Non Invasive Cardiac system (NICaS)
Whole Body Electrical Bio Impedance
Bio Impedance Technology

Study Review

January 2014
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CARDIAC OUTPUT MONITORING
Reviewing the Evidence on Four Systems

CLINICAL ENGINEERING COMMUNICATION TIPS

INTEROPERABILITY CERTIFICATION FROM IHE

SAFETY MATTERS
Proposed Changes to Defibrillator Regulations
Sentinel Event Alert on Alarms
Reducing Pharmacotherapy Errors
... And More
GO WITH THE FLOW

THERMODILUTION USING A PULMONARY ARTERY CATHETER IS CONSIDERED THE GOLD STANDARD IN MEASURING CARDIAC OUTPUT. HOWEVER, DRAWBACKS ASSOCIATED WITH THE TECHNIQUE HAVE PROMPTED CLINICIANS TO SEEK LESS INVASIVE OPTIONS. BUT THESE ALTERNATIVES HAVE THEIR OWN LIMITATIONS. WE EXAMINE THE EVIDENCE ON FOUR DEVICES THAT MEASURE CARDIAC OUTPUT USING MINIMALLY INVASIVE AND NONINVASIVE TECHNIQUES.

Measuring a patient's cardiac output—the amount of blood pumped by the heart per minute—can aid in diagnosing diseases of the cardiovascular system and in managing high-risk patients (e.g., those suffering from burns, sepsis, or shock) and patients undergoing major surgical procedures. The cardiac output value can be derived from heart rate and stroke volume (the amount of blood pumped by the heart per beat) using the relationship

$$\text{cardiac output} = \text{stroke volume} \times \text{heart rate}$$

The traditional approach to monitoring cardiac output is pulmonary artery catheterization using thermodilution as the measurement method. However, the drawbacks associated with this technique—including the risk of pulmonary artery rupture and air embolism—have led clinicians to seek less invasive alternatives.

In our December 2009 issue, we looked at some minimally invasive and noninvasive alternatives to pulmonary artery catheterization for cardiac output monitoring and reviewed the evidence regarding their effectiveness. This article serves as an update to that piece. We profile four additional cardiac output monitoring systems and review the evidence regarding their accuracy compared to other cardiac output monitoring techniques, particularly thermodilution. We also examine evidence regarding improved clinical outcomes with use of these devices.

We look at the following systems:

- **ConMed ECOM.** The literature we reviewed did not show the ECOM to be an acceptable alternative to the reference techniques; however, two studies found that the monitor was useful in predicting fluid responsiveness in abdominal and cardiac surgery patients. When the monitor is used in the OR with electrosurgical equipment, interruptions in monitoring could occur. We did not find any studies addressing clinical outcomes.

- **Edwards Lifesciences FloTrac sensor.** Previously reviewed literature showed the FloTrac sensor to be comparable to thermodilution in stable cardiac surgery patients. Studies on the latest generation of the FloTrac sensor, however, found that the device may be less reliable than thermodilution in hemodynamically unstable patients such as those undergoing abdominal surgery.
or liver transplantation, those on vasopressor therapy, or those with sepsis. Two studies reported improved clinical outcomes (reduced complications and hospital length of stay) when the FloTrac sensor was used to guide fluid management in abdominal surgery patients.

- **Edwards Lifesciences VolumeView sensor.** The VolumeView sensor is relatively new; therefore, the evidence on it is limited. More independent studies on varied patient populations are required to determine its efficacy. We did not find any studies addressing clinical outcomes.

- **NI Medical NICaS.** Six studies examined in our literature review found that the NICaS is an acceptable alternative to the reference techniques for cardiac output measurements in cardiac patients and heart failure patients. Two of those studies found it to be more accurate than thoracic impedance cardiography. We did not find any studies addressing clinical outcomes. Of these systems, only NI Medical’s NICaS is noninvasive; the remaining three systems are considered minimally invasive.

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**Cardiac Output Monitoring Techniques**

### Pulmonary Artery Thermodilution

Traditionally, cardiac output is measured using a technique known as pulmonary artery thermodilution, which incorporates the use of a pulmonary artery catheter, or PAC. Pulmonary artery thermodilution is considered the gold standard in cardiac output monitoring. There are two basic versions of this technique: bolus and continuous. In bolus, or intermittent, thermodilution, a bolus of an injectate at a known temperature is infused into the bloodstream, and the change in temperature caused by the injectate is measured at some downstream location using temperature sensors incorporated into a PAC. One drawback to bolus thermodilution is that it does not provide a continuous measurement of...
cardiac output and therefore cannot detect rapid and sudden changes in the hemodynamic status of high-risk patients.

Continuous thermodilution involves measuring the change in the temperature of blood at a downstream location after introducing a heating filament upstream. Typically, the heating filament is placed in the right ventricle and powered on intermittently, and blood temperature is measured in the pulmonary artery. The displayed cardiac output is an average of measurements taken over three to six minutes.

The use of a PAC adds a degree of risk to the technique: PACs are both invasive and associated with a number of complications, most of which are related to the insertion of the catheter; these include pulmonary artery rupture, air embolism, and arrhythmias. Additionally, evidence regarding the efficacy of PACs in improving clinical outcomes is weak; therefore, this technique is being used on a small and declining percentage of critical care patients (Schwann et al. 2011, Wheeler et al. 2006, Wiener et al. 2007).

ALTERNATIVE TECHNIQUES

The drawbacks associated with pulmonary artery thermodilution have spurred the development of less invasive alternatives for monitoring cardiac output. These alternative technologies, although less invasive than pulmonary artery thermodilution, have their own drawbacks, and the evidence regarding their usefulness can be limited. All currently marketed cardiac output monitoring systems fall into one or more of the following categories.

Arterial waveform analysis. This minimally invasive technique uses an arterial pressure line and is based on the principle that changes in arterial blood volume during a cardiac cycle are accompanied by changes in pulse pressure. Stroke volume can be determined by converting the change in pulse pressure obtained from the arterial pressure waveform to a corresponding change in blood volume. Pulse pressure changes that correspond to a change in blood volume are dependent on arterial characteristics such as aortic compliance and peripheral resistance.

Systems using arterial waveform analysis often need to compensate for changes in individual arterial/aortic characteristics that might occur during the measurement period, due either to physiologic changes or to changes associated with treatment. Most devices compensate for these changes using an independent measure of stroke volume (e.g., thermodilution). However, some devices don’t use any external calibration and instead use proprietary algorithms that frequently update specific calculation parameters based on the patient’s demographic and physiologic information.

Devices that use arterial waveform analysis might not be accurate in patients with certain arrhythmias or arterial tree pathologies (conditions that affect the shape of the arterial pressure waveform) or in the presence of circulatory assist devices such as intra-aortic balloon pumps.

Three of the systems we reviewed use this technique: the ConMed ECOM (which uses a combination of arterial waveform analysis and impedance cardiography [described under Electrical, below]) and the Edwards Lifesciences FloTrac and VolumeView.

Esophageal Doppler. This minimally invasive approach uses Doppler ultrasound techniques to measure blood flow in the aorta, and can be used in the absence of any peripheral or central line. In this technique, an ultrasonic wave is directed toward the aorta. Measurements are performed using ultrasound probes that are inserted into the esophagus and aimed at the aorta. The frequency of the wave reflected back by the moving blood cells (in the aorta) is different from the originally transmitted ultrasound frequency; this shift in frequency can be used to obtain the velocity of the blood in the aorta. That velocity can be used to calculate the distance traveled by the blood in the aorta during systole, known as the stroke distance. The stroke distance is then used to estimate stroke volume using the cross-sectional area of the aorta, which is estimated using the patient’s age, height, and weight. This technique is typically used on intubated patients.

Electrical. In this noninvasive technique, cardiac output is derived by applying an electrical signal across certain areas of the body (e.g., chest, ankle) using electrodes...
placed on the patient. Changes in the applied signal are then measured during each cardiac cycle. Observed changes in impedance and phase shift can be related to changes in blood volume. Devices using these techniques are typically susceptible to motion artifacts that might prove a hindrance to continuous monitoring.

One of the more common electrical techniques is known as impedance cardiography (ICG), which is based on the theory that changes in blood volume in the aorta during each cardiac cycle result in impedance changes that can be used to estimate stroke volume. The impedance changes can be derived by measuring voltage changes to an applied electrical signal. Traditionally, the ICG technique uses electrodes placed on the patient's neck and chest (known as thoracic ICG). One drawback of these locations is the susceptibility to noise. In addition to blood flow, the electrodes may pick up other signals such as airflow through the lungs. Two systems we review use ICG: the ConMed ECOM (which uses a combination of ICG and arterial waveform analysis) and the Nitric Medical NICaS.

**Rebreathing.** The noninvasive rebreathing technique is based on the principle that intake or elimination of a gas (as indicated by the difference in the concentration of the gas entering and exiting the lungs) is proportional to the amount of blood flow to the lungs that is involved in the gas exchange. The amount of gas consumed/produced is used as an indication of pulmonary blood flow, and in the absence of significant intrapulmonary shunt (blood flow to the lungs not involved in gas exchange) or intracardiac shunt (blood flow across the chambers of the heart), pulmonary blood flow can be equated to systemic blood flow or cardiac output. Devices using this technique may be inaccurate in patients with abnormally high intrapulmonary or intracardiac shunts (which can occur in the presence of some respiratory or cardiac diseases).

**Transesophageal echocardiography.** In transthoracic echoangiography, or TTE, an ultrasound probe is placed on the chest to measure the velocity of blood across the aortic or pulmonary valve. This, combined with the cross-sectional area of the valves, allows calculation of left or right stroke volume and cardiac output. This noninvasive technique may be inaccurate in patients with valve and flow-pattern abnormalities.

### PRODUCT REVIEWS

Pulmonary artery thermodilution is considered the gold standard for cardiac output measurement. Therefore, the tables that accompany our product reviews compare the evidence on each product with the evidence on thermodilution. But because comparisons to other methods can also be useful (see the box on page 180), the discussions in each review also take into consideration studies comparing the products to other cardiac output techniques.

**ConMed ECOM**

Supplier. ConMed Corp. (101345), Utica, NY (USA): +1 (800) 448-6506, +1 (315) 797-8375; www.conmed.com

Procedure. The ECOM (which stands for Endotracheal Cardiac Output Monitor) is a minimally invasive system that measures cardiac output and other related hemodynamic parameters using a combination of two different techniques: ICG and arterial waveform analysis. The monitor obtains an impedance waveform with the ICG technique and uses this in conjunction with the arterial waveform analysis technique to determine cardiac output.

The monitor consists of an endotracheal tube with a printed electrode array that applies the electrical signal required for ICG. The electrode array consists of a single electrode at the proximal end of the tube and six electrodes at the distal end. When the patient is intubated, the distal electrodes are located adjacent to the ascending aorta, thus facilitating aortic blood flow measurements. The electrode array also detects the R-wave and uses the R-R interval to obtain heart rate measurements. Arterial pressure data is obtained from an existing arterial pressure line and, in addition to cardiac output, facilitates estimation of other hemodynamic parameters such as systemic vascular resistance and stroke volume variation (neither of which can be obtained from ICG). At the beginning of the procedure, the clinician must enter the patient's height, weight, and age, which are used along with the measured ICG signal to estimate stroke volume. According to the vendor, since the electrodes are in such close proximity to the aorta, the ECOM is less susceptible to noise compared to traditional ICG methods.

**Clinical uses.** According to the vendor, the ECOM is used primarily in the OR for short-term continuous monitoring and is indicated for use in patients who are expected to be intubated for 24 hours or less. Although ICG technology in general is susceptible to motion artifacts, this may not be an issue with this device since intubated patients in the OR are also typically sedated.

**Disposables.** The monitor requires a proprietary disposable endotracheal tube.
LITERATURE REVIEW: CONMED ECOM COMPARED TO THERMODILUTION

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<th>Study</th>
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<th>Reference method</th>
<th>Outcomes</th>
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<tr>
<td>Ball et al. 2010</td>
<td>40 cardiac surgery patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With a percentage error of 50% and a correlation coefficient of r = 0.49, the two methods were not considered comparable.</td>
</tr>
<tr>
<td>Gennart et al. 2012 (conference abstract)</td>
<td>14 cardiac surgery patients</td>
<td>Thermodilution*</td>
<td>With percentage errors of 41% and 59% (based on arterial line location), the two methods were not considered comparable.</td>
</tr>
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<td>Maus et al. 2011</td>
<td>29 coronary artery bypass graft patients</td>
<td>Balus pulmonary artery thermodilution and transesophageal echocardiography</td>
<td>The percentage error was 50% compared to thermodilution and 48% compared to echocardiography. However, the authors report acceptable trending of cardiac output.</td>
</tr>
<tr>
<td>Moller-Sorensen et al. 2012</td>
<td>25 coronary artery bypass graft patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With percentage errors ranging from 37% to 43% based on patient position, the two methods were not considered comparable. The study also reported poor trending of cardiac output by the ECOM monitor.</td>
</tr>
<tr>
<td>Van der Kleij et al. 2012 (conference abstract)</td>
<td>20 coronary artery bypass graft patients</td>
<td>Pulmonary artery thermodilution**</td>
<td>The abstract reports poor correlation (r = 0.23) between the ECOM monitor and the reference method in postoperative patients.</td>
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</table>

* The abstract does not specify what type of thermodilution was used.
** The abstract does not specify whether the method of thermodilution used was continuous or intermittent.

Evidence. We reviewed eight clinical studies that compared the ECOM monitor to other methods of cardiac output measurement. The studies involved cardiac surgery and abdominal surgery patients, and the number of patients in the studies ranged from 12 to 40. In five of the eight studies, the ECOM monitor was compared to pulmonary artery thermodilution; these studies are outlined in the table on this page. In the remaining three studies, the reference methods were transpulmonary thermodilution (which uses a central venous catheter rather than a PAC) (Fellahi et al. 2012), esophageal Doppler (Jorgensen et al. 2012), and the FloTrac sensor (Bairamian et al. 2011; see our review of this system below). In addition, three of the eight studies (Bairamian et al. 2011, Gennart et al. 2012, Van der Kleij et al. 2012) were reported as conference abstracts only; therefore, they may not represent the final results and conclusions of the studies.

In all eight studies, the authors concluded that the device was not comparable to the reference method. The evidence regarding the monitor's ability to trend cardiac output is inconsistent, with one study (Maus et al. 2011) reporting good trending (based on the correlation between the ECOM monitor and the reference techniques) and two studies (Jorgensen et al. 2012, Moller-Sorensen et al. 2012) reporting poor trending. Two studies (Bairamian et al. 2011, Fellahi et al. 2012) conclude that the technique may be useful for predicting fluid responsiveness (using stroke volume variation). Two other studies (Ball et al. 2010, Moller-Sorensen et al. 2012) found that the ECOM was susceptible to interference from electrocautery equipment used during surgeries, leading to intermittent loss of signal during electrocautery and sometimes several seconds after electrocautery was discontinued.

We did not find any studies addressing clinical outcomes.

**Edwards Lifesciences FloTrac Sensor**

*Although the authors use the term "electrocautery," we believe the intent was "electrosurgery."

Procedure. The FloTrac sensor uses arterial waveform analysis to estimate continuous cardiac output using the FloTrac algorithm. According to the vendor, the algorithm constantly monitors the arterial pressure waveform and compensates for changes in arterial/aortic characteristics. The FloTrac sensor can be used with either the EV1000 or the Vigileo monitor offered by Edwards Lifesciences.

The FloTrac sensor can be used only on patients who have an existing arterial line that can be connected to the sensor. The sensor has two output lines: One is connected to the arterial pressure cable of a bedside monitor, and the other is connected to the EV1000/Vigileo monitor. The sensor, once connected, sends arterial pressure waveform information to both monitors. The cardiac output monitor (either the EV1000 or the Vigileo) uses this information in conjunction with patient demographic information entered by the user (e.g., age, gender, height, weight) to estimate cardiac output.

We covered the FloTrac sensor in our December 2009 Guidance Article. Since then, the vendor has updated the device's algorithm. The literature reviewed in the
LITERATURE REVIEW: EDWARDS LIFESCIENCES FLOTRAC COMPARED TO THERMODILUTION

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<td>Biancuzzo et al. 2011</td>
<td>21 liver transplantation patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With a percentage error of 37% and a correlation coefficient of r = 0.65, the agreement between the two methods was not considered clinically acceptable.</td>
</tr>
<tr>
<td>De Backer et al. 2011</td>
<td>58 septic patients</td>
<td>Balus and continuous pulmonary artery thermodilution</td>
<td>With a percentage error of 30.4%, the FloTrac sensor was considered to be at least as accurate as the reference methods.</td>
</tr>
<tr>
<td>Marque et al. 2013</td>
<td>18 septic shock patients</td>
<td>Continuous pulmonary artery thermodilution</td>
<td>With an overall percentage error of 64%, the two methods were not considered comparable.</td>
</tr>
<tr>
<td>Slagt et al. 2013</td>
<td>19 septic shock patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With an overall percentage error of 53%, the two methods were not considered comparable. The authors conclude that the trending ability of the FloTrac sensor is fair.</td>
</tr>
<tr>
<td>Su et al. 2012</td>
<td>28 liver transplantation patients</td>
<td>Continuous pulmonary artery thermodilution</td>
<td>With a percentage error of 75%, the two methods were not considered comparable. The authors also report poor trending of cardiac output by the FloTrac sensor.</td>
</tr>
<tr>
<td>Tsai et al. 2012</td>
<td>20 liver transplantation patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With a percentage error of 54.93%, the authors report poor correlation between the two methods.</td>
</tr>
<tr>
<td>Vasdev et al. 2012</td>
<td>38 coronary artery bypass graft patients</td>
<td>Balus pulmonary artery thermodilution</td>
<td>With percentage errors of 20% and 22% depending on the monitoring site (radial vs. femoral), the two methods were considered comparable.</td>
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Evidence section below deals only with the performance of the updated algorithm.

Clinical uses. The FloTrac sensor can be used for long-term continuous monitoring of patients who are already connected to an invasive blood pressure monitor with preexisting arterial line access.

Disposable. The system requires the proprietary, disposable FloTrac sensor. It does not require any proprietary catheters.

Evidence. We reviewed 16 studies published since 2010 that compared the performance of the newer generation of the FloTrac sensor with other cardiac output monitoring techniques. Seven of the 16 studies (see the table above) compared the FloTrac to pulmonary artery thermodilution, four studies compared it to transpulmonary thermodilution, and the remaining five compared it to Doppler echocardiography. The studies involved cardiac surgery, liver transplantation, sepsis, and abdominal surgery patients, and the number of patients in the studies ranged from 18 to 60.

In our previous review, the earlier generation of the FloTrac sensor was found to be comparable to thermodilution in stable cardiac surgery patients, and the one recent study we reviewed that looked at cardiac surgery patients (Vasdev et al. 2012) reports that this is the case with the new version of the FloTrac.

Most studies on the newer generation of the sensor examined its performance in hemodynamically unstable patient populations (e.g., septic patients, liver transplantation patients). In 10 of the 16 studies examined in our current review, the authors conclude that the latest generation of the FloTrac sensor is not comparable to the reference techniques; patient populations in these studies include patients undergoing abdominal surgery, patients undergoing liver transplantation, and patients undergoing vasopressor therapy (which could affect arterial compliance). Among studies comparing FloTrac to thermodilution for patients with sepsis, one study (De Backer et al. 2011) reported good accuracy, whereas two others (Marque et al. 2013, Slagt et al. 2013) reported a high percentage error. Two studies (Benes et al. 2010, Mayer et al. 2010) looked at patient outcomes.
when the FloTrac sensor was used for fluid management during major abdominal surgery compared to standard fluid management approaches (using mean arterial pressure and central venous pressure to guide therapy). Both studies showed that the length of stay and incidence of complications decreased when the FloTrac sensor was used. (Note that the Mayer study was funded by Edwards Lifesciences.)

**LITERATURE REVIEW: EDWARDS LIFESCIENCES VOLUMEVIEW COMPARED TO THERMODILUTION**

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<th>Reference method</th>
<th>Outcomes</th>
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<tr>
<td>Costa et al.</td>
<td>3 patients undergoing liver transplantation</td>
<td>Bolus and continuous pulmonary artery thermodilution</td>
<td>With percentage errors of 49% and 63% when compared to bolus and continuous thermodilution, the VolumeView was not considered comparable to the reference methods.</td>
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**Edwards Lifesciences VolumeView Sensor**

Supplier. Edwards Lifesciences Corp. [374501], Irvine, CA (USA); +1 (800) 424-3278, +1 (949) 250-2500; www.edwards.com

Procedure. The VolumeView sensor is part of the VolumeView set and is used in conjunction with the EV1000 monitor for continuous cardiac output monitoring. The sensor uses the arterial waveform analysis technique to estimate continuous cardiac output, and the arterial waveform is obtained using the VolumeView femoral catheter. However, unlike the FloTrac sensor, which does not use any external calibration, the VolumeView sensor requires calibration using an external cardiac output measurement. Typically, calibration is recommended for arterial waveform analysis techniques for unstable or critically ill patients at defined intervals of time (can range from every 30 minutes to every eight hours based on patient condition) or before undertaking any therapeutic interventions. The vendor offers the ability to perform transpulmonary thermodilution using the VolumeView set, and the resulting cardiac output measurements can be used to periodically calibrate the VolumeView sensor measurements.

Transpulmonary thermodilution technique can also be used to obtain volume measurements such as global end-diastolic volume, global ejection fraction, and extravascular lung water.

Clinical uses. The VolumeView set can be used for long-term continuous monitoring of patients who have an existing central venous line.

**Disposables.** The VolumeView set, which includes the VolumeView sensor and the VolumeView femoral catheter.

Evidence. The evidence on the VolumeView sensor is limited, since the device was introduced in 2011 and is therefore relatively new. We only found two studies that compared the VolumeView sensor with other cardiac output monitoring techniques in human patients. Costa et al. (2012) compared the cardiac output measurements from the VolumeView sensor to those obtained from pulmonary artery thermodilution with PACs in five patients undergoing liver transplantation (see the table above). The study found that the VolumeView results were not comparable to the values obtained from thermodilution. This study was only reported as a conference abstract; thus, the results reported may not represent the final results and conclusions of the study. The other study, Kiefer et al. (2012), compared the VolumeView sensor with another arterial waveform analysis technique that also uses transpulmonary thermodilution for calibration. This study was performed on critically ill patients and found that the VolumeView results were comparable to those from the reference method; note that the study was funded by Edwards Lifesciences.

We did not find any studies addressing clinical outcomes with this device.

**NI Medical NICaS Monitor**

Supplier. NI Medical USA [457874], Akron, OH (USA); +1 (800) 979-2904; www.nimedical.com

Procedure. The NICaS (which stands for Non Invasive Cardiac System) consists of a laptop and one pair of wrist-ankle ICG electrodes. The system is based on the ICG technique, which is based on the theory that changes in the voltage of an electrical signal applied across an area of the body are due to changes in impedance (which in turn are associated with changes in blood volume during each cardiac cycle).
Most cardiac output monitors that use this model measure changes in thoracic impedance with electrodes placed on the chest; however, the NICaS monitor measures impedance through two ICG electrodes—one on the patient's wrist and the other on the contralateral ankle.

At the beginning of the procedure, the clinician must enter the patient's gender, age, weight, and height. This data is used in conjunction with the impedance data obtained from the wrist and ankle electrodes to estimate stroke volume. The electrodes also provide heart rate and a single-channel electrocardiogram (ECG). The ECG waveform, the impedance waveform, and the hemodynamic parameters are all displayed on the laptop. Standard ECG electrodes are provided as an option with the monitor and can be used in addition to the ICG electrodes to obtain three-channel ECG.

Clinical uses. The ICG technology is inherently susceptible to motion artifacts, and typically patients need to be still while measurements are being taken. Thus, this monitor, like others that use the ICG model, is more suitable for spot-check measurement of cardiac output and other hemodynamic parameters than for continuous monitoring. Another issue to consider is that since this monitor is laptop-based, infection control risks must be taken into account, as the presence of a keyboard complicates cleaning of the device. As a result, additional precautions (e.g., special keyboard covers) may be needed, particularly when the device is used in the OR.

Disposables. One pair of wrist-ankle electrodes.

Evidence. We reviewed six studies comparing cardiac output measurements from the NICaS monitor with those from other reference methods. Five of these studies used thermodilution as the reference method (see the table on this page), and the remaining study (Leitman et al. 2006) used Doppler echocardiography. One of the studies (Goor 2006) was reported as a conference abstract only; therefore, the reported findings may represent only preliminary results and not the final results and conclusions of the study. The studies involved cardiac patients, and the number of patients in the studies ranged from 35 to 122.

All six studies found good correlation between the NICaS system and the reference method. Two of the studies (Cotter et al. 2006, Goor 2006) also compared thoracic ICG, in addition to the NICaS monitor, to thermodilution for the same patients, and found the NICaS system to better correlate with thermodilution.

We did not find any studies addressing clinical outcomes with this device.

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<th>LITERATURE REVIEW: NI MEDICAL NICAS COMPARED TO THERMODILUTION</th>
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<td><strong>Study</strong></td>
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<td>Cotter, Moshkovitz, et al. 2004</td>
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<td>Cotter, Torre-Amiot, et al. 2004</td>
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<td>Cotter et al. 2006</td>
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<td>Goor 2006 (conference abstract)</td>
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<td>Pareides et al. 2006</td>
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* The abstract does not specify what type of thermodilution was used.
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FloTrac sensor (Edwards Lifesciences, LLC) for noninvasive cardiac output monitoring [product output brief]. Custom Hotline Service. 2012 Dec 6.


DO YOU HAVE A QUESTION ABOUT CARDIAC OUTPUT MONITORING?

For example, are you wondering . . .

- What factors do I need to consider when purchasing a minimally invasive or noninvasive cardiac output monitor?
- How widespread is the use of cardiac output monitoring in clinical practice?
- What is the most established alternative technique in monitoring cardiac output?

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Take our physiologic monitoring system survey. We want your thoughts on your physiologic monitoring system’s ease of use, functionality, and reliability. Take a few minutes to fill out our user experience survey, available through your member home page or at https://survey.ecri.org/Survey.aspx?d=2178a562844402e9d0159fc16290bce. When done, you’ll be automatically entered to win an iPad Mini.

See the results of our CT survey. The results of our CT system user experience survey are now available. Find out how your peers ranked the top vendors and models on the market in terms of their functions, features, and service. View the results at https://members2.ecri.org/Components/UserExperience/Pages/ct_scanners/userexp_main.aspx.
Noninvasive and Simple Assessment of Cardiac Output and Pulmonary Vascular Resistance With Whole-Body Impedance Cardiography Is Useful for Monitoring Patients With Pulmonary Hypertension

Yu Taniguchi, MD; Noriaki Emoto, MD, PhD; Kazuya Miyagawa, MD, PhD; Kazuhiko Nakayama, MD, PhD; Hiroto Kinutani, MD; Hidekazu Tanaka, MD, PhD; Toshiro Shinke, MD, PhD; Ken-ichi Hirata, MD, PhD

Background: Right heart catheterization (RHC) is the gold standard for the diagnosis of pulmonary hypertension (PH) and a useful tool for monitoring PH. However, there are some disadvantages in the regular use of RHC because it is invasive. Noninvasive methods for monitoring hemodynamics are needed to manage patients with PH. In this study, we aimed to evaluate the reliability of noninvasive hemodynamic assessment with whole-body impedance cardiography (Non-Invasive Cardiac System [NICaS]) for PH.

Methods and Results: We investigated 65 consecutive patients undergoing RHC. Two-thirds of them had pulmonary arterial hypertension and one-third had chronic thromboembolic PH; 25% of the patients were receiving medical therapy. Cardiac output (CO) was estimated by NICaS (NI-CO), thermodilution (TD-CO), and the Fick method (Fick-CO). There was a strong correlation between NI-CO and TD-CO (r=0.715, P<0.0001) and Fick-CO (r=0.653, P<0.0001). Noninvasive pulmonary vascular resistance (PVR) was estimated using a conventional invasive equation with NI-CO, mean pulmonary arterial pressure was calculated by echocardiographic measurement, and pulmonary capillary wedge pressure was estimated at 10 mmHg in all cases. NICaS-derived PVR was very strongly correlated with invasive PVR (TD-PVR: r=0.704, P<0.0001; Fick-PVR: r=0.702, P<0.0001).

Conclusions: Noninvasive measurement of CO and PVR using NICaS and echocardiography is a useful tool for the assessment of PH.

Key Words: Cardiac output; Noninvasive assessment; Pulmonary hypertension; Pulmonary vascular resistance; Whole-body impedance cardiography

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated pulmonary vascular resistance (PVR) because of pulmonary vascular remodeling. This leads to a decrease in cardiac output (CO) and ultimately death. Recently, targeted medical therapy for PAH patients with endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs has been established, and the prognosis of PAH has improved. However, there is no universally accepted consensus on the treatment goals or follow-up strategy for PAH patients. Right heart catheterization (RHC) is not only the gold standard for the diagnosis of PAH, but is also a useful tool for monitoring PAH, and is recommended 3–6 months after new treatments and in the case of clinical worsening. Hemodynamic monitoring with RHC is predictive of survival and effective in a goal-oriented treatment strategy, and has been recommended by a recent guideline; however, there are some disadvantages in the regular use of RHC as a follow-up procedure, especially with regard to invasiveness. Noninvasive and less complicated methods for monitoring hemodynamics are needed to manage patients with pulmonary hypertension (PH). Less invasive hemodynamic monitoring has recently been suggested as feasible in some situations. The Non-Invasive Cardiac System (NICaS; NI Medical, Hod-Hasharon, Israel) is a device for calculating CO noninvasively with whole-body impedance cardiography (ICGωn). The NICaS-derived CO (NI-CO) has been shown to be as reliable as the RHC-derived CO and is applicable for the noninvasive assessment of cardiac function.
in patients with left-sided chronic heart failure, but its feasibility in patients with PH has not been evaluated. The purpose of this study was to evaluate the reliability of noninvasive measurement of CO and PVR with ICGw in patients with PH.

**Editorial p????**

**Methods**

This study was approved by Kobe University Hospital Institutional Review Board and the patients provided written informed consent to participate.

**Patients**

We enrolled 65 consecutive patients with known or suspected pulmonary hypertension hospitalized in Kobe University Hospital from April 2010 to August 2011. All patients who were scheduled for RHC without fulfilling one of the exclusion criteria were eligible for the study. The exclusion criteria included restlessness and/or unstable patient condition, severe aortic valve regurgitation and/or aortic stenosis, aortic aneurysm, heart rate >130 beats/min, intra- and extracardiac shunts, severe peripheral vascular disease, severe pitting edema, sep-

| Table 1. Clinical Characteristics of All Patients at Initial Hospitalization |
|-----------------------------|-----------------------------|
| Age (years)                    | 62±14                      |
| Female (%)                     | 39 (65)                    |
| Diagnosis (%)                  |                            |
| PAH                           | 38 (63)                    |
| IPAH                          | 12 (20)                    |
| CTD-PAH                       | 24 (40)                    |
| Po-PAH                        | 2 (3)                      |
| PH associated with respiratory disorders | 3 (5)                |
| CTPH                          | 20 (33)                    |
| WHO-fc (%)                    |                            |
| 1                             | 1 (1.7)                    |
| 2                             | 22 (37.3)                  |
| 3                             | 32 (54.2)                  |
| 4                             | 4 (6.8)                    |
| Treatment (%)                 | 25 (24)                    |
| Bosentan                      | 13 (22)                    |
| Sildenafil                    | 14 (23)                    |
| Beraprost                     | 10 (17)                    |

| Hemodynamic variables          |                             |
| sPAP (mmHg)                    | 53.9±21.3                  |
| mPAP (mmHg)                    | 31.7±12.0                  |
| RAP (mmHg)                     | 3.7±4.2                    |
| PCWP (mmHg)                    | 7.0±4.3                    |
| CO (TD) (L/min)                | 4.90±1.62                  |
| CO (Fick) (L/min)              | 3.92±2.08                  |
| PVR (TD) (dyn·s⁻¹·cm⁻⁵)        | 433±244                    |
| PVR (Fick) (dyn·s⁻¹·cm⁻⁵)      | 581±344                    |
| HR (beats/min)                 | 73±11                      |

**Table 2. Hemodynamic Measurements**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD-CO (L/min)</td>
<td>4.92±1.56</td>
</tr>
<tr>
<td>Fick-CO (L/min)</td>
<td>3.87±1.24</td>
</tr>
<tr>
<td>Echo-CO (L/min)</td>
<td>4.34±1.11</td>
</tr>
<tr>
<td>NI-CO (L/min)</td>
<td>4.40±1.32</td>
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<tr>
<td>TD-PVR (dyn·s⁻¹·cm⁻⁵)</td>
<td>446±249</td>
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<tr>
<td>Fick-PVR (dyn·s⁻¹·cm⁻⁵)</td>
<td>583±362</td>
</tr>
<tr>
<td>Echo-PVR (dyn·s⁻¹·cm⁻⁵)</td>
<td>660±363</td>
</tr>
<tr>
<td>NI-PVR (dyn·s⁻¹·cm⁻⁵)</td>
<td>544±316</td>
</tr>
</tbody>
</table>

Echo-CO, echocardiography-derived cardiac output; Echo-PVR, echocardiography-derived PVR; Fick-CO, cardiac output derived by the modified Fick method; Fick-PVR, PVR derived by modified Fick method; NI-CO, NICaS-derived cardiac output; NI-PVR, NICaS with echocardiography-derived PVR; PVR, pulmonary vascular resistance; TD-CO, thermodilution-derived cardiac output; TD-PVR, thermodilution-derived PVR.

**Hemodynamics**

Hemodynamic data were derived from standard RHC in all patients using a 6Fr Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA). The catheter was introduced into the pulmonary artery under fluoroscopic guidance. Mean pulmonary arterial pressure (mPAP), systolic and end-diastolic pulmonary arterial pressure (sPAP and dPAP), mean right atrial pressure, and PCWP were measured. CO was measured using the following techniques.

**Thermodilution-Derived CO (TD-CO)** A 5-ml bolus of iced 5% glucose solution was injected 5 times at the same rate. The results of 3 injections within 15% of their extreme disparity were averaged to derive the TD-CO value.

**Modified Fick method (Fick-CO)** Blood samples were obtained from systemic and pulmonary arteries. All samples were measured for oxygen saturation with the same device (Radiometer ABL 715, Copenhagen, Denmark).

**NI-CO** These measurements were performed simultaneously with the measurement of TD-CO and Fick-CO during RHC. The measurement of NI-CO followed the method as previously reported: an alternating electrical current of 1.4 mA with a 30-kHz frequency is passed through the patient via 2 pairs of tetrapolar electrodes – 1 pair placed on the wrist above the radial pulse, and the other pair placed on the contralateral ankle above the posterior tibialis arterial pulse. If the arterial pulses in the legs are either absent or of poor quality, the second pair of electrodes is placed on the contralateral wrist.

The NICaS apparatus calculates the stroke volume (SV) by Frimerman’s formula:

\[ SV = \frac{dR}{R} \times \frac{\rho}{L} \times \frac{1}{2} \times (\alpha + \beta) \times KW \times HF \]

where \( dR \) is the impedance change; \( R \) is the basal resistance; \( \rho \) is the blood electrical resistivity; \( L \) is the patient’s height; \( Ri \) is the corrected basal resistance according to sex and age; \( KW \) is a correction factor for weight according to ideal values; \( HF \) is the hydration factor, which takes into account the body water composition. \( \alpha + \beta \) is equal to the ECG R-R wave interval...
Noninvasive Assessment of PH

Measurement of PVR

PVR (dyn·s⁻¹·cm⁻⁵) was calculated using RHC from the equation:

\[ \text{PVR} = 80 \times \frac{(\text{mPAP} - \text{PCWP})}{\text{CO}} \]

PVR was also estimated noninvasively using a combination of NICaS and echocardiography, and by echocardiography alone. \(^9\) Echo-mPAP was calculated as Echo-sPAP plus estimated right atrial pressure (Echo-RAP). \(^9\)

Statistical Analysis

Quantitative data are presented as mean±SD. The correlations

and \( \beta \) is the diastolic time interval. To calculate the CO, SV is multiplied by the heart rate. Because the NI-CO values are calculated every 20 s, the average of 3 measurements obtained consecutively during 60 s of monitoring is considered to be the NI-CO value for each individual case.

Echocardiography

Echocardiography was performed using a Vivid 5 system and a 3.5-MHz transducer (GE Vingmed Ultrasound AS, Horten, Norway). Two-dimensional Doppler examinations were performed in the usual manner. CO was measured by tracing the left ventricular ejection flow (Echo-CO). Echo-sPAP was estimated from the peak velocity of the tricuspid regurgitation jet plus estimated right atrial pressure (Echo-RAP). \(^9\)

Measurement of PVR

PVR (dyn·s⁻¹·cm⁻⁵) was calculated using RHC from the equation:

\[ \text{PVR} = 80 \times \frac{(\text{mPAP} - \text{PCWP})}{\text{CO}} \]

PVR was also estimated noninvasively using a combination of NICaS and echocardiography, and by echocardiography alone. \(^9\) Echo-mPAP was calculated as Echo-sPAP plus estimated right atrial pressure (Echo-RAP). \(^9\)

Statistical Analysis

Quantitative data are presented as mean±SD. The correlations
Among TD-CO, Fick-CO, Echo-CO, and NI-CO and between Echo-mPAP and mPAP measured by RHC (RHC-mPAP) were determined by calculating the Spearman’s rank correlation coefficient. P<0.05 was considered to be significant. Agreement between methods was analyzed by the Bland-Altman method. The limits of the agreement were expressed as the mean±SD. The 95% confidence intervals (CIs) of the bias were also calculated. Receiver-operating characteristic (ROC) curves were generated for the detection of elevated PVR defined as > 240 dyn·s⁻¹·cm⁻⁵ (3 Wood units [WU]). The area under the curve (AUC), cut-off value, sensitivity, and specificity were estimated by the ROC curves. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA).

Results
The baseline characteristics of all patients at initial hospitalization are summarized in Table 1. Approximately two-thirds of the patients had PAH (World Health Organization [WHO] classification of PH group 1) and the other one-third of the patients had chronic thromboembolic PH (CTEPH: WHO group 4); 5% of the patients were classified as WHO group 3. At enrollment, 24% of the patients were receiving medical therapy.

Relationships Among Parameters
The mean CO values from all measurements in these subjects for TD-CO, Fick-CO, Echo-CO, and NI-CO were 4.92±1.56 L/min, 3.87±1.24 L/min, 4.34±1.11 L/min, and 4.40±1.32 L/min, respectively (Table 2). A significant and very strong correlation was observed between TD-CO and NI-CO (r=0.715, P<0.0001) and between TD-CO and Fick-CO (r=0.795, P<0.0001) by 2-tailed Spearman’s rank correlation test (Figure 1). There was a strong correlation between Fick-CO and NI-CO (r=0.653, P<0.0001). However, the correlation between Echo-CO and TD-CO or Fick-CO was significant but not strong (r=0.512 or 0.461, P<0.0001, respectively). The differences between 2 measurements were plotted according to the Bland-Altman method (Figure 2). The mean bias and limits of agreement between TD-CO and NI-CO, Fick-CO and NI-CO, and TD-CO and Fick-CO were 0.50±1.08 L/min, –0.54±1.04 L/min, and 1.02±0.86 L/min, respectively. The limits of agreement between TD-CO and Echo-CO, and Fick-CO and Echo-CO were 0.64±1.33 L/min and –0.42±1.18 L/min, respectively. The mean values of all measurements of invasive mPAP and Echo-mPAP were 32.9±1.28 mmHg and 43.0±1.59 mmHg, respectively. There was a very strong correlation between inva-
Noninvasive Assessment of PH

We demonstrated strong correlations among the NICaS, TD, and the Fick method for the measurement of CO. Although the limits of agreement between NI-CO and TD-CO or Fick-CO estimated by the Bland-Altman approach were not small, they were acceptable when compared with previous reports. Therefore, we believe that NICaS can be a reliable tool for the noninvasive assessment of CO in PH. However, compared with NI-CO, the correlation between Echo-CO and TD-CO or Fick-CO was weaker and the limits of agreements were larger. The relative inaccuracy of CO measured by echocardiography was consistent with a previous report, and may be a consequence of using the Doppler method, severe tricuspid regurgitation, and operator-dependency.

We also demonstrated the feasibility of noninvasive and simple measurement of PVR using a combination of NICaS and echocardiography. Kouzu et al showed that tricuspid regurgitant pressure gradient (TRPG)/right ventricular time-velocity integral (TVI) is reliable for the estimation of PVR. However, the correlation between PVR measured by invasive methods and Echo-PVR was not as strong (r=0.602 or 0.603, P=0.0001, respectively; Figures 4G, J) as that between invasive methods and NI-PVR. Figure 4B and dyn·s⁻¹·cm⁻² shows the Bland-Altman plots of the differences between TD-PVR, Fick-PVR, and NI-PVR. The limits of agreement between TD-PVR and NI-PVR, Fick-PVR and NI-PVR, and TD-PVR and Fick-PVR were −195±265 (715 to 326) dyn·s⁻¹·cm⁻², −35±325 (673 to 603) dyn·s⁻¹·cm⁻², and −135±164 (457 to 187) dyn·s⁻¹·cm⁻², respectively. The limits of agreement between TD-PVR and Echo-PVR, and Fick-PVR and Echo-PVR were −191±266 (713 to 330) dyn·s⁻¹·cm⁻², and −33±341 (703 to 635) dyn·s⁻¹·cm⁻², respectively (Figures 4H, K). The AUC for NI-PVR to detect increased PVR >240 dyn·s⁻¹·cm⁻² (3 WU) against TD and Fick-PVR were 0.84 (95% CI, 0.72–0.96) and 0.92 (95% CI, 0.84–0.99), respectively (Figures 3C, F), and optimal cut-off values were 411 dyn·s⁻¹·cm⁻² (sensitivity: 81.3%, specificity: 75%) and 400 dyn·s⁻¹·cm⁻² (sensitivity: 80.3%, specificity: 100%), respectively. The AUC for Echo-PVR against TD and Fick-PVR were lower: 0.75 (95% CI, 0.57–0.92) and 0.83 (95% CI, 0.66–0.99) (Figures 4L, L) compared with that for NI-PVR against TD and Fick-PVR.

Discussion

We report on the reliability of a noninvasive and simple method of assessing CO and PVR using ICGw in patients with PH. Previous reports have indicated the feasibility of hemodynamic assessment using various methods in comparison with RHC in a range of clinical settings; however, a reliable method for the assessment of PH has not yet been established. In our study, the value for TD-CO was significantly higher than the CO values with other methods, including Fick-CO, and therefore, the value of TD-PVR was underestimated. This
could be caused by overestimation of the value of TD-CO in the presence of low CO, consistent with previous reports.23

**Study Limitations**

The main limitation of this study was the need to measure the Doppler parameter for estimating NI-PVR. Proper alignment of the ultrasound beam is crucial for the Doppler parameter to be determined appropriately. This may have resulted in bias in the measurement of NI-PVR. In our study, the Doppler parameter needed in order to estimate NI-PVR was only TRPG, and there was no patient in whom we were unable to obtain that value. Second, we used the conventional invasive equation for estimating NI-PVR. We had to estimate PCWP at 10 mmHg in all cases as previously reported,10 which may also have re-
sulted in the measurement of NI-PVR; however, in general, a wide variation in PCWP is not usually observed among patients with PH. Third, because CO measurement using NICaS in patients with cardiac shunts is known to be unreliable,\textsuperscript{24} we excluded cases of PAH associated with cardiac shunts. Fourth, noninvasive estimation of CO and PVR with NICaS was feasible; however, there were some patients who had large divergence between NI-CO or NI-PVR and invasive CO or PVR. Further studies are needed to clarify the factors that lead to inaccurate measurements of CO and PVR. Fifth, in our study, the number of patients with WHO functional class 4 was small. Most patients were WHO functional class 2 or 3. The reliability of NICaS in patients with severe PH is to be examined in future studies. Finally, the study sample size was relatively small and originated from a single center. We believe that a larger, multicenter study is needed to appropriately confirm the reliability of the method.

Although recent advances in treatment options and management have improved the outcomes for patients with PH, treatment goals and follow-up strategy are still not well defined. Hemodynamic monitoring with RHC is recommended in a goal-oriented treatment strategy for PH\textsuperscript{1} and is the gold standard for the assessment of PAH; however, the invasiveness of RHC is a critical factoring its regular use as a follow-up procedure. A noninvasive, accurate, and simple method is required for the management of patients with PH. We have demonstrated noninvasive measurement of CO and PVR using only simple parameters. Echo-sPAP is needed to estimate PVR, but Echo-sPAP has been established as a simple, reliable screening parameter for PH.\textsuperscript{28} This noninvasive, reliable, and simple assessment can be a useful tool for monitoring and managing patients with PH.

**Conclusion**

Noninvasive measurement of CO and PVR using NICaS is as reliable as invasive RHC. This simple assessment could help physicians to manage their patients with PH.

**Disclosures**

None.

**References**


**Supplementary Files**

**Supplementary File 1**

**Figure S1.** Linear correlation between NI-CO and TD-CO (A) or Fick-CO (B) in IPAH (●, red line), CTD-PAH (●, blue line) and CTEPH (▲, green line). Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-13-0172
Cardiac power index: staging heart failure for mechanical circulatory support
SG Hall, J Garcia, DF Larson and R Smith
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What is This?
Cardiac power index: staging heart failure for mechanical circulatory support

SG Hall, J Garcia, DF Larson and R Smith

Abstract
Cardiac power output has been shown to quantify cardiac reserve. Cardiac reserve is defined as the difference between basal and maximal cardiac performance. We compared cardiac power index to other commonly used hemodynamic parameters to validate its usefulness to stage heart failure patients and determine the optimal time for implantation of mechanical circulatory support. A retrospective study of twenty-eight heart failure patients implanted with mechanical circulatory support was analyzed at three levels of drug therapy. Subjects were further separated into two categories: survived versus deceased. Cardiac power index was the only statistically significant hemodynamic parameter that identified cardiac reserve (p<0.05) in this patient population. These results showed that a cardiac power index at or below 0.34 Watts/m² resulted in increased mortality rate, ninety days post-implantation.

Conclusion: Cardiac reserve was a determinant of post-device survival; therefore, these data suggest that device implantation should occur prior to the 0.34 Watts/m² threshold.

Keywords
cardiac power output; cardiac reserve; mechanical circulatory support; hemodynamics; cardiac power index

Introduction
Cardiac power output is the hydraulic energy required by the heart to provide enough blood flow to the systemic circulation. Cardiac power output measured at exercise reflects the peak cardiac performance attainable by the heart. Comparing maximum cardiac power output with resting cardiac power output represents the heart’s cardiac reserve. In heart failure patients, cardiac reserve is severely limited. Patients performing exercise tests or positive inotrope infusion tests tend to show little difference in cardiac performance due to poor cardiac reserve. It has been demonstrated in several studies that heart failure patients with higher cardiac reserves have better survival rates. As heart failure progresses in these patients, cardiac reserve continues to decline.

Once cardiac performance can no longer be improved through inotropic drug therapy, heart failure patients may require mechanical circulatory support. Because end-organ damage is a predictor of poor prognosis in patients who receive mechanical circulatory support, it is important to implant devices before heart failure has become so severe that irreparable systemic damage has occurred. Symptomatic assessment, drug tolerance, and myocardial oxygen consumption are commonly used to determine the severity of heart failure, but are unable to provide all the information necessary to reflect true cardiac reserve. Myocardial oxygen consumption provides an indirect measurement of cardiac output; however, given that cardiac power output incorporates cardiac output as well as systemic pressures, this distinguishes it as a rational marker of cardiac performance when compared to myocardial oxygen consumption. Cardiac power output has been used to assess cardiac performance and prognosis in cardiogenic shock and acute and chronic heart failure patients. The purpose of this study was to retrospectively analyze the application of cardiac power output to stage the severity of heart failure in patients who have received mechanical circulatory support.

Methods
Twenty-eight patients, twenty-four male and four female, with a history of heart failure were referred to the

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University of Arizona Medical Center for mechanical circulatory support. Patients were admitted due to increased heart failure symptoms or were medically transferred from outside institutions. The studied population consisted of New York Heart Association (NYHA) classes III and IV and American College of Cardiology (ACC-AHA) stages C and D. Patient data was taken from July 2008 to April 2011. Approval of the data review was granted by the University of Arizona Medical Center, Tucson and the Institutional Committee on Human Research.

Patient data was collected at three levels of drug therapy from right heart catheterizations, Swan-Ganz catheters, and/or echocardiography exams. Hemodynamic data was initially collected when patients were first admitted to the intensive care unit and before they received inotropic drug therapy. Patients were then assessed when they were first placed on inotropic support. The initial inotropic dose was documented within four hours of administration. The most common inotropic drugs prescribed included one or more of the following: dobutamine, milrinone, and dopamine. Throughout the patients’ admission, medical management was adjusted based on declining heart function and/or drug tolerance. The third level of drug therapy assessed was the peak inotropic dose prescribed where current inotropic type was changed before the patients became non-responsive to medication and required mechanical circulatory support. Patients were further subdivided into two groups: survived versus deceased. Patients in the survived group survived at least ninety days after receiving mechanical circulatory support. The deceased group consisted of patients who died within ninety days of receiving mechanical circulatory support. Survival was assessed at ninety days to account for delayed organ failure due to prolonged hypoperfusion.

Six hemodynamic parameters were compared to assess the remaining cardiac reserve in the twenty-eight heart failure patients studied: heart rate(HR) – beats per minute (bpm); mean arterial pressure – mmHg, [(2 x diastolic) + systolic]/3; stroke volume – ml, (cardiac output(CO)/HR); ejection Fraction - %, (stroke volume (SV)/end-diastolic volume (EDV)) x 100; cardiac index (CI) - L/min/m², [(HR x SV)/body surface area (BSA)]; and cardiac power index (CPI) - W/m², [(MAP x CO) x 0.0022]/BSA.

Statistics

Statistical analysis was done using Data Analysis and Statistical Software Stata 11 (StataCorp LP, College Station, TX, USA). An independent two-sample t-test with unequal variance was used to identify if contractile reserve still existed in the failing heart. Mechanical circulatory support hemodynamic standards were tested to determine which hemodynamic parameter gave a better representation of the remaining contractile reserve. All data are presented as mean ± SEM.

Results

Of the twenty-eight patients studied, twenty-one survived and seven died within ninety days of receiving an implanted device. Six of the seven patients died from end-organ failure and one died from systemic inflammatory response syndrome within six months of receiving mechanical circulatory support. The twenty-one patients who survived ninety days from receiving mechanical circulatory support were classified as “destination therapy” or “bridge to transplant” patients.

Baseline hemodynamic values, seen in Table 1, indicated abnormal values for all subjects, with the exception of heart rate and mean arterial pressure. Baseline values were recorded as patients were on standard heart failure medications (ß-blocker, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, and angiotensin receptor blockers (ARBs)). The other hemodynamic parameters (ejection fraction, left ventricular stroke work index, cardiac output, cardiac index, and cardiac power) were all below healthy adult ranges. Table 2 displays documented mean inotropic therapy while patients were in the intensive care unit.

Heart rate and mean arterial pressure (Figure 1A & 1B) were not found to be statistically significant between the “survived” and “deceased” groups. Heart rate increased below healthy adult ranges. Table 2 displays documented mean inotropic therapy while patients were in the intensive care unit.

<table>
<thead>
<tr>
<th>Characteristic (n=28)</th>
<th>Datum</th>
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<tr>
<td>Age (year)</td>
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<tr>
<td>BSA (m²)</td>
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<tr>
<td>HF Etiology</td>
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<tr>
<td></td>
<td>Non-ischemic 15 (54%)</td>
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<tr>
<td>ICD</td>
<td>19 (68%)</td>
</tr>
<tr>
<td>HR (BPM)</td>
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<td>MAP (mmHg)</td>
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<tr>
<td>CVP (mmHg)</td>
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<td>PCWP (mmHg)</td>
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<td>15 ± 1.92</td>
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<tr>
<td>CO (L/min)</td>
<td>3.14 ± 0.3</td>
</tr>
</tbody>
</table>

Abbreviations. BSA: body surface area; ICD: implantable cardioverter defibrillator; HF: heart failure; HR: heart rate; MAP: mean arterial pressure; SVR: systemic vascular resistance; CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; LVSWI: left ventricular stroke work index; EF: ejection fraction; CO: cardiac output. Values are expressed as mean ± SEM or number (% within studied population).
in both the “survived” and “deceased” groups when compared across all three levels of drug therapy. Mean arterial pressure of the “deceased” group declined despite inotropic drug intervention. Those in the “survived” group maintained a consistent level of mean arterial pressure across all three levels of drug therapy.

Stroke volume was well below the healthy adult ranges (Figure 1D), but was not found to be statistically significant between the “survived” and “deceased” groups. Stroke volume did not increase in the “deceased” group after the initial inotropic drug therapy; however, when peak inotropic drug therapy was administered, stroke volume decreased. On the other hand, the “survived” group displayed an increase in stroke volume at each level of drug therapy.

Left ventricular ejection fraction (Figure 1C) derived from echocardiography was not significantly different between the “survived” or “deceased” groups. When placed on the initial inotropic treatment, both the “survived” and “deceased” groups had an increased ejection fraction; however, the “deceased” was less (31.50 ± 7.5% to 22.76 ± 13.17 %). There was a large variance in the “deceased” group due to a few having diastolic heart failure with preserved ejection fraction. Those with diastolic heart failure had poor cardiac performance, but because their chamber size was unchanged or even decreased despite ventricular wall thickening, the overall percentage of blood ejected from the heart with each contraction was still elevated due to a decrease in overall ventricular chamber size.

Cardiac output was used to calculate cardiac index in order to account for the distribution of blood across the body surface area. In Figure 1E, the “survived” and “deceased” patients presented with a cardiac index of 1.65 ± 0.83 and 1.52 ± 0.13 L/min/m², respectively. With the initial inotropic treatment, the “survived” group’s cardiac index increased to 2.14 ± 0.54 L/min/m², but remained constant with the peak inotropic treatment at 2.17 ± 0.47 L/min/m². The “deceased” group displayed a moderate increase in cardiac index during the initial inotropic treatment (1.86 ± 0.62 L/min/m²), however, this decreased on peak inotropic support (1.69 ± 0.26 L/min/m²). Cardiac index was not a functional hemodynamic marker to identify if contractile reserve remained or whether it was able to detect survival outcomes between the survived and deceased groups.

Cardiac power output was used to calculate cardiac power index to adjust for blood volume distribution across the body surface area. The baseline administered inotropic dose increased cardiac power index, but revealed no statistical difference when compared to the deceased group (Figure 1F). When peak inotropic doses were administered, cardiac power index continued to decline in the deceased group, but was able to distinguish the contractile reserve between the two groups. The mean cardiac power index of patients who survived was 0.34 ± 0.07 W/m² at peak inotropic drug therapy. A cardiac power index below 0.34 W/m² identified patients who did not survive ninety days past the implantation of mechanical circulatory support because all patients in the deceased group had a cardiac power index below 0.34 W/m². Comparing cardiac power index between the survived and deceased groups showed significantly increased mortality rates once values fell below this point (p<0.05).

Discussion

Current hemodynamic guidelines use left ventricular ejection fraction and myocardial oxygen consumption as criteria to assess cardiac and systemic degeneration for possible mechanical circulatory support. As shown by Marmor et al., the present study demonstrates that ejection fraction did not display any significant differences between the “survived” and “deceased” groups during maximal cardiac performance resulting from peak inotropic drug therapy.9 In addition, results from prior myocardial oxygen consumption studies on patients in end-stage heart failure have shown to be inconclusive when peak cardiac function was measured.3,10,11 Patients with NYHA classes III and IV symptoms are severely compromised when tested physically for myocardial oxygen consumption due to progressive muscle deconditioning, poor vascular circulation, compromised lung capacity, and anemia. Although ejection fraction and myocardial oxygen consumption tests have their respective roles in measuring specific parameters of heart function, they may not be completely reliable assessments of cardiac function in these severely compromised patients.

Right heart catheterization provides very useful information in gathering pressure and volume changes in specific areas of the heart. This method requires that patients

<table>
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<tr>
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</tr>
<tr>
<td>Milrinone</td>
</tr>
<tr>
<td>Dopamine</td>
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</tbody>
</table>

Inotropic doses are expressed as mean values for the two levels of inotropic drug therapies studied.
be placed in a supine position without simulating peak cardiac contractility. This is a significant limitation, as assessing heart function in this manner does not allow for measuring the difference between basal and maximal cardiac performance in order to determine true cardiac reserve. Resting values alone do not provide a sufficient amount of information on cardiac performance in healthy versus diseased hearts; however, positive inotropic stimulation that achieves peak contractility is when diseased hearts can become distinguishable from healthy hearts.

Figure 1. Hemodynamic parameters of the survived and deceased.

*Normal hemodynamic values are from reference numbers 5-8. Values are expressed as mean ± standard error of the mean. *p=0.009.
With the limited physical and physiological abilities of this population, an effective method to assess true cardiac reserve is through the use of stress tests using inotropic drug infusion. This method has proven to be equivalent to results produced by maximal exercise tests. In severely compromised patients, this may be the only practical method to use in order to determine existing contractile energy. The current study used this concept by gathering data while patients were placed on initial inotropic support in order to stimulate the remaining contractile reserve, if any existed. As heart failure progressed in these patients and inotropic support was increased or altered, therapeutic saturation was met, eventually, due to the heart already functioning at its maximum contractile capacity. This indicated a lack of existing reserve in these patients, due to their basal cardiac performance equaling their maximum.

Cardiac power index was the only hemodynamic parameter that distinguished between the cardiac reserve of patients who survived ninety days post-implant versus those who died. Although invasive inotropic stimulation may not be the first choice to assess cardiac contractile reserve, measuring peak cardiac power index invasively may provide information on whether pharmacological support is still efficacious and if any contractile reserve still remains. Non-invasive methods to evaluate cardiac power output have been used for over five years and have been shown to effectively determine the severity of heart failure. With the availability of non-invasive equipment utilizing an inert gas re-breathing technique, patients in earlier stages of heart failure can be readily assessed for existing cardiac reserve. Cardiac power index can be a useful prognostic tool in order to determine if cardiac reserve exists in these patients and when to intervene with pharmacological support or mechanical circulatory support before the systemic effects of heart failure become irreparable.

**Limitations**

Because this was a single-center study, our data were non-randomized and our cohort of patients was relatively small. Due to the novelty of the population, having a large number of subjects is a difficult limitation to overcome when performing studies on patients receiving mechanical circulatory support. The variation in medical record charting between patients also limited the number of hemodynamic values that could be evaluated. Subject data were collected either by right heart catheterizations, Swan-Ganz catheters, and/or echocardiography exams, but these methods were inconsistent across the sample population. A future prospective study would be beneficial to reduce the lack of consistency between available subject data and their collection methods.

**Conclusions**

In conclusion, our data suggest that attaining cardiac index and mean arterial pressure, either invasively or non-invasively, and applying these values to the cardiac power index formula, can determine the severity of heart failure based on the heart's maximal contractile reserve. Peak cardiac power index values may also be a useful tool to determine the appropriate therapeutic approach necessary for these patients. Cardiac power index has proven to recognize remaining contractile reserve in heart failure patients in comparison to other commonly used hemodynamic parameters. In heart failure patients categorized as NYHA classes III and IV or ACC-AHA stages C and D, a peak cardiac power index below 0.34 W/m², with or without the use of drug therapy should immediately be considered for implantation of mechanical circulatory support. Patients at or below a cardiac power index of 0.34 W/m² have an increased incidence of mortality.

**Acknowledgement**

This study was supported the Steinbronn Heart Failure Research Award to DFL.

**Conflict of Interest Statement**

None declared.

**References:**

a noninvasive approach for assessment of contractile reserve. 


Non invasive measurements of Cardiac Output (CO) and Cardiac Power Index (CPI) by whole body bio impedance in patients with heart failure. A report from SICA- HF study (FP7/2007-2013/241558)

P Pellicori1, E Wright1, P Costanzo1, S Smith1, S Rimmer1, J Hobkirk1, A Torabi1, T Mabote1, J Warden1, JGF Cleland1, 1University of Hull, Department of Academic Cardiology - Hull - United Kingdom,

- **Objectives**: Haemodynamic dysfunction is often used as part of the definition for heart failure (HF), predicts an adverse outcome and could be an important target for therapy but is rarely measured in routine practice, perhaps because simple, effective, inexpensive technology is lacking. We assessed the ability of whole body electrical bioimpedance to measure haemodynamics non-invasively.

- **Methods**: Patients and controls enrolled in the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA) were included in this analysis if in sinus rhythm. Stroke volume (SV), cardiac output (CO), cardiac power index (CPI) and total body water (TBW) were measured non-invasively using whole body bio-impedance (NICaS) after two minutes rest in the supine position. Results were compared amongst HF patients according to tercile of amino-terminal pro-brain natriuretic peptide (NT-proBNP) and left ventricular ejection fraction (LVEF).

- **Results**: The median age of the 51 patients with HF was 71 years (IQR:63–77), 15 were women (29%), median LVEF was 36% (IQR:29-44) and median body mass index (BMI) was 30kg/m² (IQR:26-33). The median age of 15 control subjects was 66 years (IQR:56-75), 4 were women (27%) and median BMI was 29kg/m² (IQR:26-37). As expected, compared with controls, patients with HF had higher plasma NTproBNP, worse renal function, lower CPI (0.64±0.25w/m² vs. 0.47±0.18w/m²; p< 0.01) but TBW was similar (47±9% vs. 46±8%; p=0.74).

- **Patients** were divided into terciles of NTproBNP (lower and upper limits of the mid-tercile were 373 and 1063ng/L). Patients in the highest tercile of NTproBNP had lower BMI (32±5kg/m² vs. 29±5kg/m² vs.28±4kg/m² respectively ; p=0.02), LVEF (42±5% vs. 37±9% vs. 29±8%; p<0.01), CPI (0.52±0.2w/m² vs. 0.50±0.2w/m² vs. 0.38±0.1w/m²; p=0.04) and poorer renal function (Creatinine: 91±28μmol/l vs. 113±35μmol/l vs. 130±47μmol/l; p=0.02) and increased TBW (41±6% vs. 47±7% vs. 48±9%; p=0.02). No differences in CO or SV were found. In the lowest tercile of LVEF, SV (83±24ml vs. 67±23ml vs.68±9ml;p=0.01), CO (5.7±1.9/l/min vs. 4.3±1.6/l/min vs. 3.9±0.8/l/min; p <0.01) and CPI (0.58±0.2W/m² vs. 0.45± 0.2W/m² vs. 0.38±0.1W/m²; p<0.01) were all significantly lower, but TBW was similar across terciles (43±6% vs. 46±7% vs. 48±9%; p = 0.28).

- **Conclusion**: In patients with HF and sinus rhythm, whole body bio-impedance might be a useful method of monitoring the haemodynamic severity of heart failure that is quick, simple and inexpensive. Whether it is as or more useful than NTproBNP as a marker of outcome awaits the results of large long-term studies. (European Journal of Heart Failure Supplements (2012) 11 (S1), S91)
Letter to the Editor

Detection of left ventricular systolic dysfunction using a newly developed, laptop based, impedance cardiographic index

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Congestive heart failure (CHF) is a major cause of morbidity and mortality worldwide [1]. The development of left ventricular systolic dysfunction (LVSD) is a marker of poor prognosis. Mild reduction in EF progresses with time and when EF gets to <40%, most patients develop CHF and their prognosis is dismal [2,3]. Simple, cheap techniques that will reliably detect mild reduction of the EF, typical for LVSD, will thus be of enormous value to reduce the occurrence of CHF and cardiac mortality [3–7].

Impedance Cardiography (ICG) is a noninvasive method of determining hemodynamic status and reliable estimates of myocardial contractility (and EF) can be obtained using indices based on systolic time intervals [8–10]. We have recently developed an index—Granov Goor Index (GGI)—that combines time interval and impedance parameters in order to identify subjects with LVSD. The GGI is obtained from a regional ICG signal—measured using wrist and ankle electrodes [10–13]. In this manuscript we determined the accuracy of GGI in identifying subjects with LVSD (in a “training” cohort of 100 individuals) and validated the findings in an additional cohort of 201 subjects.

The regional ICG signal is obtained from 2 pairs of tetra-polar electrodes: one on the wrist, above the radial artery, and the other on the contra-lateral ankle above the posterior tibial artery. The detailed description of the system and measured parameters can be reviewed in previous publications [10–13]. The GGI is designed to assess the systolic contractile function of the LV and is obtained from the following formula:

$$\text{GGI} = \frac{\Delta R}{R} \times \alpha \times HR(\text{corrected})$$

where $R$ is the basal impedance and $\Delta R$ is the change in impedance, $\alpha$ is the time to peak $\Delta R$ and HR is the heart rate. The GGI takes into account both $\Delta R$ as an estimate of stroke volume and $\alpha$ as a time interval parameter. HR and $R$ are used as normalization factors so that the result is a dimensionless index that reflects the systolic function of the LV.

The entire system (electrode, signal analysis and calculations) can replace the CD ROM in a regular computer, transforming any laptop into a simple diagnostic device—ideal for screening.

Echocardiography was performed using GE Vivid 7 (GE Vingmed Ultrasound A/S, Norway). EF was calculated using the biplane Simpson’s technique [14]. Echocardiography and ICG were performed on the same day.

Patients who were referred for screening echocardiography at the outpatient clinic of the E. Wolfson Medical Center were considered for this trial.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution’s human research committee.

Optimal cutoff value for the GGI for detection of LVSD was determined from the Receiver Operating Characteristic (ROC) curve of the training set. Sensitivity specificity and predictive accuracy of GGI to detect LVSD were determined using standard technique. Statistical analysis was performed using MedCalc® software (Broekstraat, Belgium version 9.5.2.0).

Tables 1 and 2 describe the demographic echocardiographic and ICG results. The superiority of GGI in detecting LVSD is confirmed using ROC curve analysis (Fig. 1). The area under curve (AUC) of ROC curves of $\Delta R/R$ and $\alpha$ as predictors of LVSD were 0.84 and 0.75 respectively, significantly lower (p<0.001) than the value for GGI (0.97 CI 0.92 to 0.99). For a GGI cutoff value of 10 the sensitivity, specificity positive and negative predictive values are 86%, 100%, 100% and 96% respectively.

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Patients in the validation set were slightly older with a tendency for lower prevalence of smoking. Echocardiographic and ICG values were similar in these two sets of patients (Tables 1 and 2). A GGI cutoff of 10 was 89% sensitive and 96% specific for detection of LVSD, confirming the excellent results of the training set. Positive and negative predictive values were 78% and 98% respectively.

False positives and false negatives of GGI as a predictor of EF are extremely rare (Fig. 2) reflecting the accuracy of GGI to detect LVSD. Careful observation of the data points suggests that rather than a simple correlation, the relation between EF and GGI is more like a step function with a GGI<10 corresponding to a wide range of EF<55% while a GGI≥10 corresponds to varying levels of EF≥55%.

In this study we were able to demonstrate that a simple regional impedance based technology can reliably detect LVSD. Regional (as compared to thoracic) ICG enables more accurate determination of stroke volume and cardiac output [10–12]. The addition of α, a time interval parameter, with the resulting GGI adds significantly to the accuracy of this method to identify subjects with LVSD (increasing the AUC from 0.84 to 0.97). Most importantly, also those at the asymptomatic stage of mild LVSD are accurately detected.

Some of the energy of the LV contraction produces forward blood flow during systole, while a significant amount is briefly stored as potential energy in the distended arteries—maintaining the forward flow during diastole [15]. The information provided by α relates to this stored energy while the ΔR is related to the stroke volume. The incorporation of both these parameters into the GGI makes the GGI a more reliable index of the energy generated by the contraction of the LV. Time interval parameters were used in the past from the ICG curve to try to estimate the EF. Despite significant correlation [9] the coefficient values (typically approximately 0.5) are not high enough for clinical purpose. Thus accurate estimation of the value of EF is limited but, as we have showed, the GGI very accurately determines whether the LVEF is normal or abnormal (step function rather than simple correlation).

The natural history of patients with ALVSD is dismal [4]. Compared with those with normal LV, patients with ALVSD had 5-fold increase risk of CHF and death. Early detection of ALVSD requires a search for CAD as a possible etiology. When CAD is causing reversible dysfunction prompt revascularization is essential to improve outcome; preventing CHF and early arrhythmic death [16–19]. In those with irreversible ALVSD; further deterioration can be attenuated by the use of appropriate drug therapy [3].

Since early intervention in subjects with ALVSD is beneficial, screening programs need to be implemented to identify these individuals. Echocardiography—the “gold standard” in the assessment of LVSD—is impractical for general screening since it is very expensive. Thus an effective screening program should use an inexpensive, non-invasive diagnostic test (such as GGI) to identify those who are likely to have ALVSD.

The use of appropriate drug therapy [3].

Even though we excluded patients with symptoms of suggestive of heart disease the decision to refer patients for echocardiography biases the population so that data was not collected from the true target population—asymptomatic individuals with no prior history of heart disease. However the likelihood that this will change the observed relation between GGI and EF is small.

The GGI can accurately detect LVSD in subjects at risk (referred for echocardiography). The GGI can be easily obtained from regional ICG signal using any laptop by replacing the CD ROM with the measuring hardware and software. This laptop based device is cheap and easy to operate making it an attractive tool to screen for LVSD. Additional trials are required to prove the efficacy of this device in the target population of asymptomatic patients at risk.

Table 1
Clinical characteristics of subjects in the training and validation cohorts.

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</table>

BMI=body mass index.

Fig. 1. Receiver operating characteristic (ROC) curve of ΔR/R, α×HR and GGI as diagnostic tests for LVSD (EF<55%).

Please cite this article as: Rozenman Y, et al, Detection of left ventricular systolic dysfunction using a newly developed, laptop based, non-invasive, regional cardiac index, Int J Cardiol (2011), doi:10.1016/j.ijcard.2011.02.029
Fig. 2. Scatter plot of EF vs. GGI demonstrating the diagnostic power GGI (with cutoff value of 10) to detect LVSD (EF < 55%) (data from the entire cohort, n = 301).

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [20].

References

Measurement Precision in the Optimization of Cardiac Resynchronization Therapy
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Measurement Precision in the Optimization of Cardiac Resynchronization Therapy

Robert G. Turcott, MD, PhD; Ronald M. Witteles, MD, FACC; Paul J. Wang, MD; Randall H. Vagelos, MD, FACC; Michael B. Fowler, MB, FRCP, FACC; Euan A. Ashley, MRCP, DPhil

Background—Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether atrioventricular (AV) and interventricular (VV) pacing interval optimization confers further clinical improvement remains unclear. A variety of techniques are used to estimate optimum AV/VV intervals; however, the precision of their estimates and the ramifications of an imprecise estimate have not been characterized previously.

Methods and Results—An objective methodology for quantifying the precision of estimated optimum AV/VV intervals was developed, allowing physiologic effects to be distinguished from measurement variability. Optimization using multiple conventional techniques was conducted in individual sessions with 20 patients. Measures of stroke volume and dyssynchrony were obtained using impedance cardiography and echocardiographic methods, specifically, aortic velocity-time integral, mitral velocity-time integral, A-wave truncation, and septal-posterior wall motion delay. Echocardiographic methods yielded statistically insignificant data in the majority of patients (62%–82%). In contrast, impedance cardiography yielded statistically significant results in 84% and 75% of patients for AV and VV interval optimization, respectively. Individual cases demonstrated that accepting a plausible but statistically insignificant estimated optimum AV or VV interval can result in worse cardiac function than default values.

Conclusions—Consideration of statistical significance is critical for validating clinical optimization data in individual patients and for comparing competing optimization techniques. Accepting an estimated optimum without knowledge of its precision can result in worse cardiac function than default settings and a misinterpretation of observed changes over time. In this study, only impedance cardiography yielded statistically significant AV and VV interval optimization data in the majority of patients. (Circ Heart Fail. 2010;3:395-404.)

Key Words: cardiac resynchronization therapy ■ pacing optimization ■ AV delay ■ interventricular interval ■ echocardiography ■ impedance cardiography

Cardiac resynchronization therapy (CRT) decreases morbidity and mortality in populations with reduced cardiac function and conduction abnormalities1–3; however, approximately one third of these patients do not experience benefit.4 Atrioventricular (AV) and interventricular (VV) pacing interval optimization improve hemodynamics acutely5–7 and may enhance the response to CRT relative to default interval settings among both the traditional responder and nonresponder groups. To date, however, results of prospective randomized trials have been mixed.8–12

Clinical Perspective on p 404

The clarification of fundamental issues in pacing interval optimization is still at an early stage. For example, the extent to which optimum AV/VV intervals change with body position and exertion remains unclear;13–16 and data assessing the stability of optima over time have been inconsistent.17,18 Even the definitions of pacing intervals vary among manufacturers, with identical programmed intervals corresponding to very different ventricular pace timing.19 Perhaps the most important fundamental weakness is the lack of statistical tools to quantitatively evaluate the significance of the measured data and to characterize the precision of the estimated optimum AV/VV interval.11,20–22

In this study, we examined multiple commonly used AV/VV interval optimization techniques. Central to our approach is the recognition that the underlying dependence of cardiac function on AV/VV interval is obscured to some degree by measurement noise and that the optimum interval identified by a given technique is in fact an estimation of the true physiologic optimum. The degree to which measured optimization data demonstrate a significant dependence on pacing interval and the precision of estimated optima were rigorously evaluated using new statistical tools based on

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34 of 158.
Table 1. Patient Demographics

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<td>66</td>
<td>F</td>
<td>52</td>
<td>HCM</td>
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</table>

AS indicates aortic stenosis; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation.

*Dual-chamber device. †No LV capture. §No atrial lead.

Table 1. Patient Demographics

Methods

Patient Selection

Data were obtained from consecutive patients referred for clinical pacing interval optimization with institutional review board approval. Patients with dual-chamber or biventricular pacemakers or implantable cardioverter defibrillators were included without regard to underlying etiology (Table 1).

Optimization Techniques

AV/VV interval optimization was conducted using multiple techniques, as follows:

1. Noninvasive, beat-to-beat estimates of stroke volume (SV) were acquired continuously using impedance cardiography (ICG; BioZ, CardioDynamics, San Diego, Calif) (Figure 1A).24–26 With ICG, changes in thoracic impedance are measured using surface electrodes and then processed by a proprietary algorithm to estimate SV and other hemodynamic parameters. Each test interval was delivered for 60 seconds, with all beats recorded during the last 30 seconds included in the analysis.

2. The remaining techniques were derived from echocardiography using a Philips iE33 System (Philips International B.V., Amsterdam, The Netherlands). The aortic velocity-time integral (A-VTI), which is directly proportional to SV, was obtained by numerically integrating the ejection velocity envelope obtained by continuous-wave Doppler directed in line with aortic flow in the apical 5-chamber view (Figure 1B).20,21 For this and the other echocardiographic techniques, a 10- to 20-second equilibration period followed each programming change. Data then were recorded over 1 to 2 respiratory cycles, with premature and postpremature beats excluded.

3. Mitral inflow velocity-time integral (M-VTI), which is directly proportional to inflow volume, was obtained using pulsed-wave Doppler with the sample volume placed just apical to the mitral leaflets in the apical 4-chamber view (Figure 1C).20,21

4. In contrast to the techniques described above, which attempt to characterize cardiac function by estimates of forward flow, septal-posterior wall-motion delay (SPWMD) provides an assessment of left ventricular (LV) mechanical synchrony.20 As shown in Figure 1D, the transducer signal was directed across the septum and the posterior LV wall in the parasternal long-axis view. Color M-mode Doppler was used to highlight the relative motion of the 2 walls, with minimum lag taken to represent optimal ventricular synchrony.

5. A-wave truncation identifies the optimum AV delay as the shortest pacing interval that avoids truncation of the A-wave21 and is based on the same Doppler waveform as M-VTI. Figure 1E shows an A-wave truncated at 150 milliseconds and untruncated at 180 milliseconds.

Optimization techniques were compared in terms of their ability to detect underlying physiologic changes with pacing interval. Specifically, the statistical significance of the data was quantitatively estimated, as described below. Because A-wave truncation yields a binary assessment at each test interval (A wave is or is not truncated), it is not amenable to the analytic paradigm used for the other techniques. Therefore, for A-wave truncation, we report the number of times each of the 3 readers, blinded to other results, was able to estimate an optimum pacing interval.

Summary statistics were obtained based on all patients referred for clinical optimization and, in addition, with hypertrophic cardiomyopathy patients excluded. Because ICG allows a greater number of data points to be obtained compared with echocardiographic methods, the AV interval optimization analysis was repeated for ICG data using the same number of measurements that were obtained in the corresponding A-VTI data set at each test interval.

Statistical Methods

A third-degree polynomial was fit to the data, and the location of the maximum was taken as the estimated optimum interval. For SPWMD, the location of the minimum absolute value of the polynomial was taken as the optimum. Use of a continuous function, such as a polynomial, allows interpolation between test intervals and averaging both at and across test intervals provided that the number of free parameters of the function is smaller than the number of unique test intervals.

The test for statistical significance was based on the formulation of the alternative hypothesis that the measured data do not depend on pacing interval. The probability of obtaining the observed data under this null hypothesis was estimated using bootstrapping.22,23 A test statistic $s$ was defined to be equal to the area bounded above by the best-fitting polynomial and below by the minimum value of the polynomial, as illustrated in Figure 2. The test statistic is not unique; other measures also would be acceptable if they possess the property that their value varies depending on how “physiological” the optimization data are. Specifically, if an underlying physiologic optimum exists, and if the range of test intervals was appropriately selected to span the optimum, then the test statistic should be larger than what would be obtained under the null hypothesis in which there is no dependence on pacing interval. The greater the difference in cardiac function at the optimum pacing interval and the extreme of the test range, the greater the value of $s$. For each optimization data set, 1000 surrogate bootstrapped data sets were generated by randomly selecting data points from the original data set with replacement and without regard to test interval. This process yields surrogate data sets with the same number of data points at each test interval as the original but replaces the original mapping between

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Figure 1. Raw optimization data. A, Impedance cardiography is measured noninvasively using surface electrodes and provides estimates of multiple hemodynamic parameters, including stroke volume (SV). B, Aortic velocity-time integral is measured with continuous-wave Doppler at the left ventricular outflow tract and is directly proportional to ejected SV. C, Mitral velocity-time integral (M-VTI) is measured with pulsed-wave Doppler echocardiography and is directly proportional to inflow volume. D, Septal-posterior wall-motion delay is obtained using tissue Doppler imaging. The VV interval that minimizes the delay is taken as representing optimum synchrony. E, A-wave truncation uses the same images as M-VTI to identify the pacing interval at which the A-wave becomes truncated by ventricular systole. The image shows the A-wave truncated when a 150-ms AV delay is used and untruncated with a 180-ms AV delay.
measured data and test interval with a random pairing. Each surrogate bootstrapped data set thus represents a single realization of data that would be observed under the null hypothesis while preserving the amplitude statistics of the original data. The test statistic $s$ was calculated for each surrogate data set, and the fraction that was greater than or equal to that of the original data estimates the probability that a test statistic at least as large as that associated with the original data would be observed under the null hypothesis. For $P\leq0.05$, the null hypothesis was rejected, and the data were interpreted as demonstrating a statistically significant dependence on pacing interval.

The 95% CI of the estimated optimum pacing interval was obtained by generating an additional 1000 bootstrapped data sets in which the original data were randomly selected with replacement while preserving the mapping to test interval. In this case, with the mapping between test interval and measured data retained, the collection of best-fitting polynomials of the bootstrapped data sets reflects the variability in the best-fitting polynomial of the original data that is attributable to the statistical variability in the measurements. The locations of the maxima of the surrogate data sets were ordered from smallest to largest, and the cutoff point of the smallest and largest 2.5% of the surrogate optima were taken as the 95% CI of optimum estimated from the original data.

**Assessment of A-VTI Variability**

The variability of the measured A-VTI data was quantified by calculating the average and SD over all measurements made at an AV delay of 120 ms, which by protocol were acquired over at least 1 respiratory cycle at 4 different times during the recording session. To allow comparison with previously published values, a transformation was derived that converts the coefficient of variation (defined as SD divided by mean) to the average difference of successive measurements. Specifically, $\mu_y = CV \sqrt{2/\pi}$, where $\mu_y$ is the average difference in successive measurements, and $CV$ is the coefficient of variation. This result is based on the transformation $y_i = (x_i - x_0)/\mu_y$, where the $x_i$ represents successive A-VTI measurements at a given pacing interval in a given patient; $y_i$, the normalized difference in A-VTI measures in a given patient, and the subscript $i$, patient-specific values. The derivation assumes that $x_{i1}$ and $x_{i2}$ are independently drawn from a Gaussian distribution whose mean $\mu_i$ and SD $\sigma_i$ can vary among patients but whose coefficient of variation $CV_i$ remains fixed for all patients, that is, $CV_i = \sigma_i/\mu_i = \text{constant}$. Data acquisition and device programming are summarized in Table 2.
**Results**

Patient demographics are presented in Table 1. Of the 20 sequential, unique patients referred for clinical pacing optimization, 18 had biventricular pacemakers or implantable cardioverter defibrillators and 2 had dual-chamber devices. The LV lead in 1 patient failed to capture, and another patient with chronic atrial fibrillation had a biventricular device without an atrial lead. Patients who underwent AV delay optimization were in sinus rhythm with the AV delay initiated by an atrial sensed-event in all cases.

AV delay optimization data from a single patient are presented in Figure 3. As with the ICG data shown here (left panel), when statistically significant data were obtained they typically exhibited an inverted U appearance, indicating that the estimated optimum interval was in the interior of the range of test intervals. Statistically insignificant data typically had a best-fitting polynomial that was flat relative to the intrinsic variability of the data.

The average and SD of the measured A-VTI data were calculated over all beats (10 to 31, median 20) recorded from each patient during AV optimization at the 120-ms test interval. The ranges of the per-patient average and SD of the A-VTI data were 6.7 to 56 cm and 0.73 to 5.1 cm, respectively. The median sample coefficient of variation was 0.075, which corresponds to an average normalized difference in successive measurements of $\mu_\gamma=0.12$, consistent with previous reports of $\mu_\gamma=0.1\pm0.1$.

The VV optimization data shown in Figure 4 are from the same patient whose AV optimization results are presented in Figure 3. As with this individual, for most patients, VV optimization yielded insignificant results more frequently than did AV optimization.

The number of statistically significant data sets is summarized in Table 3. For both AV and VV optimization, A-VTI, M-VTI, and SPWMD yielded data that were indistinguishable from the null hypothesis (ie, failed to demonstrate a statistically significant dependence on pacing interval) the majority of the time. As shown in Table 3, this finding remained true whether patients with hypertrophic cardiomyopathy were included or excluded from the analysis. ICG was significantly different from the null hypothesis 84% of the time for AV delay optimization and 75% of the time for VV interval optimization. Excluding patients with hypertrophic cardiomyopathy from the analysis, the null hypothesis could be rejected 81% and 75% of the time, respectively.

![Figure 3. AV delay optimization. Data were obtained from an individual patient at a single optimization session. Impedance cardiography (ICG) and aortic velocity-time integral (A-VTI) yielded statistically significant results, although the 95% CI of the estimated optimum was much narrower for ICG than for A-VTI. Mitral velocity-time integral (M-VTI) data were not statistically significant. Solid curve indicates best-fitting third-degree polynomial; X, location of estimated optimum pacing interval; horizontal line, 95% CI of estimated optimum.](http://circheartfailure.ahajournals.org/Downloaded from)
Among the statistically significant data sets, the optimum AV delay estimated by ICG differed from the default value (120 ms) by an average magnitude of 57 ms, and 63% of the estimates differed from default by at least 50 ms. Among the statistically significant, ICG-derived VV interval data sets, estimated optima differed from the default value (0 ms) by an average of 52 ms, and 75% of the estimates differed by at least 30 ms. Repeating the ICG AV interval optimization analysis using the same number of measurements at each test interval as the A-VTI recordings continued to yield statistically significant results in the majority of patients, with 81% of the reduced ICG data sets having $P$ values $<0.05$.

An optimum AV delay could be estimated by 3 independent readers using A-wave truncation 69%, 75%, and 94% of the time. The estimates of each reader are compared with ICG results in Table 4. The relationship between optima predicted by ICG and A-wave truncation was variable, with the Pearson correlation coefficient ranging from 0.02 to 0.67 for the 3 readers.

Although the analysis presented above is based on unique patient visits, 1 patient underwent both ICG and echocardiographic optimization on 2 separate occasions separated by 3.5 months. As shown in Figure 5, in both cases ICG yielded similar-appearing, statistically significant results. The estimates of the optimum pacing intervals were precise, with narrow 95% CIs, and had good concordance, with 91 ms at the first optimization and 67 ms 3.5 months later. In contrast, in neither optimization session did A-VTI yield statistically significant results. The wide 95% CI of the initial A-VTI optimum predicted that subsequent optimization attempts would be unlikely to identify a similar optimum interval.

**Discussion**

In this study, multiple clinically accepted AV and VV interval optimization techniques were used in single sessions in a heterogeneous group of 20 patients. For 62% to 86% of patients, A-VTI, M-VTI, and SPWMD yielded data that were statistically indistinguishable from the null hypothesis; that is, the majority of the time these measures yielded data that did not show a significant dependence on AV or VV interval. With A-wave truncation, it was possible for 3 independent readers to estimate an optimum AV delay 69%, 75%, and 94% of the time. ICG performed better than the echocardiography methods, yielding statistically significant data 84% of the time for AV delay optimization and 75% of the time for VV interval optimization. Notably, the echocardiography techniques tested here represent the most commonly used approaches to AV/VV interval optimization.28

In previous studies, SPWMD failed to predict a response to CRT,29,30 and interval optimization using A-VTI neither improved clinical outcomes12 nor yielded acute data that were distinguishable from a negative control.31 The poor precision of these techniques demonstrated in this study may account for the lack of clinical utility seen in the earlier work.

AV/VV interval optimization traditionally has been conducted without consideration of the intrinsic variability of the measured data. Test intervals often are delivered in a nonrandom order, sweeping systematically from one end of the test range to the other, and the AV or VV interval associated with the best average measure of cardiac function typically is taken at face value to represent the underlying physiologic optimum.11,20 Although efficient, the traditional approach has important drawbacks. A nonrandom order of test intervals allows systematic error to be introduced into the measured data in a way that cannot be subsequently corrected by averaging (eg, with subtle drift of the Doppler angle over the course of data collection). Furthermore, without considering the intrinsic variability of the measured data, it is not possible to characterize the precision of the estimated optimum AV/VV interval.

In the absence of knowledge about its precision, an estimated optimum AV/VV interval may in fact be spurious and associated with worse cardiac function than the population-derived, default setting (eg, a sensed AV delay of 120 milliseconds) (Figures 2, 3, and 5). In addition, although multiple studies have suggested that optimum pacing inter-
Table 3. *P* Value Associated With Measured Optimization Data

<table>
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All patients

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HCM excluded

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HCM indicates hypertrophic cardiomyopathy; AV, atrioventricular; W, interventricular; ICG, impedance cardiography; A-VTI, aortic velocity-time integral; M-VTI, mitral velocity-time integral; SPWMD, septal-posterior wall-motion delay.

Table 4. Estimated Optima: ICG and A-Wave Truncation

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Percent interpretable was as follows: Reader 1, 94%; Reader 2, 69%; Reader 3, 75%. Correlation coefficients were as follows: Reader 1, 0.02; Reader 2, 0.67; Reader 3, 0.48.

*Reader indicated that A-wave truncation could not be reliably identified. ICG indicates impedance cardiography; CI, confidence interval.

The trial will not address the question of whether the experimental technique is superior to default settings. In contrast, another clinical trial uses a 3-arm design in which patients are randomized to the experimental technique, a control arm in which population-derived default settings are used, and a conventional optimization arm in which a specific optimization technique is uniformly used. This study design allows direct comparisons between the experimental technique and both default settings and the specific conventional optimization method, and for comparison of the conventional technique to default settings.

Statistical significance testing may provide a useful way to evaluate the quality of competing optimization techniques. It avoids prespecifying a gold standard, and although demonstration of improved clinical outcomes in well-designed trials ultimately is required, the approach presented here offers a way to narrow the very wide field of plausible optimization techniques without the resource requirements of a prospective clinical trial.

Although a rigorous, quantitative analysis is desirable, statistical significance can be evaluated informally by plotting the measured data against pacing interval. With test intervals delivered in a random order, if the data exhibit the expected inverted U shape and are tightly clustered about the overall curve, then one can be confident that the estimation of optimum AV/VV interval is precise; repeating the process
likely would yield a similar result. On the other hand, if the plot is relatively flat compared with the intrinsic variability of the measured data, then the estimate of the underlying optimum is imprecise and heavily influenced by measurement variability. In this case, repeating the optimization process likely would yield a very different estimated optimum AV/VV interval. The statistical tools used here along with plotting capability have been made available on the Internet.35

In the majority of patients examined in the present study, ICG generated precise estimates and A-wave truncation yielded data from which an optimum could be inferred, although often with significant interreader variability and marginal correlation with the ICG-predicted optima. Notably, neither ICG nor A-wave truncation has been clinically validated in prospective interval optimization studies. In addition, unanswered fundamental questions include whether the physiologic optimum interval evolves over time and whether it changes between rest and exertion or between supine and upright posture. A study that compares estimated optimum intervals obtained at both supine rest and upright exertion in the same patient, perhaps using motion-tolerant ICG, would add important insight into these basic questions. In the absence of such data and given the theoretical potential benefit of pacing optimization, our approach is to accept an estimated optimum interval if quantitative and qualitative analyses suggest that the estimate has good precision. Particular attention should be paid to the effect of outliers and the overall shape of the curve compared with the measurement variability.

That ICG continued to yield statistically significant data in the majority of patients, even when using an identical number of data points as the A-VTI analysis, suggests that it has a superior intrinsic signal-to-noise ratio and that the acquisition time can be substantially shortened from the 60 s per test interval that was used in this study. The superior noise properties of ICG may be partly due to the automatic and objective nature of data acquisition and analysis in contrast to A-VTI, which requires the sonographer to physically hold the probe in a fixed position and the reader to manually demarcate the envelope of the velocity waveform.

A wide variety of optimization techniques have been advocated, including multiple approaches to the assessment of systolic function, diastolic function, and electrical and mechanical synchrony.9,19 –21,24 –26,30,36 – 40 Although each has a rationale that is mechanistically plausible, consideration of the neurohormonal derangements of heart failure and the therapeutic interventions that have been successful lead us to view SV and its surrogates as parameters that when optimized are most likely to translate into clinical benefit. Specifically, it is now well established that ameliorating the effects of sympathetic tone in these patients leads to improved clinical outcomes.41 For a given cardiac output, maximizing SV would minimize sympathetic tone. Indeed, the effects on the neurohormonal system of increased mechanical efficiency may contribute to the salutary effects of CRT, which remains the only contractility-enhancing intervention demonstrated to prolong life.42 Theoretical arguments may not account for important effects, however. For example, an increase in SV at the expense of greater oxygen consumption may not benefit
the patient with ischemic heart failure. Ultimately, any proposed optimization technique must be validated by randomized prospective trials with hard clinical end points, a goal which to date has not been frequently achieved.8–12

Limitations
The study was based on a small and heterogeneous population comprising successive patients referred for clinical pacing interval optimization. Multiple conventional optimization techniques were examined for their ability to yield statistically significant results. This property is necessary but not sufficient for improved clinical outcomes, which were not examined in this study.

Conclusions
Optimization of AV and interventricular intervals in CRT requires assessment of the variability of the measured data. Accepting an estimated optimum without considering its precision may result in worse cardiac function than default settings in the individual patient and confound results in clinical trials. In the small, heterogeneous pacemaker population examined here, echocardiographic techniques yielded statistically insignificant data in the majority of patients. In contrast, ICG yielded precise estimates of the optimum AV and VV interval in most patients. Further research is necessary to confirm these results, to validate the accuracy of the impedance-predicted optima, and to demonstrate clinical improvement with pacing interval optimization compared to population-derived default settings.

Sources of Funding
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Disclosures
Dr Witteles has received honoraria from Medtronic. Dr Wang has received honoraria and research support from and has served as a consultant to Medtronic and received honoraria from Medtronic. Dr Fowler has received honoraria from Medtronic and Boston Scientific.

References
Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether further clinical benefit is possible with atrioventricular and interventricular pacing interval optimization remains unclear. Tools to assess the statistical significance of the measured optimization data have not been available previously. In the study reported here, an objective methodology for quantifying the statistical precision of estimated optimum pacing intervals was developed and applied to a number of commonly used optimization techniques. Many of the techniques did not yield statistically significant data in a majority of patients referred for atrioventricular and interventricular interval optimization, a finding that raises questions about the ability of pacing interval optimization to enhance clinical outcomes. The data demonstrated that accepting an estimated optimum interval without consideration of its statistical significance can result in worse cardiac function than default settings and can lead to the erroneous conclusion that the physiological optimum has changed over time. These results highlight the importance of evaluating the precision of measured data when conducting pacing interval optimization for the individual patient and when interpreting the results of clinical trials.

**CLINICAL PERSPECTIVE**

Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether further clinical benefit is possible with atrioventricular and interventricular pacing interval optimization remains unclear. Tools to assess the statistical significance of the measured optimization data have not been available previously. In the study reported here, an objective methodology for quantifying the statistical precision of estimated optimum pacing intervals was developed and applied to a number of commonly used optimization techniques. Many of the techniques did not yield statistically significant data in a majority of patients referred for atrioventricular and interventricular interval optimization, a finding that raises questions about the ability of pacing interval optimization to enhance clinical outcomes. The data demonstrated that accepting an estimated optimum interval without consideration of its statistical significance can result in worse cardiac function than default settings and can lead to the erroneous conclusion that the physiological optimum has changed over time. These results highlight the importance of evaluating the precision of measured data when conducting pacing interval optimization for the individual patient and when interpreting the results of clinical trials.
Whole Body Bioimpedance Monitoring for Outpatient Chronic Heart Failure Follow up

Yusuke Tanino, MD; Junya Shite, MD; Oscar L Paredes, MD; Toshiro Shinke, MD; Daisuke Ogawawara, MD; Takahiro Sawada, MD; Hiroyuki Kawamori, MD; Naoki Miyoshi, MD; Hiroki Kato, MD; Naoki Yoshino, MD; Ken-ichi Hirata, MD

Background: Although cardiac output index (CI), stroke volume index (SVI), and total systemic vascular resistance (TSVR) are important hemodynamic parameters for the prognosis of chronic heart failure (CHF), they are difficult to measure in an outpatient setting. Whole body bioimpedance monitoring using a Non-Invasive Cardiac System (NICaS) allows for easy, non-invasive estimation of these parameters. Here, whether NICaS-derived hemodynamic parameters are clinically significant was investigated by relating them to other conventional cardiovascular functional indices, and by evaluating their predictive accuracy for CHF readmission.

Methods and Results: Study subjects of 68 patients with CHF were enrolled in the study immediately upon discharge from the hospital. NICaS-derived CI, -SVI, and -TSVR values obtained at an outpatient clinic were significantly related with left ventricular ejection fraction (LVEF) measured by echocardiography, serum B-type natriuretic peptide (BNP), and exercise tolerance. During the 100±98 days follow-up, 15 patients were readmitted to our hospital for CHF recurrence. Multivariate analysis indicated that LVEF, NICaS-derived CI, NICaS-derived SVI, and plasma BNP were significant indicators (receiver operating characteristic curve cut-off point, LVEF: 37%, NICaS-derived CI: 2.49 L·min⁻¹·m⁻², NICaS-derived SVI: 27.2 ml/m², plasma BNP: 344 pg/ml) for readmission.

Conclusions: Hemodynamic parameters derived by NICaS are applicable for the non-invasive assessment of cardiac function in outpatient CHF follow up. (Circ J 2009; 73: 1074–1079)

Key Words: Bioimpedance; Cardiac output; Congestive heart failure; Non-invasive cardiac monitoring system; Prediction of readmission

The growing geriatric population and increased number of survivors of acute heart failure have dramatically increased the number of outpatients with chronic heart failure (CHF). Hemodynamic parameters, such as stroke volume (SV), cardiac output (CO), total systemic vascular resistance (TSVR), and plasma level of B-type natriuretic peptide (BNP) are thought to be important for predicting the long-term prognosis and guiding the optimal treatment of CHF. Until recently, hemodynamic parameters could only be obtained using the invasive thermodilution method with a Swan–Ganz catheter placed in the pulmonary artery. A non-invasive and low-cost method for measuring hemodynamic parameters would be useful for the clinical assessment of CHF in an outpatient setting.

Several non-invasive technologies for measuring hemodynamics are now available. Non-Invasive Cardiac System (NICaS) (NI Medical; Hod-Hasharon, Israel) is a new device for calculating SV, CO, and TSVR utilizing whole body bioimpedance cardiography with electrodes placed on one wrist and on the contralateral ankle. We previously established that NICaS-derived CO (NI-CO) is a reliable parameter when compared with thermodilution CO or modified Fick CO.

The purpose of the present study was to evaluate the feasibility of using NICaS in outpatients with CHF and to assess whether NICaS-derived hemodynamic parameters in CHF are clinically significant by relating them to other conventional cardiovascular functional indices, and to assess the predictive accuracy of NICaS-derived parameters for CHF-related readmission.

Methods

Patient Selection and Exclusion Criteria

In the present study, patients who met the following criteria were enrolled: (1) hospitalized because of acute CHF; (2) had a stable condition after optimal medical therapy including diuretics, vasodilators, ACE-inhibitors; (3) had no renal dysfunction (defined as a creatinine value >2.0 mg/dl); and (4) had no significant severe valve diseases. The cardinal manifestations of heart failure were dyspnea and fatigue caused by cardiac dysfunction.

The study population comprised 68 CHF patients (56 men, 12 women, mean age 64.9±10.8 years); 20 patients were classified as New York Heart Association (NYHA) class I and 48 were NYHA class II patients (Table 1). The Institutional Ethics Committee of the Kobe University Hospital approved the study protocol and all patients provided informed consent to participate in the study.

In most patients, CHF coexisted with multiple underlying heart diseases, as shown in Table 1. Three patients...
had atrial fibrillation when CO was measured. In addition, 20 cases (29.4%) had a moderate degree of mitral valve regurgitation, 7 cases (10.3%) had a moderate degree of aortic valve regurgitation, and 1 case (1.5%) had moderate aortic valve stenosis. The cardiovascular medicines taken by the patients comprised: diuretics (n=44, 68.7%), digitalis (n=7, 10.9%), angiotensin-converting enzyme inhibitors (n=28, 43.7%), angiotensin receptor blockers (n=42, 65.6%), beta blockers (n=53, 82.8%), nitrates (n=8, 12.5%), calcium channel blockers (n=13, 20.3%), and oral inotropic agents (n=10, 15.6%).

The exclusion criteria for the NICaS measurements included restless and/or unstable patient condition, severe aortic valve regurgitation and/or aortic stenosis, aortic aneurysm, heart rate above 130 beats/min, intra- and extra-cardiac shunts, severe peripheral vascular disease, severe pitting edema, sepsis, and dialysis, all of which interfere with the accurate measurement of impedance-derived SV as previously described. All patients were followed up at the outpatient clinic of the Cardiovascular Division of Kobe University hospital and had no walking disability. We measured the cardiac parameters once the patients’ attended the outpatient department, which was the first routine visit to our hospital 1 month after discharge from the hospital for the first heart failure admission. At the same visit, serum BNP levels were measured and a questionnaire about exercise tolerance was administered.

Cardiac Indicators Derived by NICaS

To measure NI-CO, an alternating electrical current of 1.4 mA with a 30 kHz frequency was passed through the patient via 2 pairs of tetrapolar electrodes, 1 pair placed on the wrist above the radial artery, and the other pair placed on the contralateral side above the posterior tibialis artery. If the arterial pulses were either absent or of poor quality, a second pair of electrodes was placed on the contralateral site. The NICaS apparatus calculated the SV using Tsoglin and Frineman’s formula:

\[ \text{SV} = \frac{\text{dR} \times \rho \times L^2}{\text{Ri} \times (\alpha + \beta) \times \beta \times \text{KW} \times \text{HF}} \]

where \( \text{dR} \) is the change in impedance, \( R \) is the basal resistance, \( \rho \) is the blood electrical resistivity, \( L \) is the patient height, \( \text{Ri} \) is the corrected basal resistance according to gender and age\(^{8-12} \), \( \text{KW} \) is a correction of weight according to ideal values\(^{9-13} \), \( \text{HF} \) is a hydration factor that takes into account body water composition\(^{11} \), \( \alpha + \beta \) is equal to the ECG R–R wave interval, and \( \beta \) is the diastolic time interval.

Because the NI-CO results are calculated every 20 s, the average of 3 measurements obtained consecutively during 60 s of monitoring was considered to be the NI-CO value for each individual case. By using the NI-CO value, the following parameters were calculated: NI-CO index (NI-CI = NI-CO/body surface area), SV index (NI-SVI = NI-CI/heart rate), and TSVR (NI-TSVR = Mean arterial pressure/CO*80 [dyne·s\(^{-1} \)·cm\(^{-2} \)]).

Plasma BNP Measurements

Blood samples were obtained from the patient in a resting condition after NICaS measurement. The samples were drawn into plastic syringes, transferred to chilled siliconized disposable tubes containing aprotinin (1,000 kallikrein inactivator in units/ml; Ohkura Pharmaceutical, Kyoto, Japan) and ethylenediaminetetraacetic acid (1 mg/ml), immediately placed on ice, and then centrifuged at –48°C. An aliquot of the plasma was immediately frozen at –80°C and thawed only once at the time of the assay, which was performed within 1 week. The plasma BNP concentration was measured using a specific immunoradiometric assay kit (Shionogi Co, Osaka, Japan), as previously reported\(^{4} \).

Echocardiography Measurement of the Ejection Fraction (EF) and the Ratio of Early-to-Atrial Filling of Transmitral Flow (E/A)

B-mode recordings were obtained with a commercially available instrument (SONOS 5500\(^{TM} \), Agilent Technologies Inc, Palo Alto, CA, USA) operating at 2.5 MHz. Two-dimensional imaging examinations were performed in the standard manner from apical 4 and 2 chamber views, and the left ventricular (LV) EFs were measured from B-mode images according to the modified Simpson’s method. Also, pulsed-Doppler findings of transmural flow were obtained to calculate the E/A.

Exercise Tolerance Estimation

Each patient underwent a questionnaire-based interview for the estimation of the exercise tolerance threshold (ET) according to a specific activity scale\(^{15} \).

Statistical Analysis

MedCalc version 9.6 (MedCalc Software, Mariakerke, Belgium) was used for data analysis. The quantitative data are expressed as mean±SD. A Student’s t-test was used for descriptive statistics. The Mann–Whitney U-test was used for non-parametric data sets. A two-tailed Pearson’s correlation was used to compare the relationship between LVEF, log BNP, and NI-CI, NI-SVI, and NI-TSVR. Spearman’s coefficient of rank correlation (rho) was used to estimate the probability of correlations with ET. We used the multiple regression analysis in order to detect the predictors for CHF readmission, and also used receiver operating characteristic curve (ROC) analysis for BNP, NI-CI, NI-SVI, NI-TSVR, LVEF and ET to determine the thresholds between the readmission group and the non-readmission group. A two-tailed P-value of less than 0.05 was considered to be significant.

Results

Relationship Between NICaS-Derived Hemodynamic Parameters and LVEF, Plasma logBNP and ET

There were significant but weak correlations between LVEF and NI-CI (LVEF=22.70+5.21*NI-CI, r=0.3148, P=0.0089), NI-SVI (LVEF=22.80+0.38*NI-SVI, r=0.3257, P=0.0067), NI-TSVR (LVEF=46.02–0.003*NI-TSVR, r=0.2636, P=0.0298; Figure 1). There were significant moderate correlations between log BNP and NI-CI (log BNP=
Figure 1. Scatter plots showing the correlation between left ventricular ejection fraction (EF) and Non-Invasive Cardiac System (NICaS) derived cardiac output index (NI-CI) [A], EF and NICaS derived stroke volume index (NI-SVI) [B], EF and NICaS derived total systemic vascular resistance (NI-TSVR) [C]. The 2-tailed Pearson’s correlation test (r) was used for the analyses.

\[ y = 22.70 + 5.21 \times \quad r = 0.3148 \quad P = 0.0089 \]

\[ y = 22.80 + 0.38 \times \quad r = 0.3257 \quad P = 0.0067 \]

\[ y = 46.02 - 0.003 \times \quad r = -0.2636 \quad P = 0.0298 \]

Figure 2. Scatter plots showing the correlation between the logarithmic serum B-type natriuretic peptide (BNP) levels with NI-CI [A]; BNP and NI-SVI [B], BNP and NI-TSVR [C]. The 2-tailed Pearson’s correlation test (r) was used for the analyses. NI, non-invasive; CI, cardiac output index; SVI, stroke volume index; TSVR, total systemic vascular resistance.

\[ \text{Log}(y) = 3.20 - 0.38 \times \quad r = -0.4585 \quad P < 0.001 \]

\[ \text{Log}(y) = 3.20 - 0.028 \times \quad r = -0.4737 \quad P < 0.0001 \]

\[ \text{Log}(y) = 1.33 + 0.0003 \times \quad r = 0.4803 \quad P < 0.0001 \]
3.20–0.38*NI-CI, \( r=–0.4585, P=0.0001 \), NI-SVI (log BNP = 3.20–0.028*NI-SVI, \( r=–0.4737, P<0.0001 \)), and NI-TSVR (log BNP = 1.33+0.0003*NI-TSVR, \( r=0.4803, P<0.0001 \); Figure 2). There was a significant correlation between ET and NI-CI (\( \rho =0.412, P=0.0025 \)), NI-SVI (\( \rho =0.575, P<0.0001 \)), and NI-TSVR (\( \rho =–0.357, P=0.0087 \); Figure 3). There was no significant relationship between ET and E/A (Figure 4).

**Predictive Factors for CHF Readmission**

During the 100±98 days (95%CI for the mean: 46–154) follow-up, 15 patients were readmitted to our hospital because of CHF recurrence (readmission group) whereas 53 patients were not readmitted because of CHF recurrence (no-readmission group). There was a significant difference in NI-CI between the readmission and non-readmission groups (1.86±0.37 L·min⁻¹·m⁻² vs 2.92±0.63 L·min⁻¹·m⁻², \( P<0.0001 \)). Similarly, there were significant differences between groups in NI-SVI (24.2±7.9 ml·min⁻¹·m⁻² vs 40.4 ml·min⁻¹·m⁻², \( P<0.0001 \)), NI-TSVR (3,786±1,162 dynes·cm⁻⁵·m⁻² vs 2,420±583 dynes·cm⁻⁵·m⁻², \( P=0.0007 \)), LVEF (27.4±8.4% vs 39.3±11.7%, \( P=0.0005 \)), ET (2.89–3.11 metabolic equivalents vs 5.00–7.00 metabolic equivalents in 95%CI for median, \( P<0.0001 \)), and BNP (696.5 pg/ml [95%CI: 487.5–995.1] vs 98.1 pg/ml [95%CI: 69.8–138.1], \( P<0.0001 \)). Receiver operator characteristic curves for sensitivity, specificity, positive predictive value, and negative predictive value for readmission for each parameter are shown in Table 2. Multivariate analysis for readmission showed that LVEF measured by echocardiography, NI-CI, NI-SVI, and plasma BNP were significant predictors of readmission (Table 3).

**Discussion**

We have previously reported the reliability of NICaS-derived hemodynamic parameters when compared with those obtained by the Swan–Ganz catheter. Overall, 2-tailed
According to our data, BNP had 93.3% sensitivity and 88.7% specificity for the future occurrence of heart failure. An NICaS-derived CI of less than 55% was significant for predicting the future recurrence of heart failure. ET was significantly worse in the readmission group than in the non-readmission group. In our study subjects, diastolic dysfunction did not have a significant effect, probably because of the small number of subjects used.

It is widely believed that exercise capacity is related to LV diastolic function, but not to the LVEF, which in the present study was closely correlated to CI and SVI. We did not, however, find a significant relationship between E/A and ET. Also, in our study subjects, 3 patients were thought to have a purely diastolic dysfunction because they had a preserved EF of more than 55% and an E/A with the transmitral Doppler echocardiogram of less than 1 during their first visit to the outpatient department, and were not in the readmission group. Thus, in our study subjects, diastolic dysfunction did not have a significant effect, probably because of the small number of subjects used.

Although NICaS might be useful for estimating cardiac performance in patients who are not exercise tolerant or who have difficulty walking, it might not be reliable when applied to patients who match the exclusion criteria described above, including those with arteriosclerosis obliterans and severe pitting edema of the limbs.

### Table 2. Receiver Operating Curve Analysis for Readmission

<table>
<thead>
<tr>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUC</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>93.3</td>
<td>88.7</td>
<td>70.0</td>
<td>97.9</td>
<td>0.95</td>
</tr>
<tr>
<td>NI-CI</td>
<td>100</td>
<td>79.3</td>
<td>57.7</td>
<td>100</td>
<td>0.93</td>
</tr>
<tr>
<td>NI-SVI</td>
<td>80</td>
<td>98.1</td>
<td>92.3</td>
<td>94.4</td>
<td>0.91</td>
</tr>
<tr>
<td>NI-TSVR</td>
<td>100</td>
<td>68.6</td>
<td>46.7</td>
<td>100</td>
<td>0.89</td>
</tr>
<tr>
<td>LVEF</td>
<td>86.6</td>
<td>64.2</td>
<td>40.6</td>
<td>94.4</td>
<td>0.80</td>
</tr>
<tr>
<td>ET</td>
<td>100</td>
<td>71.4</td>
<td>52.0</td>
<td>100</td>
<td>0.88</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; BNP, B-type natriuretic peptide; CI, NICaS derived cardiac index; SVI, NICaS derived stroke volume index; TSVR, NICaS derived total systemic vascular resistance; LVEF, left ventricular ejection fraction; ET, exercise tolerence tolerance threshold.

### Table 3. Multivariate Analysis for Factors of Readmission

<table>
<thead>
<tr>
<th>OR (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0429 (0.9530–1.1414)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.3235 (0.0593–1.7647)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.8918 (0.8205–0.9693)</td>
</tr>
<tr>
<td>NI-CI</td>
<td>0.0318 (0.0023–4.4241)</td>
</tr>
<tr>
<td>NI-SVI</td>
<td>0.8121 (0.681–0.9540)</td>
</tr>
<tr>
<td>BNP</td>
<td>1.0068 (1.0019–1.0117)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.0456 (0.9805–1.0138)</td>
</tr>
<tr>
<td>SBP</td>
<td>1.0118 (0.9711–1.0542)</td>
</tr>
</tbody>
</table>

OR, odds ratio; SBP, systolic blood pressure. Other abbreviations as in Table 2.
Conclusions

NICaS-derived hemodynamic parameters obtained by monitoring whole body bioimpedance are applicable for the non-invasive assessment of cardiac function for the follow up of outpatients with CHF.

References

Impedance cardiography: a useful and reliable tool in optimization of cardiac resynchronization devices

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Aims Optimizing cardiac resynchronization therapy (CRT) devices has become more complex since modification of both atrioventricular (AV) and interventricular (VV) stimulation intervals has become possible. The current paper presents data from the routine use of impedance cardiography (IC)-based cardiac output (CO) measurements to guide the optimization of AV- and VV-interval timing of CRT devices.

Methods and results Forty-six patients with heart failure (left ventricular ejection fraction <35%, New York Heart Association (NYHA) III–IV) and left bundle branch block (LBBB). Atrial fibrillation and ventricular conduction delay caused in part by left bundle branch block (LBBB). CRT reduces clinical symptoms of heart failure and hospitalization, improves haemodynamic parameters (including ventricular performance), and has been shown to reduce mortality.

Conclusion Modification of both AV and VV intervals in patients with a CRT device significantly improves CO compared with standard simultaneous biventricular pacing and no pacing. IC is a useful non-invasive technique for guiding this modification. Marked variability of optimal AV and VV intervals between patients requires optimization of these intervals for each patient individually.

KEYWORDS
Cardiac resynchronization therapy; Non-invasive optimization; Impedance cardiography

Introduction

Cardiac resynchronization therapy (CRT) has developed from an experimental method to an established adjunctive treatment for patients with advanced heart failure. CRT aims to improve cardiac output (CO) by lessening the interval and intra-ventricular conduction delay caused in part by left bundle branch block (LBBB). CRT reduces clinical symptoms of heart failure and hospitalization, improves haemodynamic parameters (including ventricular performance), and has been shown to reduce mortality.

Successful CRT in any given patient depends upon many variables, such as the appropriate positioning of the LV lead, and also on achieving optimal biventricular stimulation timing. This latter variable has attracted particular interest recently in an attempt to reduce the substantial proportion (20–30%) of patients who derive no apparent benefit from CRT, despite meeting appropriate implantation criteria and having had technically straightforward device implantation (‘non-responders’).

CRT devices have become significantly more complex recently. Many now have the facility to programme different atrioventricular (AV) and interventricular (VV) stimulation timing intervals. Data exist to show that tailoring these intervals to suit the patient in hand further improves the haemodynamic benefits brought by CRT. However, questions remain as to which method of haemodynamic assessment is best for guiding the adjustment of the device settings to suit any given post-implant patient.

In the measurement of cardiac function, invasive methods (e.g. dp/dt estimation of contractility or the thermodilution method for CO) are the gold standards but are not suitable for routine use during routine follow-up of patients with implanted CRT devices. Non-invasive methods used in optimizing device settings include echocardiographic techniques, radionucleotide ventriculography, finger photoplethysmography, and more recently, impedance cardiography (IC).

IC is an established technique for haemodynamic assessment and is capable of calculating CO on a beat-to-beat basis. It relies upon changes in impedance (resistance) to current flow through the chest between strategically placed electrodes. Given that most current takes the path

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of least resistance (principally the blood-filled aorta) and that the impedance changes with blood flow, these variables can be used to calculate CO. IC has been used in patients receiving dual chamber pacemakers and in the assessment of patients with heart failure. IC as a technique may supplement or even replace invasive measurements and Doppler echocardiography in the optimization of implanted CRT devices.

This paper presents data from the routine use of IC in optimizing CRT by adjusting AV and VV intervals to obtain maximum CO in post-implant patients. To our knowledge, this is the first report on the combined manipulation of AV- and VV-interval timing in biventricular pacing devices using IC.

Methods

Patient characteristics

Forty-six consecutive patients (37 males, 9 females, mean age 63 ± 9 years) with heart failure [left ventricular ejection fraction (LVEF) <35%; NYHA III–IV], LBBB (>130 ms), and sinus rhythm were evaluated 3–5 days after implantation of a CRT device. Baseline characteristics of study patients are detailed in Table 1. All patients had been receiving optimal (guideline compliant) medical treatment for heart failure for at least 1 month before device implantation. Evaluation of patients before CRT included 12-lead surface ECG. Echocardiography was undertaken pre-implant, and post-CRT device optimization according to a standard template was performed with a System FiVe (GE VingMed) machine coupled to a 2.5 MHz transducer. In all patients, measurement of left ventricular (LV) dimensions, LVEF and evaluation for valve disease, particularly mitral regurgitation was undertaken. Transmitral flow was assessed using pulsed wave Doppler imaging in the apical 4-chamber view. Coronary angiography was performed in patients who had not previously had this done or where patients had symptoms of active coronary disease requiring further imaging. The echocardiography and coronary angiography form part of our standard patient ‘work-up’ for device implantation, but these results were not part of the prospectively chosen datasets gathered for the purpose of the study.

Device implantation

All patients received a CRT device in combination with a cardioverter–defibrillator (Contak Renewal, Guidant, St. Paul, MN, USA) except one patient who received only a CRT device (Contak Renewal). Forty-five of the 46 CRT devices were implanted in our catheterization laboratory by a cardiologist and a cardiac surgeon. The other patient received a device with epicardial leads implanted during surgical mitral valve reconstruction. Device implantation was similar in all cases. Initially the right ventricular (RV) lead was placed in the RV apex, then the coronary sinus lead was positioned using the over-the-wire technique, and finally the right atrial lead was implanted. The device was programmed in DDD-Mode with a lower rate limit at 40–50 bpm, producing atrial synchronous biventricular tracking of the intrinsic sinus rhythm (VAT-Mode). The AV interval was set at 120 ms as a standard value without LV or RV pre-excitation (VV interval = 0). This ‘standard’ pacing set-up was kept from implantation until optimization.

Impedance cardiography

Optimization of biventricular pacing was performed using a commercially available system for IC (Task Force Monitor Systems, CNSystems, Graz, Austria) as described by Braun et al. Two electrodes were placed bilaterally to the inferior chest wall in combination with one electrode at the neck. Low-amplitude high-frequency current was delivered via these surface electrodes, and transthoracic impedance (resistance) to this current flow was measured. Changes in transthoracic impedance (mainly influenced by changes of systolic aortic blood flow) were measured by means of four additional surface electrodes: one pair placed bilaterally to the sternum and the second pair bilaterally to the abdomen. Cardiac output was calculated on a beat-to-beat basis from the transthoracic impedance signal. Figure 1 shows an example of the IC measurement acquired by the Task Force Monitor System.

Table 1 Patient characteristics

| Patients | 46 |
| Age (years) | 63 ± 9 |
| Gender (female/male) | 9/37 |
| % CAD/% DCM | 20/80 |
| QRS | 187 ± 26 ms |
| PQ | 197 ± 40 ms |
| LVEF | 27 ± 8% |

Figure 1 Example of the impedance cardiography measurement acquired by the Task Force Monitor System. There are two paced beats and one beat without pacing. From top to bottom: lead II from the surface ECG, blood pressure, and the first derivative dZ/dt of the impedance. DBP, diastolic blood pressure; SBP, systolic blood pressure; B, aortic valve opening; dZ/dt max, maximum of the first derivative of the impedance signal; X, aortic valve closure.
Pacing study protocol

To optimize the CRT set-up, all patients were examined in the supine position in a silent environment to reduce the impact of sympathetic activation by external stimuli.

A standard protocol involving a period of stabilization and equilibration followed by VV-interval optimization and then AV-interval optimization was employed in all patients. Pacemakers were programmed in a DDD-Mode with a lower rate limit of 40 bpm to avoid effects of atrial pacing on the AV interval. During data acquisition, telemetry between the implanted device and the programmer was disconnected to prevent interference with the measurement of impedance. AV-interval values relate to the atrioRV stimulation interval, and VV intervals relate to interventricular interval with negative figures implying LV pre-excitation.

The first stage of the pacing protocol was a period of stabilization and equilibration. The baseline CO without pacing was recorded, and this was alternated three times with 'standard' simultaneous biventricular pacing with an AV interval of 120 ms for 50 s at each setting. Once consistent values for CO in both modes were confirmed, we proceeded to the 'optimization' stage of the pacing protocol.

With the AV interval fixed at 120 ms, VV intervals were adjusted through a set of seven steps ranging from LV pre-excitation of −60 ms to an LV delay of 60 ms in steps of 20 ms (as reported previously). The CO was recorded for 50 s at each setting. Then, the VV interval was set at zero while the AV interval was adjusted from 80 to 140 ms stepwise in 20 ms increments. Again, CO at each setting was recorded. We found that 10 s were sufficient for stabilization in values after any change in the stimulation set-up. Finally, the device was set at whichever combination of AV and VV intervals produced highest CO in that patient.

We defined an increase in CO of greater than 10% above baseline (i.e. without pacing) as a 'positive response' to biventricular pacing, in keeping with data previously published. Where maximum CO was identified by IC to occur at very short AV intervals (i.e. A to RV or A to LV of <80 ms), an echocardiogram was performed to exclude a truncated A wave caused by atrial contraction against closed AV valves.

Statistics

All data are presented as means ± standard error. Statistical analysis was performed using multiple analysis of variance, Kruskal–Wallis test, and Fisher's exact test to compare more than two sets of data. For a comparison of two sets of data, a student's t-test was performed. A P-value of < 0.05 was considered to be significant. Data was processed using commercially available software (Statgraphics Plus for Windows).

Results

Cardiac resynchronization therapy

Forty-six CRT devices were successfully implanted, 45 by the transvenous approach and 1 by the transthoracic approach during surgical mitral valve repair. The LV lead was placed in a posterolateral (n = 35) or an anterolateral (n = 10) side branch. There were no complications.

There were no significant differences between the heart rates without pacing (75.1 ± 10.7 bpm), with initial simultaneous biventricular pacing (74.7 ± 10.9 bpm), or optimized biventricular pacing (74.8 ± 10.2 bpm, P > 0.05). Thus, results for CO obtained at each CRT set-up were unaffected by the heart rate.

Cardiac output without pacing vs. simultaneous biventricular pacing vs. optimized biventricular pacing

The alternation between three cycles of no pacing with simultaneous biventricular pacing during stabilization and equilibration revealed (across all patients) a mean increase in CO of 21.6 ± 22.1% (P < 0.05) with pacing. The mean range (i.e. variation) between the three recordings (in each patient) without pacing was 10.1% and between the three recordings with pacing was 11.8%.

Figure 2 shows data obtained for a typical patient at different VV intervals with a fixed AV interval of 120 ms. In this patient, the maximum CO was measured during LV pre-excitation of 20 and 40 ms relative to RV stimulation. Still, earlier LV pre-excitation, simultaneous biventricular pacing, and RV pre-excitation resulted in a lower CO.

Data collected from all patients at each stimulation set-up with VV optimization at a fixed AV interval of 120 ms and with AV optimization at a VV interval set to zero are shown in Figure 3.

In detail, the maximum CO was achieved with the following VV intervals (when combined with an AV interval of 120 ms): −60 ms in 15 pts, −40 ms in 6 pts, −20 ms in 9 pts, ±0 ms in 5 pts, +20 ms in 2 pts, +40 ms in 2 pts, and +60 ms in 3 pts, so the majority of patients (30 of 46 patients) achieved peak CO with LV pre-excitation. The remaining four patients achieved maximum CO with simultaneous biventricular pacing, two with an AV interval of 80 ms, and two with an AV interval of 140 ms.

The combination of an AV interval of 120 ms and LV pre-excitation of 40 ms yielded the highest mean CO of

![Figure 2](http://europace.oxfordjournals.org/Downloaded from compact.oxfordjournals.org)
4.57 ± 1.1 L/min. Similar values were obtained by LV pre-excitation of 20 and 60 ms (4.51 ± 1.3 and 4.50 ± 1.2 L/min, respectively). The optimal pacing set-up varied widely from patient to patient. As a result of this variability, there was no significant difference in CO when the results from different AV and VV intervals were compared. No single combination of AV and VV intervals could be recommended for application to the whole study population, because no single combination of intervals showed statistically significant superiority over other combinations.

For the population as a whole, when the CO obtained with ‘optimized’ biventricular pacing (i.e. the CO measured at whichever AV and VV intervals produced the highest value in that patient) is compared with the CO obtained with ‘standard’ simultaneous biventricular pacing and compared with the CO obtained with no pacing, a statistically significant difference is seen (Figure 3). CO without pacing was 3.66 ± 0.85 L/min. CO increased to 4.40 ± 1.1 L/min (P < 0.05) with simultaneous biventricular pacing using a standard AV interval of 120 ms.

The mean increase in CO changing from no pacing to simultaneous biventricular pacing was 21.6 ± 22.1% (P < 0.05). ‘Optimizing’ VV and AV intervals further increased the mean CO to 4.86 ± 1.1 L/min. This corresponds to an increase in mean CO of 32.8% without pacing and an increase of 11.2% compared with simultaneous biventricular pacing, all three set-ups resulting in significantly different CO (P < 0.05, Figure 4).

Taking an increase in CO ≥10% as a definition of a positive haemodynamic response to CRT,39 16 of the 46 patients (35%) were ‘non-responders’ with standard simultaneous biventricular CRT. In five of these patients, CO with standard biventricular pacing was lower than without any pacing. The mean CO in this group of 16 ‘non-responders’ (with standard biventricular CRT) was 100.8 ± 4.9% (where CO without pacing was 100%). After optimization, 9 of these 16 patients (who were ‘non-responders’ to standard simultaneous biventricular CRT) experienced an increase of ≥10% in CO to become ‘responders’. In this group of nine patients, the mean CO increased significantly from 101.3 ± 3.6% to 121 ± 5.1% (P ≤ 0.05). In the seven patients who failed to respond despite ‘optimization,’ the mean CO was 106.6 ± 2.6% with optimized pacing. Nevertheless, after modification of AV and VV intervals to produce the
Assessment of optimal biventricular stimulation: current methods

Although invasive measurements of CO and other parameters remain the ‘gold standard’ for the evaluation of haemodynamics, they are not suitable for routine follow-up and optimization of CRT device settings because such invasive procedures are unpleasant for the patient and have potentially serious complications.8,40

Most units favour non-invasive methods for the optimization of CRT devices. The use of echocardiographic techniques for this purpose has received more attention in the literature, although there is no consensus as to which of the many echo-based parameters is the best surrogate for CO in the context of CRT optimization.

Mitral44 and aortic42 valve Doppler velocity time integrals (VTI) as well as several other24 echocardiographic parameters have been assessed as an alternative to invasive measures and as a surrogate for CO in the optimization of pacing devices. Recently, there has been promising data using advanced tissue Doppler imaging techniques and real-time 3-D echo (particularly in selecting the optimal lead positioning for biventricular pacing), but despite these advances, the echocardiographic lead optimization of CRT remains complex and time consuming. It requires an experienced operator and has significant problems relating to reproducibility and objectivity.

Impedance cardiography: a reliable alternative technique?

Several studies have demonstrated that IC is capable of providing a reliable and accurate measurement of CO when compared with invasive methods.28,32,43 The utility of IC has been shown in patients with decompensated cardiac failure33 and in optimizing dual chamber pacemakers.44 A direct comparison of IC and echo techniques in optimizing AV intervals for pacemakers has been made in several studies30,31 with a recurring theme being that optimal AV intervals calculated by IC tend to be shorter than those obtained by echocardiography.45 Recently, Braun et al.6 provided data using IC to guide the manipulation (primarily) of AV intervals and showed that IC-based optimization is comparable with transaortic VTI, but IC was felt to be more sensitive to small changes in CO and easier to apply.

Limitations of impedance cardiography

The limitations of IC was usefully reviewed by Kinderman.46 In a study of 14 patients with dual chamber pacemakers, data from IC overestimated CO if very short AV intervals were programmed. This phenomenon seems to be attributable to a decrease in the thoracic impedance caused by a retrograde flow into the great thoracic veins induced by atrial contraction against closed AV valves. In these cases, optimization of AV interval solely according to the impedance signal would result in a truncated A wave of the transmitral flow, causing potentially deleterious effects. In our study, if IC indicated that optimum CO was seen at more than one AV or VV interval, the longer AV interval and the shorter VV interval were programmed. If IC indicated optimum CO at short AV intervals (below 80 ms), transmitral flow was checked by Doppler echocardiography to exclude a truncated A wave. Of the 46 patients in the present study, this echocardiographic ‘check’ was required in two, neither of whom required a lengthening of AV interval.

Importance of optimizing both VV and AV intervals

The early generations of CRT devices enabled programming of the AV interval only.

Discussion

In the present study, we described the use of IC to guide optimization of the AV and VV timing following CRT. To our knowledge, this is the first report of both AV and VV manipulation using IC as a guide in CRT optimization. We found IC to be simple to apply and capable of yielding rapid results in a reliable and reproducible fashion. We found that the optimal CRT-timing settings varied substantially between patients underlining the need to optimize each patient’s device individually in order to gain most benefit from device. Using this technique, we were able to significantly improve CO by manipulating both AV and VV intervals. By optimizing both settings, we were able to further improve the CRT-related increase in CO in ‘responders’ and, furthermore, could produce a significant increase in CO in patients who, with ‘standard’ or simultaneous biventricular pacing, had demonstrated no increase in CO (‘non-responders’). In part, this reflects the importance of ‘electrical repositioning’ of the LV lead by VV-interval manipulation. Thus, using this technique, we were able to reduce the rate of non-responders to CRT by 56% (from 35 to 15%) by IC haemodynamic criteria.

Assessment of optimal biventricular stimulation: current methods

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Figure 5 Comparison of the percentage of ‘non-responders’ to cardiac resynchronization therapy (definition see text) with simultaneous biventricular pacing (with an atrioventricular interval of 120 ms) vs. atrioventricular- and ventriculo-ventricular-interval optimized biventricular pacing according to the cardiac output measured by impedance cardiography for the whole study population.

maximum CO, the number of haemodynamic ‘non-responders’ was reduced to 7 of the 46 patients, i.e. the number of non-responders was reduced by 56% (Figure 5).

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The early generations of CRT devices enabled programming of the AV interval only. Most units favour non-invasive methods for the optimization of CRT devices. The use of echocardiographic techniques for this purpose has received more attention in the literature, although there is no consensus as to which of the many echo-based parameters is the best surrogate for CO in the context of CRT optimization.

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Importance of optimizing both VV and AV intervals

The early generations of CRT devices enabled programming of the AV interval only.
Prospective randomized trial data have shown that AV-interval optimization not only improves the haemodynamic response to CRT, but also improves NYHA functional class and quality of life scores.47

The current generation of devices allows the manipulation of both AV and VV intervals.

Since activation of the interventricular septum is mainly influenced by the RV lead, modification of the VV interval affects not only inter-ventricular dyssynchrony, but also intra-ventricular dyssynchrony of the LV. The capacity to manipulate VV intervals may thus further improve the haemodynamic response to CRT.

There is increasing evidence that sequential biventricular pacing is superior to simultaneous biventricular pacing in many patients with a CRT device.

Perego et al. examined the impact of sequential biventricular pacing while invasively monitoring dp/dt in both ventricles simultaneously. Simultaneous ventricular pacing produced an increase in dp/dt of 29% over baseline, but sequential pacing produced a significantly greater increase of 35% (p < 0.01). The mean optimal VV interval was LV pre-excitation of 25 ms, and there was no detriment to RV function.38 Similar findings were reported by van Gelder et al.40

This pattern of haemodynamic improvement with both AV and VV optimization has been verified using Doppler echocardiography,48 3-D echocardiography49 and radionuclide ventriculography.55 The largest benefit is obtained in most cases by LV pre-excitation. Our study is the first to validate the previous data, showing the additional benefit of optimizing both AV and VV intervals using IC as the method of assessment.

Where no facility for optimizing CRT devices in individual patients exists, we would recommend an AV interval of 120 ms and LV pre-excitation of 20–40 ms as empirical intervals in CRT programming. However, due to significant heterogeneity between patients, we were unable to identify any single set of AV and VV intervals as being superior and thus suitable for application to the whole CRT population on an empirical basis. This variation between patients is to be expected, since there is a substantial heterogeneity between patients of conduction pattern, ventricular size, scar tissue formation, ventricular function (especially with respect to regional wall motion abnormalities) CRT lead placement positions, and other variables. The facility to manipulate VV intervals in effect allows the operator to 'electrically reposition' the LV lead to help overcome some of these variations to maximize the haemodynamic response to the device.

This work has been an early, descriptive study of the feasibility of using IC to manipulate both AV and VV intervals in optimizing CRT devices. Further work is required before this technique can enter mainstream use. For instance, in any given patient, since AV and VV intervals are likely to be interdependent, the ideal IC protocol would test every AV-interval setting against every VV-interval setting and vice versa. With current equipment, this would be impractical. Another simpler method of combining these interdependent values of AV and VV intervals would be to identify the optimal VV interval (i.e. A to LV interval) and keeping this fixed (rather than re-setting this to zero as our protocol did), and then adjusting the AV (i.e. A to V interval) to identify the optimal CO. We suspect that this method of combined optimization of AV and VV intervals by IC may yield still higher CO values, and hence hopefully reduce the number of non-responders. Further studies are required.

Conclusions

The present paper is the first to report the utility of IC in the optimization of both AV and VV intervals in biventricular pacemaker set-up in routine clinical practice. Using IC, we demonstrated that manipulating both AV and VV intervals is feasible and may result in a significant improvement in the haemodynamic response to CRT compared with 'standard' simultaneous biventricular pacing and no pacing. The results show the importance of optimizing CRT set-up in each patient individually, since the variability between patients' means that no single set of intervals can be identified as being suitable for all or even most patients.

In our opinion, IC is a promising method of CRT optimization and may compare well with other techniques in routine use. It carries less risk of complications than invasive techniques and is more comfortable for the patient. The validity and reliability of IC has now been reported by several authors.28,31–33,43 Notwithstanding its limitations, which include a tendency to relative CO overestimation and the potential for selecting inappropriately short AV intervals, IC has an emerging role in the optimization of CRT parameters in routine clinical practice. Further work is required to make best use of IC derived data in combining AV and VV intervals to ideally suit any given patient.

Conflict of interest: none declared.

References


17. Doshi RN. Optimizing resynchronization therapy: can we increase the number of true responders? J Cardiovasc Electrophysiol 2005;16(Suppl. 1):548–51.


Cardiac power output predicts mortality across a broad spectrum of patients with acute cardiac disease

Dorinna D. Mendoza, MD, Howard A. Cooper, MD, and Julio A. Panza, MD Washington, DC

**Background** Cardiac power output (CPO) is a novel hemodynamic measurement that represents cardiac pumping ability. The prognostic value of CPO in a broad spectrum of patients with acute cardiac disease undergoing pulmonary artery catheterization (PAC) has not been examined.

**Methods** Consecutive patients with a primary cardiac diagnosis who were undergoing PAC in a single coronary care unit were included. The relationship between initial CPO [(mean arterial pressure × cardiac output [CO])/451] and inhospital mortality was evaluated. CPO was analyzed both as a dichotomous variable (using a cutoff value previously established among patients with cardiogenic shock) and as a continuous variable.

**Results** Data were available for 349 patients. The mean CPO was 0.88 ± 0.37 W. The inhospital mortality rate was significantly higher among patients with a CPO ≤0.53 W (n = 53) compared with those with a CPO >0.53 W (n = 296) (49% vs 20%, \( P < .001 \)). In separate multivariate analyses, both CPO and CO were associated with inhospital mortality. However, when both terms were included simultaneously, CPO remained strongly associated with mortality (odds ratio 0.63, 95% CI 0.43-0.91, \( P = .01 \)), whereas CO did not (odds ratio 1.05, 95% CI 0.75-1.48, \( P = .78 \)).

**Conclusions** Cardiac power output is a strong, independent predictor of inhospital mortality in a broad spectrum of patients with primary cardiac disease undergoing PAC. (Am Heart J 2007;153:366-70.)

Pulmonary artery catheterization (PAC) remains in common usage in the coronary care unit (CCU) setting despite questions regarding the use of this procedure in critically ill patients. The decision to use PAC is based on the concept that invasive hemodynamic measurements provide a more precise understanding of the status of the cardiovascular system, which in turn allows close monitoring of the response to therapeutic interventions. However, traditional hemodynamic measurements obtained from PAC, such as cardiac output (CO), do not fully describe the fundamental state of the cardiovascular system in the setting of severe illness. In particular, because of its critical dependence on preload and afterload, measured CO provides a limited estimation of ventricular function.

Cardiac power output (CPO) is a novel hemodynamic measure that is the product of simultaneously measured CO and mean arterial pressure (MAP). By incorporating both the pressure and flow domains of the cardiovascular system, CPO is an integrative measure of cardiac hydraulic pumping ability. Cardiac power output has been shown to be a powerful predictor of mortality in patients with chronic heart failure (HF) and in those with cardiogenic shock. Recently, a report from the SHOCK Trial Registry found that CPO was the strongest independent hemodynamic correlate of inhospital mortality in patients with cardiogenic shock. We hypothesized that CPO would provide important prognostic information across a broad spectrum of patients with acute cardiac disease. Accordingly, we analyzed the relationship between CPO and short-term mortality in a consecutive series of patients undergoing PAC in a single CCU.

**Methods**

**Study design and data collection**

The institutional review board for human research at the Washington Hospital Center approved this research protocol. Data were collected prospectively for consecutive patients admitted to the CCU between October 2002 and February 2006. Based on all available information, the attending physician determined the primary clinical diagnosis requiring admission to the CCU. Patients with a noncardiac primary diagnosis were excluded from this analysis. Persistent cardiogenic shock was determined to be present by using conventional clinical criteria of hypotension and signs of peripheral hypoperfusion in the presence of pulmonary congestion that did not rapidly resolve. Left ventricular ejection fraction (EF) was visually estimated from 2-dimensional echocardiography.
obtained during the index admission, or from left ventricular angiography (when available) if echocardiography was not performed.

For each patient, the first set of hemodynamic measurements obtained in the CCU was used for analysis. Measurements included those made while receiving support with inotropes and/or an intra-aortic balloon pump. Cardiac output was measured by the thermodilution method, taking the average of 3 to 5 readings. Mean arterial pressure was determined by invasive arterial monitoring if available; otherwise, automated sphygmomanometry was used. Cardiac power output was calculated as $\text{MAP} \times \text{CO} = 451$. Treatment decisions were made without specific regard to CPO measurements.

Statistical considerations

Previously, the SHOCK investigators determined that the cutoff value of CPO that most accurately predicted inhospital mortality in their patient cohort was 0.53 W. Accordingly, we analyzed CPO both as a dichotomous variable ($\geq 0.53$ W vs $\leq 0.53$ W) and as a continuous variable (per 0.2-W increments). Baseline variables were compared using standard statistical tests. The relationship between baseline variables and inhospital mortality was assessed with univariate logistic regression analysis. Multivariate logistic regression analysis was performed to examine the independent relationship between CPO (as a continuous variable) and inhospital mortality. A comprehensive logistic regression model was constructed including the following covariates: age, sex, race (white or nonwhite), treated diabetes mellitus, current or recent smoking, chronic renal failure requiring dialysis, prior coronary artery bypass grafting, intra-aortic balloon counterpulsation, mechanical ventilation, inotrope use, persistent cardiogenic shock, EF, heart rate, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, and CPO. A reduced model was then created that included only those covariates significantly associated with inhospital mortality. Cardiac output was subsequently forced into this reduced model. A 2-sided $P$ value less than .05 was considered to represent statistical significance.

Results

Baseline characteristics

Complete data were available for 349 patients. The primary admission diagnoses are listed in Table I. The most common diagnoses were acute myocardial infarction, cardiomyopathy, coronary atherosclerosis, and unstable angina. Baseline patient characteristics and hemodynamics are presented in Table II. The mean age was 64 years, 59% were men, and 39% were of nonwhite race. Patients had severe illness, as evidenced by the fact that 50% required an intra-aortic balloon pump, 51% required mechanical ventilation, and 55% required intravenous inotropic support.

The CPO ranged from 0.17 to 2.48 W, with a mean of 0.88 ± 0.37 W. Compared with patients with a CPO $>0.53$ W ($n = 296$), patients with a CPO $\leq 0.53$ W ($n = 53$) were older (69 vs 63 years, $P = .004$) and more likely to be women (64% vs 34%, $P < .001$). As expected, those with CPO $\leq 0.53$ W had a lower MAP, CO, and cardiac index, and a higher systemic vascular resistance (all $P < .001$). Of note, the EF was similar among patients with CPO $>0.53$ W and patients with CPO $\leq 0.53$ W (31% vs 28%, $P = 0.0$ significant).

Outcomes

Patients with a CPO $\leq 0.53$ W had a significantly higher inhospital mortality rate than those with a CPO $>0.53$ W (49% vs 20%, $P < .001$), corresponding to a positive predictive value of 49% and a negative predictive value of 80%. On univariate analysis, predictors of mortality were age, diabetes mellitus, need for mechanical ventilation, persistent cardiogenic shock, MAP, CO, cardiac index, heart rate, central venous pressure, and CPO (Table III). In the final reduced multivariate model, CPO remained independently associated with a reduced risk of inhospital mortality (odds ratio [OR] 0.65, 95% CI 0.54-0.78, $P < .001$) (Table IV). Other independent predictors were heart rate ($P = .01$), diabetes mellitus ($P = .02$), and the need for mechanical ventilation ($P < .001$). When CO was forced into this model, the relationship between CPO and inhospital mortality was not substantially altered (OR 0.63, 95% CI 0.43-0.91, $P = .01$), whereas there was no significant relationship between CO and mortality (OR 1.05, 95% CI 0.75-1.48, $P = .78$).

Cardiogenic shock

Persistent cardiogenic shock was diagnosed in 73 patients (21%). Mortality in patients with persistent

<table>
<thead>
<tr>
<th>Table I. Primary diagnosis</th>
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<tbody>
<tr>
<td>Primary diagnosis (N = 349)</td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>Non-ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Acute mycarditis</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>Tako-Tsubo cardiomyopathy</td>
</tr>
<tr>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Complete heart block</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
</tr>
</tbody>
</table>
Cardiogenic shock was higher than mortality among patients without this condition (37% vs 21%, \( P < .001 \)). After excluding patients with persistent cardiogenic shock, CPO remained independently associated with inhospital mortality (OR 0.64, 95% CI 0.50 to 0.81, \( P < .001 \)).

### Table II. Baseline characteristics and initial hemodynamic measurements

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 349)</th>
<th>CPO &gt;0.53 (n = 296)</th>
<th>CPO ≤0.53 (n = 53)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64 ± 14</td>
<td>63 ± 14</td>
<td>69 ± 11</td>
<td>.004</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>206 (59)</td>
<td>188 (64)</td>
<td>18 (34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonwhite race, n (%)</td>
<td>135 (39)</td>
<td>113 (38)</td>
<td>22 (42)</td>
<td>.65</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting, n (%)</td>
<td>61 (18)</td>
<td>51 (17)</td>
<td>10 (19)</td>
<td>.77</td>
</tr>
<tr>
<td>Percutaneous coronary intervention, n (%)</td>
<td>46 (13)</td>
<td>37 (13)</td>
<td>9 (17)</td>
<td>.37</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>79 (23)</td>
<td>67 (23)</td>
<td>12 (23)</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>27 (8)</td>
<td>25 (8)</td>
<td>2 (4)</td>
<td>.40</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>14 (4)</td>
<td>13 (4)</td>
<td>1 (2)</td>
<td>.70</td>
</tr>
<tr>
<td>Intra-aortic balloon pump, n (%)</td>
<td>175 (50)</td>
<td>155 (52)</td>
<td>20 (38)</td>
<td>.05</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>177 (51)</td>
<td>147 (50)</td>
<td>30 (57)</td>
<td>.35</td>
</tr>
<tr>
<td>Acute myocardial infarction, n (%)</td>
<td>175 (59)</td>
<td>175 (59)</td>
<td>26 (49)</td>
<td>.17</td>
</tr>
<tr>
<td>Persistent cardiogenic shock, n (%)</td>
<td>73 (21)</td>
<td>60 (20)</td>
<td>13 (25)</td>
<td>.48</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>80 ± 13</td>
<td>82 ± 13</td>
<td>70 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.9 ± 1.8</td>
<td>5.2 ± 1.7</td>
<td>2.8 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac index (L min^{-1} m^{-2})</td>
<td>2.5 ± 0.8</td>
<td>2.6 ± 0.8</td>
<td>1.6 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne s/cm(^5))</td>
<td>1297 ± 597</td>
<td>1207 ± 535</td>
<td>1824 ± 668</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 ± 19</td>
<td>90 ± 18</td>
<td>86 ± 19</td>
<td>.23</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>20 ± 7</td>
<td>19 ± 7</td>
<td>21 ± 7</td>
<td>.15</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>13 ± 7</td>
<td>12 ± 5</td>
<td>15 ± 12</td>
<td>.12</td>
</tr>
<tr>
<td>Any inotrope, n (%)</td>
<td>193 (55)</td>
<td>161 (54)</td>
<td>32 (60)</td>
<td>.42</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>30 ± 13</td>
<td>31 ± 13</td>
<td>28 ± 12</td>
<td>.14</td>
</tr>
</tbody>
</table>

### Table III. Univariate logistic regression results for inhospital mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.00-1.04)</td>
<td>.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.75 (0.46-1.22)</td>
<td>.24</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>0.74 (0.44-1.24)</td>
<td>.25</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>1.15 (0.61-2.16)</td>
<td>.66</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>1.13 (0.56-2.30)</td>
<td>.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.94 (1.12-3.36)</td>
<td>.02</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.37 (0.11-1.27)</td>
<td>.11</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0.89 (0.23-3.14)</td>
<td>.81</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.04 (0.63-1.71)</td>
<td>.88</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>1.12 (0.69-1.84)</td>
<td>.64</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4.30 (2.46-7.52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persistent cardiogenic shock</td>
<td>2.26 (1.29-3.94)</td>
<td>.004</td>
</tr>
<tr>
<td>Any inotrope</td>
<td>1.18 (0.72-1.93)</td>
<td>.52</td>
</tr>
<tr>
<td>MAP</td>
<td>0.96 (0.93-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CO</td>
<td>0.74 (0.63-0.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.47 (0.32-0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>1.00 (1.00-1.00)</td>
<td>.44</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01 (1.00-1.03)</td>
<td>.03</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>1.01 (0.98-1.05)</td>
<td>.45</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>1.05 (1.01-1.10)</td>
<td>.01</td>
</tr>
<tr>
<td>EF</td>
<td>1.00 (0.98-1.02)</td>
<td>.98</td>
</tr>
<tr>
<td>CPO</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Table IV. Multivariate logistic regression analysis for inhospital mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPO</td>
<td>0.65 (0.54-0.78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.02 (1.01-1.04)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.10 (1.13-3.89)</td>
<td>.02</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3.76 (2.08-6.82)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Discussion

To our knowledge, the current study is the largest reported analysis of CPO in a broad spectrum of patients with critical cardiac illness undergoing PAC. The major findings were the following: (1) inhospital mortality was substantially higher in patients with a low initial CPO, (2) CPO was independently associated with inhospital mortality after controlling for important covariates, and (3) the association between CPO and inhospital mortality was stronger than that of the more traditional CO.

Our findings suggest that measurement of CPO is useful for risk stratification in patients with primary cardiac disease undergoing PAC in the CCU setting. CPO represents the rate of energy input that the systemic vasculature receives from the heart, incorporating both pressure and flow domains of the cardiovascular system.\(^4\) It is therefore logical that such a measure of cardiac pumping ability would predict outcomes for patients with cardiogenic shock and severe HF, as has been demonstrated previously.\(^4\)\(^6\)\(^8\)
Our analysis extends these findings to a broader spectrum of patients with critical cardiac illness, including those with acute coronary syndromes, cardiomyopathies of various etiologies, valvular heart disease, cardiac arrhythmias, and complicated post-percutaneous coronary intervention courses.

As expected, patients in our analysis had CPO values considerably higher (mean 0.88 W) than those in a more select group with acute myocardial infarction and cardiogenic shock in the SHOCK trial registry (mean 0.62 W). Despite the substantial differences in patient populations and absolute CPO values, however, the relationship between CPO and in-hospital mortality was remarkably similar in the 2 analyses: an OR of 0.65 per 0.2-W increase in CPO in the current study compared with an OR of 0.60 in the SHOCK trial registry. Furthermore, among the subset of our patients diagnosed with persistent cardiogenic shock (n = 73), the positive and negative predictive values using a cutoff of 0.53 W were nearly identical in the 2 studies (62% vs 58% and 68% vs 71%, respectively). This concordance of results suggests both that the relationship between CPO and short-term mortality is consistent across a broad spectrum of cardiac diagnoses and a wide range of CPO values, and is reproducible across studies.

Cardiac power output is calculated from the more familiar hemodynamic variables, CO and MAP. Therefore, from a statistical standpoint, it cannot provide additional prognostic information beyond that contained within the 2 individual components. However, CPO combines information from these 2 separate hemodynamic axes (flow and pressure) into a single, easily understandable variable that can potentially be targeted for therapy. For this reason, the concept of CPO appears to provide clinically useful information above and beyond that provided by standard hemodynamic variables alone.

Recent studies have questioned the use of PAC in guiding treatment in critically ill patients, including patients with severe CHF. Possible explanations for these negative results include complications related to the PAC procedure itself (arrhythmias, infection); misinterpretation of the obtained data; incorrect action in response to even appropriately interpreted data; or unanticipated deleterious effects of treatments implemented in response to these data. In patients with cardiac disease, treatments are typically targeted to the CO (or cardiac index) and pulmonary capillary wedge pressure. However, CO is a measure of cardiovascular flow, not cardiac contractility, whereas pulmonary capillary wedge pressure is a measure of intracardiac pressure not directly representing cardiac performance. Theoretically, therefore, CPO—a measure of cardiac pumping ability—might be a more appropriate target for medical therapy. In addition, CPO can be simply and accurately determined noninvasively in most patients by using whole-body electrical bioimpedance to determine CO, thereby eliminating any direct complications of PAC. Clinical studies in which noninvasively determined CPO is targeted for treatment appear to be indicated.

Our study has several potential limitations. First, this was a single-center retrospective analysis, subject to the limitations inherent in such a study design. However, measurements of CPO were not used by the CCU physicians to make therapeutic decisions. Hence, we are confident that the observed prognostic value of CPO was not influenced by bias introduced from knowledge of this information. Second, although we attempted to control for important differences in baseline characteristics between patients, residual confounding might remain. Third, we were unable to distinguish between hemodynamic measurements made with and without support from inotropes and/or an intra-aortic balloon pump. Because both types of interventions are likely to increase CPO, this might affect the relationship between CPO and mortality. However, this relationship was maintained after including the use of these interventions in the multivariate model. Indeed, the relationship between CPO and mortality might be stronger in the absence of such support measures. Finally, we must emphasize that our findings demonstrate an association between CPO and outcome without providing a direct assessment of whether CPO should be used as a clinical end point for therapeutic interventions.

Conclusions

Cardiac power output is a novel and useful prognostic tool in patients with acute cardiac disease undergoing PAC in the CCU setting. Further studies in which CPO is targeted for treatment appear to be warranted.

References

6. Williams SG, Cooke GA, Wright DJ, et al. Peak exercise cardiac power output; a direct indicator of cardiac function strongly...


Impedance Cardiography for Cardiac Output Estimation
— Reliability of Wrist-to-Ankle Electrode Configuration —

Oscar Luis Paredes, MD; Junya Shite, MD; Toshiro Shinke, MD; Satoshi Watanabe, MD; Hiromasa Otake, MD; Daisuke Matsumoto, MD; Yusuke Imuro, MD; Daisuke Ogasawara, MD; Takahiro Sawada, MD; Mitsuhiro Yokoyama, MD

Background  Non-invasive measurement of cardiac output (CO) may become an important modality for the treatment of heart failure. Among the several methods proposed, impedance cardiography (ICG) has gained particular attention. There are 2 basic technologies of ICG: thoracic and whole-body ICG whereby the electrodes are applied either to the chest or to the limbs. The present study is aimed to test the effectiveness of the Non-Invasive Cardiac System (NICaS), a new ICG device working with a wrist-to-ankle configuration

Methods and Results  To evaluate the reliability of NICaS derived CO (NI-CO), 50 CO measurements were taken simultaneously with thermodilution (TD-CO) and modified Fick (Fick-CO) in 35 cardiac patients, with the TD-CO serving as the gold-standard for the evaluation. Overall, 2-tailed Pearson’s correlation and Bland-Altman limits of agreement between NI-CO and TD-CO were r=0.91 and −1.06 and 0.68 L/min and between Fick-CO and TD-CO, r=0.80 and −1.52 and 0.88 L/min, respectively. Good correlation was observed in patients with loading conditions altered by nitroglycerin and also in patients with moderate valvular diseases.

Conclusion  Agreement between NI-CO and TD-CO is within the boundaries of the FDA guidelines of bio-equivalence. NI-CO is applicable for non-invasive assessment of cardiac function. (Circ J 2006; 70: 1164–1168)

Key Words:  Cardiac output; Impedance cardiography; Thermodilution method

Several studies suggest the importance of cardiac power output calculation, which is derived from cardiac output (CO) and mean blood pressure, to predict the prognosis in heart failure patients not only in hospital but also in the outpatient setting. CO measured by the thermodilution method with a Swan-Ganz catheter placed in the pulmonary artery has become one of the most widely accepted and used methods of monitor cardiac function, despite its certain limitations. A noninvasive and low cost method for measuring CO would be relevant for the widespread clinical use of cardiac power output.

Some noninvasive techniques of measuring CO have been proposed over the past years. The indirect Fick method of re-breathing carbon dioxide and Doppler flow measurement of the left ventricular outflow tract have been shown to be accurate; however, their applications require expensive equipments and trained operators. Other promising results have been observed with devices based on electrical bioimpedance technology and 2 basic technologies of impedance cardiography (ICG) are currently in use. The first is called whole-body ICG (ICGr), which was introduced in 1964, and the electrodes are placed on the root of the neck and on the lower chest. When the CO is measured in subjects with healthy hearts, the results from both these technologies are usually reliable, but the reliability of CO measurements taken by ICGr is compromised in patients with cardiac diseases. According to the Food and Drug Administration (FDA) standard of bio-equivalence the disparity between 2 tech-
nologies should not exceed the range of 20%. The purpose of this study was to evaluate the reliability and feasibility of the new Non-Invasive Cardiac System (NICaS: NI Medical, Hod-Hasharon, Israel), which calculates the CO by measuring ICG in a tetrapolar mode, derived from electrodes placed on one wrist and the contra-lateral ankle (Fig 1).

### Methods

#### The Trial

This study prospectively enrolled 35 patients. The thermodilution-derived CO (TD-CO) was measured using a Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA), followed immediately by the modified Fick (Fick-CO) and with the NICaS (NI-CO). In 15 subjects, a second round of CO measurements was carried out using the 3 technologies after NTG injection. Twelve patients presented with congestive heart failure (CHF) and 4 patients had atrial fibrillation. The study population comprised 35 patients (17 men, 18 women, mean age 65.5±13.7 years). In most patients there was coexistence of multiple underlying heart diseases, including hypertension (n=15), diabetes mellitus (n=13), coronary artery disease (n=21) and idiopathic dilated cardiomyopathy (n=3). Twelve patients presented with congestive heart failure (CHF) and 4 patients had atrial fibrillation when CO was measured. In addition, our study subjects included 7 cases of moderate degree of valve regurgitation (aortic regurgitation 2 cases, mitral regurgitation 4 cases, mild tricuspid regurgitation 1 case) and 7 cases of moderate aortic valve stenosis.

#### Measuring CO

All operators were unaware of the CO results obtained by the various measuring techniques.

**TD-CO** Right heart catheterization using a 6 or 8Fr Swan-Ganz catheter was performed according to the standard institutional protocol. The catheter was advanced to the pulmonary artery under fluoroscopic guidance and verified with the pressure waveforms registered on the polygraph. TD-CO was measured 5 times by injecting 5 ml bolus of iced 9% saline solution at the same rate. Therefore, the 3 results of the saline injections that were within 15% of their extreme disparity were averaged for the TD-CO result.

**Fick-CO** For arterial oxygen saturation, blood samples were obtained from the arterial access sheath, and for venous oxygen saturation, blood samples were withdrawn using the distal edge lumen of the Swan-Ganz catheter placed in the pulmonary artery. All samples were immediately measured for oxygen saturation using the same device (Radiometer ABL 715, Copenhagen, Denmark).

**NI-CO** To measure the CO with the NICaS apparatus, an alternating electrical current of 1.4mA with a 30kHz frequency is passed through the patient via 2 pairs of tetrapolar electrodes, one pair placed on the wrist above the radial pulse, and the other pair on the contralateral ankle above the posterior tibialis arterial pulse. If the arterial pulses in the legs are either absent or of poor quality, the second pair of electrodes is placed on the contralateral wrist. The NICaS apparatus calculates the stroke volume by Frinerman's formula:

\[
\text{Stroke volume} = \frac{dR}{R_i \times \frac{L^2}{R_i \times (I + I)}} \times K \times H \times F \tag{1}
\]

where \(dR\) is the impedance change, \(R\) is the basal resistance, \(L\) is the blood electrical resistivity, \(K\) is the patient's height, \(I\) is the corrected basal resistance according to gender and age, \(K\) is a correction of weight according to ideal values, \(H\) is the hydration factor, which takes into account the body water composition, and \(F\) is the diastolic time interval.

Because the NI-CO results are calculated every 20 s, the average of 3 measurements obtained consecutively during 60 s of monitoring was considered to be the NI-CO value for each individual case.

### Table 1: Statistical Analysis of CO Measurements Performed by NI-CO and Indirect Fick-CO Compared With TD-CO

<table>
<thead>
<tr>
<th></th>
<th>All measurements in 35 patients (n=50)</th>
<th>Measurements after NTG injection (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NI-CO vs TD-CO</td>
<td>Fick-CO vs TD-CO</td>
</tr>
<tr>
<td>Correlation</td>
<td>0.91±0.16</td>
<td>0.80±0.16</td>
</tr>
<tr>
<td>Bias (L/min)</td>
<td>-0.18</td>
<td>-0.32</td>
</tr>
<tr>
<td>SD (L/min)</td>
<td>0.43</td>
<td>0.60</td>
</tr>
<tr>
<td>Average CO ± SD (L/min)</td>
<td>4.18±0.10</td>
<td>4.36±0.13</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Correlation was calculated using Pearson's 2-tailed test.

\[a p < 0.0001, \] \[b p < 0.001, \] \[c p < 0.001, \] \[d p = 0.001. \]

CO, cardiac output; NI-CO, Non-Invasive Cardiac System derived CO; Fick-CO, modified Fick derived CO; TD-CO, thermodilution-derived CO; NTG, nitroglycerine.
Statistical Analysis

The quantitative data are expressed as mean ± SD. For descriptive statistic, Student's t-test was used. To compare the results of NI-CO, Fick-CO and TD-CO, 2-tailed Pearson's correlation and the Bland-Altman limits of agreement were used. The gold-standard for determining accuracy of the results was the TD-CO. Values of p<0.05 were considered to be significant.

Results

The average values of CO in the study subjects for TD-CO, NI-CO and Fick-CO were 4.18±1.01 L/min, 4.36±1.03 L/min, and 4.05±0.89 L/min, respectively. There were
no significant differences between the 3 groups (Table 1). The overall results of the Pearson correlation analysis were as follows: NI-CO vs TD-CO: r=0.91, p<0.0001; Fick-CO vs TD-CO: r=0.80, p<0.0001 and NI-CO vs Fick-CO: r=0.85, p<0.0001 (Fig 2). The Bland-Altman 2-standard deviation limit of agreement between the NI-CO and TD-CO was ±0.87 (–1.06 and 0.68) L/min, and the agreement between the Fick-CO and TD-CO was ±1.20 (–1.52 and 0.88) L/min (Fig 3). The calculated percentage of disparity between the NI-CO and TD-CO would thus be 19.95% (0.87 L/min ± 4.36 L/min), which was less than that between Fick-CO and TD-CO (29.63% [1.20 L/min ± 4.05 L/min]). Nevertheless, there are 3 cases in this series in which the disparity between the NI-CO and TD-CO was greater than 20%, indicating that the disparity here is not equal, but close to FDA bio-equivalence (Note that the mathematical model of the FDA for determining bio-equivalence was not used here. Yet the simple model of limits of agreement, which was used, offers an acceptable appraisal of the good interrelationships between the 2 statistical approaches).

When we analyzed the subgroup of measurements before and after nitroglycerine injection to alter vascular resistance, identical changes in CO were observed with the NI-CO and TD-CO (TD-CO: 4.42±1.00 L/min ± 3.59±0.76 L/min, NI-CO: 4.07±1.07 L/min ± 3.85±0.85 L/min (Fig 4)). The relation between NI-CO and TD-CO after nitroglycerine injection was r=0.96, p<0.0001, n=15. All other statistical details are summarized in Table 1.

In the other subgroups of moderate degree of valvular regurgitation (n=7) and aortic valve stenosis (n=7), the correlation of NI-CO with TD-CO was r=0.92, p<0.0001, with a lower limit of agreement of –0.97 L/min and upper limit of agreement of 0.73 L/min.

Discussion

According to Bland and Altman and Raaijmakers et al when averages of repeated measurement results are used to compare the performance of a new medical device with a gold-standard, there is an overestimation of the correlation coefficient. In the present investigation the preferable single measurement design was used; namely, each test consisted of a TD-CO measurement, followed immediately by a NI-CO and a Fick-CO measurement. In 20 patients, only 1 study was performed, whereas in the remaining 15 patients 2 studies were done: before and after nitroglycerine injection. However, each of the second tests was conducted in the manner of an independent comparative measurement.

According to the definition of the FDA, if there is bio-equivalence between the gold-standard and a new technology, all the comparative results should be within a range of 20% disparity. Previous studies reported limits of agreement between ICGr-CO vs TD-CO of –2.2 to 2.2 L/min at best27–29 ICGWB-CO (JR Medical-Tallinn, Estonia) vs TD-CO of –1.37 to 1.87 L/min,4 and bipolar NI-CO vs TD-CO of –1.25 to 1.30 L/min (Table 2)! Based on these reports, it can be calculated that the disparity between ICGr-CO, ICGWB-CO, bipolar NI-CO vs TD-CO is 40%, 32.4% and 26%, respectively. Our result for tetrapolar NI-CO vs TD-CO (–1.06 to 0.68 L/min, disparity 20%) is better than those results. The reason for the better result with NICaS may be related to the most upgraded calculation formula.

An important fringe benefit of this trial is the data produced by the Fick-CO technology. This method, which enjoys increasing popularity among practical cardiologists, is still considered controversial. According to the present results, the limits of agreement between Fick-CO and TD-CO are –1.52 and 0.88 L/min (average ±1.20 L/min). In the presence of a mean Fick-CO of 4.05 L/min, the disparity between the 2 technologies is 30%, better than that of ICGr but inferior to that of NI-CO.

Among the established exclusion criteria related to the use of the NICaS are: severe aortic stenosis, in which the NI-CO is usually underestimated, and significant aortic regurgitation, in which the NI-CO tends to be overestimated. In the present trial, however, 7 cases of moderate aortic stenosis and 2 with mild–moderate aortic regurgitation were involved, indicating that NICaS is applicable in cases of mild to moderate aortic valve disease.

From the 15 measurements that were obtained after nitroglycerine injection, we observed a decrease in the mean CO output, all the comparative results should be within a range of 20% disparity. Previous studies reported limits of agreement between ICGr-CO vs TD-CO of –2.2 to 2.2 L/min at best27–29 ICGWB-CO (JR Medical-Tallinn, Estonia) vs TD-CO of –1.37 to 1.87 L/min,4 and bipolar NI-CO vs TD-CO of –1.25 to 1.30 L/min (Table 2)! Based on these reports, it can be calculated that the disparity between ICGr-CO, ICGWB-CO, bipolar NI-CO vs TD-CO is 40%, 32.4% and 26%, respectively. Our result for tetrapolar NI-CO vs TD-CO (–1.06 to 0.68 L/min, disparity 20%) is better than those results. The reason for the better result with NICaS may be related to the most upgraded calculation formula.

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From the 15 measurements that were obtained after nitroglycerine injection, we observed a decrease in the mean CO

<table>
<thead>
<tr>
<th>Authors</th>
<th>Method</th>
<th>Condition</th>
<th>Year published</th>
<th>Limits of agreement between ICG and TD (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drazner M, et al27</td>
<td>ICGT</td>
<td>CHF</td>
<td>2002</td>
<td>–2.2 to 2.2</td>
</tr>
<tr>
<td>Leslie S J, et al27</td>
<td>ICGT</td>
<td>CHF</td>
<td>2004</td>
<td>–2.2 to 2.2</td>
</tr>
<tr>
<td>Koobi T, et al10</td>
<td>ICGWB</td>
<td>CABG</td>
<td>1997</td>
<td>–1.37 to 1.87</td>
</tr>
<tr>
<td>Cotter G, et al4</td>
<td>NICaS</td>
<td>CABG, CHF</td>
<td>2004</td>
<td>1.25 to 1.30</td>
</tr>
</tbody>
</table>

Values are mean, ICG, impedance cardiography; ICGT, thoracic ICG; ICGWB, whole-body ICG; TD, thermodilution; CHF, congestive heart failure; CABG, coronary artery bypass graft; NICaS, Non-Invasive Cardiac System ICG. Other abbreviations as in Table 1.
levels. However, the accuracy of the results remained unaltered in NI-CO, which suggests that NICaS is also applicable even when the arterial resistance has changed.

Clinical Implications
Recent studies have shown that the calculation of cardiac power output (CO × mean arterial pressure) and systemic vascular resistance are important for the management of various cardiac diseases.3–5 Cardiac power output was found to be the strongest independent predictor of in-hospital mortality in patients admitted with cardiogenic shock3 and is an important tool for assessing the clinical response to drug therapy. In addition, there is enough evidence that ambulatory monitoring of cardiac power would benefit patients with CHF, resulting in better titration of medication and possibly less readmission to hospital. By introducing NICaS apparatus, wide-spread clinical use of cardiac power calculation would become feasible.

Conclusion and Limitations of NICaS
The present study indicates that NICaS performs at least as accurately as the thermodilution method. However, the reliability of the NICaS method depends on an alignment with exclusion criteria. This allows for the use of NICaS in approximately 80–85% of patients needing the examination.

References
Impedance cardiography revisited

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Abstract

Previously reported comparisons between cardiac output (CO) results in patients with cardiac conditions measured by thoracic impedance cardiography (TIC) versus thermodilution (TD) reveal upper and lower limits of agreement with two standard deviations (2SD) of approximately ±2.2 l min⁻¹, a 44% disparity between the two technologies. We show here that if the electrodes are placed on one wrist and on a contralateral ankle instead of on the chest, a configuration designated as regional impedance cardiography (RIC), the 2SD limit of agreement between RIC and TD is ±1.0 l min⁻¹, approximately 20% disparity between the two methods. To compare the performances of the TIC and RIC algorithms, the raw data of peripheral impedance changes yielded by RIC in 43 cardiac patients were used here for software processing and calculating the CO with the TIC algorithm. The 2SD between the TIC and TD was ±1.7 l min⁻¹, and after annexing the correcting factors of the RIC formula to the TIC formula, the disparity between TIC and TD further declined to ±1.25 l min⁻¹. Conclusions: (1) in cardiac conditions, the RIC technology is twice as accurate as TIC; (2) the advantage of RIC is the use of peripheral rather than thoracic impedance signals, supported by correcting factors.

Keywords: cardiac output measurements, thoracic bioimpedance, whole-body bioimpedance, impedance cardiography

Introduction

Three basic technologies are currently in use for impedance cardiography (ICG): (1) the thoracic ICG (TIC), where the electrodes are placed on the root of the neck and the lower part of the chest, being the dominant method in the market (Patterson et al 1964, Kubicek
et al 1966, 1974); (2) the whole-body ICG (ICGWB), where four pairs of electrodes are used, one pair on each limb (Tischenko 1973, Koobi et al 1999); (3) the regional ICG (RIC), a technology which is used by the NICaS (noninvasive cardiac system). In this technology, which is the subject of this report, only two pairs of electrodes are used, performing best when placed on one wrist and on the contralateral ankle (Cohen et al 1998, Cotter et al 2004, Torre-Amione et al 2004).

Two comprehensive reviews of the literature on clinical experience in measuring the cardiac output (CO) by TIC determined that in patients with cardiac conditions the TIC-CO results are unreliable (Raaijmakers et al 1999, Handelsman 1991). According to Patterson (1985) and Wang et al (2001), a number of sources in the chest, such as the lungs, vena cava, and systemic and pulmonary arterial vasculatures, generate systolic impedance reductions, while the heart generates signals of increased impedance. In addition to these multifarious sources of $\Delta Z$, variations in the electrical conductivities between the sources of impedance changes and the TIC electrodes (Kim et al 1988, Kauppinen et al 1998), and between the various impedance sources (Wtorek 2000) have been described. These model experimentation indicated that the thoracic $\Delta Z$ is not a reliable signal for calculation of the SV due to the multiple sources of $dZ/dt$ (Kim et al 1988, Wang and Patterson 1995, Kauppinen et al 1998, Wtorek 2000), providing the explanations for the above-mentioned unsatisfactory clinical results obtained by TIC (Raaijmakers et al 1999, Handelsman 1991).

In this report, an attempt is made to define the differences between the peripheral and thoracic impedance signals, and based on this, to explain the differences in the performance of RIC and TIC.

As we are capable of saving raw data from the wrist-ankle (peripheral) impedance signals, we were able to use the peripheral impedance waveforms and base impedance values to calculate stroke volumes, using various algorithms that have been associated with TIC calculations. This enabled us to prove that (1) the performance of RIC is twice as accurate as reported TIC results; (2) the reasons for this are as follows: (a) the impedance changes which are yielded by the limb electrodes are more suitable than the impedance changes of the thoracic electrodes for calculating the stroke volume and (b) the use of properly designed coefficient improved the accuracy of the CO results by at least an additional 25%.

Methods

The data for this project were gathered from two patient series. In both, comparisons were made between cardiac output results measured by the NICaS versus thermodilution. One series, which was studied in hospital A, consisted of 30 patients who were studied immediately upon arrival at the ICU following an open heart operation. In 11 (36%), despite the intravenous administration of adrenalin, cardiac index (CI) was lower than 2.5 l min$^{-1}$ m$^{-2}$. The second series included 13 cases of acute heart failure that were studied in hospital B. CI was lower than 2.5 l min$^{-1}$ m$^{-2}$ in seven (54%), and in the combined group of 43 cases of the two hospitals, it was lower than 2.5 l min$^{-1}$ m$^{-2}$ in 18 (43%).

The purpose of this study was to use peripheral impedance waveforms to calculate stroke volume by means of four different ICG algorithms and to compare each of these SV values with the thermodilution SV result.

Of the 55 and 31 studies conducted in hospitals A and B, respectively, raw data were successfully retrieved from only the last 30 consecutive patients of hospital A and the last 13

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4 In the ICGWB and RIC, where the impedance changes are depicted in the periphery, the impedance value is automatically converted into the real parts ($R_0$ and $\Delta R$) of the measured impedance signals (Lamberts et al 1984).
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Figure 1. Unedited print of the ECG and $\Delta R$ waveforms to demonstrate the definition of $\alpha$ and $\beta$.

consecutive cases of hospital B. It quickly became apparent that these 43 source data were retrieved from only one of the two NICaS devices that were being used in the two hospitals. The reason for this was that we did not realize that the software designed for source data retrieval was not implemented in one of the two NICaS devices that were used interchangeably during these trials.

Measuring the CO

Thermodilution. The standard techniques for measuring the thermodilution CO (TDCO) used in these two hospitals have been reported elsewhere (Cotter et al. 2004).

NICaS. To measure the CO with the NICaS (NICO), which is a tetrapolar device, two electrodes are placed on a wrist above the radial pulse and two on the contralateral ankle above the posterior tibialis arterial pulse. If the arterial pulses in the legs are either absent or of poor quality, the second pair of electrodes is placed on the contralateral wrist. The NICaS device calculates the SV by means of the following Frinerman formula5 (Cohen et al. 1998):

$$SV = \frac{\Delta R \cdot L^2 (\alpha + \beta) K_w \times HF}{R_i \beta}.$$

where SV is the cardiac stroke volume (ml), $\Delta R$ is the resistance change during the cardiac cycle ($\Omega$), $R$ is the basal resistance ($\Omega$), $R_i$ is a corrected basal $R$ ($\Omega$), $\rho$ is the blood electrical resistivity ($\Omega$ cm), $L$ is the patient’s height (cm), $K_w$ is a correcting factor for the body weight, HF is the hydration factor related to the body water composition and $(\alpha + \beta)/\beta$ is the ratio of the systolic time plus the diastolic time divided by the diastolic time of the $\Delta R$ waveform (figur 1).

5 The present formula is principally the same as the formula in Cohen et al (1998), but is written differently. The original formula was

$$SV = \frac{Hct_{cor} \times K_{cl} \times K_{weight} \times IB \times H_2 \Delta R}{R \times (\alpha + \beta)/\beta}.$$

The values of the hematocrit (Hct) and Na (el) are now represented by $\rho$, which is the electrical resistivity of the blood. $K_{sex age}$, which affects the basal resistance ($R$), is now represented by $R_i$, and IB (index body) is now represented by HF (hydration factor). The correction of $H^2$ is no longer included in the formula, but in patients whose arms are disproportionately long, the electrodes should be placed 5 cm proximally to their regular position.
Definition and principles of the correcting coefficients of the Frinerman formula

The basic impedance part of Frinerman’s formula consists of the following Bonjer equation (1950):

\[ SV = \frac{dR\rho L^2}{R^2}, \]  
\[(3)\]

to which Frinerman’s correcting factors were added. These coefficients were designed to neutralize the individual effects of gender, age, body water composition and anthropomorphic variabilities of each patient.

According to RIC studies, the basal \( R_0 \) is higher in females than in males, a fact which is in accordance with the literature (Organ et al 1994, Lukaski et al 1986, Hoffer et al 1970, Lamberts et al 1984, Ward et al 2000), and it tends to rise with age (Organ et al 1994).

Based on reported values of basal resistances related to sex and age (Organ et al 1994, Lukaski et al 1986, Ward et al 2000), a coefficient is calculated to determine an ideal value of \( R_0 \) for the studied patient. Ideal here means an ideal weight compared to height in healthy condition. By dividing the measured \( R_0 \) of the patient by the calculated ideal \( R_0 \), a correcting coefficient is obtained. By multiplying the measured \( R \) by the correcting coefficient the \( R \) variable is determined and placed in the denominator of the formula.

Similarly, a correcting coefficient (\( K_w \)) for the body weight is calculated by dividing the measured weight by the calculated weight according to Hamwi’s formula (1964) of ideal weight. \( K_w \) is required for compensation of the reduced electrical conductance in the fat, and this coefficient is placed in the numerator of the formula, affecting the value of \( \Delta R \). In a similar fashion, the hydration factor, \( HR \), is calculated by the patient’s body water composition, and this coefficient is placed in the numerator of the formula, either to reduce or to increase \( \Delta R \) in over- or under-hydrated patients, respectively.

The variable \((\alpha + \beta) / \beta\) is based on the Windkessel principle (Frank 1926, Faes et al 1999), where a distinction is made between the aortic inflow \( \alpha \), which is incurred by the systolic left ventricular ejection, and the aortic outflow \((\alpha + \beta)\), which extends throughout the cardiac cycle (figure 1).

Comparative calculation of CO by software simulation

The impedance raw data of the compiled 43 investigative patients were retrieved and their CO were calculated by the following formulae: (1) Frinerman’s formula, as measured by the NICaS; (2) Bonjer’s equation of 1950 (Bonjer 1950), which was expressed differently by Patterson’s first version of the TIC formula (Patterson et al 1964):

\[ \Delta V = \rho \left( \frac{L}{Z} \right)^2 \Delta Z; \]  
\[(4)\]

(3) Patterson’s formula of the first derivative (Patterson 1965):

\[ SV = \frac{dZ}{dt} \times T \times \rho \times \left( \frac{L}{Z} \right)^2, \]  
\[(5)\]

where \( SV \) is the cardiac stroke volume (cm), \( dZ/dt \) is the peak of the first derivative of the impedance change during systole (\( \Omega \) s\(^{-1}\)), \( T \) is the cardiac ejection time (s), \( L \) is the length between voltage pick-up electrodes (cm) and \( Z \) is the base impedance value (\( \Omega \)), which is still used by the TIC technology (Kubicek et al 1974); (4) a combined formula which includes Patterson’s equation together with Frinerman’s correcting factors (table 1, figure 2 and 3):
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Figure 2. Scatter plot comparing CO results calculated by four impedance algorithms versus thermodilution.

Table 1. Correlations and limits of agreement between four algorithms versus TD. Comparison of four different algorithms in 43 patients for measuring cardiac output (CO) of the same raw data: (a) Frinerman (NICaS); (b) Bonjer; (c) Patterson–Kubicek; (d) Patterson–Kubicek–Frinerman. Each of these was compared with thermodilution.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>TD</th>
<th>Frinerman NICaS</th>
<th>Bonjer</th>
<th>Patterson–Kubicek</th>
<th>Patterson–Kubicek–Frinerman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average CO (l min⁻¹)</td>
<td>5.12</td>
<td>5.05</td>
<td>5.33</td>
<td>5.00</td>
<td>5.09</td>
</tr>
<tr>
<td>SD</td>
<td>1.952</td>
<td>2.043</td>
<td>2.218</td>
<td>1.781</td>
<td>1.986</td>
</tr>
<tr>
<td>Correlation with TD</td>
<td>0.969</td>
<td>0.841</td>
<td>0.897</td>
<td>0.950</td>
<td></td>
</tr>
<tr>
<td>p value versus NICaS⁴</td>
<td>–</td>
<td>&lt;0.001</td>
<td>&lt;0.0005</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>−0.0698</td>
<td>0.2107</td>
<td>−0.1116</td>
<td>−0.0302</td>
<td></td>
</tr>
<tr>
<td>SD of Bias</td>
<td>0.509</td>
<td>1.203</td>
<td>0.864</td>
<td>0.624</td>
<td></td>
</tr>
<tr>
<td>LL agreement</td>
<td>−1.088</td>
<td>−2.196</td>
<td>−1.840</td>
<td>−1.277</td>
<td>−1.277</td>
</tr>
<tr>
<td>UL agreement</td>
<td>0.949</td>
<td>2.617</td>
<td>1.617</td>
<td>1.217</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; LL agreement = lower limit of agreement; UL agreement = upper limit of agreement.

⁴ Bonferroni adjusted p values for testing equality of correlation NICaS TD as compared with Bonjer TD (<0.0001), Patterson–Kubicek TD (<0.0005), Patterson–Kubicek–Frinerman TD (0.33).

\[
SV = \frac{dR \times T}{dt \times R} \times \frac{\rho \times L^2(\alpha + \beta)}{R_i \beta} \times K_w \times HF, \tag{6}
\]

where Frinerman’s \( \Delta R \) was replaced by \( dZ/dt \times T \) and \( (\alpha + \beta)/\beta \) was deleted.

Patient selection

Restlessness, aortic insufficiency, abdominal aneurysm, heart rate above 130 beats min⁻¹, arrhythmia with significant irregular heart rate, severe peripheral vascular disease, two or more
Figure 3. Scatter plots of Bland–Altman difference-against-average of the CO results calculated by the four impedance algorithms versus thermodilution results (based on table 1).

pitting edema and dialysis all interfere with the proper measurements of the SV; therefore, this patient population, which amounts to 15% of the candidates, is a priori excluded from the ICG studies. Also excluded are RIC measurements of the CO in thoracoabdominal operations, such as esophagectomies and pancreatectomies, where plasma loss and heavy intravenous volume loads due to significant bleeding undermine the stability of the basal R and the reliability of the CO results (Critchley et al 1996).

Statistical analysis

Thermodilution (TD) was used as the ‘gold standard’, and agreement between the four ICG formulae and TD was analyzed according to the Bland–Altman approach (Bland and Altman 1986).

Results

The results of the four algorithms revealed a rather similar average of the NICO in the range of 5 l min$^{-1}$ (table 1). The Pearson correlation coefficient were $r = 0.969, 0.841, 0.897$ and $0.950$ with the formulae of Frinerman, Bonjer (1950), Patterson–Kubicek (Patterson 1965, Kubicek et al 1974) and the combined Patterson–Kubicek–Frinerman formula, respectively (table 1, figure 2 and 3). The Bland–Altman 2SD lower and upper limits of agreement with TD were $-1.088$ and $0.949$, $-2.196$ and $2.617$, $-1.840$ and $1.617$, and $-1.277$ and $1.217$, according to the same order of formulae as above (table 1, figure 3).

6 To calculate the SV with the Bonjer, Patterson–Kubicek and Patterson–Kubicek–Frinerman formulae, the raw data of the 43 patients were e-mailed to Professor Robert Patterson, the inventor of the TIC technology (Patterson et al 1964, Patterson 1965), who made these calculations at the University of Minnesota.
Discussion

To compare the performance of the currently used TIC technology with RIC, we used three recent reports representing TIC results in patients with chronic stable congestive heart failure, which revealed similar values (Drazner et al. 2002, Van De Water et al. 2003, Leslie et al. 2004) and could serve as a paradigm of the performance of TIC in the presence of cardiac conditions. A relatively recent publication by Sageman et al. (2002) could not be included here because (a) only CI values were provided, (b) these values are characteristic of patients with normal cardiac functions and (c) the patients’ CO results were averages of up to 20 measurements, an approach which is not used clinically.

The average cardiac output in each of the three TIC series was in the range of 5 l min\(^{-1}\). Comparison in each series of the results with thermodilution (TD) revealed a Bland–Altman limit of agreement with a 2SD of approximately ±2.2 l min\(^{-1}\)—a 44% deviation compared to TD (Drazner et al. 2002, Van De Water et al. 2003, Leslie et al. 2004). Despite the fact that the present series did not include cases of chronic congestive heart failure, it is comparable with the TIC studies because (a) the patients were actively managed for cardiac conditions, (b) a CI < 2.5 l min\(^{-1}\) m\(^{-2}\) was observed in 43% of the cases and (c) the average CO was in the range of 5 l min\(^{-1}\), as in the TIC paradigm.

When the Patterson–Kubicek algorithm was fed by impedance raw data yielded by the peripheral wrist–ankle rather than by thoracic electrodes, the disparity compared to TD was ±1.7 l min\(^{-1}\), which is a 34% difference (figure 2 and 3). When the Patterson–Kubicek algorithm was reinforced by the correcting factors of the NICaS formula and the peripheral raw data were used, there was a further decline in the disparity between ICG and TD to the range of ±1.25 l min\(^{-1}\), a 25% difference. This is almost as good as the 20% disparity between the NICaS and the TD.

Judging by the 20% deviation between the NICaS and TD CO results, and by the 44% deviation between the reported TIC and TD CO results, it is evident that the accuracy of the NICaS is higher by a factor of more than 2, than the reported values of TIC (Raajmakers et al. 1999, Handelsman 1991, Drazner et al. 2002, Van De Water et al. 2003, Leslie et al. 2004).

Moreover, according to the FDA standard of bioequivalence (Guidance for Industry 2001), the comparative results of new and gold-standard technologies should be contained within a range of 20% disparity. This 20% range is determined by the 10% repeatability rate of each of the two methods. Judging by figure 3(A), the agreement between the NICaS and the TD is in very close proximity to the FDA standard bioequivalence.

About the validity of correcting coefficients

To appreciate the competence of the correcting factors, it is sufficient to compare the CO results of Frinerman’s and Bonjer’s formulae (figure 3(A) and (B)). As stated earlier, the only difference between these two equations is the addition of Frinerman’s correcting factors to Bonjer’s formula. \( R_e \), for example, which is the corrected \( R_0 \), may reach twice the value of the measured \( R_0 \). \( K_w \) may increase the measured \( \Delta R \) by up to 45%. The HF may either reduce or increase the value of \( \Delta R \) by only slight to moderate degrees. Thus, it can be discerned that when using Bonjer’s equation alone (figure 3(B)) the 2SD limits of agreement are approximately ±2.4 l min\(^{-1}\), and when Frinerman’s variables are added (figure 3(A)) the 2SD limits of agreement are ±1.0 l min\(^{-1}\). There is a 20% disparity between the NICaS and the TD, and a 45% improvement of Bonjer’s reinforced performance.

Similarly, annexing the Frinerman correcting coefficient to the TIC \( dZ/dt \times T \) formula dramatically improved the calculated CO results, from 2SD limits of agreement of
approximately ±1.7 l min⁻¹ (table 1, figure 3(C)) to 2SD limits of agreement of approximately ±1.25 l min⁻¹ (table 1, figure 3(D)).

It has been repeatedly shown by Hoffer et al. (1970), Lukaski et al. (1986), Organ et al. (1994), Ward et al. (2000) and others that the body is not a homogeneous conductor, and its basal resistance, and consequently the spatial distribution of conductivities, is a function of the body composition. It is also recognized that the two main factors which determine the impedance variabilities are the percentages of body water and fat. As shown here, by using the RIC approach, the variabilities of age, sex, height and weight can be quantitated and translated to the effective correcting coefficients.

About the validity of the wrist–ankle electrodes

The most significant advantage of RIC in comparison to TIC is the use of the peripheral impedance signal for calculation of the SV. According to Kauppinen et al. (2000), 75% of the peripheral (RIC) impedance waveform is borne by the systolic blood volume pulsations of the arterial vasculature of the upper and lower limbs, and the remaining 25% arrives from the trunk (thorax). Still, the sole source of the peripheral signal is generated by the blood volume pulse of the arterial vasculature.

It must be borne in mind that the aorta and its peripheral ramification comprise a single anatomophysiological structure, and the pulse waveform, which evolves throughout its length, occurs almost at the same time. This is possible only because the velocity of the pulse wave is so rapid that the arterial expansion is completed before the termination of the left ventricular contraction (Guyton and Hall 2000). The mean value of the pulse wave velocity (PWV) from the thorax to the calves is approximately 7–10 m s⁻¹ (Guyton and Hall 2000). Similarly, the impedance volume pulse travels at approximately the same rate as reported by Risacher et al. (1995).

Thus, in accordance with the existing knowledge of the cardiac role in the formation of the pulse (McVeigh et al. 2002), the RIC peripheral volumetric signal is borne throughout the length of the arterial tree beginning with the left ventricular stroke volume ejection.

In contrast, the thoracic (TIC) waveform is generated by multiple sources, including the aorta, lungs, atria, vena cava and artifacts due to heart movements (Wang et al. 2001, Kauppinen et al. 1998, Wtorek 2000). In normal people, some studies have shown that TIC gives reasonably reliable CO results (Raaijmakers et al. 1999), but in the presence of cardiac conditions, distortions of the TIC waveforms were already observed in the earliest days of the emergence of this technology (Kubicek et al. 1974). This is contrary to RIC, where we see very few changes, if any, in the waveform shape incurred by the different cardiac conditions.

The immunity of the peripheral impedance waveform to the distorting influence of cardiac conditions is reflecte by the results of the present study. The average disparity between TIC-CO and TD-CO measured in cardiac patients is 44%. In the present trial, the average disparity between TD-CO and ICG-CO, which was calculated by the combination of the TIC algorithm and a peripheral impedance waveform, was 34%. This 23% higher accuracy, which is obtained by the standard TIC algorithm, can be attributed only to one factor, the reliance for calculation of the SV on the peripheral, rather than the thoracic, impedance signal.

The fact that the RIC region consists of only part of the whole body but can be used to calculate the CO of the whole body is explained by the electrophysiological relationships which exist between RIC and ICGWB. In the ICGWB technique, electrodes are placed on all four limbs, and yet, despite the fact that the head which consumes 13% of the CO is not

7 Significant differences exist in these values, depending on the elasticity of the arterial vasculature.
included in the electrical field the reliability of the CO results of this technology has been validated (Tischenko 1973, Koobi et al 1999).

The common electrophysiological denominator of RIC and ICGWB is in that the same basal R of a body that is measured by RIC is twice the value measured by ICGWB. As measured in this series, and by and large as measured by others (Kauppinen et al 2000, Lukaski et al 1986, Organ et al 1994), the basal R of the region between the wrist and the ankle is approximately 450 Ω. This, when the value of the basal R of ICGWB is in the range of 200–250 Ω (Tischenko 1973, Lamberts et al 1984, Kauppinen et al 2000). The 2:1 ratio of the basal R in RIC versus ICGWB is attributed to the fact that in ICGWB the two upper and the two lower limbs are measured in parallel. Consequently, the cross-sectional area of the limbs is twice as large in ICGWB, resulting in the reduction of the electrical resistance to one-half. Thus, it is the same physiological mechanism which facilitates the appropriate measurement of the total CO by ICGWB, which also holds for the exceptionally accurate RIC results.

Conclusions

The present CO results measured by the NICaS device indicate that, with regard to accuracy of measuring the CO, the RIC technology outperforms any other ICG technology, being twice as accurate as TIC.

The peripheral systolic impedance changes are more reliable than the TIC impedance changes for calculating the cardiac stroke volume.

The main disadvantage of the RIC technology is that in approximately 15% of the patients who need the test, there are exclusion criteria which preclude the use of the NICaS, a problem which is also shared by other impedance technologies.

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8 It should be borne in mind that in females the electrical resistance between the wrist and the ankle is higher than in males by 80–100 Ω (Organ et al 1994, Lukaski et al 1986, Hoffler et al 1970). Furthermore, there are differences in the basal R values of different ethnic populations (Ward et al 2000), where different anthropometric characteristics exist. In the present series, the average basal R of the postoperative cases was lower by 100 Ω compared to the non-operative cardiac patients, and this is attributed to the over-hydration induced during the surgery.


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Value of Noninvasive Hemodynamics to Achieve Blood Pressure Control in Hypertensive Subjects

Ronald D. Smith, Pavel Levy, Carlos M. Ferrario and for the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels

Study Group

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Value of Noninvasive Hemodynamics to Achieve Blood Pressure Control in Hypertensive Subjects

Ronald D. Smith, Pavel Levy, Carlos M. Ferrario; for the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels Study Group

Abstract—Abnormal hemodynamics play a central role in the development and perpetuation of high blood pressure. We hypothesized that hypertension therapy guided by noninvasive hemodynamics with impedance cardiography could aid primary care physicians in reducing blood pressure more effectively. Uncontrolled hypertensive patients on 1 to 3 medications were randomized by 3:2 ratio to either a standard arm or hemodynamic arm that used impedance cardiography (BioZ, CardioDynamics). Each patient completed 5 study visits with a 2-week washout period followed by 3 months of treatment. A total of 164 patients from 11 centers completed the study, 95 in the standard arm and 69 in the hemodynamic arm. At baseline and after washout, there were no differences between arms in number of medications or demographic, blood pressure, or hemodynamic characteristics. Systolic blood pressure reductions in the hemodynamic arm were greater from baseline (19 mm Hg versus 11 mm Hg; \( P < 0.01 \)) and after washout (25 mm Hg versus 19 mm Hg; \( P < 0.05 \)). Diastolic blood pressure reductions were also greater in the hemodynamic arm from baseline (12 mm Hg versus 5 mm Hg; \( P < 0.001 \)) and after washout (17 mm Hg versus 10 mm Hg; \( P < 0.001 \)). The hemodynamic arm achieved goal blood pressure (<140/90 mm Hg) more frequently (77% versus 57%; \( P < 0.01 \)) and a more aggressive blood pressure level (<130/85 mm Hg) more frequently (55% versus 27%; \( P < 0.0001 \)). These study results indicate that antihypertensive therapy guided by impedance cardiography in uncontrolled hypertensive patients on \( \geq 1 \) medications is more effective than standard care. (Hypertension. 2006;47:771-777.)

Key Words: hemodynamics ■ cardiac output ■ vascular resistance ■ hypertension, arterial ■ hypertension, essential ■ blood pressure

Approximately 65 million people in the United States\(^1\) and 1 billion people worldwide\(^2\) have hypertension; it is the most common reason adults visit US physicians.\(^3\) Hypertension is a major public health concern, because it significantly increases risk of coronary artery disease, heart failure, renal disease, and stroke.\(^4\) In spite of major public health and medical education efforts and availability of effective antihypertensive agents, blood pressure (BP) control rates in the United States remain low, with only 31% of hypertensives and 54% of those actively treated and taking medications achieving BP <140/90 mm Hg.\(^5\) Why is BP control such an elusive goal? The reasons are numerous and complex. However, inadequate pharmacological treatment remains the most common cause of uncontrolled BP in actively treated patients.\(^6\)

Hypertension is a hemodynamic-related disorder. BP rises as the result of increased systemic vascular resistance (SVR), cardiac output (CO), fluid volume, or a combination of these factors.\(^7,8\) Consequently, antihypertensive agents lower BP by reducing SVR, CO, fluid volume, or combinations thereof.\(^9\)

Previous authors hypothesized that hemodynamic information could help tailor therapy and subsequently improve BP control.\(^10\) Invasive procedures for hemodynamic profiling are not warranted in outpatient clinics, and noninvasive procedures, such as echocardiography, are costly and operator dependent.\(^11\)

Impedance cardiography (ICG) has emerged as a reliable noninvasive method to measure hemodynamics in physician offices. In a randomized, controlled trial, ICG-guided treatment improved BP control rates in resistant hypertension treated by hypertension specialists.\(^12\) We hypothesized that ICG-guided treatment could aid physicians in reducing BP more effectively than standard care in a population of uncontrolled hypertensive patients receiving 1 to 3 medications in a primary care setting.

Methods

Eligibility

Male and female patients (age range, 18 to 75 years) were eligible if they had a diagnosis of essential hypertension and were currently on
1 to 3 antihypertensive medications with systolic BP of 140 to 179 mm Hg and/or diastolic BP of 90 to 109 mm Hg. Patients were excluded if they were on >3 antihypertensive agents; had abnormal laboratory findings; or had history of heart failure, left ventricular ejection fraction <40%, atrial fibrillation, severe valvular disease, cerebrovascular event within 3 months, severe renal disease, nephrotic syndrome, or cirrhosis. Patients in whom ICG might be subject to technical limitations were excluded (height <47 or >75 inches or weight <66 or >341 pounds, presence of activated minute-ventilation pacemaker, known hypersensitivity to sensor gel or adhesive, or skin lesion interfering with sensor placement). Patients who were enrolled and subsequently found to have not met the inclusion/exclusion criteria were terminated and excluded from analysis. Therefore, this was not an intention-to-treat analysis. The study was approved by an independent institutional review board, which adheres to the Declaration of Helsinki and US Code of Federal Regulations. These hypertensive outpatients provided written informed consent and had study procedures consistent with the protocol (no. 20021400).

Hemodynamic Evaluation Assignment
Eligible patients (N=164) underwent a 2-week washout period at which time all of the antihypertensive medications were discontinued according to the manufacturer’s recommendations. After screening and medication washout, each patient had 3 monthly office visits (Figure 1). After the 2-week washout period, patients meeting inclusion/exclusion criteria were randomized in a 3:2 ratio to the standard arm (n=95) or ICG-aided hemodynamic arm (n=69) using a central telephone service and stratified by site. All of the physicians were educated on the hemodynamic treatment strategy illustrated in Figure 2.

Procedures
BP determinations were made in the seated position using the oscillometric technique. ICG data were collected by trained technicians at each visit in all of the patients, but ICG findings were not revealed in the standard arm to treating physicians or patients. ICG was performed with patients in the supine position, resting for 5 minutes before measurement (BioZ ICG Monitor, CardioDynamics). ICG involves the measurement of thoracic impedance through placement of 4 dual sensors, 2 on the neck and 2 on the chest. Electrical impedance changes are digitally processed to calculate CO, SVR, and thoracic fluid content (TFC). CO and SVR are normalized for body size by indexing to each patient’s body surface area to obtain cardiac index (CI) and SVR index (SVRI). TFC is the inverse of baseline chest impedance, and any changes in TFC are directly proportional to total fluid (intravascular and extravascular) changes. TFC has different normal ranges for each gender that are displayed and printed for reference. The reproducibility of this ICG device in stable outpatients has been established, and accuracy
has been validated versus invasive methods in patients with various cardiovascular disorders.\textsuperscript{16,17}

**Outcome Measures**

Physician investigators were instructed that the treatment goal was to reduce systolic and diastolic BP as low as they believed would be beneficial to the patient and to achieve sustained BP <140/90 mm Hg. The primary study end points were reductions in systolic and diastolic BP from baseline and post-washout visit. Additional study end points were achievement of: (1) goal BP <140/90 mm Hg, (2) more aggressive BP of <130/85 mm Hg, and (3) BP of <140/90 mm Hg with normal values of CI and SVRI. Normal range for CI was defined as 2.5 to 4.2 L/min per m\(^2\) and for SVRI as 1680 to 2580 dynes/cm\(^5\)/m\(^2\). Isolated systolic hypertension was defined as systolic BP >140 mm Hg and diastolic BP <90 mm Hg.

**Interventions**

After randomization, therapy was initiated in all of the patients at the post-washout visit, 2 weeks after screening. Physician investigators prescribed medications consistent with published guidelines, their usual practice patterns, and patient clinical characteristics. In the hemodynamic arm, the treating physician was also encouraged to use a hemodynamic treatment strategy to guide therapeutic decisions about pharmacological agents and dosing (Figure 2).

Physicians could share ICG information with patients in the hemodynamic arm, and patients in both arms received education on the importance of medication compliance, which was reinforced with a nurse telephone call midway between each study visit. Compliance was assessed at each visit by asking patients to estimate the percentage of prescribed pills they had taken over the previous month. Patients were considered compliant with the prescribed protocol if pill count was >85% over the prior month.

**Statistical Analysis**

Data from case report forms were collected by study coordinators and entered into a locked database. Statistical analysis was performed with SAS statistical analysis software, version 8.2. Continuous variables were expressed as mean\(\pm SD\) and categorical variables as n (%). Differences in continuous variables between treatment groups were examined by the Student t test and by ANOVA and in discrete variables using Fisher’s exact tests. Subgroup analysis was performed in subjects with isolated systolic hypertension, age \(\geq 55\) years, and those receiving a thiazide diuretic. Additional evaluation of age-specific results was performed by a 2-way ANOVA for achievement of BP end points, in which treatment arm and dichotomized age (\(\geq 55\) years) were included in the model. In combination agents, each class and dosage was counted separately for analysis. Equivalency of defined daily doses for each class of medication was calculated using World Health Organization criteria.\textsuperscript{18} Medication changes were evaluated in visits where such changes affected BP end points (visits 2 versus 1, 3 versus 2, and 4 versus 3). Medication class and dose were compared with the prior study visit, with any change in class or dose counted separately. Sample size was powered using the importance of medication compliance, which was reinforced with a nurse telephone call midway between each study visit. Compliance was assessed at each visit by asking patients to estimate the percentage of prescribed pills they had taken over the previous month. Patients were considered compliant with the prescribed protocol if pill count was >85% over the prior month.

**Results**

Eleven primary care centers participated in the study between November 2002 and November 2004. Of 262 patients screened, 184 were randomized. A total of 164 patients (95 in the standard arm and 69 in the hemodynamic arm) completed the study and were analyzed. There were 20 early terminations, including 2 who withdrew and 18 who were randomized but were subsequently found not to have met BP enrollment criteria (BP >140/90 mm Hg at screening) and were removed as protocol violations. No reported adverse events (minor or serious) were attributable to ICG.

There were no differences in the number of antihypertensive medications, patient demographic, clinical, BP, or ICG variables at baseline or after washout (Table 1). At baseline, there were no differences in the percentage of patients in the standard versus hemodynamic arm on 1 (42% versus 45%; \(P>0.05\)), 2 (48% versus 44%; \(P>0.05\)), or 3 (6% versus 10%; \(P>0.05\)) medications. Baseline medication usage in the

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Care (n=95)</th>
<th>Hemodynamic Care (n=69)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.5±9.4</td>
<td>55.2±9.2</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>30.2±6.3</td>
<td>30.8±5.1</td>
<td>ns</td>
</tr>
<tr>
<td>Men</td>
<td>51 (53.4)</td>
<td>38 (55.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>75 (79.0)</td>
<td>53 (76.8)</td>
<td>ns</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>7 (7.4)</td>
<td>5 (7.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Black</td>
<td>6 (8.4)</td>
<td>6 (8.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (3.2)</td>
<td>3 (4.4)</td>
<td>ns</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>4 (4.2)</td>
<td>3 (4.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2 (2.1)</td>
<td>5 (7.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (14.7)</td>
<td>12 (17.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline BP and hemodynamics</td>
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<td></td>
<td></td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>147±8</td>
<td>148±12</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>87±10</td>
<td>89±8</td>
<td>ns</td>
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<tr>
<td>Heart rate, bpm</td>
<td>75±12</td>
<td>74±13</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac index, L/min/m(^2)</td>
<td>2.8±0.5</td>
<td>2.9±0.6</td>
<td>ns</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dynes×s×m(^2)/cm(^2)</td>
<td>2933±576</td>
<td>2956±605</td>
<td>ns</td>
</tr>
<tr>
<td>Thoracic fluid content, /kOhm</td>
<td>28.6±4.9</td>
<td>28.0±4.8</td>
<td>ns</td>
</tr>
<tr>
<td>Isolated systolic hypertension at baseline</td>
<td>46 (48.4)</td>
<td>31 (44.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Post-washout BP and hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>156±13</td>
<td>155±13</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>92±9</td>
<td>94±9</td>
<td>ns</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±12</td>
<td>78±14</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac index, L/min/m(^2)</td>
<td>2.9±0.5</td>
<td>2.9±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dynes×s×m(^2)/cm(^2)</td>
<td>3083±630</td>
<td>3122±672</td>
<td>ns</td>
</tr>
<tr>
<td>Thoracic fluid content, /kOhm</td>
<td>29.1±5.0</td>
<td>28.4±4.3</td>
<td>ns</td>
</tr>
<tr>
<td>Medications</td>
<td>Total antihypertensive medications</td>
<td>1.7±0.8</td>
<td>1.7±0.7</td>
</tr>
</tbody>
</table>

Categorical variables expressed as n (%), continuous variables as mean±SD; ns indicates not significant.
Patients with isolated systolic hypertension in the hemodynamic arm (n=31) had greater systolic BP reductions from baseline (22±16 versus 11±17 mm Hg; P<0.01) and post-washout (28±16 versus 18±16 mm Hg; P<0.05) than those in the standard arm (n=46). Patients ≥55 years in the hemodynamic arm (n=33) had greater systolic BP reductions compared with the standard arm (n=51) from baseline (21±17 versus 11±20 mm Hg; P<0.05) and trended greater from post-washout (26±20 versus 21±19 mm Hg; P>0.05). Diastolic BP reductions were also greater in those ≥55 years in the hemodynamic arm from baseline (13±11 versus 4±12 mm Hg; P<0.001) and post-washout (16±11 versus 10±12 mm Hg; P<0.05). In patients ≥55 years, goal BP (<140/90 mm Hg) was achieved more frequently in the hemodynamic arm (76% versus 53%; P<0.01), and the more aggressive BP (<130/85 mm Hg) was also achieved more often (55% versus 27%; P<0.0001).

Patients who achieved systolic hypertension in the hemodynamic arm had a small but significant reduction in TFC from baseline and post-washout visits are shown in Table 2. Systolic BP reductions were greater in the hemodynamic arm from baseline (19±17 versus 11±18 mm Hg; P<0.01) and post-washout (25±18 versus 19±17 mm Hg; P<0.05). Diastolic BP reductions were also greater in the hemodynamic arm from baseline (12±11 versus 5±12 mm Hg; P<0.001) and post-washout (17±12 versus 10±11 mm Hg; P<0.001). Final BP was lower in the hemodynamic arm (129/76±14/11 versus 136/82±15/10 mm Hg; P<0.01). Figure 3 demonstrates that goal BP (<140/90 mm Hg) was achieved more frequently in the hemodynamic arm (77% versus 57%; P<0.01), and the more aggressive BP (<130/85 mm Hg) was also achieved more often (55% versus 27%; P<0.0001).

Patients with isolated systolic hypertension in the hemodynamic arm (n=31) had greater systolic BP reductions from baseline (22±16 versus 11±17 mm Hg; P<0.01) and post-washout (28±16 versus 18±16 mm Hg; P<0.05) than those in the standard arm (n=46). Patients ≥55 years in the hemodynamic arm (n=33) had greater systolic BP reductions compared with the standard arm (n=51) from baseline (21±17 versus 11±20 mm Hg; P<0.05) and trended greater from post-washout (26±20 versus 21±19 mm Hg; P>0.05). Diastolic BP reductions were also greater in those ≥55 years in the hemodynamic arm from baseline (13±11 versus 4±12 mm Hg; P<0.001) and post-washout (16±11 versus 10±12 mm Hg; P<0.05). In patients ≥55 years, goal BP (<140/90 mm Hg) was achieved more frequently in the hemodynamic arm (76% versus 53%; P<0.05), and the more aggressive BP (<130/85 mm Hg) was also achieved more often (58% versus 27%; P<0.01). ANOVA also indicated that age ≥55 years had no effect on study end points (P>0.05).

SVRI was reduced to a greater extent in the hemodynamic arm than in the standard arm from baseline and post-washout. There were no significant differences between arms at the final visit for heart rate, CI, or TFC. However, the standard arm had a small but significant reduction in TFC from post-washout to final. The percentage of patients achieving normal hemodynamic values defined as simultaneously normal values of BP, CI, and SVRI was 52% in the hemodynamic arm and 29% in the standard arm (P<0.01). Patients in either arm who achieved BP <130/85 mm Hg had lower SVRI (2646±592 versus 2855±606 dyne×s×cm⁻²/m²; P<0.05) and lower CI (2.7±0.5 versus 2.9±0.5 L/min/m²; P<0.05) than those who did not achieve BP <130/85 mm Hg. Patients in the hemodynamic arm who achieved BP <130/85 mm Hg trended toward lower SVRI (2446±580 versus 2573±612 dyne×s×cm⁻²/m²; P>0.05) and higher CI (2.8±0.5 versus 2.6±0.5 L/min/m²; P>0.05) than those in the standard care arm who achieved BP <130/85 mm Hg.

In the visit after medication washout, patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB, or CCB (92.8% versus 80.0%; P<0.05). Over

### Table 2. Final BP and Hemodynamic Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Care (n=95)</th>
<th>Hemodynamic Care (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>136±15</td>
<td>129±14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>−11±18</td>
<td>−19±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>−19±17</td>
<td>−25±18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>82±10</td>
<td>76±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>−5±12</td>
<td>−12±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>−10±11</td>
<td>−17±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>77±13</td>
<td>76±11</td>
<td>ns</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>2±12</td>
<td>2±13</td>
<td>ns</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>−2±13</td>
<td>−2±13</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>2.9±0.5</td>
<td>2.9±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>0±0.5</td>
<td>0±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>0±0.5</td>
<td>0±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne×s×cm⁻²/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>2714±619</td>
<td>2523±581</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>−219±667</td>
<td>−433±660</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>−369±642</td>
<td>−599±738</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thoracic fluid content, kOhm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>27.8±4.1</td>
<td>28.2±4.9</td>
<td>ns</td>
</tr>
<tr>
<td>Δ baseline to final</td>
<td>−0.8±3.6</td>
<td>0.1±3.0</td>
<td>ns</td>
</tr>
<tr>
<td>Δ post-washout to final</td>
<td>−1.2±3.3</td>
<td>−0.2±2.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Variables expressed as mean±SD; ns indicates not significant.
the course of the study, patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB, or CCB when their SVRI was high, per the hemodynamic treatment strategy (78.3% versus 67.1%; P < 0.05). However, there were no differences in the other 2 treatments encouraged by the hemodynamic treatment strategy, β blocker use based on high CI, or in diuretic use when TFC did not decrease in response to diuretic initiation or increase. Patients in the hemodynamic arm were more likely to avoid β blocker use or to have their β blocker reduced in the presence of low or normal CI (85.4% versus 77.0%; P < 0.05) as the hemodynamic strategy suggested. Direct vasodilators were not used, and, therefore, changes in vasodilator use in the presence of normal SVRI were not evaluated. Table 3 lists all of the medications at the final visit. Patients in the standard arm were on 2.0±0.8 medications compared with 2.1±0.9 for the hemodynamic arm (P > 0.05). In the hemodynamic arm, ARB use was higher (46.4% versus 30.5%; P < 0.05), and ACEI use was similar (49.3% versus 53.7%; P > 0.05). However, the percentage of patients in the hemodynamic arm who were prescribed either an ACEI or ARB was not significantly different (87.0% versus 76.8%; P > 0.05). There were no differences in the percentage of patients in the hemodynamic care on 1 (25% versus 26%), 2 (48% versus 53%), 3 (19% versus 15%), 4 (9% versus 5%), or 5 (0% versus 1%) medications at the final visit (P > 0.05 for all). There were a greater number of medication dose increases in the standard versus hemodynamic arm (3.6±1.3 versus 3.0±1.2; P < 0.001), as well as a greater number of dose decreases (2.7±1.3 versus 1.7±1.0; P < 0.001). Medication class changes in the standard and hemodynamic arm were similar in both class initiation (1.0±0.9 versus 1.1±0.9; P > 0.05) and removal (0.8±0.8 versus 0.7±0.8; P > 0.05).

Thiazide diuretic use at baseline was similar in the standard versus hemodynamic arm (28.4% versus 24.6%; P > 0.05). A similar proportion of patients were prescribed thiazide diuretics at some point during the trial in both the standard and hemodynamic arms (44.2% versus 40.2%; P > 0.05), and use was similar at the final visit (33.7% versus 34.8%; P > 0.05). Medication doses were not different between arms except that patients in the standard arm were on higher doses of thiazide diuretics (18.9±8.3 versus 13.0±2.6 mg/day; P < 0.01). There were no differences in the hemodynamic arm in the dosing of ACEIs (19.1 versus 19.1 mg/day; P > 0.05), ARBs (93.9 versus 87.0 mg/day; P > 0.05), β blockers (65.6 versus 80.9 mg/day; P > 0.05), or CCBs (7.9 versus 7.9 mg/day; P > 0.05). The greater mean dose of thiazide diuretics was because of a higher percentage of patients taking ≥ 25 mg/day versus 12.5 mg/day in the standard arm (40.1% versus 8.3%; P < 0.05). When the study end points were analyzed only for patients on a thiazide diuretic in the final visit, patients in hemodynamic arm had greater decreases in systolic BP from baseline (26±19 versus 8±17 mm Hg; P < 0.001) and post-washout (36±17 versus 21±20 mm Hg; P < 0.01) and greater decreases in diastolic BP from baseline (16±11 versus 3±14 mm Hg; P < 0.001) and post-washout (20±12 versus 11±13 mm Hg; P < 0.01). There were no differences in patient-reported compliance between the standard and hemodynamic arm in visit 3 (96.8% versus 97.1%; P > 0.05), 4 (96.8% versus 98.6%; P > 0.05), or 5 (100% versus 100%; P > 0.05) or when these visits were combined (97.9% versus 98.6%; P > 0.05).

### Discussion

Our results demonstrate that ICG-guided antihypertensive treatment was more effective in reducing BP than standard therapy and empiric selection of antihypertensive medications. Patients in the 2 arms of our study were not significantly different at baseline, and each patient underwent a medication washout period to additionally equalize the 2 groups. The 57% BP control rate in the standard arm was substantial and compared favorably to BP control rates of long durations in large antihypertensive trials. However, the 77% BP control rate in the hemodynamic arm was even more impressive with an 8/7 mm Hg greater BP reduction from baseline and a 6/7 mm Hg greater BP reduction from post-washout. As a result, patients in the hemodynamic arm achieved goal BP of <140/90 mm Hg 35% more often (77% versus 57%) and the more aggressive level of BP control (<130/85 mm Hg) 104% more often (55 versus 27%) than those in the standard arm. The hemodynamic arm maintained superiority in 3 key subgroups: patients who were older, on thiazide diuretics, or had isolated systolic hypertension.

Why did the hemodynamic arm achieve greater reductions in BP and higher BP control rates than the standard arm? The fundamental difference between the two arms was that patient treatment in the hemodynamic arm was individualized and targeted at the hemodynamic abnormality associated with the elevated BP. This approach led to greater reductions in SVRI in the hemodynamic arm, which allowed greater decreases in both systolic and diastolic BP. The mechanistic and hemodynamically based improvement in BP was also demonstrated in patients achieving BP <130/85 mm Hg through significantly lower SVRI and higher CI in both arms. In theory, the larger drop in SVRI and BP levels in the hemodynamic arm could have occurred through use of more

### Table 3. Final Antihypertensive Medications

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
<th>Standard Care (n=95)</th>
<th>Hemodynamic Care (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at final visit</td>
<td>2.0 ± 0.8</td>
<td>2.1 ± 0.9</td>
<td>ns</td>
</tr>
<tr>
<td>α Blocker</td>
<td>1 (1.0)</td>
<td>1 (1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>ACEI</td>
<td>51 (53.7)</td>
<td>34 (49.3)</td>
<td>ns</td>
</tr>
<tr>
<td>ARB</td>
<td>29 (30.5)</td>
<td>32 (46.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>β Blocker</td>
<td>18 (19.0)</td>
<td>6 (8.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium channel blocker, dihydropyridine</td>
<td>36 (37.9)</td>
<td>28 (40.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium channel blocker, nondihydropyridine</td>
<td>6 (6.3)</td>
<td>7 (10.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Central acting agent</td>
<td>0 (0.0)</td>
<td>1 (1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretic, thiazide</td>
<td>32 (33.7)</td>
<td>24 (34.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretic, loop</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretic, potassium sparing</td>
<td>6 (6.3)</td>
<td>3 (4.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Categorical variables expressed as n (%); ns indicates not significant.
medications, more effective medications, greater dosing intensity, more effective combination therapy, or better patient compliance. Our study allowed full discretion by the physician in choosing the agents, and a multitude of classes and doses within classes were used. The study was not powered to find small disparities in medication use, and most medication differences did not reach statistical significance.

On the other hand, some differences are worth noting. Patients in the standard arm were more likely to experience both increases and decreases in their medication doses, whereas medication class changes were not different between arms. This result might have been expected, because treatment in the standard arm followed guidelines and usual practice patterns in which a stepped approach to therapy contributes to a “trial-and-error” method of determining whether agents and doses are working. In the hemodynamic arm, the initial selection of antihypertensive medications appears to have been influenced by the hemodynamic data, because these patients were more likely to be prescribed a vasodilating agent to reduce SVRI. Additionally, the hemodynamic treatment strategy influenced medication use when SVRI was considered high, because patients in the hemodynamic arm were more likely to have received an ACEI, ARB, or CCB, as was suggested. The hemodynamic treatment strategy did not influence the prescription of β blockers in the presence of high CI or in diuretic use in response to TFC changes. However, β-blocker use was lower or reduced in the presence of low or normal CI in the hemodynamic arm. Although the final number of antihypertensive medications given to patients in both arms of the study was similar, patients in the hemodynamic arm were more likely to be prescribed an ARB. However, when ACEI and ARB use was combined into a single category (renin–angiotensin–aldosterone system inhibitors), the hemodynamic arm only trended toward greater use at the final visit (87.0% versus 76.8%).

Thiazide diuretic use increased during the study but was lower than in some pharmacological trials and what hypertension guidelines currently suggest. However, the percentage of patients in both arms who were prescribed a thiazide diuretic at the final visit was very similar to the 35.6% usage that was reported in recent analysis of over 25,000 hypertensive patients. The lower use of diuretics and β blockers also follows the previously recognized physician preference for other antihypertensive agents. Some might hypothesize that greater BP reductions could have been achieved in the standard arm if diuretics were used more frequently. However, when patients taking a thiazide diuretic were examined as a subgroup, the hemodynamic arm maintained its superiority. Additionally, although the higher doses of thiazide diuretics in the standard arm may have contributed to a greater drop in TFC from the post-washout visit, they did not lead to better BP control.

Our study was not intended to evaluate whether a particular antihypertensive agent was more effective at reducing BP than another. Rather, it was designed to determine whether providing hemodynamic data to the physician and patient could more effectively reduce BP. Whether hemodynamic data led to a more tailored approach to selection and monitoring of antihypertensive agents or by other factors, it resulted in greater reduction in BP and SVRI and better BP control. Physicians cannot adequately estimate hemodynamics from routine clinical examination or BP measurements, because at similar levels of BP, SVR and CO can vary widely. Therefore, the addition of accurate, noninvasive, and readily obtainable hemodynamic measurements is clinically relevant.

Importantly, the current study also showed that patients in the hemodynamic arm were almost twice as likely to achieve BP control with normalization of both CI and SVRI. Improvements in vascular resistance may result in greater benefits in reducing cardiovascular risk than improvement in BP alone, and differences in SVRI at the same BP may explain poorer prognosis for men versus women and black versus nonblack patients. Hemodynamics are also known to change with age. In older subjects, decreased arterial compliance and CI lead to increased SVRI, arterial BP, and pulse pressure. In spite of the expected differences in the hemodynamics of older patients, this study demonstrated that hemodynamically driven, individualized therapy was similarly effective regardless of age or existence of isolated systolic hypertension.

The use of ICG to achieve greater BP control offers the potential for better short-term use of healthcare resources. In addition, the long-term benefits of even small levels of BP reduction are well known. A sustained BP reduction of 4/3 mm Hg is expected to reduce stroke risk 23%, coronary heart disease events 15%, heart failure 16%, and overall mortality 14%. Accordingly, a recent meta-analysis of major hypertension trials reveals that an antihypertensive agent is judged favorably when it produces mean BP improvements versus placebo of only 3 or 4 mm Hg or versus another antihypertensive agent of only 1 or 2 mm Hg.

Previously, ICG has been used to profile hemodynamic variability across BP values and to identify left ventricular dysfunction. Changes in ICG parameters have demonstrated the hemodynamic effect of antihypertensive agents and dietary sodium. ICG-guided therapy has shown benefit in a case series, observational study, and a randomized trial in resistant hypertensive patients. In the randomized trial, ICG-guided therapy resulted in better final BP and greater BP control. Similar to our study, that study showed no differences in the number of medications between arms. In contrast to our study with lower diuretic doses and fewer medication changes in the hemodynamic arm, resistant hypertension patients receiving ICG-guided therapy had higher diuretic doses and more medication changes. The differences between the studies might be expected because of the difference in patients (severe hypertension on more medications versus milder hypertension on fewer medications) and setting (specialist versus generalist). However, in both studies, ICG-guided therapy led to more effective treatment as evidenced by better BP outcomes.

The conclusions of this study may be limited to its duration of 3 months. However, in pharmacological trials, short-term reductions in BP are typically sustained over longer periods. Another limitation may be in our use of patient-reported medication compliance. Without using automatic counting procedures, our goal was to educate both arms equally and to reinforce patient compliance with follow-up phone calls.
Lastly, treatment differences in the hemodynamic arm do not imply superiority of one medication over another, because the study was not designed to evaluate this question.

**Perspectives**

The results of this study indicate that ICG-guided antihypertensive therapy in uncontrolled hypertensive patients on 1 to 3 antihypertensive medications is more effective than standard care. This was evident by greater reductions in systolic and diastolic BP and by achieving a better level of BP control. Our study showed that, in clinical practice, inclusion of ICG hemodynamic assessment may improve BP control rates in patients who are not controlled on initial therapy.

**Acknowledgments**

Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL) Site Investigators: Fred E. Abbo, Douglas C. Beatty, Donald M. Brandon, Milan L. Brandon, Anthony V. Dallas, Jr, Lawrence Dinnenberg, Mazhar El Amir, Nigar Enayat, Neil W. Hirschenbein, Dorothy Lebeau, Bernard A. Michlin, John Millsapgh, Nell Nestor, Melissa Noble, Robin F. Spiering, Joseph Taylor, and Allen R. Walker. Statistical support was provided by Gerard Smits and the study was sponsored by CardioDynamics (San Diego, CA).

**References**

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85 of 158.
Non-invasive measurement of cardiac output by whole-body bio-impedance during dobutamine stress echocardiography: Clinical implications in patients with left ventricular dysfunction and ischaemia

Marina Leitman, Edgar Sucher, Edo Kaluski, Ruth Wolf, Eli Peleg, Yaron Moshkovitz, Olga Milo-Cotter, Zvi Vered, Gad Cotter

Abstract

Objectives: To compare non-invasive determination of cardiac index (CI) by whole body electrical bioimpedance using the NICaS apparatus and Doppler echocardiography, and the role of cardiac power index (Cpi) and total peripheral resistance index (TPRi) calculation during dobutamine stress echocardiography (DSE).

Subjects and methods: We enrolled 60 consecutive patients undergoing DSE. Patients were prospectively divided into 3 groups: Group 1 (n=20): normal DSE (control). Group 2 (n=20): EF<40% without significant ischaemia. Group 3 (n=20): patients with significant ischaemia on DSE. Measurements of CI were performed at the end of each stage of DSE by both echocardiographic left ventricular outflow track flow and the NICaS apparatus, using whole-body bio-impedance. MAP was measured simultaneously and TPRi and Cpi were calculated.

Results: The correlation between non-invasive CI as determined by NICaS and echocardiography was 0.81, although Echocardiographic readings of CI were higher during administration of higher doses of dobutamine. Lower EF correlated with lower Cpi, especially stress induced Cpi. Hence, patients with reduced EF (group 2) had a blunted increase in Cpi during stress. Patients with ischaemia (group 3) had a blunted increase in Cpi as well as a decrease in Cpi and increase in TPRi during the last stages of DSE.

Conclusion: Measurement of CI by NICaS correlated well with Doppler derived CI. The calculation of Cpi and TPRi changes during dobutamine stress may provide important clinical information.

Keywords: Cardiac index; Cardiac power; Bioimpedance

1. Background and aims

Cardiac power index (Cpi) is the product of simultaneously measured cardiac index (CI) and mean arterial blood pressure (MAP). Cpi increases — cardiac power reserve during stress [1,2] or dobutamine administration [3] was shown in previous studies to be an important measure of systolic cardiac contractile reserve, better than VO₂ and echocardiographic ejection fraction (EF). Recently, Samejima et al. [4] demonstrated that CO increase during stress using non-invasive CO determination with bioimpedance was correlated with stress induced dyspnea.

The use of hemodynamic measures such as increase in vascular resistance for the detection of ischaemia was suggested almost a decade ago [5]. However, this research avenue has not been pursued due to the lack of simple non-invasive devices for CO measurement. Recently Weiss et al.
demonstrated that in patients with significant ischaemia during stress, CO increase by bio-impedance is lower than in patients without ischaemia.

The NICaS apparatus uses whole body bio-impedance and the Tsoglin–Frinerman formula for non-invasive determination of CI [7]. In short, a small electrical current is transferred from the left wrist to the right foot, and the impedance to its transit is detected (termed whole-body bio-impedance). The instantaneous change in bio-impedance has previously been shown to be related to the pulsatile changes in the volume of the great arteries. The Tsoglin–Frinerman formula uses this change in bio-impedance ($\Delta R$) as well as population based constants correcting for age, sex, weight and body composition (electrolytes, haematocrit and changes in baseline bio-impedance) to calculate the stroke volume (SV). Thereafter by electrocardiographically measuring the pulse rate it calculates cardiac output and CI. In a few recently published studies [7–9], NICaS measurements of CI in patients with various cardiac conditions showed good reproducibility and correlated well with thermodilution ($R=0.81$), with no bias and precision of approximately 0.6 L/min/M$^2$.

The aim of the present study was two fold: first, to compare CI measurements by NICaS and Doppler echocardiography over a wide range of values during dobutamine stimulation and, secondly, to determine whether the non-invasive continuous measurement of CI and MAP and calculation of Cpi and TPRi changes during dobutamine stress could be used for diagnosis of significant left ventricular (LV) dysfunction or myocardial ischaemia as determined by dobutamine stress echocardiography (DSE).

### 2. Patients and methods

We enrolled 60 consecutive patients undergoing standard DSE using incremental dobutamine infusion from 10 to 40 µg/min and atropine up to 1 mg as required to reach the pre-determined target heart rate. Patients were recruited in our outpatient clinic during a once weekly session. All consecutive patients attending the clinic during that day for the purpose of DSE were considered for the study. Patients were divided into 3 groups: Group 1: Control. Normal DSE, including baseline EF >40% and no significant ischaemia, Group 2: LV systolic dysfunction as determined by baseline echocardiographic EF <40% without significant ischaemia and Group 3: Significant ischaemia as determined by improvement of contractility during low-dose dobutamine infusion followed by decreased contractility during high dose dobutamine infusion in at least one non-infarcted myocardial segment.

Exclusion criteria were inability to achieve good echocardiographic visualization, significant hypotensive or hypertensive reactions or tachy or bradyarrhythmias during dobutamine infusion and inability to reach the pre-determined heart rate.

### 2.1. Study protocol

DSE was performed according to a standard protocol by 2 DSE teams. NICaS CI was measured by one NICaS operator. CI was determined by both echocardiographic left ventricular outflow track (LVOT) diameter and flow velocity as well as the NICaS apparatus. Operators measuring CI by one method were blinded to the result of the other method throughout the examination. Thereafter, based on NICaS determined CI, we calculated Cpi and total peripheral vascular resistance (TPRi) for each of the above mentioned time-points. NICaS and Doppler determined CI were not calculated during dobutamine administration in 3 patients (5%) in whom it was judged by...
the operator that LVOT obstruction occurred due to dobutamine administration.

2.2. Study end-points

(1) The correlation between NICaS and Doppler echocardiography derived CI and (2) the absolute and relative changes in NICaS determined Cpi and TPRi during dobutamine stress in the 3 groups.

2.3. Statistical methods

All data is reported based on pre-determined group allocations. To compare the baseline characteristics of the groups we used the Student’s *t*-test to compare continuous variables and the chi-square test to compare categorical variables. Since the cardiac index and cardiac power measurements were not normally distributed we used the Spearman-rank test for comparison of NICaS and echocardiographically determined CI and for comparison of resting EF and Cpi during the different stages of DSE. Since both NICaS and Doppler echocardiography are not regarded as gold standard for CI determination, when comparing the two methods we used the Bland and Altman [10] recommendations and for each dobutamine stage, as well as for the whole cohort, we determined bias (mean difference between the 2 methods) and the limits of agreement (precision) calculated as 2 SD of the bias. Analysis of variance with repeated measurements (time * group) was used to compare changes in Cpi and TPRi over time in the different groups. All *P* values <0.05 were considered significant.

3. Results

Sixty consecutive patients where enrolled in the 3 prospectively defined groups. The baseline characteristics of the three groups are presented in Table 1. As expected, patients differed with respect to baseline echocardiographic EF, age and severity of background diseases.

The correlation between CI as determined by echocardiographic LVOT area and mean flow velocity and the NICaS apparatus was \( R = 0.81 \) (Fig. 1). The Bland–Altman distribution of CI measurements is depicted in Fig. 2. The correlation was better for CI measurements at baseline and during the infusion of dobutamine at doses of up to 20 \( \mu \text{g/min} \) than for CI determinations during administration of dobutamine at a rate of 30 and 40 \( \mu \text{g/min} \) (Table 2, Fig. 2), due to increasing bias (i.e., CI measurements by Doppler echocardiography tending to be higher) and lower precision. Therefore, the CI increase in the different stages of DSE was similar by both techniques (Fig. 3). Again, a slight tendency was observed for higher increase in the Doppler echocardiography determined CI during the last phase of dobutamine infusion.

<table>
<thead>
<tr>
<th>Dobutamine infusion rate</th>
<th>Mean NICaS-CI</th>
<th>Mean echo-Doppler CI</th>
<th>Spearman Rank Correlation</th>
<th>Bias</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.9±0.6</td>
<td>2.8±0.6</td>
<td>0.77</td>
<td>−0.06</td>
<td>0.39</td>
</tr>
<tr>
<td>10 ( \mu \text{g/min} )</td>
<td>3.4±0.9</td>
<td>3.4±1.1</td>
<td>0.81</td>
<td>0.04</td>
<td>0.71</td>
</tr>
<tr>
<td>20 ( \mu \text{g/min} )</td>
<td>4.1±1.1</td>
<td>4.2±1.5</td>
<td>0.87</td>
<td>0.16</td>
<td>0.8</td>
</tr>
<tr>
<td>30 ( \mu \text{g/min} )</td>
<td>4.7±1.4</td>
<td>4.9±1.5</td>
<td>0.81</td>
<td>0.24</td>
<td>1.16</td>
</tr>
<tr>
<td>40 ( \mu \text{g/min} )</td>
<td>4.7±1.2</td>
<td>5.2±1.4</td>
<td>0.62</td>
<td>0.49</td>
<td>1.18</td>
</tr>
<tr>
<td>All measurements</td>
<td>3.9±1.3</td>
<td>4.1±1.5</td>
<td>0.81</td>
<td>0.17</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Fig. 2. Difference of CI measurements by Doppler echocardiography and NICaS vs. their mean (Bland and Altman analysis).
We have observed a significant correlation between EF and Cpi based both on echocardiographically determined CI and on NICAS-CI (Table 3). Interestingly, and consistent with previous studies [11], this correlation was better for stress Cpi than for rest Cpi.

During dobutamine infusion, NICaS determined Cpi increase was significantly different in the three groups (Fig. 4). Cpi increase was smallest in the group of patients with LV dysfunction followed by the group of patients with significant ischaemia and highest in patients with normal DSE ($p=0.002$ comparing LV dysfunction with normal DSE, $p=0.03$ comparing patients with ischaemia with patients with normal DSE and $p=0.02$ comparing patients with ischaemia to patients with LV dysfunction).

Baseline TPRi was significantly higher at baseline in the LV systolic dysfunction group as compared to patients with normal DSE (3120±1020 vs. 2450±940 dynes s M$^{-2}$, $p=0.04$) however, during dobutamine stress it decreased steeply in all 3 groups, to a similar degree.

A significant difference was observed in Cpi and TPRi changes during the last phase of dobutamine infusion in patients in the significant ischaemia group. As compared to patients in the control as well as the systolic LV dysfunction group, patients who were found by DSE to have significant ischaemia had during the last phase of DES a significant decrease in Cpi ($-0.16±0.15$ vs. $+0.1±0.15$ W/M$^{2}$, $p=0.0002$) and increase in TPRi. ($+279±636$ vs. $-59±169$ dynes s M$^{2}$; $P=0.022$).

No significant adverse events were recorded during the dobutamine stress test.

4. Discussion

The results of the present study demonstrate that CI determination by whole-body bio-impedance using the NICaS device is correlated well with CI determination by Doppler echocardiography. However, during infusion of higher doses of dobutamine ($\geq 30$ mg/min), the correlation became less accurate, mainly due to significant bias, i.e. Doppler echocardiography CI measurements tended to be significantly higher than NICaS readings.

In the overall cohort we found a correlation between severity of LV dysfunction by resting EF and Cpi at rest and especially Cpi during the dobutamine stress; i.e., the lower the EF the lower the rest and peak DSE Cpi. Hence, in the group of patients with reduced baseline EF (group 2), Cpi increase during exercise was significantly blunted. This finding is substantiated by the results of previous studies showing that lower Cpi increase during stress (lower cardiac power reserve) is correlated with poor outcome — although this correlation was superior to the correlation of EF and outcome. In the present study, the small number of patients enrolled did not allow for outcome analysis, however, it is possible that accurate non-invasive CI determination and calculation of Cpi reserve by whole body bio-impedance during stress may become a useful predictor of outcome in patients with reduced left ventricular function.

The results of the present cohort, in concordance with previous studies [5,6] show that during significant ischaemia, cardiac power tends to decrease and vascular resistance increases. Again, such non invasive calculation may enable an additional important indication for significant ischaemia in addition to conventional signs on DSE.

Importantly, all haemodynamic data was obtained in the present study using a simple non-invasive device. Although
the size of the present cohort does not allow for far-reaching conclusions, if these results are reproduced by additional, larger studies, cardiac power and vascular resistance changes could be used for non-invasive detection of left ventricular dysfunction and ischaemia during simple stress tests such as electrocardiographic exercise stress test or mental stress test. Moreover, serial changes in these measures may be useful for improving detection of ischaemia in patients at home using telemedicine.

4.1. Study limitations

The study included a small, select group of patients referred for DSE due to various symptoms. Hence, the results require further confirmation in a larger study including a non-selected group of outpatients.

5. Conclusion

The results of the present study suggest that a simple stress test using dobutamine infusion and non-invasive determination of CI by the NICaS™ 2001 apparatus and calculation of Cpi and TPRi can be used for easy out-patient screening of patients for systolic LV dysfunction and myocardial ischaemia.

References

Impact of Impedance Cardiography on Diagnosis and Therapy of Emergent Dyspnea: The ED-IMPACT Trial

W. Frank Peacock, MD, Richard L. Summers, MD, Jody Vogel, MD, Charles E. Emerman, MD

Abstract

Background: Dyspnea is one of the most common emergency department (ED) symptoms, but early diagnosis and treatment are challenging because of multiple potential causes. Impedance cardiography (ICG) is a noninvasive method to measure hemodynamics that may assist in early ED decision making.

Objectives: To determine the rate of change in working diagnosis and initial treatment plan by adding ICG data during the course of ED clinical evaluation of elder patients presenting with dyspnea.

Methods: The authors studied a convenience sample of dyspneic patients 65 years and older who were presenting to the EDs of two urban academic centers. The attending emergency physician was initially blinded to the ICG data, which was collected by research staff not involved in patient care. At initial ED presentation, after history and physical but before central lab or radiograph data were returned, the attending ED physician completed a case report form documenting diagnosis and treatment plan. The physician then was shown the ICG data and the same information was again recorded. Pre- and post-ICG differences were analyzed.

Results: Eighty-nine patients were enrolled, with a mean age of 74.8 ± 7.0 years; 52 (58%) were African American, 42 (47%) were male. Congestive heart failure and chronic obstructive pulmonary disease were the most common final diagnoses, occurring in 43 (48%), and 20 (22%), respectively. ICG data changed the working diagnosis in 12 (13%; 95% CI = 7% to 22%) and medications administered in 35 (39%; 95% CI = 29% to 50%).

Conclusions: Impedance cardiography data result in significant changes in ED physician diagnosis and therapeutic plan during the evaluation of dyspneic patients 65 years and older.


Keywords: dyspnea, hemodynamics, impedance cardiography, bioimpedance, cardiac output, systemic vascular resistance, noninvasive
Including cardiac output, systemic vascular resistance, and fluid status, may provide important information and aid decision making beyond what is possible from history and physical examination alone. Unfortunately, hemodynamic parameters cannot be accurately determined by patient history or physical examination.2–5 Until recently, hemodynamic data could only be obtained by pulmonary artery catheterization. Because this invasive procedure is not practical in the ED, physicians typically are left to make diagnosis and treatment decisions without reliable information about a patient’s hemodynamic status.

Noninvasive hemodynamic monitoring by impedance cardiography (ICG) has been used in more than four million patients. Cardiac output (CO) by ICG has been shown to correlate well with CO obtained by invasive methods in hospitalized patient populations with correlation coefficients for CO by ICG and thermodilution ranging from 0.76 to 0.89.6–10 ICG also has been used as an alternative to invasive monitoring in the critical care setting.11 In the ED setting, ICG has been studied for the differential diagnosis of dyspnea12–14 and the identification of pulmonary edema15,16 and provides prognostic information about hospitalization costs and length of stay.17 ICG results are available within a few minutes, allowing more rapid patient evaluation than that afforded by radiographic or laboratory studies.

Given the high rate of morbidity, mortality, and hospital readmissions for patients with dyspnea and acute decompensated HF, there is an urgent need to examine technologies that could lead to improvements in care in the ED. The present study examines an aspect of therapeutic efficacy18 as it relates to ICG and the acutely dyspneic emergency patient, and not simply the performance of ICG as a testing modality. Put into context, previous studies of commonly used ED tools, such as pulse oximetry,19,20 and B-type natriuretic peptide (BNP) testing,21 suggest that a 5% to 11% rate of change in diagnosis, or 10% rate of change in therapy, is clinically relevant. The effect of ICG-derived hemodynamics on diagnosis and treatment of dyspnea in the ED is not yet known. The purpose of this study was to determine the rate of change in diagnosis and therapy resulting from the availability of ICG data during the initial evaluation of older ED patients presenting with dyspnea.

METHODS

Study Design
This was a prospective study of dyspneic patients that was designed to determine the frequency of change in the ED physician’s initial diagnosis and therapeutic plan after physician access to noninvasive ICG hemodynamic data. The study was approved by each hospital’s institutional review board. All patients gave informed consent before enrollment in the study.

Study Setting and Population
The setting was two large urban academic EDs with experience in using noninvasive hemodynamic monitoring. A convenience sample was obtained from patients age 65 years or older who were presenting with a chief complaint of dyspnea or symptoms of HF, as determined by the ED physician. Because ICG is not currently recommended (per U.S. Food and Drug Administration guidelines) for the diagnosis of acute coronary syndromes, including acute myocardial infarction (MI), patients were excluded if electrocardiogram (ECG) or serum markers were positive for acute MI. Additional exclusions included the following: if ICG monitoring was not possible because of inability to place electrodes, if the patient’s weight was greater than 341 pounds, or if the patient had an activated minute ventilation pacemaker (which uses an impedance signal). Also, although severe aortic regurgitation that could give a falsely elevated ICG CO is rare and generally evident on ED evaluation, we excluded those with aortic regurgitation by past history, and those with the typical diastolic murmur. Last, because the treatment and disposition actions for patients needing immediate intubation and mechanical ventilation are generally well defined from the emergency physician point of view, and because it was our intent to study the diagnostically most challenging patients, those requiring urgent intubation and mechanical ventilation upon presentation to the ED were excluded.

Study Protocol
Project coordinators screened candidates and an independent research nurse, not involved in the diagnosis or treatment of the patient, obtained hemodynamic data. Hemodynamic data were collected by using the BioZ ICG monitor (CardioDynamics, San Diego, CA), as has been described elsewhere.22 ICG data are obtained by the following technique: four dual sensors (each sensor consisting of two electrodes) are placed on the patient, as shown in Figure 1, on opposite sides of the neck at a level between the ears and shoulders and on either side of the chest in the mid-axillary line at the level of the xiphoid process. The outer electrodes in each sensor transmit a low-amplitude, high-frequency current (2.5 mA, 70 kHZ), and the inner electrodes detect thoracic voltage changes. Changes in voltage are used to calculate changes in impedance (Z). Baseline, static impedance is indicative of chest fluid volume, and dynamic impedance

Figure 1. Front view of impedance cardiography method.
is affected by aortic blood volume and velocity. Beat-
to-beat changes in thoracic impedance are processed to
calculate blood flow per heartbeat (stroke volume) and
calculate per minute (cardiac output). By using standard equations,
other hemodynamic parameters, such as systemic vascular
resistance, are calculated. The reciprocal of baseline
thoracic impedance can provide an index of intrathoracic
lar resistance, are calculated. The reciprocal of baseline
other hemodynamic parameters, such as systemic vascu-
lar resistance, are calculated. The reciprocal of baseline
thoracic fluid content (TFC). TFC has
been used to identify intravascular and extravascular
fluid changes and to titrate diuretic therapy.

Before study initiation, participating physicians re-
ceived instruction regarding the interpretation of the
hemodynamic values obtained by the ICG device.
Attending physicians, all of whom were board-certified
or board-eligible in emergency medicine, were given a
description of ICG technology and hemodynamic param-
eters provided on the ICG report, including definitions
and normal values for cardiac index (CI), resistance, tho-
racic fluid content, and measures reflecting left ventricu-
lar performance. This was performed at departmental
grand rounds and at the monthly attending-physician
staff meeting. Additional information was disseminated
in hardcopy by mailing and was duplicated by e-mail.
The pathophysiology of HF and hemodynamic findings
most suggestive of dyspnea caused by decompenated
HF (reduced CI, elevated systemic vascular resistance,
and increased TFC) were described. The expected effects
of various medications on hemodynamic parameters
were discussed, including use of diuretics, vasodilators,
and drugs affecting contractility. Additionally, physicians
were provided personal reference cards for use at their
discretion that detailed normative values for all ICG
data. Copies of the data card were also kept fixed to the
ICG device. These data were also shown at the time of
ICG unbinding. For any given parameter, ICG data are
presented as a bar indicating the normal human range.
The average result and the currently measured data point
then are indicated on this bar, such that variations from
normal are readily apparent.

All staff involved with patient care were blinded to the
ICG data until after the initial history and physical ex-
amination by the attending physician. After the initial his-
tory and physical exam, but before initiation of therapy
(other than supplemental oxygen), and before obtaining
any central laboratory or radiographic data, the attend-
ing physician completed a case report form indicating
his or her working diagnoses and short-term therapeutic
plans. The physician was then immediately shown the
ICG hemodynamic data and was asked to complete the
case report form again, this time with consideration of
the ICG data. All patient care then proceeded according
to usual ED routine. Blood tests, including electrolytes,
blood urea nitrogen (BUN), serum creatinine (Cr), and
BNP levels, were obtained in the majority of cases.
Although these data were not mandated as part of the
protocol, they were used in most cases to determine final
ED diagnosis.

Measures
The two primary endpoints were 1) the rates of change
in working diagnosis and 2) medical therapy after the
addition of ICG data to the physician’s initial clinical
assessment and therapeutic plan. In the cases in which
the diagnosis changed on the basis of ICG data, a com-
parison to the final diagnosis was made to determine
whether the pre- or post-ICG diagnosis was more consis-
tent with the final ED diagnosis. The final ED primary di-
agnosis was defined as the principal diagnosis at the end
of the ED visit after all diagnostic testing was completed
and reviewed by the ED physician responsible for dispo-
sition. A change in therapy was defined as the addition or
subtraction of a drug or procedure. Changing the dose of
a previously ordered drug was not considered a thera-
peutic change. Adverse events were defined as cardiac
arrest, intubation for respiratory failure, urgent cardio-
version, or blood transfusion.

Data Analysis
The size of the study was prospectively determined on the
basis of the number needed to detect a 5% rate of change
in diagnosis or therapy. Given an alpha of 0.05 and a beta
of 0.20, a sample size of 100 was needed to detect a statis-
tically significant change. Data were analyzed by an inde-
pendent statistician using SAS Software (Cary, NC).

Demographic data are reported descriptively. Continuous
variables are reported as mean ± standard deviation
(SD). Rates of change were calculated by dividing the
number of patients in whom diagnosis or therapeutic
plan changed by the total number of patients and were
reported as percentages. An analysis of variance was
performed to assess for differences among vital signs
and ICG parameters in the final diagnosis categories.

RESULTS
Eighty-nine patients, cared for by 31 ED staff physicians,
were enrolled from December 2001 through July 2003
and are included in the analysis. No adverse event,
defined as cardiac arrest, intubation, cardioversion, or
blood transfusion, occurred during the course of the
ED observation during this study.

The patient characteristics and vital signs are summa-
rized in Table 1. The mean (±SD) age of the subjects
was 74.8 (±7.0) years. Fifty-eight percent of the patients
were African American, and 61% had a history of HF,
including 13% with a history of both HF and chronic lung disease. The prevalence of chronic lung disease, including asthma, was 38%. The average respiratory rate was 22.2 ($\pm 5.1$) min$^{-1}$ with systolic BP and heart rate of 145.5 ($\pm 29.3$) mm Hg and 84.6 ($\pm 18.8$) min$^{-1}$, respectively. The hemodynamic values for the population as a whole are listed in Table 2.

Patients could be categorized by final primary diagnosis at the time of ED discharge or hospital admission into three major groups: 1) HF ($n = 43$); 2) chronic obstructive pulmonary disease (COPD; 20); and 3) “other” (26). The other group included other cardiovascular and lung conditions not included in the HF or COPD groups: atrial fibrillation ($n = 4$), bronchitis (4), hypertension (2), pneumonia (2), pulmonary hypertension (2), anemia (1), influenza (1), lung cancer (1), palpitations (1), upper respiratory infection (1), atypical chest pain (1), hypoxia (1), intra-abdominal abscess (1), non-cardiac shortness of breath (1), pulmonary fibrosis (1), vertigo (1), and dehydration (1).

Chest radiographs and ECG results were recorded by the ED physician in 85 patients (96%). The various ECG and radiographic findings are summarized in Table 3. ECG findings were described as normal or nonspecific in the vast majority (82%), and the chest radiograph was normal or nondiagnostic in nearly half, with only 16% showing either HF or upper zone redistribution consistent with pulmonary venous congestion.

<table>
<thead>
<tr>
<th>Electrocardiographic and Chest Radiographic Findings</th>
<th>$n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, nonspecific, or “nondiagnostic ECG”</td>
<td>70 (82)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Normal or no acute disease</td>
<td>42 (49)</td>
</tr>
<tr>
<td>Increased cardiothoracic ratio (&gt;0.5)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>or cardiomegaly</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Pulmonary edema or “heart failure”</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Upper zone redistribution</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Pulmonary infiltrate</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

For each finding group, $n = 85$. Because of multiple findings, total for ECG diagnoses is greater than 85.

Diagnosis Changes
A summary of the rates of diagnosis and therapy change that resulted from ICG data are presented in Figure 2. ICG data changed the working diagnosis in 12 (13%; 95% CI = 7% to 22%). When diagnoses were categorized as either cardiac or noncardiac, the post-ICG diagnosis was the same as the final diagnosis in 8 of 12 patients in whom ICG resulted in a change (67%, 95% CI = 35% to 90%). Of the four patients in whom a change in diagnosis after ICG did not match the final ED diagnosis, one who was ultimately diagnosed with a cardiac cause of dyspnea had normal hemodynamic parameters, suggesting a pulmonary cause. In another patient, altered hemodynamic parameters suggested cardiac dyspnea that was later attributed to an exacerbation of COPD. One patient with lung cancer had hemodynamic findings consistent with diastolic HF. Finally, one patient who initially was thought to have pulmonary dyspnea had altered hemodynamic findings that were believed to be nondiagnostic by the evaluating physician; that patient was eventually treated for fluid overload and discharged home.

Results Grouped by Final Diagnosis
A summary of the patient vital signs and hemodynamic characteristics grouped by final ED diagnosis is listed in Table 4. No diagnosis group had vital sign data that were significantly different from those of any other group ($p = 0.1332$). Of the hemodynamic parameters, cardiac index, systemic vascular resistance index, and thoracic fluid content had one diagnosis group that differed significantly from the other two ($p < 0.02$). HF patients had greater amounts of lung water, as reflected by a mean TFC (38.5 $\pm 12.3$ kOhm$^{-1}$) that was significantly higher than that of the other two diagnosis groups (30.4 $\pm 5.6$ for the COPD and other groups, respectively). Patients with COPD had higher CI (3.08 $\pm 0.57$ vs. 2.39 $\pm 0.56$ and 2.48 $\pm 0.65$) and lower SVR (1,361 $\pm 407$ vs. 1,772 $\pm 565$ and 1,789 $\pm 638$) than did patients in the HF or other groups, respectively.

Laboratory measurements, including electrolytes, BUN, Cr, WBC, Hgb, and BNP were analyzed by final diagnosis. Of the laboratory measurements, only BNP, measured in 72 patients, exhibited a statistically
significant difference (p < 0.0001) among the three diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups. The HF group had a significantly higher mean BNP level (940 pg/mL) than did the other diagnosis groups.

Table 4
Initial Vital Signs and Selected Hemodynamic Parameters by Final Diagnosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic Failure (n = 43)</th>
<th>Obstructive Pulmonary Disease (n = 20)</th>
<th>Other (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>36.4 ± 0.7</td>
<td>36.6 ± 0.8</td>
<td>36.7 ± 0.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>149.5 ± 30.5</td>
<td>135.6 ± 19.1</td>
<td>146.8 ± 32.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.2 ± 18.0</td>
<td>75.7 ± 13.0</td>
<td>78.5 ± 21.2</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>84.1 ± 18.0</td>
<td>88.2 ± 19.4</td>
<td>82.9 ± 20.1</td>
</tr>
<tr>
<td>Respiration rate (min⁻¹)</td>
<td>22.1 ± 5.7</td>
<td>23.8 ± 3.8</td>
<td>21.0 ± 4.6</td>
</tr>
<tr>
<td>Thoracic fluid content (kOhm⁻¹)</td>
<td>38.5 ± 12.3*</td>
<td>30.0 ± 6.0</td>
<td>30.4 ± 5.6</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne sec cm⁻⁵)</td>
<td>1,772 ± 565</td>
<td>1,361 ± 407*</td>
<td>1,789 ± 638</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.39 ± 0.56</td>
<td>3.08 ± 0.57*</td>
<td>2.48 ± 0.65</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100.0 ± 20.0</td>
<td>98.5 ± 14.2</td>
<td>100.7 ± 21.8</td>
</tr>
<tr>
<td>Stroke index (mL/m²)</td>
<td>29.7 ± 9.9</td>
<td>36.3 ± 9.7</td>
<td>31.6 ± 10.0</td>
</tr>
</tbody>
</table>

Data are mean ± SD. * Different from other two categories, p < 0.02.

**DISCUSSION**

In cases of elderly dyspeptic patients who may require urgent treatment, the ED physician must assess status, formulate a working diagnosis, and institute therapy, in many cases before all information is available. Hemodynamic information, which reflects the contribution of the cardiovascular system to the current presentation, may have an important impact on the process of care. Our results demonstrate that knowledge of ICG data leads to a change of working primary diagnosis in 13% of elderly patients presenting with dyspepsia to the ED. When changes in diagnosis were made, they were consistent with the final diagnosis at time of ED disposition in two-thirds of cases. In addition to changes in diagnosis, ED physicians made medication changes on the basis of ICG-derived hemodynamic information in 39% of cases. Finally, unlike vital signs, which were similar across the various diagnostic groups, hemodynamic data varied based on causes of dyspepsia. These findings are consistent with the hypothesis that hemodynamic information is relevant and actionable in the ongoing evaluation and treatment of such patients.

Patients presenting with dyspepsia are commonly at risk for exacerbation of either cardiac or pulmonary disease. Those with acute HF typically have reduced cardiac output and elevated vascular resistance. Those with a pulmonary or other noncardiac cause of their dyspepsia typically have normal cardiac output and hemodynamic parameters. Because the accuracy and reproducibility of ICG have been validated in a variety of patient populations and settings, it is not surprising that physicians used this information to help guide diagnosis and treatment in dyspeptic patients. Our finding of different values of hemodynamic parameters among the diagnostic groups is consistent with this paradigm. The relatively high rate of change of diagnosis, when ICG-derived information was revealed to treating physicians, suggests acceptance of the technical and diagnostic accuracy efficacies of the test. Not only does the information result in altered diagnosis, but the noninvasive hemodynamic data provided by ICG was applied by the physicians to therapeutic decision making, an indication of therapeutic efficacy, as defined by Perl.¹⁸ Thus, our results support the potential value of such information and support a practical role for this technology in the ED assessment of such patients.

Recently, BNP testing has been shown to be a useful bedside tool to aid in diagnosis of patients presenting with shortness of breath.²⁰ However, despite the availability of point-of-care laboratory testing, real-time diagnosis and treatment can be delayed. In fact, one large trial of cardiac markers found that even with point-of-care testing, the door-to-brain time (the time from ED arrival until cardiac marker results are available for the physician to act upon) exceeded one hour.²⁵ ICG data are available within several minutes. And, unlike the hemodynamic information obtained by a pulmonary artery

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catheter, performance of ICG is noninvasive and can be readily accomplished in the ED without specialized training and at minimal risk to the patient.

The magnitude of the changes in diagnosis and treatment resulting from ICG-derived hemodynamic data can be compared with that from other technologies that are currently the standard of care in most EDs. Historically, changes in therapy on the order of 5% to 11% appear to define utility of testing in the ED. In one study, Summers et al.\textsuperscript{19} reported that the ED physician assessment of patient severity of illness was changed by pulse oximetry in 3% of cases. Kosowky et al.,\textsuperscript{21} evaluating BNP testing in patients older than 40 years of age, found that BNP data changed the diagnosis in 10%, and treatment in 11%, of cases. These trials suggest that the rate of change that resulted from ICG use in the present study would be clinically significant in the ED environment. Moreover, ICG can be performed concurrently with existing diagnostic and therapeutic strategies, such that the information is incremental in the decision-making process.

The changes in ED decision making from esophageal Doppler results, a more invasive and less common form of cardiac output measurement, have been studied elsewhere.\textsuperscript{28} Those investigators found a change in management decisions in 31% of cases. Our results show a greater change in therapy alone, perhaps because of the incremental information provided by systemic vascular resistance and thoracic fluid content parameters. Although most ED physicians would not subject a patient to esophageal monitoring to obtain hemodynamic measurements, it is likely that many would consider the collection of ICG data, which requires little more time or inconvenience than obtaining an electrocardiogram. We did not measure the time required to obtain ICG data; however, in routine use, these data can be obtained in about 3 to 5 minutes and require 30 to 60 seconds to interpret. Because ICG provides early and accurate data, there is a potential for significant clinical impact from its use. We did not specifically study the financial effects of ICG in this study or how it might have affected length of ED stay or hospital admission rate. However, at a procedural cost for each test of less than $20 and with the cost of a day in intensive care at more than $1,000, the provision of ICG would be cost-effective even if, for example, it reduced hospital length of stay by only one day for every 50 patients monitored.

**LIMITATIONS**

We acknowledge several limitations. This study evaluated the effect of ICG on working diagnosis and initial treatment plan before the results of chest radiograph, ECG, or BNP level. Thus, it is impossible to gauge the relative importance of the information obtained from ICG to that obtained by these other tests or to judge the additional contribution of ICG for cases in which the results of other tests were available before performing ICG. Although blood work and various ancillary testing such as chest radiography are part of the complete ED evaluation of such patients, the results are generally not available within the first few minutes of patient assessment. By design, this study evaluated ICG’s effect on working diagnosis and therapy in a manner that would be consistent with clinical practice in the ED, where patients presenting with dyspnea might be evaluated with ICG either before or within minutes of the ED physician’s initial assessment. Furthermore, as seen in our study, the findings of ECGs and chest radiographs are often normal or nonspecific and may not provide significant diagnostic certainty. Because ICG is not part of the diagnostic criteria for acute coronary syndromes, including acute MI, we did exclude patients with evidence of myocardial necrosis from analysis. Therefore, the role of ICG in providing possible clues in the evaluation of patients with dyspnea as a manifestation of MI cannot be assessed by the present study.

Our study was also limited by the use of the final ED diagnosis as the criterion standard for diagnostic categorization. Although it is possible that this diagnosis was incorrect or incomplete in some patients, this represents the real-life diagnosis based on current evaluation strategies during the patient’s ED visit. It is also possible that a physician had the right diagnosis and treatment plan before reviewing ICG results and that ICG data resulted in inappropriate therapies. A larger prospective outcome-based study will be required to determine the potential for this to occur.

In our study, ICG data were available and likely contributed to the final ED diagnosis, thereby introducing possible bias. However, the goal of this study was not to assess technical accuracy of the technology, which has been evaluated in previous studies. In contrast, this study was designed to assess whether physicians would incorporate early hemodynamic information into the process of formulating an initial working diagnosis and treatment plan. In addition, the study design does not allow us to draw conclusions about the sensitivity or specificity of ICG criteria, or to compare diagnostic accuracy to other measures, such as BNP or chest radiography. The accuracy of the post-ICG diagnosis based on these hemodynamic criteria could only be verified by a more standardized diagnostic approach including cardiac imaging studies, blinded reviews of subsequent hospital records with adjudication of discordant diagnoses, and long-term follow-up, which were not within the scope of the current study.

**CONCLUSIONS**

Knowledge of ICG data early in the ED evaluation of patients older than 65 years of age presenting with dyspnea results in significant changes in diagnosis and treatment plan. Whether changes in diagnosis, diagnostic certainty, or therapy from ICG improve outcomes or are cost-effective will require a prospective, randomized clinical trial with longer periods of clinical follow-up.

The authors thank Gerard Smits, PhD, for his statistical assistance.

**References**


Hypertension as a Hemodynamic Disease: The Role of Impedance Cardiography in Diagnostic, Prognostic, and Therapeutic Decision Making

Hector O. Ventura, Sandra J. Taler, and John E. Strobeck

Hypertension is the most common cardiovascular disease, affecting approximately 60 million Americans. Despite the importance of this condition, only the minority of patients are appropriately identified and treated to reach recommended blood pressure (BP) goals. Although historically defined as an elevation of BP alone, hypertension is characterized by abnormalities of cardiac output, systemic vascular resistance, and arterial compliance. These hemodynamic aspects of hypertension have implications for diagnosis, risk stratification, and treatment. Impedance cardiography (ICG) has emerged as a unique and highly accurate noninvasive tool that is used to assess hemodynamic parameters. Measurement of the various hemodynamic components using ICG in those with hypertension allows more complete characterization of the condition, a greater ability to identify those at highest risk, and allows more effectively targeted drug management. This article reviews the importance of hemodynamic factors in hypertension and the evolving role of ICG technology in the assessment and management of this important cardiovascular condition.

Key Words: Hypertension, hemodynamics, impedance cardiography.

When functioning properly, the cardiovascular system provides normal blood flow to the various tissues of the body under normal arterial blood pressure (BP). Historically, BP is the most commonly measured parameter of cardiovascular function. Hypertension—typically defined by BP levels of 140/90 mm Hg and higher—leads to increased rates of coronary artery disease, heart failure, renal disease, and stroke. Therefore, BP control is of paramount importance for both individual and public health considerations.

Blood pressure by itself is an incomplete indicator of the status of the cardiovascular system. Mean arterial pressure (MAP) is the product of two hemodynamic components: cardiac output (CO), the flow of blood pumped by the heart each minute; and systemic vascular resistance (SVR), the force the left ventricle must overcome to expel blood into the systemic vasculature, also called total peripheral resistance. Hypertension results from elevations of CO, SVR, or both. Because “hemodynamics” literally refers to blood flow–related parameters of the arterial system, CO and SVR are fundamental to obtaining greater insight into the pathophysiology of hypertension, and they can help to guide diagnostic, prognostic, and therapeutic management decisions. Thus, the hemodynamic model of hypertension has intrigued scientists and clinicians since the early part of the last century and has been reviewed extensively by leaders in the field.

The hemodynamic components of BP, CO, and SVR, and other related parameters such as arterial compliance provide insight into mechanisms of hypertension and have implications for management of patients with this condition. Historically, most hemodynamic information used in research has been obtained using invasive techniques, including arterial cannulation and placement of a pulmonary artery catheter for the measurement of cardiac output and determination of SVR. However, invasive procedures are not feasible in the routine care of patients with hypertension. Echocardiography provided early noninvasive measurement of cardiac output, but it is costly and highly operator dependent, and it is therefore impractical for frequent serial measurements in the clinical setting.

Recent advancements in noninvasive hemodynamic monitoring with impedance cardiography (ICG) have been achieved, elevating its role as a unique and valuable noninvasive tool for the assessment of hemodynamic status in patients with hypertension.

This review describes the historical use of hemodynamics in hypertension and reveals the growing body of evi-
Hypertension: Definition and Clinical Presentation

Hypertension is most commonly defined as a systolic BP (SBP) of $\geq 140$ mm Hg or a diastolic BP (DBP) of $\geq 90$ mm Hg. In patients at high risk for complications from elevated BP levels, such as those with diabetes or chronic renal disease, lower levels of BP (eg, <130/80 mm Hg) are recommended. Between BP levels of 115/75 mm Hg and 185/115 mm Hg, each 20-mm Hg increase in SBP or 10-mm Hg increase in DBP doubles the risk of a cardiovascular event. In recognition of this increase in risk from levels as low as 115/75 mm Hg, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recently identified “prehypertension” (defined as a BP of 120 to 139/80 to 89 mm Hg) as a significant health problem associated with “increased risk for progression to hypertension.” The JNC 7 recommended lifestyle modifications for the management of prehypertension. Table 1 lists the stages of hypertension as defined in the JNC 7 classification.

Secondary hypertension results from an identifiable cause such as renal, adrenal, or vascular pathology. In contrast, 90% of patients have no identifiable cause of their BP elevation and are thus diagnosed with essential hypertension. Most patients with hypertension are asymptomatic and do not show evidence of acute pathologic changes; their clinical presentation has been termed “benign,” although their long-term risk of cardiovascular complications is significantly greater than in normotensive persons without so-called benign hypertension. Severe elevation of BP, associated with papilledema on fundoscopic examination, is termed “malignant hypertension.” Similar levels of BP elevation with congestive heart failure, anginal symptoms, or other evidence for accelerated end-organ injury (but without papilledema) are termed “hypertensive urgencies” or “hypertensive emergencies.” The etiologies of hypertension (essential versus secondary) and the various clinical presentations (benign, malignant, unspecified and with or without associated co-morbidities) are reflected in the World Health Organization’s International Classification of Diseases, Ninth Revision (ICD-9), coding for hypertension (Table 2).

Hypertension: Magnitude of the Problem

Hypertension affects up to 60 million Americans and as many as 1 billion persons worldwide; and it is the most common reason that patients in the United States visit their physicians. The incidence of hypertension increases significantly with advancing age (Fig. 1), such that a normotensive adult in the United States 55 years of age still has a 90% lifetime risk of developing hypertension. In fact, the most common group with hypertension is comprised of elderly patients with systolic hypertension. Although controlling BP levels reduces the incidence of stroke and other cardiovascular complications, BP control in the US is well below stated goals. For an individual patient, this may be due to the lack of recognition of the condition, failure to institute effective treatment, or the result of a suboptimal long-term medical regimen (Table 3). There remains a substantial need for improvement in the effectiveness of hypertension treatment. As reported in JNC 7, only 34% of adults aged 18 to 74 years with hypertension have achieved BP control, despite a published goal of 50%. In the elderly population, BP control is even less successful: fewer than 20% of treated patients 70 years or more of age attain BP levels of <140/90 mm Hg. Hypertension treatment commonly requires multiple medications. “Refractory hypertension” has been defined as hypertension that is not controlled on two or more antihypertensive medications. “Resistant hypertension” has been defined by some as BP readings of $\geq 140/90$ mm Hg “despite an optimal two-drug regimen that has had adequate time to work (at least 1 month since last drug or dosage adjustment).” As defined by Gifford, resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. The JNC 7 recommends a goal BP of $<140/90$ mm Hg for the general population, with the tighter goal of $<130/80$ mm Hg for persons with chronic renal disease or diabetes mellitus.

Hypertension substantially increases the incidence of cardiovascular events, especially the risk of stroke. Wilking et al, in data from the Framingham study, reported on the prognostic significance of systolic hypertension. They found that for men and women, the relative risk of cardiovascular disease event adjusted for age was approximately 2.5 times greater for persons with isolated systolic hypertension compared with those with BP levels $<140/95$ mm Hg. Lower BP levels are thus associated with improved prognosis and decreased incidence of morbidity and mortality. From pooled data of more than 60

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**Table 1. JNC 7 Classification of blood pressure for adults $\geq 18$ years of age**

<table>
<thead>
<tr>
<th>BP classification</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>$&lt;120$</td>
<td>$&lt;80$</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>$\geq 160$</td>
<td>$\geq 100$</td>
</tr>
</tbody>
</table>

prospective studies and 1 million patients, Lewington et al.\textsuperscript{17} report that 10–mm Hg reductions in systolic BP would be expected to reduce stroke mortality by as much as 40%.

Importantly, the authors note that even a 2–mm Hg reduction in systolic BP is associated with a 10% lower death rate from stroke. These reductions in risk apply all the way to BP levels of 115/75 mm Hg. Thus, the failure to lower BP even modestly in patients with hypertension is responsible for a significant number of preventable cardiovascular events each year.

The financial implications of hypertension and hypertension management are substantial.\textsuperscript{18} The direct costs of treating hypertension exceeded $37 billion in the year 2003, and additional costs due to loss of productivity were more than $13 billion (Table 4). Of the ten medical conditions evaluated for their effects on absenteeism from work and loss of productivity, hypertension was the most

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**Table 2. International Classification of Diseases codes for hypertension**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>401.0</td>
<td>Essential hypertension; Malignant</td>
</tr>
<tr>
<td>401.1</td>
<td>Benign essential hypertension</td>
</tr>
<tr>
<td>401.9</td>
<td>Unspecified essential hypertension</td>
</tr>
<tr>
<td>402.00</td>
<td>Hypertensive heart disease; malignant; without congestive heart failure</td>
</tr>
<tr>
<td>402.01</td>
<td>Hypertensive heart disease; malignant; with congestive heart failure</td>
</tr>
<tr>
<td>402.10</td>
<td>Hypertensive heart disease; benign; without congestive heart failure</td>
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<tr>
<td>402.11</td>
<td>Hypertensive heart disease; benign; with congestive heart failure</td>
</tr>
<tr>
<td>402.90</td>
<td>Hypertensive heart disease; unspecified; without congestive heart failure</td>
</tr>
<tr>
<td>402.91</td>
<td>Hypertensive heart disease; unspecified; with congestive heart failure</td>
</tr>
<tr>
<td>403.00</td>
<td>Hypertensive renal disease; malignant; without mention of renal failure</td>
</tr>
<tr>
<td>403.01</td>
<td>Hypertensive renal disease; malignant; with renal failure</td>
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<tr>
<td>403.10</td>
<td>Hypertensive renal disease; benign; without mention of renal failure</td>
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<tr>
<td>403.11</td>
<td>Hypertensive renal disease; benign; with renal failure</td>
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<td>Hypertensive renal disease; unspecified; without mention of renal failure</td>
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<tr>
<td>403.91</td>
<td>Hypertensive renal disease; unspecified; with renal failure</td>
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<tr>
<td>404.00</td>
<td>Hypertensive heart and renal disease; malignant; w/o mention of congestive</td>
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<tr>
<td></td>
<td>heart failure or renal failure</td>
</tr>
<tr>
<td>404.01</td>
<td>Hypertensive heart and renal disease; malignant; with congestive heart</td>
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<td></td>
<td>failure and renal failure</td>
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<td></td>
<td>failure</td>
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<td>404.92</td>
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<tr>
<td>404.93</td>
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<td></td>
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<td>Secondary hypertension; benign; renovascular</td>
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<td>405.91</td>
<td>Secondary hypertension; unspecified; renovascular</td>
</tr>
<tr>
<td>405.99</td>
<td>Secondary hypertension; unspecified; other</td>
</tr>
</tbody>
</table>

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**FIG. 1** Prevalence of hypertension by age.

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expensive—costing businesses an average of $392 per eligible employee per year. Improving the efficiency and effectiveness of drug management in the hypertensive population would likely reduce these costs in addition to decreasing morbidity and mortality associated with the condition.

**Hemodynamic Measurements Using ICG**

The historical use of BP without CO or SVR is, in part, because it has been impractical to estimate or measure these parameters in most clinical settings. The assessment of the hemodynamic components of hypertension from clinical evaluation alone is unreliable. Even in patients with acute conditions such as those requiring the emergency department or patients with decompensated congestive heart failure (in whom hemodynamic derangements are greater than those in patients with essential hypertension), clinicians are generally unable to estimate CO or SVR with accuracy.20,21

Echocardiography has been used to measure cardiac output and in some studies has demonstrated acceptable correlation with invasive techniques.22 However, in a comparison with ICG, echocardiography is considerably more time consuming and technically demanding.23 In the office setting, CO is not generally reported by most physicians interpreting echocardiograms in clinical practice. Thus, until recently, CO and SVR were commonly measured only in the intensive care setting or catheterization laboratory setting using invasive means such as a pulmonary artery catheter.

In recent years, ICG has emerged as an accurate, safe, and inexpensive tool with which to measure hemodynamic parameters by noninvasive means. The procedure is most commonly performed in the physician office setting by medical assistants or nurses, requiring about 5 min to complete the test. Using four sets of paired sensors on the neck and chest, ICG measures the instantaneous change of an electrical signal across the thoracic cavity (Fig. 2). As the changes of thoracic impedance during the cardiac cycle are most dependent on the changes in the size and the blood volume of the thoracic aorta, ICG is able to calculate the amount of blood ejected from the left ventricle (that is, the stroke volume [SV]). The product of heart rate (HR) and SV yields CO. In addition, ICG-derived parameters related to the changes of thoracic impedance are indicative of aortic blood velocity and acceleration, and they correlate with measures of inotropic state and cardiac performance. As fluid is the best conductor of the electrical signal through the chest (when

![Fig. 2](image-url) Measurement of impedance signal using four sets of paired sensors. Sensors transmit and record electrical signal from which multiple hemodynamic parameters are derived.
compared with bone, air and fat, in particular), the total thoracic impedance is inversely related to an index of fluid termed the “thoracic fluid content” (TFC). Finally, using a simultaneous electrocardiographic recording, ICG measures the pre-ejection period and LV ejection time—timing intervals that relate to cardiac performance.

Representative simultaneous tracings of an electrocardiogram, change in thoracic impedance ($\Delta Z$), and first-time derivative of impedance (dZ/dt) are shown in Fig. 3. From the measured variables and from HR and mean BP determined by oscillometry, SVR and other parameters are calculated and displayed. An ICG test report is shown in Fig. 4. A more detailed description of selected parameters is provided in Table 5.

Validation of Current ICG Technology

Placement of a pulmonary artery catheter is a costly procedure requiring special training and expertise; and it is associated with risks of bleeding, infection, and damage to vascular and other structures. Because of the risks inherent in invasive methods for measuring hemodynamics, studies comparing ICG to invasive techniques of hemodynamic measurement are only available from populations with significant underlying cardiovascular conditions or situations that justify the risks associated with pulmonary artery catheter placement. In such clinical settings and patient populations, multiple studies have shown that current ICG technology, using advanced data processing and modeling techniques, yields data that are significantly more accurate than those obtained with prior generations of ICG devices. Five additional validation studies of ICG presented since 1998, using refined ICG technology (BioZ ICG Monitor, CardioDynamics, San Diego, CA), demonstrate the high correlation and accuracy available with ICG when compared with invasive techniques (Table 6).

The ability to measure changes in hemodynamic parameters reliably in a given patient is critically important from a clinical perspective, as the changes in serial measurements are the basis for evaluating patients’ disease progression, response to therapy, and need for further intervention. Thermodilution, using a pulmonary artery catheter, has traditionally been the standard to which ICG has been compared. Van De Water et al assessed the relative reproducibility of ICG and thermodilution cardiac outputs in hospitalized patients in whom a pulmonary artery catheter was placed for hemodynamic monitoring after bypass surgery. Serial ICG measurements in a given patient showed better reproducibility than serial CO measurements using thermodilution technique (Table 7). The investigators concluded that current ICG technology has advanced such that ICG provides “a level of agreement that is equivalent to thermodilution.” Their finding support the clinical utility of ICG for serial measurements in patients with cardiovascular disease.

In a stable group of patients in the outpatient setting, Verhoeve et al demonstrated a high reproducibility of measurements performed on the same day and appropriate sensitivity for the physiologic variations expected from day to day. The variation in the average of readings for CO, SVR, and thoracic fluid content (TFC) ranged between 3% and 7% for serial measurements 1 week apart. Figure 5 illustrates the high degree of correlation between stroke index measured on day 1 and then 1 week later in 96 patients who were clinically stable.

The ICG technique is widely applicable, and reliable information can be obtained in minutes at virtually no
risk to the patient. However, ICG has some limitations related to the technology and patient factors. Although ICG equations have demonstrated accuracy over a wide range of conditions and patient populations, ICG has not been evaluated extensively in patients weighing 66 pounds or 342 pounds. Severe aortic insufficiency may affect ICG reliability, but it has not been fully studied and validated in such patients. In addition, a few models of permanent pacemakers use impedance technology to measure minute ventilation. If the minute ventilation function is activated, the paced rate may increase because of ICG signals; therefore, patients with such pacemakers must have the minute ventilation sensor function inactivated before ICG testing. In patients with atrial fibrillation or frequent premature ventricular contractions, marked irregularity in heart rhythm can affect data collection and analysis of wave forms.

### Hemodynamic Parameters in Hypertension

Hypertension is the result of complex cardiac, renal, neurohormonal, and vascular mechanisms that are modulated by both genetic and environmental factors. The interactions of these many factors result in endothelial dysfunction and hemodynamic derangements of arterial compliance, CO, and SVR. As noted earlier, MAP is the product of CO and SVR, and elevations of BP can result...
from elevation of either or both of these hemodynamic parameters. Pulse pressure (PP), that is, the difference between systolic BP and diastolic BP, is determined by SV and total arterial compliance (TAC). Arterial compliance is a complex parameter that is most closely approximated using a complicated and sophisticated model (the three-element Windkessel model) that incorporates the ratio of the decay time constant to peripheral resistance.\textsuperscript{33,34} True arterial compliance is thus tedious and time-consuming to measure and is not clinically useful. However, studies have shown that arterial compliance can be reliably estimated as the ratio of SV to PP.\textsuperscript{34,35} Relationships among the hemodynamic parameters including PP, SV, MAP, CO, and SVR are shown in Fig. 6. The hemodynamics of hypertension have been studied for decades, and previously various aspects have been extensively reviewed.\textsuperscript{3,36-39}

**Hemodynamics of Hypertension: Diagnostic Considerations**

Numerous studies using either invasive or noninvasive techniques have demonstrated that there are distinct hemodynamic subsets among various groups of patients with hypertension. Hemodynamic measurements allow the differentiation of patients with primarily elevated CO from those in which elevated SVR (signifying a vasoconstricted state) is the primary mechanism of their hypertension. Moreover, hemodynamic measurements can elucidate the relative contributions of SV and arterial compliance to elevations in PP.

**Invasive Hemodynamic and Echocardiographic Studies**

In the Tecumseh, Michigan study,\textsuperscript{40} patients were studied using echocardiographic techniques and investigators found that 37\% of patients with hypertension were “hyperkinetic,” as define by increased cardiac index, HR, forearm blood flow and plasma norepinephrine levels. The distribution of cardiac index in this population study is shown in Fig. 7. The wide distribution of cardiac index values in these patients provides corroboration that hypertension represents a heterogeneous mix of various hemodynamic subsets.

In general, aging is associated with decreases in CO and increases in SVR, as shown in Fig. 8. In young adults, hypertension may be more commonly associated with increased CO, whereas in older adults it is more commonly associated with elevated SVR. Lund-Johansen\textsuperscript{41} found a change in hemodynamic pattern in patients with borderline hypertension at 10 and 17 years of follow-up. There was a significant and progressive decrease in CO over time, associated with an increase in SVR.

Age-related changes in hemodynamic status, as evidenced by changes in arterial compliance, occur in patients with hypertension even in the absence of changes in CO or SVR. Slotwiner et al.\textsuperscript{42} used echocardiographic estimates of cardiac output to study hemodynamic parameters in 272 patients who were 25 to 80 years of age and had mild hypertension. These investigators found that in their study group, CO and SVR levels did not vary significantly with age. However, vascular stiffness, as reflecte by the ratio of PP to SV (the reciprocal of TAC) increased with age, which is possibly the mechanism for increased rates of cardiovascular events in elderly individuals. Others have noted that arterial stiffness exerts deleterious effects due to increases in central aortic pressure—another hemodynamic mechanism that is key in the pathophysiology of hypertensive cardiovascular disease.\textsuperscript{43}

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Correlation (r value)</th>
<th>SD (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD 2 v TD 1</td>
<td>0.83</td>
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<td>TD 3 v TD 2</td>
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<tr>
<td>ICG 3 v ICG 1</td>
<td>0.97</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Adapted from Van De Water et al.\textsuperscript{24}

**FIG. 5** Reproducibility of stroke index (SI) measurements made 1 week apart. Adapted from Verhoeve et al.\textsuperscript{30}

**FIG. 6** Components of mean arterial pressure (MAP) and pulse pressure (PP). CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.

**TABLE 7.** Reproducibility of serial measurements: impedance cardiography (ICG) versus thermodilution (TD)

<table>
<thead>
<tr>
<th>Comparison</th>
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Adapted from Van De Water et al.\textsuperscript{24}

**FIG. 6** Components of mean arterial pressure (MAP) and pulse pressure (PP). CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.
Other factors besides age appear to predict general trends in the hemodynamic parameters in hypertensive populations. Hemodynamic parameters differ between hypertensive men and women. Messerli et al.\(^44\) measured PP, CO, and SVR using invasive techniques in 200 subjects. Despite equal levels of arterial BP, women had significantly higher CO, PP, and lower SVR compared with men. Isometric exercise was associated with an increase in arterial pressure that was nearly 50% greater in men than in women. The hemodynamic differences between men and women were confined to premenopausal women, suggesting that estrogens play a significant role in the cardiovascular and hemodynamic responses in patients with hypertension. The mechanisms of hypertension seen with acute stressors, such as public speaking or mental arithmetic, also vary based on gender. Studies have shown that men and postmenopausal women have a more significant increase in SVR in response to acute stressors, whereas premenopausal women exhibit a hypertensive response that is due primarily to increases in CO. Some studies have suggested that hypertension early in the course of diabetes and with obesity are associated with increased CO and relatively normal SVR.\(^45\) Others have shown that the earliest hemodynamic abnormalities may be changes in arterial compliance.\(^46\) To a significant degree, hypertension in patients on dialysis results from volume expansion and can be associated with signs of sympathetic stimulation such as increased HR and SV.

### Impedance Cardiographic Studies

Impedance cardiography has been used to evaluate the hemodynamic parameters in normotensive individuals at different ages and in various hypertensive populations. In a study of 640 normal transplant donors, Taler et al.\(^47\) found that increasing age was associated with increasing BP, increasing SVR, and decreasing CO due to decreased SV. Hemodynamic changes with age were similar in men and women, although BP and CO were lower and HR and SVR were higher in women. Age-related changes included an increase in total thoracic impedance, equivalent to a decrease in its reciprocal TFC and consistent with decreasing cardiopulmonary volume or muscle mass or both.

In a study comparing hemodynamic variables between pre-menopausal and post-menopausal women, Hinderliter et al.\(^48\) showed that post-menopausal women had lower CO and higher SVR for any given BP level compared with pre-menopausal women. Importantly, these significant changes in CO and SVR occurred without significant changes in BP levels, suggesting that the hemodynamic parameters underlying BP provide more information than does MAP alone. This is also seen in data from a study by Galarza et al.\(^49\) in which, despite relatively stable DBP levels in patients from the third to seventh decades of life, the investigators found significant increases in SVRI of nearly 50% and decreases in cardiac index of 27%. Alfi et al.\(^50\) used impedance techniques to show that elevations in the difference between SBP and DBP (pulse pressure [PP]) occurred due to different hemodynamic mechanisms in men <30 years of age compared with those middle aged and older. In younger men, increased PP was associated with increases in stroke index, reflecting preserved hemodynamic load with normal arterial compliance. In contrast, after age 50 years, men showed increases in PP associated with decreases in stroke index, reflecting age-related decreases in arterial compliance. Thus, BP readings alone did not reflect the underlying hemodynamic differences in groups with presumably different cardiovascular risk despite similar levels of MAP and PP. Gender differences are seen in impedance studies of the hypertensive response to caffeine: men who show hypertensive responses to caffeine increase their SVR, whereas women primarily increase SV and CO.\(^51\) Yu et al.\(^52\) studied hemodynamic parameters in patients with different mood states. Findings of correlation of CO and SVR—but not SBP, DBP, or

![FIG. 7](image)

**FIG. 7** Distribution of cardiac index values in Tecumseh, Michigan study. Cardiac index values for the hypertensive population show a bimodal distribution. From Julius et al.\(^40\)

![FIG. 8](image)

**FIG. 8** Age-related changes in cardiac output and peripheral resistance. With increasing age, peripheral resistance rises in the hypertensive population and at higher levels it is associated with decreasing cardiac output and ultimately congestive heart failure.
SBP and SVR at rest and during exercise correlated with parameters in individual patients with hypertension. This supports the need for measurement of hemodynamic parameters that cannot reliably be predicted on the basis of age, gender, or ethnic background. Moreover, that hemodynamic values cannot identify hemodynamic status of an individual patient cannot be clinically identified. The heterogeneity of hemodynamic subsets within various groups clinically identified.

Hinderliter reported that African American men and women had increased SVR, decreased CO, and associated LV remodeling compared with Caucasian men and women despite similar BP readings. In normotensive African Americans, Calhoun et al postulated that vasoconstrictor responses seen with mental stress and cold presser testing may contribute to elevated SVR and the development of hypertension.

These and other studies using ICG technology show that within any given population SVR, CO, and TAC show significant variation. The heterogeneity of hemodynamic finding within various cohorts is evidence that the specific hemodynamic status of an individual patient cannot reliably be predicted on the basis of age, gender, or ethnic background. Moreover, that hemodynamic values cannot be identified by BP levels or clinical assessment alone supports the need for measurement of hemodynamic parameters in individual patients with hypertension.

### Hemodynamics of Hypertension: Prognostic Considerations

The underlying hemodynamic abnormalities in hypertension result in structural and functional changes in the cardiovascular system that adversely affect prognosis, ie, that increase risk of morbidity or mortality. Increases in hemodynamic measures such as SVR and reductions in arterial compliance provide prognostic information in addition to that obtained by BP measurements alone.

### Invasive Hemodynamic and Echocardiographic Studies

Elevated arterial BP is the result of increased arterial stiffness and increased SVR. This results in increased LV wall stress, the best measure of LV afterload. Using catheterization techniques, Fagard et al demonstrated that SBP and SVR at rest and during exercise correlated with the risk of cardiovascular events and total mortality at an average of 16.2 years of follow-up. In this study, exercise SVR—but not exercise BP—added prognostic value to parameters measured at rest, suggesting that hemodynamic variables other than BP might have greater prognostic value.

A subsequent article reported the relationship between another hemodynamic parameter, namely, the ratio of PP to stroke index (PP-to-SVi ratio), and outcomes in patients followed for an average of 16.5 years. In this study, the PP-to-SVi ratio, that is, the reciprocal of TAC index, was independently associated with cardiovascular events or death. Each increase in PP-to-SVi ratio of 0.75 mm Hg/(mL/m²) was associated with a 79% increase in the risk of a cardiovascular event (P = .01) and greater than double the risk of all-cause mortality (P = .01). As shown in Table 8, the increased hazard rates with PP-to-SVi ratio compared with PP alone demonstrates the additional predictive value when the hemodynamic parameter of flo (SVi) is added to the pressure measurement alone.

De Simone et al studied the effects of TAC on cardiovascular events over a 10-year period. They found that risks of fatal and total cardiovascular events were independently correlated with age, LV mass, and lower levels of arterial compliance, define as decreasing values of the measured ratio of echocardiographic SV to PP (SV/PP) to that predicted from previously developed equations (% SV/PP). Moreover, consistent with the results of Fagard et al, the investigators found that systolic BP, mean BP, or PP alone (without including the flow-relate hemodynamic parameter of SV) were not independent predictors of prognosis. After adjustment for age and LVH there remained an independent effect of % SV/PP on cardiovascular endpoints at 10-year follow-up (Fig. 9). These investigators found that hemodynamic parameters such as arterial compliance and percent predicted arterial compliance correlated better with changes in cardiac structure (ie, hypertrophy and remodeling) than did BP levels alone.

<table>
<thead>
<tr>
<th>Table 8. Improved predictive power of pulse pressure (PP) to stroke volume index ratio (SVIR) compared with pulse pressure alone*</th>
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<tbody>
<tr>
<td><strong>Hazard rate, CV event</strong></td>
</tr>
<tr>
<td>PP</td>
</tr>
<tr>
<td>PP to SVIR</td>
</tr>
</tbody>
</table>

CV = cardiovascular.

Values and 95% confidence intervals for 1-SD increase in the variable of interest.

Adapted from Fagard et al.

* Adjusted for age, gender, mean arterial pressure, and heart rate; † P = NS; ‡ P < .01.

MAP—with affective state is further evidence of the heterogeneity of hemodynamic subsets within various groups clinically identified.

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Gender has long been known to affect prognosis in patients with hypertension. In 1913, Janeway published the observation that women with hypertension tended to have a better prognosis than men. More recent studies have suggested that this difference may be related to different hemodynamic substrates in men compared to women with elevated BP levels. Messerli et al suggested that the disparate prognosis between men and women might be explained on the basis of differing hemodynamic mechanisms: “For any level of arterial pressure, total peripheral resistance (and therefore the risk of hypertensive cardiovascular disease) was lower in women than in men.”

The mechanism of the adverse prognosis from hypertension is in part related to structural changes in the heart that result from elevated wall stress. Prolonged increases in wall stress lead to left ventricular (LV) structural changes with relative increases in wall thickness, overall LV mass or both. In concentric remodeling, there is a relative increase in LV thickness without increase in overall LV mass. This structural change appears to be related to increased pressure load but with relative decrease in volume as evidenced by low normal CO (termed “volume underload”). Concentric left ventricular hypertrophy (LVH) is characterized by an increase in wall thickness with increase in LV mass or mass index and also results from pressure overload caused by long-term hypertension. Eccentric hypertrophy is defined as increased LV mass index with preserved relative wall thickness and is associated with both pressure and volume overload. This pattern, a common result of the afterload and volume excesses in long-standing severe aortic insufficiency results in spherical remodeling of the LV. Interestingly, in this study of hypertensive individuals, both eccentric hypertrophy and concentric remodeling were more common than the “classic” pattern of hypertensive heart disease, namely, concentric LVH.

Nonetheless, LVH is a powerful predictor of cardiovascular risk and is independently associated with mortality in patients with coronary artery disease. For example, Vakili et al reported on the pooled results of 20 published studies of LVH as defined by electrocardiographic or echocardiographic criteria. They demonstrated a weighted mean relative risk of cardiovascular morbidity and mortality from LVH of 2.3, independent of all covariates analyzed. As reported by Ichkhan et al, LVH is associated with abnormalities of ventricular repolarization and at least a twofold increase in the risk of serious ventricular arrhythmias.

Hypertension results in abnormalities of endothelial function, affecting hemodynamic factors such as arterial compliance. Gomez-Cerezo et al demonstrated impaired brachial artery flow–mediate dilation, a common test of endothelial function, in patients with sustained or labile hypertension. They found that flow–mediate dilation was abnormal to a similar degree in patients with sustained essential hypertension or “white-coat hypertension” but was normal in individuals with normal BP levels. Others have evaluated measures of arterial compliance (or, alternatively, arterial stiffness) using the measure of pulse wave velocity.

Additional structural changes occurring at the level of the heart and blood vessel have prognostic significance in persons with hypertension, including vascular remodeling with changes in lumen to wall thickness. Apoptosis, or programmed cell death, contributes to the vascular changes (ie, remodeling) in hypertension. Inflammation and fibrosis similarly contribute with the accumulation of various components in the extracellular matrix such as collagen and fibronectin Intengan and Schiffin reviewed the factors that result in arterial remodeling and altered hemodynamic parameters in patients with hypertension.

Importantly, studies have shown that treatment with antihypertensive agents may result in regression of the structural abnormalities caused by long-standing hypertension and may result in improved prognosis. Mathew et al, reporting on data from the Heart Outcomes Prevention Evaluation (HOPE) study, demonstrated that treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril was associated with regression of LVH by electrocardiographic criteria compared with placebo control. That BP showed minimal difference between the treatment and control groups is consistent with other studies demonstrating improvement in overall hemodynamics (as shown by significant decreases in SVR and parallel increases in CO) that are not evident from BP levels alone. Ofil et al, in an echocardiographic substudy of the Systolic Hypertension in the Elderly Program (SHEP), demonstrated partial regression of LVH in patients treated with a diuretic-based regimen for a minimum of 3 years. In a meta-analysis of >1000 patients with serial echocardiography during treatment of essential hypertension, Verdecchia et al demonstrated that patients whose LVH regressed during treatment had significantly fewer cardiovascular events compared with those in whom LV mass increased, consistent with the hypothesis that improvements in hemodynamics correlate with improved prognosis in patients with appropriately treated hypertension.

**Impedance Cardiographic Studies**

The ICG technique has been used to explore age-related changes in hemodynamic variables and their correlation with cardiovascular risk and the adverse prognosis. These studies support previous finding that future risk in patients with hypertension may not be reflecte in BP levels alone. Alfi et al demonstrated that despite similar elevations in PP, younger men had preserved stroke index (and arterial compliance) compared with older men. They concluded that preserved arterial compliance and cardiac pump function may explain the lack of prognostic significance of elevated PP in younger men. These finding lend further support to the value of the incremental information
provided by the hemodynamic components of BP and PP levels.

Hemodynamic differences have been demonstrated in patients who have experienced complications of hypertension compared with those with hypertension alone. In a study of hemodynamic status in hypertensive patients with and without a history of stroke, Galarza et al.75 found lower cardiac index and higher SVR index in those with history of stroke. These differences occurred in the absence of differences in BP or antihypertensive treatment, providing another example of the unreliability of BP to reflect the severity of underlying hemodynamic abnormalities.

**Hemodynamics of Hypertension: Therapeutic Considerations**

Hypertension management includes hygienic measures such as sodium restriction and weight loss; and, in most cases, it requires the use of one or more antihypertensive agents. Antihypertensive medications exert their BP-lowering effects by reductions in SVR or CO. Hemodynamic effects can be used to classify antihypertensive agents, predict the response to antihypertensive therapy, and guide both the initiation and titration of these agents.76–78

Just as interpretation and treatment of serum cholesterol level improves when its components (HDL-cholesterol and LDL-cholesterol) are measured, hypertension may be better diagnosed and treated by examining its hemodynamic components (CO and SVR). As MAP is the product of CO and SVR, elevated mean BP results from elevated CO, SVR, or both. As shown in Fig. 10, CO is the product of HR and SV. Stroke volume is determined in part by LV filling (preload) and contractile (inotropic) state. Hypertension can thus result from increases in SVR (vasoconstriction), HR (hyperchronotropy), preload (hypervolemia), or contractility (hyperinotropy).

**Invasive and Echocardiographic Studies**

In a small group of men with severe hypertension, Sullivan et al.79 studied the relationship between baseline hemodynamic status and the response to various antihypertensive agents that were randomly selected. Patients with elevated SVR responded with decreases in SVR, and those with elevated CO had BP control associated with normalization of CO.

Treatment targeted at the specific hemodynamic cause of hypertension has predictable and appropriate results. Easterling et al.80 studied noninvasive hemodynamic parameters using Doppler echocardiography in 19 pregnant hypertensive women. Ten patients had elevated CO, whereas nine patients had elevated SVR, demonstrating hemodynamic heterogeneity within this apparently homogeneous population. Patients with elevated CO were treated with a β-blocker (atenolol) and those with elevated SVR were treated with hydralazine, a vasodilator targeted at elevated SVR. Patients given hydralazine had dramatic improvements in CO in association with decreases in SVR; those given atenolol for elevated CO had improvement in BP and normalization of CO. The investigators suggest that the failure of previous studies to show consistent results in the drug management of hypertension in pregnancy may have resulted from treating a heterogeneous hemodynamic group with a single regimen. The implication of their study is that hemodynamically guided therapy would be expected to show more consistent results in hemodynamically diverse populations.

Differential effects of antihypertensive medications on hemodynamic variables may not be evident from changes in BP alone. Resnick and Lester81 studied the effects of various BP medications on arterial compliance in patients referred to an outpatient practice specializing in hypertension. The changes in compliance of the large arteries (capacitive compliance) and in smaller arteries (reflective compliance) were evaluated during treatment with ACE inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), and β-blockers. The researchers found that despite similar changes in SBP, DBP, and PP during treatment, there were improvements in arterial compliance with ACE inhibitors, ARB, and CCB but not with β-blockers. These researchers suggest that choosing medications that have favorable effects on both BP and arterial compliance “might further enhance the potential clinical benefit of drug therapy in hypertension.” Similarly, Zusman78 reported that despite similar degrees of BP reduction, the hemodynamic effects of the CCB nifedipine were favorable when compared with the β-blocker atenolol, resulting in decreased SVR, increased CO and improved measures of LV contractility and diastolic function. Others have shown significantly different hemodynamic effects between various β-blockers such as between metoprolol and carvedilol due to the α-adrenergic blocking properties of the latter.82

Studies suggest that most patients require multiple medications to achieve BP control. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),83 a large randomized trial comparing outcomes in patients treated with different classes of antihypertensive agents, 90% of patients were
Rationale for an ICG-Guided Approach to Antihypertensive Therapy

The foregoing discussion has presented data on the role of hemodynamic information for diagnostic, prognostic, and therapeutic decision making for patients with hypertension. The use of ICG-derived hemodynamic information to improve BP control requires accurate assessment of baseline hemodynamic state, creation of a therapeutic regimen based on hemodynamic status, and timely measurement of changes in various hemodynamic parameters in response to therapy. Studies have shown that it is very difficult—i not impossible—to make an accurate assessment of CO and SVR at the bedside by physical examination alone. Therefore, it is not likely to be possible to use physical examination to reliably identify baseline hemodynamic subsets or changes in hemodynamic status so as to optimize therapy.

Clinicians have used ICG in various patient care settings to assess its applicability in the assessment and treatment of hypertension. As noted earlier here and in Fig. 7, there is significant hemodynamic heterogeneity among individuals with hypertension, suggesting that BP level alone is not adequate to categorize patients into clinically meaningful subgroups. De Divitiis et al used ICG to confirm the presence of distinct hemodynamic profile in patients with hypertension: 1) elevated CO in association with normal or nearly normal SVR, and 2) predominantly elevated SVR. Margulis et al evaluated other hemodynamic parameters in untreated patients with hypertension. They found impairment of cardiac performance with decreased indices of contractility and evidence for increased thoracic fluid content, suggesting increased water content of the lungs or thoracic wall tissues.

Thoracic fluid content, the reciprocal of total thoracic

<table>
<thead>
<tr>
<th>Effect</th>
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<th>Stroke volume</th>
<th>Heart rate</th>
<th>Intravascular volume</th>
<th>LVH</th>
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<tbody>
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<td>Diuretics</td>
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ACE = angiotensin converting enzyme; CO = cardiac output; LVH = left ventricular hypertrophy; NC = no change; SVR = systemic vascular resistance; ↑ = increase, ↓ = decrease.
impedance, is strongly correlated with amount of fluid in the chest cavity, whether intravascular or extravascular. In patients undergoing thoracentesis, Petersen et al \(^{97}\) demonstrated a strong correlation between the volume of pleural fluid removed and the change in total thoracic impedance (correlation coefficient 0.97). In studies using lower-body negative pressure to create pooling of venous blood in the lower extremities, Ebert et al \(^{98}\) found a nearly perfect linear correlation with changes in central venous pressure and changes in thoracic impedance. Thus, TFC has been used to monitor changes in fluid volume and guide diuretic therapy in patients with hypertension.

Linb et al \(^{89}\) reported that BP reductions resulted from improvements in baseline hemodynamic abnormalities; patients with elevated CO responded to targeted therapy with a \(\beta\)-blocker (propranolol), whereas those with elevated SVR responded to treatment with the vasodilating CCB (nifedipine). Mattar et al \(^{96}\) showed that an intensive regimen of diet and exercise resulted in improvements in hemodynamic parameters with substantial increases in CO and decreases in SVR despite only modest changes in MAP. Moreover, the investigators speculated that failure of some hypertensive patients to show hemodynamic improvement on serial ICG measures resulted from the inappropriate choice of medications that were not targeted toward the underlying hemodynamic abnormalities.

Hemodynamic parameters derived from ICG have been used to evaluate the differential effects of medications in patients with essential hypertension. In a study of the effects of a cardioselective \(\beta\)-blocker compared with a \(\beta\)-blocker with intrinsic sympathomimetic activity, Toth et al \(^{100}\) studied 57 patients randomized to treatment with either atenolol or pindolol for 12 weeks. Pindolol therapy was associated with a 12% decrease in SVR compared with minimal change with atenolol. Atenolol-related improvement in BP resulted from decrease in HR and cardiac index. Breithaupt-Grogler et al \(^{87}\) reported on the differential hemodynamic effects of combination therapy with verapamil/trandolapril (Vera/Tran) compared with metoprolol/hydrochlorothiazide (Meto/HCTZ) in 26 patients after 6 months of therapy. In addition to ICG-derived CO and SVR, the authors measured carotid/iliac pulse wave velocity as a measure of arterial stiffness. The combination of CCB and ACE inhibitor (Vera/Tran) reduced diastolic BP to a greater degree than Meto/HCTZ and lowered SVR by about 15% compared with minimal change with the \(\beta\)-blocker/diuretic combination. Treatment with Meto/HCTZ was associated with a significant reduction in CO compared with baseline, which was not seen with Vera/Tran. However, pulse wave velocity decreased with Vera/Tran but not with Meto/HCTZ, suggesting an improvement in the elastic properties of the aorta with the former drug regimen.

The ICG technique has been used to assess the hemodynamic effects of sodium restriction in a small group of subjects with mild hypertension. \(^{101}\) During sodium restriction, ICG-derived measures of SV decreased in association with fall in diastolic BP. An increase in overall thoracic impedance (the reciprocal of TFC) was consistent with a decrease in extracellular fluid volume. In addition, ICG has been used to explore the mechanisms of responses to ACE inhibitors and prostaglandin inhibitors in patients who are either salt sensitive or salt insensitive. \(^{102}\) These examples illustrate the use of ICG in assessing the mechanisms of BP elevation and the hemodynamic effects of nonpharmacologic interventions in hypertension.

As noted above, antihypertensive medications ultimately act on one or more of the hemodynamic components that determine BP. \(^{79,80}\) Once the baseline hemodynamic status is known, an appropriate medical regimen can be designed based on the expected hemodynamic effects of various medications. However, individual patients vary in their responses to antihypertensive drugs such that the actual hemodynamic effects and side effects cannot reliably be predicted. Therefore, empiric selection of drug combinations based on their general hemodynamic actions as a class may not be successful in managing a specific patient, even if the baseline hemodynamic status is known. The ICG technique is unique in that it can provide not only an accurate hemodynamic profile noninvasively but can guide therapy toward a drug regimen that is most appropriate for the specific patient based on serial measurements. Periodic measurements of hemodynamic status allow the physician to monitor therapy when results are suboptimal or unexpected. It is for these reasons that ICG has emerged as a valuable tool in the evaluation and treatment of patients with hypertension.

**Outcome Studies Using ICG-Guided Therapy in Hypertension**

The observation that hypertension is a hemodynamic disease implies that measurement of hemodynamic parameters can be used to guide medication selection, to titrate dose, and to evaluate efficacy of the medical regimen. Several studies have used ICG to evaluate hemodynamic parameters and demonstrated that ICG-guided therapy improves BP control. Taler et al \(^{103}\) randomized 104 patients with hypertension uncontrolled on two or more drugs to a 3-month trial of ICG-guided therapy or standard therapy directed by a hypertension specialist. In this study, BP control (define as achieving BP \(<140/90\) mm Hg) occurred 70% more often in the ICG-guided group (Fig. 11). Use of ICG resulted in greater reductions in SVR index and more intensive use of diuretic therapy, guided by levels of TFC. According to the study investigators, measurement of hemodynamic and impedance parameters was more effective than clinical judgment alone in guiding selection of antihypertensive therapy patients resistant to empiric therapy.

Sharman et al \(^{104}\) studied a cohort of patients in the primary care office setting with drug-resistant hypertension, define as systolic BP \(\geq140\) mm Hg or diastolic BP \(\geq90\) mm Hg during treatment with two antihypertensive
medications. Patients were treated based on a published ICG-guided treatment algorithm (Fig. 12) for an average of 7 months. In this study, ICG resulted in BP control in 57.1% of patients who were not controlled before the use of ICG-guided therapy. The average number of medications increased from 2.0 at time of entry to 2.5 ± 0.7 at the end of the study period. The observation that hemodynamic information derived from ICG resulted in BP control with two medications in some patients and three or more in others is consistent with both higher intensity and more appropriate medical regimens. The investigators concluded that ICG is safe and cost-effective and could assist community-based physicians in treating uncontrolled hypertension.

Sramek et al.\textsuperscript{105} reported on a series of 322 patients with hypertension uncontrolled despite previous therapy with two or more antihypertensive agents for periods of 2 years or more. The researchers directed the management of hypertension at both control of BP and improvement in underlying hemodynamic parameters including CO and SVR. At baseline, 16% of subjects had significantly reduced CO (ie, were considered hypodynamic) and approximately 19% were hyperdynamic. In this large series of patients treated using the results of ICG evaluation, so-called normodynamic goal-oriented therapy controlled BP in 203 subjects (63%) within several weeks. The investigators highlight the observation that ICG was able to identify medications that were optimal and specific for the individual patients, resulting in an approach superior to the conventional “trial-and-error” method.

Additional Roles of ICG in Patients With Hypertension

The evidence cited above supports the use of ICG-derived hemodynamic information in guiding the selection, initiation, titration, and evaluation of antihypertensive medication. However, patients and their physicians fail to achieve adequate BP control for reasons other than the responses to specific medications. Common barriers to BP control include lack of awareness of the condition, inability to make necessary dietary and other lifestyle modifications, noncompliance with medications, complicating factors such as drug interactions, secondary causes of hypertension, and comorbidities such as kidney disease.

Testing with ICG using currently available equipment may favorably affect each of these issues. Oscillometric measurements of BP, as with the most widely used ICG equipment, are more reliable and less operator dependent than standard BP techniques. The accurate and reproducible measures of CO and SVR identify patients with abnormal hemodynamic states and may increase clinical suspicion and diagnostic sensitivity for those with borderline or prehypertensive BP readings. The ICG reports are useful teaching tools for patients and may provide motivation for the dietary and other lifestyle changes that assist in BP control.

Changes in hemodynamic parameters may identify instances when patients stop their medications or when there are complicating factors such as worsening renal function or interactions with medications such as over-the-counter nonsteroidal anti-inflammatory drugs. As noted,\textsuperscript{103} an increase in one class of hypertensive agents may result in compensatory fluid retention, leading to an increase in TFC as measured by ICG and the need for higher doses of diuretics. Similarly, fluid retention resulting from the renal effects of anti-inflammatory medications may be recognized by changes in TFC. Importantly, ICG-derived measures of cardiac performance, such as velocity index or

![FIG. 11 Percentage of patients achieving blood pressure (BP) control using impedance cardiography (ICG)-guided therapy compared with non-ICG-guided therapy. Adapted from Taler et al.\textsuperscript{103}](image1)

![FIG. 12 Algorithm for hemodynamically guided therapy of hypertension. Adapted from Sharman et al.\textsuperscript{105} and Taler et al.\textsuperscript{104} In the latter study, postural changes in total body impedance (TBI), the reciprocal of thoracic fluid content (TFC), were used as the criteria for decisions regarding fluid status.](image2)
systolic time ratio, may be the initial signs of the development of LV dysfunction.\textsuperscript{106,107}

### Implications of Hemodynamics and Future Considerations

In addition to improving the diagnosis and therapy of hypertension, hemodynamic measurements provide insights into other aspects of cardiovascular function. For example, studies have shown the importance of endothelial function in the development and progression of cardiovascular disease.\textsuperscript{108} Endothelial dysfunction, as measured by reduced flow-mediated arterial dilation, is associated with abnormal hemodynamic measures, including elevated SVR.\textsuperscript{109} In the HOPE study,\textsuperscript{110} an ACE inhibitor—a drug that both lowers SVR and improves endothelial function—reduced mortality from cardiovascular disease despite only minor effects on BP. Future studies will likely examine the significance of elevated SVR and arterial compliance in individuals with hypertension or prehypertension and will correlate ICG-derived hemodynamic parameters with other evolving markers of increased cardiovascular risk such as C-reactive protein, homocysteine level, and the metabolic syndrome.

The studies included in this supplement of the journal add to the growing body of literature that supports the accuracy, reliability, and clinical utility of ICG in diagnostic and prognostic assessment and therapeutic management of patients with hypertension. The use of ICG has added significantly to our understanding of hypertension as a disease with both hemodynamic causes and hemodynamic consequences. Just as congestive heart failure reflect abnormal flow or inappropriate ventricular filling pressures, hypertension occurs when there is abnormal flow or inappropriate vascular resistance or compliance. When hypertension impairs LV performance (either systolic or diastolic), heart failure ensues. Although these conditions often co-exist, in many cases hypertension is a step in a hemodynamic continuum that leads to further hemodynamic derangement and heart failure. It is believed that future studies will confirm recent findings that hemodynamic measurements in individual patients will improve diagnosis, risk assessment, and treatment for these patients. It is also possible that further exploration of the implications of hypertension as a hemodynamic disease will lead to studies demonstrating that earlier detection and treatment of the hemodynamic components of hypertension may change the natural history of this disease process.

### References


Whole-Body Electrical Bio-Impedance is accurate in Non Invasive Determination of Cardiac Output: A Thermodilution controlled, Prospective, Double Blind Evaluation.

Guillermo Torre-Amiot\textsuperscript{1} MD, Gad Cotter\textsuperscript{2} MD, Zvi Vered\textsuperscript{2} MD, Edo Kaluski\textsuperscript{2} MD, Karl Stang\textsuperscript{3} MD. From Baylor College of Medicine, Houston, TX, USA (\textsuperscript{1}), Assaf-Harofeh Medical Center, Israel (\textsuperscript{2}) and Charite Campus, Berlin, Germany (\textsuperscript{3}).

Background: The NICaS\textsuperscript{TM} is a novel non-invasive apparatus based on whole body electrical bio-impedance for simple non-invasive continuous CO determination.

Patients and Methods: Patients were recruited while randomized in a study evaluating the efficacy of Tezosentan (a ET-A/B endothelin antagonist) in patients admitted due to acute heart failure (CHF). Patients were randomized after having been hospitalized due to acute heart failure with dyspnea at rest, CI < 2.5 L/min/m\textsuperscript{2} and PCWP ≥ 20 mmHg. Study Protocol: At baseline and during treatment with study drug at the pre-specified time points of 0.5,1,2,3,4 and 6 hours from randomization CO was determined by both thermodilution and the NICaS\textsuperscript{TM} 2001 apparatus. At each time point CO was determined by thermodilution and NICaS\textsuperscript{TM} 2001 apparatus by a two independent, blinded operators.

Results: Out of 130 patients enrolled, in 93 CO was measured simultaneously by both methods at all the pre-determined time points. The overall Correlation between the two methods was R=0.81 (Figure). Precision and bias were 0.01±0.6 L/min. There was a difference between the two methods in cardiac output readings. When Mean CI (of both methods) was < 2 L/min/M\textsuperscript{2} CO readings were statistically significantly lower by NICaS while when CI was >3 L/min/M\textsuperscript{2}, CO readings were statistically significantly higher by NICaS. We have calculated the cardiac power index (Cpi=CI* mean arterial pressure), and found that low Cpi (indicating reduced myocardial contractile reserve) was related to higher recurrent CHF. However, Cpi based on NICaS CI measurement (NICaS Cpi) was a better predictor of recurrent CHF then thermodilution Cpi (Th Cpi), due to less accurate prediction in patients with high Cpi.

Conclusions: NICaS is a novel accurate non-invasive method for CO determination. The results of the present study suggest that NICaS might be more accurate then thermodilution for CO determination due to the tendency of thermodilution to under estimate CO when high and over estimate it when low.
Accurate, Noninvasive Continuous Monitoring of Cardiac Output by Whole-Body Electrical Bioimpedance

Gad Cotter, Yaron Moshkovitz, Edo Kaluski, Amram J. Cohen, Hilton Miller, Daniel Goor and Zvi Vered

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Accurate, Noninvasive Continuous Monitoring of Cardiac Output by Whole-Body Electrical Bioimpedance*

Gad Cotter, MD; Yaron Moshkovitz, MD; Edo Kaluski, MD; Amram J. Cohen, MD, FCCP; Hilton Miller, MD; Daniel Goor, MD; and Zvi Vered, MD

Study objectives: Cardiac output (CO) is measured but sparingly due to limitations in its measurement technique (ie, right-heart catheterization). Yet, in recent years it has been suggested that CO may be of value in the diagnosis, risk stratification, and treatment titration of cardiac patients, especially those with congestive heart failure (CHF). We examine the use of a new noninvasive, continuous whole-body bioimpedance system (NICaS; NI Medical; Hod-Hasharon, Israel) for measuring CO. The aim of the present study was to test the validity of this noninvasive cardiac output system/monitor (NICO) in a cohort of cardiac patients.

Design: Prospective, double-blind comparison of the NICO and thermodilution CO determinations.

Patients: We enrolled 122 patients in three different groups: during cardiac catheterization (n = 40); before, during, and after coronary bypass surgery (n = 51); and while being treated for acute congestive heart failure (CHF) exacerbation (n = 31).

Measurements and intervention: In all patients, CO measurements were obtained by two independent blinded operators. CO was measured by both techniques three times, and an average was determined for each time point. CO was measured at one time point in patients undergoing coronary catheterization; before, during, and after bypass surgery in patients undergoing coronary bypass surgery; and before and during vasodilator treatment in patients treated for acute heart failure.

Results: Overall, 418 paired CO measurements were obtained. The overall correlation between the NICO cardiac index (CI) and the thermodilution CI was $r = 0.886$, with a small bias (0.0009 ± 0.684 L) [mean ± 2 SD], and this finding was consistent within each group of patients. Thermodilution readings were 15% higher than NICO when CI was $< 1.5 \text{ L/min/m}^2$, and 5% lower than NICO when CI was $> 3 \text{ L/min/m}^2$. The NICO has also accurately detected CI changes during coronary bypass operation and vasodilator administration for acute CHF.

Conclusion: The results of the present study indicate that whole-body bioimpedance CO measurements obtained by the NICO are accurate in rapid, noninvasive measurement and the follow-up of CO in a wide range of cardiac clinical situations.

Key words: cardiac function test; cardiac output; congestive heart failure

Abbreviations: CABG = coronary artery bypass graft; CHF = congestive heart failure; CI = cardiac index; CO = cardiac output; Cpi = cardiac power index; ISDN = isosorbide-dinitrate; MAP = mean arterial BP; NICO = noninvasive cardiac output system/monitor; SV = stroke volume; SVRi = systemic vascular resistance index; TEB = thoracic electrical bioimpedance; WBEB = whole-body electrical bioimpedance

Measurement of cardiac output (CO) and the calculation of cardiac index (CI) has been used selectively over the last 2 decades, mainly due to the fact that CI measurement requires the invasive procedure of right-heart catheterization and placement of a Swan-Ganz catheter (Baxter Healthcare; Irvine, CA). Hence, the experience with its application for monitoring and risk stratification of cardiac patients is limited.

In recent years, however, evidence has accumulated to the effect that CI measurement and the calculation of systemic vascular resistance index (SVRi) and cardiac power index (Cpi, the product of CI...
multimodal, there may be useful for early detection of myocardial ischemia. Furthermore, changes in acute SVR (systolic vascular resistance) and Cpi (cardiac performance index) have been found to be an important tool for diagnosis and risk stratification. In patients with chronic CHF, a few studies have shown that noninvasive Cpi reserve (the increase in Cpi during exercise or dobutamine stress) is the strongest predictor of outcome (a better oxygen consumption and echocardiographic ejection fraction) in such patients. Furthermore, changes in acute SVR may be useful for early detection of myocardial ischemia. Moreover, in two separate studies examining the efficacy of vasodilators in patients with acute CHF, medication was found to be effective mainly in patients who were submitted to hemodynamic monitoring, implying that perhaps in order to be efficacious, vasodilator treatment should be monitored attentively to prevent overtreatment and undertreatment. In different studies, we have also demonstrated that careful titration of vasodilator treatment administered for acute heart failure and acute coronary syndromes is important to optimize its efficacy. In the present study, we evaluated the accuracy of a novel method of CI measurement (whole-body electrical bioimpedance [WBEB]) in different cardiac clinical settings (during cardiac catheterization and coronary artery bypass graft [CABG] surgery, and for monitoring patients with acute CHF) and over a wide range of CI values and severity of left ventricular dysfunction.

**Materials and Methods**

**Patient Populations**

*Group 1:* Group 1 consisted of 40 patients with coronary artery disease referred during March to July 1993 for left and right [CABG] surgery, and for monitoring patients with acute CHF and over a wide range of CI values and severity of left ventricular dysfunction. During the right-heart study, a pulmonary artery catheter was introduced under fluoroscopy; at a single time point, a paired measurement of CI by a noninvasive cardiac output system/monitor (NICO) [NICaS; NI Medical; Hod-Hasharon, Israel] and by thermodilution was performed.

*Group 2:* Group 2 included 51 patients undergoing CABG operations. The first 15 patients were studied at Wolfson Medical Center (Israel) during October to November 1994. The next 16 patients were studied at Johns Hopkins Medical Center during April to May 1995. The remaining 20 patients were studied again at Wolfson Medical Center during August to October 1995. A balloon-guided, Swan-Ganz catheter was introduced after the induction of anesthesia, and five paired NICO CI and thermodilution CI measurements were obtained at specific operative and postoperative stages: immediately prior to the skin incision; after sternotomy; after pericardiotomy; 10 min after weaning from the pump; and immediately after arrival to the ICU. The results obtained from the first 31 cases of this series have already been published.

*Group 3:* Group 3 consisted of 31 patients admitted during September to December 2001 to the ICU of Assaf-Harofeh Medical Center (Israel) because of an acute exacerbation of CHF. Prior to admittance, they underwent a right-heart study in the catheterization laboratory for the assessment of their cardiac condition, and a Swan-Ganz catheter was inserted under fluoroscopy. CO measurement was begun on arrival to the ICU, where three baseline measurements were obtained, 15 min apart. In 17 patients who required vasodilator therapy, four measurements were obtained during the initiation and up-titration of IV isosorbide-dinitrate (ISDN) treatment. In the 14 patients who did not require ISDN treatment, an additional (fourth) baseline measurement was obtained. All the studies were approved by the review boards and the Helsinki committees of the various hospitals. Consents for the studies were obtained from each patient.

**Measuring CI**

**Thermodilution:** In all three study groups, a No. 7F Swan-Ganz balloon flotation catheter was placed in the pulmonary artery. In groups 1 and 2, the Swan-Ganz catheter was introduced in the catheterization laboratory, and in group 2 on the operating table, following anesthesia. In the 16 patients of group 2 who were studied at Johns Hopkins Medical Center, CO measures were obtained by the 7010 Series Marquette (Marquette; Madison, WI). In the remaining 15 patients of group 2 studied at Wolfson Medical Center, and also in group 1 patients at the Tel Aviv Medical Center (Israel), the Horizon 2000 (Mennen Medical; Rohovot, Israel) was used. In group 3, the CO was measured by Marquette 5000 Clinical Information Center 419897-015 (Marquette).

A volume of 10 mL of 5% dextrose at room temperature was injected in all patients via the proximal port. Temperature changes were measured via the distal port located in the pulmonary artery, ascertained by fluoroscopy, oxygen saturation, and wedge pressure measurements. In all patients, three CI measurements were obtained; when a >15% disparity occurred between the two extreme measurements, two further injections, or more, were administered until an average of three measurements within the 15% range was obtained.

**NICO WBEB Technology**

When transmitting a small electrical current through the body, an impedance to its transmission (resistivity, R) is being measured.

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†Deceased.

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This resistivity is called bioimpedance. According to Kirchov’s law, electric current passes through conduits of higher conduction (lowest resistivity). The resistivity of blood and plasma is the lowest in the body (resistivity of blood is 150; plasma, 63; cardiac muscle, 750; lungs, 1,275; and fat, 2,500 ohm/cm). Thus, when an alternating current of 20 to 100 kHz is applied to the body, it is primarily distributed via the extracellular fluid and the blood. The changes in the body resistivity (ΔR) over time (milliseconds) are therefore related to the dynamic changes of the blood and plasma volume. This pertains particularly to the passage of the stroke volume (SV) from the left ventricle into the aorta and its branches. However, in the capillaries and in the venous system the blood volume is relatively constant, because the flow in these vessels is not pulsatile. Consequently, each systolic increase in the aortic blood volume is associated with a proportional increase in the measurable conductance of the whole body (Fig 1). Thus, for measuring the aortic SV by means of its impedance change, Frimerman and Tsoglin developed the following algorithm:

\[
SV = \frac{H_{\text{corr}} \times K_{\text{sex}, \text{age}} \times K_{\text{weight}} \times IB \times H_{\text{corr}} \Delta R}{R} \times \frac{\alpha + \beta}{\beta}
\]

in which the ΔR/R is corrected for hematocrit (Hctcorr), electrolytes (Kel), body composition (K sex, age), weight (K weight), time characteristics (α = systolic time, β = diastolic time), and index balance (IB), which measures the body water composition.

To collect patient signals, the NICO uses proprietary electrodes arranged in a wrist-to-ankle configuration (Fig 2); in certain conditions when this particular form is not applicable (as with severe peripheral edema or severe peripheral vascular disease), a wrist-to-wrist configuration is used. The precise positioning of the NICO electrodes is not critical; an untrained operator can make the attachments. An alternating current of 30 kHz, 1.4 mA is delivered through the two electrodes, and the bioimpedance and its fluctuations over time are measured. In addition, a standard three-lead ECG connection is made for measuring the pulse rate. The other variables required for SV and CI calculation (age, gender, weight, height, hematocrit, electrolytes) are introduced into the machine only at the start of monitoring. For measuring the CO, the SV is multiplied by the heart rate.

Although the idea of the WBEB was conceived and tested in the Soviet Union in 1941, it remained dormant until recently. Meanwhile another bioimpedance approach for measuring the CO was initially introduced by Kubicek et al in the United States in 1966, and further refined in 1974. His method is called thoracic electrical bioimpedance (TEB), and the tools of this approach are commercially available. Noted here are dissimilarities in the operation of the two technologies. In the NICO, one electrode is applied to the wrist and the other to the ankle; in TEB, a number of electrodes are placed at the root of the neck and another set around the lower part of the chest cage. In WBEB, the SV is measured by the impedance variation (ΔZ or ΔR) induced by the systolic volume ejected into the aorta. In the original TEB formula of 1966, the SV measurement was based on a similar principle. However, since when the electrodes are placed on the chest, the ΔZ wave could be hardly detected, Kubicek et al adopted another principle, whereby the SV measurement is based on the depiction of the aortic systolic dp/dt (instantaneous pressure change over time) for calculation of the systolic blood flow into the great arteries.
Measuring CI by the NICO

For each CI determination, three NICO measurements were obtained. Since the CO results that are displayed on the scope are updated every 20 s, for the determination of the CI an average CO is derived from a 60-s monitoring.

Statistical Methods

Agreement between the CI values of the NICO and thermodilution was evaluated in three ways: the mean CI values of the NICO and thermodilution were compared by a paired Student t test; correlation between these values was evaluated by calculating the Pearson correlation coefficient and by applying a linear regression model of the NICO on thermodilution; the differences between the paired CI values of the NICO and thermodilution were plotted against the average CI values of both methods, instead of against thermodilution alone. This statistical method was recommended by Bland and Altman for evaluating a new device (NICaS) against an established method (thermodilution), which has its own inaccuracies. Bias was defined as the mean difference between the NICO CI and thermodilution CI values. Limits of agreement (precision) were calculated as bias ± 2 SD of the differences between the NICO CI and thermodilution CI values. All three analyses were carried for the whole sample and for each specific clinical group: cardiac catheterization patients (group 1), CABG patients (group 2), and CHF patients (group 3).

We have examined the differences between the CI determination by the NICO and thermodilution at different CI readings by classifying the readings into four subgroups according to the mean CI levels: CI < 1.5, CI ≥ 1.5 and < 2, and CI ≥ 2 and < 3, and CI ≥ 3. CI readings by the NICO and thermodilution in each group were compared using the paired Student t test and presented as mean and SDs.

The sensitivity of the two methods (NICO and thermodilution) to a change in a specific medical condition was compared in the CABG group at five operative and postoperative stages. A variance analysis with repeated measures (type of method and stage) was performed, followed by contrast analysis that compared successive stages. This analysis could be performed only for patients with complete data at all the five stages. A similar analysis was performed at seven time points in CHF patients who had been treated with an IV vasodilatory drug. All statistical analyses were performed using the SAS System for Windows (version 8.01; SAS Institute; Cary, NC).

RESULTS

No significant differences between the means of NICO CI and thermodilution CI in the three clinical groups, as well as the whole cohort, were observed (Table 1). A significant, high correlation was found between the NICO CI and the thermodilution CI measurements: 0.886 in the whole cohort, and 0.881, 0.902, and 0.851 in the catheterization, bypass surgery, and CHF groups, respectively. All correlation coefficients were statistically significant (p < 0.0001).

The results of applying linear regression models to the data (Table 2, Fig 3) demonstrate similar models in the three clinical groups, as the intercepts and slopes of the regression lines are not significantly different (intercepts, p = 0.2398; slopes, p = 0.2310). Figure 4 shows differences between CI values plotted against the average value of the two methods with limits of agreement: two SDs from the mean difference.

Significant differences between the NICO CI and thermodilution CI were observed when comparing the average CI of the four CI ranges (Table 3). When CI is < 2 L/min/m², the thermodilution CI readouts

Table 1—Comparison Between the Mean CI Values of the NICO and Thermodilution in the Three Clinical Groups and in the Whole Cohort*

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Thermodilution CI, L/min/m²</th>
<th>NICO CI, L/min/m²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample</td>
<td>418</td>
<td>2.39 ± 0.70</td>
<td>2.38 ± 0.73</td>
<td>NS</td>
</tr>
<tr>
<td>Catheterization</td>
<td>40</td>
<td>2.81 ± 0.72</td>
<td>2.81 ± 0.68</td>
<td>NS</td>
</tr>
<tr>
<td>CABG</td>
<td>208</td>
<td>2.33 ± 0.72</td>
<td>2.31 ± 0.77</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>170</td>
<td>2.35 ± 0.63</td>
<td>2.38 ± 0.66</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = not significant.
are significantly higher than the NICO CI; when CI is > 3 L/min/m², the thermodilution CI is lower than the NICO CI (Table 3). When CI was between 2 L/min/m² and 3 L/min/m², there was a slight difference of only 3.28% between the two methods, with a borderline significance (Table 3).

Twenty-five patients with CABG (subgroup A) had complete information of the NICO CI and thermodilution CI results at five operative and postoperative stages (Table 4, Fig 5, top). A further 26 CABG patients (subgroup B) had incomplete data (< 5 paired measurements for each patient), yielding additional 80 paired measurements (Table 4). There were time-related changes in the CI, and the NICO and the thermodilution followed these changes by producing similar results at each time point (p = 0.0035 and p = 0.0058, respectively; Fig 5, top). A contrast analysis, performed to compare the CO in successive stages of the measurements, found that the difference between stage 3 and stage 4 was statistically significant according to the two measurements in subgroup A (NICO CI, p = 0.0135; thermodilution CI, p = 0.002; Fig 5, top). In 17 of the CHF patients in group 3 who were treated with an IV vasodilator agent, and in whom the CI was measured simultaneously at seven time points during the treatment, the total time trend was significant in the NICO (p = 0.0056) but not significant in thermodilution (Fig 5, bottom).

**DISCUSSION**

In recent years it has been suggested that CO and MAP measurement and the calculation of CI, Cpi, and SVRI might be instrumental in the diagnosis, treatment titration, and risk stratification of cardiac patients, especially those with CHF.7–10 However,
CI has been measured only during invasive right-heart catheterization, which requires intensive care admission and may be associated with complications. Therefore, CI was measured only rarely, and in the sickest patients. Therefore, a simple, reliable, noninvasive, and continuous method for CI measurement has become necessary in order to enable its application to cardiac patients with different degrees of medical severity and in diverse settings.

Currently there are four accepted methods for noninvasive CO measurement. The Doppler echocardiogram obtained from the left ventricular outflow track and CO₂ rebreathing techniques have been shown to be accurate in measuring CI. But these methods are limited by the requirement for expensive equipment and specialized personnel for their application and therefore are not simple to use, and moreover do not enable continuous measurements. Thoracic bioimpedance has been used in the last decade for continuous CO measurement. Judging by the literature, as long as the heart function is intact, TEB can be useful for monitoring the hemodynamic state in various clinical conditions such as trauma, massive surgery, sepsis, etc. But when it comes to monitoring and managing pathologic cardiac conditions TEB requires further improvement.

Thus far, eight groups of patients who submitted to CO measurements by WBEB have been reported in six published articles. Kedrov, who was the first, compared the average CI measured by the WBEB in 57 subjects with normal hearts in published results of the Fick method, revealing 3.3 ± 0.16 L/min/m² (range, 2.4 to 4.2 L/min/m²), respectively. Tischenko compared the CI results measured by WBEB in three groups of subjects with normal hearts vs three standard methods. There were 31 cases vs acetylen (r = 0.84), 28 cases vs thermodilution (r = 0.95), and 28 cases vs Fick (r = 0.99).

Using a modified Tischenko algorithm vs thermodilution.

Table 3—Differences Between the NICO CI and Thermodilution CI Within the CI Ranges

<table>
<thead>
<tr>
<th>CI Ranges by NICO CI</th>
<th>No.</th>
<th>NICO CI, Mean</th>
<th>Thermodilution CI, Mean</th>
<th>Relative Difference, %</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>30</td>
<td>1.278 ± 0.16</td>
<td>1.515 ± 0.35</td>
<td>-12.99</td>
<td>0.0002</td>
</tr>
<tr>
<td>1.5 &lt; CI &lt; 2</td>
<td>98</td>
<td>1.749 ± 0.14</td>
<td>1.876 ± 0.33</td>
<td>-6.65</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2 &lt; CI &lt; 3</td>
<td>220</td>
<td>2.433 ± 0.28</td>
<td>2.392 ± 0.40</td>
<td>3.28</td>
<td>0.0484</td>
</tr>
<tr>
<td>CI &gt; 3</td>
<td>70</td>
<td>3.594 ± 0.57</td>
<td>3.449 ± 0.64</td>
<td>4.44</td>
<td>0.0045</td>
</tr>
</tbody>
</table>
olution, Koobi et al\textsuperscript{28} obtained simultaneous measure-
mements in 74 patients with coronary disease, reaching a bias between the two methods of 0.25 L/min (SD), where the limits of agreement (2 SD) were –1.37 L/min and 1.897 L/min, respectively. Using the NICaS apparatus, Cohen et al\textsuperscript{14} compared its performance against thermodilution by measuring the CO in patients undergoing CABG operations, with a correlation of \( r = 0.91 \). Thus, this six-clinical series, which included 274 subjects, revealed similar correlation coefficients between the compared methods, just as in the present series. Moreover, in none of these publications did the authors express reservations about the performance of the WBEB. There were, nonetheless, two publications in which no correlation was found between WBEB and thermodilution; in both instances, the underlying clinical conditions are listed in the exclusion criteria of the NICO. Lamberts et al\textsuperscript{29} compared the original Tischenko equation with dye dilution CO in 10 patients, 4 of whom had significant aortic regurgitation and 1 had coarctation of the aorta. The NICO apparatus cannot measure the CO in such conditions.

Imhoff et al\textsuperscript{30} compared the NICO apparatus against thermodilution in 22 postpancreatectomy or esophagectomy patients. They were all managed postoperatively by Swan-Ganz catheters for boosting the oxygen delivery to 600 mL/min/m\(^2\) and the CI to 4.5 L/min/m\(^2\). Hence, in these patients the radical surgical procedures were followed by massive intercompartmental volume shifts due to IV administration of up to 6 L per 24 h of crystalloids and plasma, often accompanied by massive peripheral edema. In such hemodynamic situations, the baseline impedance should properly become distorted, preventing an accurate measurement of the systolic impedance variation.

In the present study, the agreement between NICO CI and thermodilution CI as tested by comparisons of the means is highly significant. The similarity between the means in the entire cohort as well as in each diagnostic group, together with the relatively large sample size, further endorses the significance of the results.

The mean difference between the NICO and thermodilution in the entire sample range was 0.0009 L/min (Table 2, Fig 4), ranging from 0.0040 to 0.0271 L/min in the three diagnostic groups. This disparity is smaller than the level of accuracy of thermodilution, which is defined to a 15% range.\textsuperscript{31} Linear regression applied to the data revealed that the line slope was close to 1.00 in the entire sample range and in each specific diagnostic group. There were no significant differences between the slopes and the intercepts of the three diagnostic groups. This indicates that the relation between the NICO and thermodilution is similar in all diagnostic groups. Following the recommendations of Bland and Altman,\textsuperscript{20} the differences between the two measurements were plotted against their means. This plot demonstrates that the range of differences is similar along the different values of the average.

Although the main purpose of this work was to compare the performance of the NICO vs thermodilution, following the suggestion in previous studies\textsuperscript{31–35} that thermodilution tends to overestimate CI when low and underestimate it when high, we have compared the NICO CI and thermodilution CI in the different CI ranges. The results of this analysis have shown that when the CI was < 2 L/min/m\(^2\), the thermodilution results were higher than the NICO results; when the CI was > 3 L/min/m\(^2\), the thermodilution results were slightly lower than the NICO results (Table 3). As a consequence, the differences of the hemodynamic responses to vasodilation therapy may be better depicted by the NICO when compared with thermodilution (Fig 5, bottom).

The link between a low CI and a higher thermodilution readout, and between a higher CI with a low thermodilution readout, is also expressed in the stability of the range of differences along the different values of the average (Fig 4). Furthermore, the

### Table 4—Trend Follow-up of the NICO CI and Thermodilution CI During the Five Operative and Postoperative Stages

<table>
<thead>
<tr>
<th>Method</th>
<th>NICO CI Mean (SD)</th>
<th>Thermodilution CI Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup A (n = 25)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.28 (0.87)</td>
<td>2.25 (0.83)</td>
</tr>
<tr>
<td>2</td>
<td>2.09 (0.38)</td>
<td>2.09 (0.37)</td>
</tr>
<tr>
<td>3</td>
<td>2.17 (0.62)</td>
<td>2.26 (0.69)</td>
</tr>
<tr>
<td>4</td>
<td>2.72 (0.79)</td>
<td>2.54 (0.81)</td>
</tr>
<tr>
<td>5</td>
<td>2.56 (0.74)</td>
<td>2.46 (0.85)</td>
</tr>
<tr>
<td><strong>Subgroup A + B (n = 51)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.22 (0.69)</td>
<td>2.22 (0.67)</td>
</tr>
<tr>
<td>2</td>
<td>2.14 (0.57)</td>
<td>2.14 (0.52)</td>
</tr>
<tr>
<td>3</td>
<td>2.15 (0.68)</td>
<td>2.22 (0.70)</td>
</tr>
<tr>
<td>4</td>
<td>2.80 (0.74)</td>
<td>2.61 (0.77)</td>
</tr>
<tr>
<td>5</td>
<td>2.61 (0.83)</td>
<td>2.53 (0.87)</td>
</tr>
</tbody>
</table>
almost identical results of thermodilution and the NICO observed in the CI \( \text{CI} < 2 \) to \( \text{CI} < 3 \) range (Table 3) yield a mutual endorsement of the technical operations of the measuring devices by the two methods. It should also be noted that the two methods switch their interrelations at CI of approximately \( \text{CI} \approx 2.5 \) L/min/m\(^2\) (Fig 5, bottom), which is close to the lower border.

Limitations of the NICO

**Diseases of the Aorta and Aortic Valve**: The NICO measures the SV of the aorta and its derivatives (including the peripheral arteries). For determining the CO, SV is multiplied by the heart rate. Any aberration in the hemodynamics of the aorta and its derivatives may interfere with the proper function of
the NICO. In aortic insufficiency, the SV is pathologically increased. Coarctation and significant aneurysms of the aorta and also severe peripheral arterial disease may produce inaccurate readouts of the SV.

Significant (+3/+4) Peripheral Edema: In significant edema, the baseline impedance of the body is occasionally very low, currently interfering with the accuracy of the results.

Shunts: Our experience with congenital heart disease is limited, but we assume that since there is no complete separation between the two circulations the impedance technique may not be appropriate.

Restlessness: The impedance test requires a motionless condition; in addition, restlessness is associated with fluctuating activation of the sympathetic system, resulting in an unstable hemodynamic state.

Arrhythmias: In most cases, there is no interference with the CO measurement, although when associated with a heart rate > 150 beats/min or when there is a severe disarray of the complexes (ECG and SV), the results may become inaccurate, as may be for any technique measuring CO.

Resections: Major abdominal and thoracic surgical resections, especially those that include major rapid shifts in fluid distribution between the intravascular and extravascular space.

CONCLUSIONS

In spite of these limitations, the NICO apparatus offers a simple, noninvasive, reliable, and continuous measurement of CI in cardiac patients with particular emphasis on CHF. This measurement combined with MAP measurement and the calculation of Cpi and SVRi is destined to become a safe, simple, rapid, noninvasive method for evaluating and treating primarily coronary patients sustaining chronic and acute exacerbations of CHF.

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Gad Cotter, Yaron Moshkovitz, Edo Kaluski, Amram J. Cohen, Hilton Miller, Daniel Goor and Zvi Vered
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The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure

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Abstract

Objective: Conventional hemodynamic indexes (cardiac index (CI), and pulmonary capillary wedge pressure) are of limited value in the diagnosis and treatment of patients with acute congestive heart failure (CHF). Patients and methods: We measured CI, wedge pressure, right atrial pressure (RAP) and mean arterial blood pressure (MAP) in 89 consecutive patients admitted due to acute CHF (exacerbated systolic CHF, n = 56; hypertensive crisis, n = 5; pulmonary edema, n = 11; and cardiogenic shock, n = 17) and in two control groups. The two control groups were 11 patients with septic shock and 20 healthy volunteers. Systemic vascular resistance index (SVRi) was calculated as SVRi = (MAP − RAP)/CI. Cardiac contractility was estimated by the cardiac power index (Cpi), calculated as CI × MAP. Results and discussion: We found that CI < 2.7 l/min/m² and wedge pressure > 12 mmHg are found consistently in patients with acute CHF. However, these measures often overlapped in patients with different acute CHF syndromes, while Cpi and SVRi permitted more accurate differentiation. Cpi was low in patients with exacerbated systolic CHF and extremely low in patients with cardiogenic shock, while SVRi was increased in patients with exacerbated systolic CHF and extremely high in patients with pulmonary edema. By using a two-dimensional presentation of Cpi vs. SVRi we found that these clinical syndromes can be accurately characterized hemodynamically. The paired measurements of each clinical group segregated into a specific region on the Cpi/SVRi diagnostic graph, that could be mathematically defined by a statistically significant line (Lambda = 0.95). Therefore, measurement of SVRi and Cpi and their two-dimensional graphic representation enables accurate hemodynamic diagnosis and follow-up of individual patients with acute CHF.

Keywords: Cardiac power; Vascular resistance; Acute congestive heart failure

1. Introduction

Acute congestive heart failure (CHF) is a common disease, accounting for over 700 000 annual admissions to hospitals in the USA alone. We have recently suggested that this disease can be divided into four major clinical syndromes [1]: (1) pulmonary edema, (2) cardiogenic shock, (3) hypertensive (HTN) crisis and (4) exacerbated systolic CHF. However, the diagnosis of these clinical syndromes of acute CHF may be difficult, due to an overlap in symptoms and signs among the different syndromes as well as lack of objective criteria for their diagnosis. For example, both cardiogenic shock and pulmonary edema patients present with severe circulatory and respiratory distress and in both cases CI is low and wedge pressure is high. However, these two clinical syndromes have a completely different course (mortality rates at 1-month in the SHOCK study [2] were approximately 60%, compared with a mortality rate of approximately 10% for pulmonary edema patients during the first 30 days in the RITZ-5 study [3]). In addition, the pathophysiology of the two clinical sy-
dromes is completely different and their treatment is almost opposite. Moreover, even the diagnosis of acute CHF is sometimes difficult, due to an overlap in signs and symptoms with those of acute exacerbations of obstructive or restrictive lung diseases and the occasional difficulty in differentiation between septic and cardiogenic shock.

Measurement of invasive hemodynamic variables, including CI and pulmonary capillary wedge pressure has been used in patients with acute decompensated and chronic compensated CHF, as well as cardiogenic shock, for more than two decades. However, despite extensive experience and numerous studies, no specific diagnostic criteria or accurate cut-off points have been determined [2,4–6]. In some studies, trends and changes in CI and wedge pressure have been used, however, no reproducible criteria for diagnosis and follow-up could be established.

Cardiac power, an index of cardiac contractility, is calculated based on the classical physical rule of fluids, i.e. power = flow × pressure, hence cardiac power index (Cpi) is the product of simultaneously measured mean arterial blood pressure (MAP) and cardiovascular flow (CI): 

$$Cpi = MAP \times CI \times 0.0022$$

The units are W/m². Cpi has been used extensively during recent years to evaluate patients with chronic and acute CHF. In three separate studies, Marmor and Schneeweiss [7], Tan et al. [8] and Cohen-Solal et al. [9] have demonstrated that Cpi increases during exercise (cardiac power reserve) and is the strongest predictor of outcome in patients with chronic CHF, stronger than O₂ consumption and echocardiographic ejection fraction. We have previously demonstrated [1] that in patients with exacerbated systolic CHF, baseline Cpi at admission is the strongest predictor of short- and long-term outcome. On the other hand, the main event preceding recurrent worsening heart failure was a steep increase in SVRi. In a recent analysis, we have also found that Cpi at baseline and during follow-up was the strongest predictor of outcome in a large cohort of cardiogenic shock patients (unpublished data).

The main hypothesis of the present study was that in patients with acute CHF, as Cpi decreases, SVRi should concomitantly increase. Therefore, for each Cpi decrease the SVRi increase may be adequate, too high or too low and, thus, Cpi/SVRi coupling may characterize the clinical-hemodynamic state. Therefore, in the present study, we examined in a two-dimensional representation, the relationship between changes in Cpi (pump work) and SVRi (resistance or work load) in the four clinical syndromes of acute CHF, (i.e. exacerbated systolic CHF, cardiogenic shock and HTN crisis), as well as in two control groups: (i.e. septic shock and normal subjects).

2. Methods

2.1. Inclusion criteria

Hemodynamic data was obtained in all patients undergoing right heart catheterization who were diagnosed by the usual clinical criteria as having acute CHF. We also enrolled two control groups: these were 11 patients with septic shock and 20 healthy volunteers.

2.2. Exclusion criteria

Significant valvular disease, significant brady- or tachy-arrhythmias or renal failure (creatinine > 2.5 mg/dl).

2.3. Clinical diagnosis criteria

2.3.1. Exacerbated systolic CHF

Patients admitted due to signs and symptoms of worsening CHF, who were in a stable clinical condition; not fulfilling the criteria for cardiogenic shock, pulmonary edema and HTN crisis and who had EF < 35% on echocardiography. (The echocardiographic criteria were used to ensure that the symptoms of dyspnea were indeed due to acute CHF.)

2.3.2. Pulmonary edema

Patients admitted due to clinical symptoms and signs of acute pulmonary congestion accompanied by findings of lung edema on chest X-ray who had severe respiratory distress accompanied by O₂ saturation < 90% in room air by pulse oxymetry during the invasive measurements.

2.3.3. Cardiogenic shock

Systolic blood pressure < 100 mmHg for at least 1 h, not responsive to percutaneous revascularization, mechanical ventilation, intra-aortic balloon-pump (IABP), IV fluid administration and dopamine of at least 10 μg/kg/min and accompanied by signs of end organ hypoperfusion but not accompanied by fever > 38° or a systemic inflammatory syndrome.

2.3.4. HTN crisis

Patients with signs and symptoms of acute CHF accompanied by high blood pressure (MAP > 130 mmHg during invasive measurements); not fulfilling the criteria for pulmonary edema.

2.3.5. Septic shock

Systolic blood pressure < 100 mmHg accompanied by fever > 38°, systemic inflammatory syndrome and signs of end organ hypoperfusion for at least 3 h not responsive to IV fluids and IV dopamine of at least 10 μg/kg/min. No evidence of an acute cardiac event.
2.4. Assessment of hemodynamic variables

Prior to enrolment in this study all patients gave written informed consent. The study protocol was approved by the local ethics review board. In all patients the hemodynamic variables were obtained during right heart catheterization using a Swan–Ganz catheter placed under fluoroscopic guidance. All measurements were obtained while patients were at least 30 s without IABP while on the same treatment used at the time the clinical diagnosis was made. Measurement of hemodynamic variables was performed at least 6 h after the last intake of an oral drug and 2 h after intravenous drug therapy.

CI was measured by thermodilution, using the mean of at least three consecutive measurements within a range of <15%. In normal subjects, right heart catheterization was not performed for ethical reasons. The values used in this cohort were obtained by standard noninvasive cuff blood pressure measurement and evaluation of CI by the FDA approved NICaS™ 2001, a noninvasive continuous cardiac output monitor [10]. Therefore, wedge pressure was not assessed in normal subjects. Instead, we used standard values documented in the literature [11].

2.5. Calculation of hemodynamic variables

Cpi was determined as MAP×CI×0.0022 and SVRi was determined as (MAP−right atrial pressure (RAP))/CI. As RAP was not measured in normal subjects, it was estimated to be 10% of MAP [11].

2.6. Echocardiographic evaluation

All patients underwent routine echocardiographic evaluation after initial stabilization. This included visual estimation of cardiac function, evaluation of valvular function and gross estimation of signs of diastolic dysfunction.

2.7. Statistical methods

The five clinical groups were compared with regard to all parameters using a one-way analysis of variance (ANOVA). Therafter, the Ryan–Einot–Gabriel–Welsch Multiple Range Test was used for pair-wise comparisons between the groups, while Dunnett’s t-test was used to compare all groups to the healthy controls.

A one-sample t-test was performed to compare mean wedge pressure in each group to the wedge pressure of normal people (<12 mmHg).

In order to determine the usefulness of the hemodynamic parameters to discriminate between the clinical syndromes, ROC curves, derived from a logistic regression model were applied to the data to determine the best cut-off point for the various parameters, in terms of highest sensitivity and specificity.

2.8. Cpi/SVRi diagnostic graph

A classification rule was developed using second order discriminant analysis. The normality of the distribution of Cpi and SVRi was examined by the Wilk-Shapiro test. Due to the skewness of the data in some groups, both variables (Cpi and SVRi) were transformed into log scale for better approximation to normality. Since the number of patients with HT crisis was small they were considered together with the exacerbated systolic CHF group. The classification used two steps. In the first step the rule separated three classes: septic shock, cardiogenic shock and a combined group, which included the normal controls, compensated CHF and pulmonary edema patients (N–C–P). If, after the first step the patient was defined as N–C–P, the second classification was used to differentiate between the normal, exacerbated systolic CHF and pulmonary edema subgroups.

All calculations were performed by SAS 6.12 (SAS Institute Inc., Cary, NC) using procedures FREQ, MEANS, GLM, DISCRIM, G PLOT.

Alfa level: 5%.

3. Results

Eighty-nine consecutive patients admitted due to acute CHF and LV dysfunction (exacerbated systolic CHF, n = 56; pulmonary edema, n = 11; cardiogenic shock, n = 17; and HTN crisis, n = 5) as well as 11 patients with septic shock and 20 healthy volunteers were enrolled in the study. Baseline characteristics of the different patient groups are presented in Table 1. The mean CI, wedge pressure, MAP, SVRi and Cpi according to clinical diagnosis are presented in Table 2.

3.1. Hemodynamic variables

3.1.1. Cardiac index (Fig. 1)

The average values of CI were significantly lower in patients with acute CHF and higher in patients with septic shock. ROC analysis found a cut-off point of CI < 2.7 1/min/m² useful for the determination that a patient had acute CHF (sensitivity = 1, specificity = 0.99). However, values between 1.2 and 2.7 1/min/m² could be found in all patients with exacerbated systolic CHF and HTN crisis as well as 73% of patients with pulmonary edema and 47% of patients with cardiogenic shock. Moreover, the mean CI of patients with pulmonary edema and cardiogenic shock was found to be almost identical (1.4 ± 0.4 vs. 1.35 ± 0.7 1/min/m², P = ns).
3.1.2. Mean arterial blood pressure

By virtue of their clinical definition, the average values of MAP were higher in patients with HTN crisis and lower in those with septic and cardiogenic shock. However, large areas of overlap were found between pulmonary edema, HTN crisis and exacerbated systolic CHF (MAP > 100 mmHg) and between exacerbated systolic CHF, cardiogenic shock and septic shock (MAP < 100 mmHg).

3.1.3. Pulmonary capillary wedge pressure (Fig. 2)

The mean wedge pressure was significantly higher in patients with acute CHF and lower in patients with septic shock. The analysis was based on normal values reported in the literature (< 12 mmHg [8]) (P = 0.001). However, the overlap of wedge pressure in the different acute CHF groups was extensive. Values between 12 and 38 mmHg were found in 82, 64, 76 and 18% of patients with exacerbated systolic CHF, pulmonary edema, cardiogenic shock and septic shock, respectively.

3.1.4. Cardiac power index (Fig. 3)

Compared with the normal controls, the mean values of Cpi were low in patients with exacerbated systolic CHF and pulmonary edema and extremely low in

---

Table 1
Baseline characteristics of the five patient groups

<table>
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<tr>
<th></th>
<th>Normal volunteers</th>
<th>Septic shock</th>
<th>Exacerbated systolic CHF</th>
<th>Pulmonary edema</th>
<th>Cardiogenic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>12:8</td>
<td>7:4</td>
<td>51:10</td>
<td>5:6</td>
<td>11:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60±8</td>
<td>55±11</td>
<td>69±10</td>
<td>73±12</td>
<td>67±11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79±14</td>
<td>77±10</td>
<td>72±8</td>
<td>70±9</td>
<td>80±14</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.92±0.22</td>
<td>1.91±0.23</td>
<td>1.88±0.21</td>
<td>1.81±0.24</td>
<td>1.92±0.24</td>
</tr>
<tr>
<td>IHD (%)</td>
<td>0</td>
<td>18</td>
<td>79</td>
<td>73</td>
<td>100</td>
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<tr>
<td>Previous MI</td>
<td>0</td>
<td>9</td>
<td>62</td>
<td>55</td>
<td>18</td>
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<tr>
<td>EF (%)</td>
<td>55±3</td>
<td>46±9</td>
<td>27±5</td>
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<td>Diabetes mellitus (%)</td>
<td>20</td>
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<td>66</td>
<td>66</td>
<td>53</td>
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<tr>
<td>Current smokers (%)</td>
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<td>Hypertension (%)</td>
<td>50</td>
<td>45</td>
<td>56</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>65</td>
<td>73</td>
<td>66</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>Baseline creatinine</td>
<td>135±75</td>
<td>124±55</td>
<td>144±81</td>
<td>110±47</td>
<td></td>
</tr>
<tr>
<td>Medications for CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>0</td>
<td>0</td>
<td>82</td>
<td>91</td>
<td>6</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>0</td>
<td>0</td>
<td>33</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>ACE inhibitor/All blocker (%)</td>
<td>0</td>
<td>9</td>
<td>95</td>
<td>91</td>
<td>29</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>0</td>
<td>9</td>
<td>62</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>Nitrate (%)</td>
<td>0</td>
<td>0</td>
<td>41</td>
<td>55</td>
<td>0</td>
</tr>
</tbody>
</table>

IHD, ischemic heart disease; MI, myocardial infarction; EF, ejection fraction; CHF, congestive heart failure.

---

Table 2
Baseline distribution of the various hemodynamic parameters in the six diagnosis groups presented as means and S.D.

<table>
<thead>
<tr>
<th></th>
<th>Exacerbated systolic CHF</th>
<th>Pulmonary edema</th>
<th>Cardiogenic shock</th>
<th>HTN crisis</th>
<th>Septic shock</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
<td>11</td>
<td>17</td>
<td>5</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>SVRi</td>
<td>44.9±8.0</td>
<td>88.2±16.7</td>
<td>55.6±31.1</td>
<td>54.3±3.2</td>
<td>11.8±1.1</td>
<td>25.2±4.1</td>
</tr>
<tr>
<td>Cpi</td>
<td>0.47±0.13</td>
<td>0.4±0.13</td>
<td>0.22±0.08</td>
<td>0.75±0.04</td>
<td>0.8±0.13</td>
<td>0.62±0.08</td>
</tr>
<tr>
<td>Wedge</td>
<td>25.5±7.2</td>
<td>32.7±8.6</td>
<td>23.3±6.5</td>
<td>28.5±4.5</td>
<td>11.4±7.7</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>101±18</td>
<td>131.4±12.7</td>
<td>72.2±11.3</td>
<td>150±10.5</td>
<td>68.2±5.4</td>
<td>87.9±8.85</td>
</tr>
<tr>
<td>CI</td>
<td>2.06±0.33</td>
<td>1.37±0.32</td>
<td>1.42±0.64</td>
<td>2.24±0.37</td>
<td>5.2±0.5</td>
<td>3.2±0.36</td>
</tr>
</tbody>
</table>

The results of the ANOVA for comparisons between exacerbated systolic CHF (CHF), pulmonary edema (edema) and cardiogenic shock (shock) patients

<table>
<thead>
<tr>
<th>Parameter groups</th>
<th>P-value for overall group comparison (ANOVA)</th>
<th>P-value for paired comparisons (Ryan–Einot–Gabriel–Welsch multiple range test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHF-edema</td>
<td>CHF-shock</td>
</tr>
<tr>
<td>CI</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>0.0037</td>
<td></td>
</tr>
<tr>
<td>SVRi</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Cpi</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

N, number of patients; SVRi, systemic vascular resistance index (wood m²); Cpi, cardiac power index (mmHg l/min/m²); wedge, pulmonary capillary wedge pressure (mmHg); MAP, mean arterial blood pressure (mmHg); CI: cardiac index (l/min/m²). +, Significant group difference.
patients with cardiogenic shock. However, some overlap was encountered among the five groups.

3.1.5. Systemic vascular resistance index (Fig. 4)

Average values of SVRi were significantly higher in all patients with exacerbated systolic CHF, HTN crisis and extremely high in patients with pulmonary edema, but were lower in patients with septic shock. SVRi was found to be instrumental in the diagnosis of pulmonary edema. All patients with this clinical syndrome had SVRi $> 67$ wood m$^{-2}$, while SVRi values in all other patient groups, as well as in normal subjects, were significantly lower than this value.

3.2. Cpi/SVRi diagnostic graph (Fig. 5)

Since the number of patients with HTN crisis was small they were included in the exacerbated systolic CHF group. Distributions of SVRi and Cpi were highly skewed. The normality of the distribution of Cpi and SVRi was assessed by the Wilk–Shapiro test. The results showed that Cpi and SVRi distribution was not normal for the normal volunteers ($P = 0.03$ for Cpi), the exacerbated systolic CHF patients ($P = 0.007$ for Cpi and $P = 0.04$ for SVRi) and the cardiogenic shock patients ($P = 0.016$ for SVRi).

However, log(SVRi) and log(Cpi) were normally distributed ($P = ns$ for both Cpi and SVRi in all patient groups). Therefore, for the analysis we used only log
Table 3
Number of observations classified into the correct clinical group using log(Cpi) or log(SVRi) only

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiogenic shock</th>
<th>Exacerbated systolic CHF</th>
<th>Normal</th>
<th>Pulmonary edema</th>
<th>Septic shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>Number of observations classified into appropriate groups: classification using log(Cpi) only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Exacerbated systolic CHF</td>
<td>1</td>
<td>44</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>61</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

(b) Number of observations classified into appropriate groups using log(SVRi) only

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiogenic shock</th>
<th>Exacerbated systolic CHF</th>
<th>Normal</th>
<th>Pulmonary edema</th>
<th>Septic shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Exacerbated systolic CHF</td>
<td>0</td>
<td>58</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>3</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 4
Number of observations classified into the correct clinical group using log(SVRi) and log(Cpi)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiogenic shock</th>
<th>Exacerbated systolic CHF</th>
<th>Normal</th>
<th>Pulmonary edema</th>
<th>Septic shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Exacerbated systolic CHF</td>
<td>0</td>
<td>60</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
For our data \( \Lambda(R/C) = 0.95 \) (S.D. (\( \Lambda \)) = 0.03) which corresponds to three errors of classification according to the classification rule, instead of 59 errors of classification according to the prior probabilities.

4. Discussion

During the last decade the pathogenesis of CHF has become clearer. The emphasis on cardiac performance as the sole pathogenic mechanism of CHF has changed to a more comprehensive understanding of the importance of the interaction between cardiac contractility, neurohormonal and inflammatory control mechanisms and vascular resistance. We have recently studied the treatment of the acute CHF syndromes of pulmonary edema and cardiogenic shock and have shown that treatment modalities with significant vascular effect are effective in improving the outcome of these patients [14–16]. These findings substantiated our theory that the SVRi reaction to the decrease in Cpi determines the hemodynamic condition and clinical syndrome of patients with acute CHF.

4.1. Classical hemodynamic monitoring

CI is the most popular parameter used in invasive hemodynamic monitoring of patients with acute CHF. However, the results of the present study as well as previous ones [2,4–6] show that CI measurements are not sufficient for the diagnosis and treatment titration in patients with acute CHF. This might be explained by the fact that CI is actually a measure of cardiovascular flow. Hence, CI (flow) is determined by both cardiac contractility and vascular resistance and, therefore, may change dramatically when Cpi decreases but also with even mild changes in SVRi. Pulmonary capillary wedge pressure is the second most popular hemodynamic variable used in hemodynamic monitoring, since it represents the hydraulic pressure transmitted backwards to the pulmonary circulation, and hence, is an important determinant of pulmonary edema. However, wedge pressure cannot be used for the exact diagnosis of the different clinical syndromes of acute CHF, due to the extent of overlapping values between patients with exacerbated systolic CHF, HTN crisis and even cardiogenic shock.

4.2. Cpi and SVRi and their role in patients with acute CHF

Cpi as measured in the present study [1,8,9] is a simplified version of a previously described method of measuring cardiac contractility [7]. This value is derived from the entire cardiac cycle (instead of instantaneous measurements) and is the product of the mean pressure and flow. Cpi has been shown to be the best predictor of outcome in chronic CHF patients [7–9], exacerbated systolic CHF [1] and cardiogenic shock (unpublished data).

In the present study, we found that in patients with exacerbated systolic CHF either Cpi was decreased or SVRi was increased or both changes occurred. In a previous study, we described the sequence of events leading to acute heart failure [1]. In most patients an acute CHF event starts with a progressive decrease in cardiac contractility and power (Cpi). Thereafter, as Cpi decreases, neurohormonal vascular control mechanisms are activated and SVRi increases [1,17]. This increase is a very important protective mechanism for two reasons:

1. The increase in SVRi in the face of decreased contractility maintains blood pressure and the perfusion of vital organs.
2. This afterload increase (while within certain limits) may improve contractility (possibly through the Gregg phenomenon [18]), which may account for the ‘normal’ Cpi we observed in some patients with echocardiographically demonstrated systolic dysfunction.

However, SVRi increase in response to Cpi decrease is not uniform. It can be appropriate (thus, leading to a compensated state), inappropriately low (thus, leading to low blood pressure, forward hypoperfusion and cardiogenic shock) or inappropriately high (thus, inducing an extreme afterload mismatch leading to pulmonary edema).

Indeed, in the present study, in patients who were clinically diagnosed as cardiogenic shock, Cpi was found to be extremely low, however, SVRi was only slightly increased. This imbalance between very low Cpi and inadequate increase in SVRi probably resulted in low blood pressure and decreased perfusion pressure of vital organs including the heart. This decrease in coronary perfusion might lead to decreased contractility inducing a vicious cycle of low contractility, low SVRi and reduced perfusion. For this reason, in a previous study [15] we treated patients with cardiogenic shock, by short-term administration of a peripheral vasoconstrictor (L-NMMA) with good clinical response.

On the other hand, in patients diagnosed as pulmonary edema, despite what appears to be a similar clinical presentation (pulmonary congestion, clammy extremities, low CI and high wedge pressure), the pathophysiological findings as well as the treatment, are the complete opposite. In patients with pulmonary edema, we measured Cpi values similar to those in exacerbated systolic CHF, however, SVRi was markedly increased. These findings are collaborated by the study by Gandhi et al. [19] showing a dramatic increase in blood pressure in patients with pulmonary edema. We hypothesize that this increase in SVRi might be an inappropriate
response, related to neurohormonal, endothelial and perhaps inflammatory activation [20,21]. This remarkable increase in SVRi induces an afterload mismatch, reducing CI and increasing intracardiac pressures, LVEDP and wedge pressure, resulting in the severe congestive symptoms of pulmonary edema. Therefore, as previously suggested [14,16,22,23], vasodilator treatment is effective in the treatment of pulmonary edema.

4.3. Two-dimensional graphic representation of Cpi/SVRi and its use in the treatment of cardiogenic shock and pulmonary edema

In the present study, we found that when plotting on a two-dimensional graph the results of Cpi and SVRi for individual patients, each clinical group of patients could be segregated into a specific area on the graph which could be bound by a mathematically defined line (Fig. 5). This graph enables exact clinical diagnosis of most (95%) patients with exacerbated systolic CHF, pulmonary edema, HTN crisis, cardiogenic shock and septic shock. Of course, the boundaries on the graph are somewhat arbitrary, since the definitions of the syndromes are as used by the medical community, and therefore, arbitrary. However, this two-dimensional representation enables a better understanding of the pathophysiology of the different syndromes of acute CHF.

We believe that this new and simple diagnostic tool may become useful for the initial evaluation of acutely decompensated patients, while the clinical diagnosis has not yet been established and initiation of appropriate disease-specific treatment is crucial. This might become even more important with the advent of new devices that accurately measure CI noninvasively. The combination of noninvasive MAP and CI measurement, Cpi and SVRi calculation and the two-dimensional Cpi/SVRi graph could enable improved diagnosis of patients even in paramedic units and in emergency rooms.

Furthermore, this method may become an important tool for monitoring the patients’ response to treatment.

4.4. Limitations

The results of the present study are based on a relatively small number of patients, and therefore, need confirmation by prospectively evaluating a larger group of patients with acute CHF. Also, the measurements in the present study were performed by thermilution, which has an inherent 10–15% deviation in measuring cardiac output. Finally, cardiac power calculations were performed using whole-cycle measurements (cardiac output and MAP). Although we recognize that the cardiovascular system operates in a pulsatile manner, cardiac power calculated according to the methodology used in the present study has previously been shown to be a useful measure of cardiac contractility and contractility reserve in chronic and acute CHF as well as in cardiogenic shock.

Appendix A: Classification rule

Given a patient with measured values of SVRi and Cpi, the classification may be performed either (A) through special calculations or (B) using the ‘Graph for classification of CHF patients (Cpi/SVRi graph)’.

(A) Classification using calculations

Step 1. Calculate three values $v_1$, $v_2$, $v_3$ according to the formulas below:

$v_1 = LCPi^2 \times 21.54 + 2 \times LCPi \times LSVRi \times 10.61 + LSVRi^2 \times 59.44 - LCPi \times 305.24 - LSVRi \times 417.70 + 1408.89$

$v_2 = LCPi^2 \times 10.12 + 2 \times LCPi \times LSVRi \times 5.67 - LSVRi^2 \times 4.99 - LCPi \times 135.81 - LSVRi \times 90.11 + 482.61$

$v_3 = LCPi^2 \times 7.29 + LCPi \times LSVRi \times 2.57 + LSVRi^2 \times 4.09 - LCPi \times 97.41 - LSVRi \times 58.22 + 368.16$

Classify the patient into the group ‘Septic shock’, if $v_1$ is the smallest value into the group ‘Cardiogenic Shock’, if $v_2$ is the smallest value if $v_3$ is the smallest value go to step 2

Step 2. Calculate three values $v_4$, $v_5$, $v_6$ according to the formula below:

$v_4 = LCPi^2 \times 6.45 - 2 \times LCPi \times LSVRi \times 0.45 + LSVRi^2 \times 16.01 - LCPi \times 65.16 - LSVRi \times 116.53 + 391.67$

$v_5 = LCPi^2 \times 17.75 + 2 \times LCPi \times LSVRi \times 26.56 + LSVRi^2 \times 54.27 - LCPi \times 420.26 - SVRi \times 758.55 + 2775.78$

$v_6 = LCPi^2 \times 32.95 + 2 \times LCPi \times LSVRi \times 3.09 + LSVRi^2 \times 19.72 - LCPi \times 390.74 - SVRi \times 161.49 + 1355.57$

Classify the patient into the group ‘Exacerbated Systolic CHF’, if $v_4$ is the smallest value among $v_4$, $v_5$, $v_6$ and $SVRi < \log(67)$ into the group ‘Pulmonary Edema’, if $v_5$ is the smallest value among $v_4$, $v_5$, $v_6$ and $SVRi > \log(67)$ into the group ‘Normal’, if $v_6$ is the smallest value among $v_4$, $v_5$, $v_6$

The value of $SVRi = 67$ was used to separate patients with exacerbated systolic CHF from patients with pulmonary edema since the group of ‘pulmonary edema’ was rather small and by classifying these patients according to the usual rule we did not receive a separating line for Cpi measures $> 250$ W/m².
(B) Classification using the diagnostic graph

Put the point (CPi, SVRi) on the diagnostic graph Fig. 5 or point (LCPi, LSVRi) and classify the patient according to the area of the graph, where the point is located.

References


Beyond the Four Quadrants: The Critical and Emerging Role of Impedance Cardiography in Heart Failure

Heart failure (HF) is a disorder characterized by hemodynamic abnormalities including a reduction in the heart's ability to deliver oxygenated blood to the body. HF is also associated with important neurohormonal abnormalities, including activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and their resulting effects on the heart and vascular endothelium. Our understanding of the neurohormonal role in the progression of HF has greatly improved in the past 10 years, and many of the therapies that significantly improve the symptoms and prognosis of patients with HF now target the underlying neurohormonal abnormalities.

As shown in Figure 1, neurohormonal activation can lead to progression of hemodynamic abnormalities resulting in reduced cardiac output (CO); increased filling pressures; and ultimately worsening symptoms of fatigue, dyspnea, and decreased exercise tolerance. Although the neurohormonal mechanisms may cause progression of the disease process, nearly all medications used in HF treatment have demonstrable effects on hemodynamics. Current acute HF treatment is aimed directly at stabilizing and improving a patient's short-term hemodynamic condition; chronic HF treatments can alter short-term and improve long-term hemodynamics.

Specific hemodynamic measurements such as CO and systemic vascular resistance are generally obtained for only the most critically ill HF patients, in large part due to the risk, discomfort, and cost of invasive procedures such as pulmonary artery catheterization. Nonetheless, understanding and measuring the factors that affect CO are central to the assessment, prognosis, and treatment of patients with HF. The four determinants of CO are the rate of the pump (heart rate), the volume of blood available to pump (preload), the pumping strength (contractility), and the force the heart must overcome to pump (afterload, generally approximated by systemic vascular resistance). Symptoms—physical findings like vital signs—and laboratory findings such as blood tests and chest radiographs are imprecise measures of hemodynamic function.

Unfortunately, they are the only data many clinicians have at their disposal when making important decisions in the care of patients with HF.

The direct cost of treating HF is estimated to be $56 billion per year in the United States and the number of HF patients in this country may reach 10 million by 2010. A significant portion of the cost of HF care is the high cost of hospitalizations for patients with acute decompensation. Through careful surveillance of patients with chronic HF using improved methods for measuring hemodynamic and neurohormonal...
status, primary care physicians and cardiologists may be able to intervene in a timely manner and prevent acute episodes leading to hospitalization, major morbidity, or death.

Warner-Stevenson5 has developed and popularized the concept of categorizing HF patients by hemodynamic subset based on perfusion with CO (warm vs. cold) and congestion with pulmonary artery wedge pressure (wet vs. dry). The four quadrants, representing the four hemodynamic classes, are shown in Figure 2. Studies have suggested that these profiles provide a useful framework to risk stratify patients with HF, predict outcomes, and identify therapeutic options. However, this framework is based on invasive pulmonary artery catheterization, with its requisite risk and cost, or on physical examination and patient history, which have been shown to lack sensitivity and specificity, even in the hands of experienced clinicians.6 HF management using hemodynamic subsets could be substantially improved by the existence of more objective data with which to classify patients and evaluate the effectiveness of subsequent pharmacologic and implantable interventions.

Impedance cardiography (ICG) is a noninvasive method of determining hemodynamic status. In the past, studies questioned the reliability of ICG technology,7,8 leading some to conclude that the technology did not have value in clinical decision making. However, refinements in signal processing and CO algorithms have greatly improved the reliability of ICG technology. The latest generation of ICG devices (BioZ ICG Monitor, CardioDynamics, San Diego, CA; and BioZ ICG Module, GE Medical Systems Information Technologies, Milwaukee, WI) are both highly reproducible and accurate in a number of clinical settings, including HF.8-11 A recent search of the literature failed to show a single citation since US Food and Drug Administration 510(k) clearances of these particular devices that suggests they are not valid for clinical applications.

ICG is a form of plethysmography that utilizes changes in thoracic electrical impedance to estimate changes in blood volume in the aorta and changes in fluid volume in the thorax. As shown in Figures 3 and 4, the ICG procedure involves the placement of four dual

### Table 1. Impedance Cardiography Parameters

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ABBREVIATION</th>
<th>MEASUREMENT/CALCULATION</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>SV</td>
<td>VI × LVET × VEPT (Z MARC algorithm)</td>
<td>mL</td>
</tr>
<tr>
<td>Stroke index</td>
<td>SI</td>
<td>SV/body surface area</td>
<td>mL/m²</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>CO</td>
<td>SV × heart rate</td>
<td>L/min</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>CI</td>
<td>CO/body surface area</td>
<td>L/min/m²</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>SVR</td>
<td>([MAP – CVP]/CO) × 80</td>
<td>dyne × s × cm²</td>
</tr>
<tr>
<td>Systemic vascular resistance index</td>
<td>SVRI</td>
<td>([MAP – CVP]/CI) × 80</td>
<td>dyne × s × cm²/m²</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preejection period</td>
<td>PEP</td>
<td>ECG Q wave to aortic valve opening</td>
<td>ms</td>
</tr>
<tr>
<td>Left ventricular ejection time</td>
<td>LVET</td>
<td>Aortic valve opening to closing</td>
<td>ms</td>
</tr>
<tr>
<td>Systolic time ratio</td>
<td>STR</td>
<td>PEP/LVET</td>
<td>No units</td>
</tr>
<tr>
<td>Velocity index</td>
<td>VI</td>
<td>First time derivative_/baseline impedance</td>
<td>1/1000/s</td>
</tr>
<tr>
<td>Acceleration index</td>
<td>ACI</td>
<td>Second time derivative_/baseline impedance</td>
<td>1/100²/s²</td>
</tr>
<tr>
<td>Left cardiac work index</td>
<td>LCWI</td>
<td>(MAP – PCWP) × CI × 0.0144</td>
<td>kg × m/m²</td>
</tr>
<tr>
<td>Fluid Status</td>
<td>TFC</td>
<td>1/baseline impedance</td>
<td>kOhm</td>
</tr>
</tbody>
</table>

VEPT=volume of electrically participating tissue; Z MARC=impedance modulating aortic compliance; CVP=central venous pressure (estimated value of 6 mm Hg); MAP=mean arterial pressure; ECG=electrocardiogram; PCWP=pulmonary capillary wedge pressure (estimated value of 10 mm Hg)
sensors on a patient’s neck and chest. A low-amplitude, high-frequency alternating current is delivered from the four outer sensors and the four inner sensors detect instantaneous changes in voltage. As suggested by Ohm’s law, when a constant current is applied to the thorax, the changes in voltage are directly proportional to the changes in measured impedance. The overall thoracic impedance, called base impedance ($Z_0$), is the sum of the impedances of the components of the thorax, including fat, cardiac and skeletal muscle, lung and vascular tissue, bone, and air. Changes from $Z_0$ occur due to changes in lung volumes with respiration and changes in the volume and velocity of blood in the great vessels during systole and diastole. The rapidly changing component of chest impedance ($\Delta Z$) is filtered to remove the respiratory variation, leaving the impedance changes due to ventricular ejection. Figure 5 details the elements contributing to $Z_0$ and $\Delta Z$, and Figure 6 illustrates how the first derivative of the impedance waveform ($\Delta Z/\Delta t$) is used with an electrocardiogram to determine the beginning of electrical systole, aortic valve opening, maximal deflection of the $\Delta Z/\Delta t$ waveform, and the closing of the aortic valve. From these fiducial points, a variety of measured and calculated parameters (Table I) are continuously displayed on the ICG device screen for monitoring purposes, or in a printed report for review (Figure 7).

The hemodynamic parameters derived from ICG can aid in the diagnostic and prognostic evaluation of patients with HF. Using ICG, a clinician is able to evaluate direct or indirect measures of each of the four major determinants of CO (preload, afterload, contractility, and heart rate). Figure 8 is a conceptual diagram of CO and its determinants, ICG parameters associated with the determinants, and the effects of pharmacologic agent classes on each determinant. Due to greater acceptance of ICG in clinical and research settings, clinicians are now able to use ICG-derived hemodynamic data to help decide when to initiate and titrate these types of medications. A summary of applications of ICG in HF is presented in Table II, demonstrating its broad clinical applicability.

In this supplement to Congestive Heart Failure, we seek to further define the role of ICG through a series of original contributions. The study by

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**Table II. Summary of Impedance Cardiography Applications in Heart Failure**

<table>
<thead>
<tr>
<th>APPLICATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment and diagnostic</td>
<td>Establish baseline hemodynamics</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Emergency department values predictive of length of stay and hospital charges</td>
</tr>
<tr>
<td>Treatment</td>
<td>Determine stability for initiation and up-titration of β-blocker and ACE-inhibitor therapy</td>
</tr>
</tbody>
</table>

**NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; LVAD=left ventricular assist device**

Yung et al. (p. 7) validates the accuracy of ICG in patients with pulmonary hypertension by comparing ICG to both direct Fick method and thermodilution CO. In doing so, the authors demonstrate the potential hazard of using thermodilution as the only reference standard for CO measurement. Parrott et al. (p. 11) compare changes in ejection fraction by echocardiography to changes in ICG parameters in established HF patients. Their findings demonstrate the ability of ICG to simply and cost-effectively identify changes in ventricular function. While pulmonary artery catheterization in patients with HF has been criticized and is largely unproven by clinical trial, an estimated 2 million such catheters are sold worldwide each year. Parrott et al. (p. 11) illustrate the role of ICG in the differential diagnosis of patients with dyspnea. Although B-type natriuretic peptide testing has gained wide attention recently as an aid to diagnose HF in the emergency department, ICG may also have a diagnostic role and provides additional value because of its ability to identify appropriate therapeutic options and monitor the response to therapy in real time. Silver et al. (page 17) report on the ability of ICG to replace pulmonary artery catheterization, which has tremendous cost implications for hospitals caring for such patients. Vijayaraghavan et al. (page 22) demonstrate the prognostic role of ICG in patients with chronic HF, and show strong association of ICG changes to changes in functional status and quality-of-life measures. Summers et al. (page 28) provide a series of case reports that illustrate ICG’s practical role in the initiation and titration of neurohormonal agents and their patient-specific hemodynamic effects.

This compilation of studies adds to the growing body of data supporting the role of ICG in the management of patients with HF. Within a year, the results of two multicenter trials studying key roles for ICG should be available: PROspective Evaluation and identification of Decompensation by Impedance Cardiography Test (PREDICT), conducted in patients with chronic HF; and the BioImpedance cardiography (BIG) substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE). PREDICT specifically addresses the ability of ICG-derived hemodynamic data to

Figure 6. Fiducial points derived from electrocardiogram (ECG) and impedance waveforms. ∆Z=change in impedance; ∆Z/∆t=first derivative of the impedance waveform; PEP=preejection period; LVET=left ventricular ejection time

Figure 7. Impedance cardiography hemodynamic status report (BioZ ICG Monitor, CardioDynamics, San Diego, CA)
identify patients at risk for death, hospitalization, or emergency department visit. The BIG substudy will evaluate the diagnostic and prognostic role of ICG in both arms of a randomized, controlled trial in pulmonary artery catheter–hemodynamic-guided management of patients admitted with an acute episode of HF.

There is now a compelling body of literature that demonstrates the validity of ICG using the most current technology. More and more studies have shown the value of ICG in clinical settings in addition to HF, including dyspnea, hypertension, and atrioventricular sequential pacemakers. The studies presented in this issue of Congestive Heart Failure further define the role of this valuable, noninvasive technology in clinical medicine. It is likely that these and other studies of ICG in HF will be used to refine our understanding and ability to assess patients and predict prognosis, expanding on the concept of the four quadrants presented in Figure 2. The impact of adding ICG hemodynamic data to the four quadrants is depicted in Figure 9. Knowledge of stroke index, cardiac index, systemic vascular resistance index, and changes in fluid with thoracic fluid content would likely provide more quantitative, objective, and sensitive measurements of hemodynamic factors, and has significant implications for the management of patients with HF.

Incorporating this model of assessment into a proposed therapeutic algorithm is shown in Figure 10. Ideally, a baseline measurement of ICG in addition to other standard clinical variables would be collected and utilized in combination to more precisely assess a patient’s perfusion, congestion, and vasoactive status. This assessment would lead to a categorization of the patient’s absolute or relative change in hemodynamic profile, facilitating assessment of short-term risk for adverse HF-related events. The change in hemodynamic status and assessment of higher risk may lead to increased clinical surveillance or a decision to intervene to prevent a negative patient outcome. In addition, ICG parameters may aid in the assessment of a stable, low-risk hemodynamic profile toward the initiation and up-titration of neurohormonal agents that are often underprescribed but are known to improve event-free survival.

Note: This supplement to Congestive Heart Failure contains articles dealing with ICG. Readers are reminded that positive statements about the clinical utility of ICG, and the BioZ ICG Monitor in particular, are solely the opinions of the authors and do not represent an official endorsement by Congestive Heart Failure, its Editors or Editorial Board, or the Heart Failure Society of America.

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ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker

Figure 10. Therapeutic algorithm for incorporating impedance cardiography (ICG) parameters into clinical assessment of heart failure. SI = stroke index; CI = cardiac index; TFC = thoracic fluid content; SVRI = systemic vascular resistance index; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.
Non-invasive measurement of cardiac output during coronary artery bypass grafting

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Abstract

Objective: A new device, using whole body bioresistance measurements and a new equation for calculating stroke volume has been developed. Using this equation, an attempt was made to correlate whole body bioresistance cardiac output with thermodilution cardiac output in patients undergoing coronary artery bypass grafting. Methods: Thirty-one adults undergoing elective coronary artery bypass grafting were studied prospectively. Simultaneous paired cardiac output measurements by whole body bioresistance and thermodilution were made at five time points during coronary artery bypass grafting: in anesthetized patients before incision (T1), after sternotomy (T2), after opening the pericardium (T3), ten min post bypass (T4), and in the intensive care unit (T5). The patients had a mean of three thermodilution cardiac outputs compared with a mean of three bioimpedance measurements at each time point. The bias and precision between the methods were calculated. Results: There was good correlation between bioresistance cardiac output (nCO) and thermodilution cardiac output (ThCO) measurements in both groups for all recorded times. The patients’ mean ThCO and nCO, as well as bias and precision between methods were calculated. Mean ThCO ranged between 4.14 and 5.06 l/min; mean nCO ranged between 4.12 and 4.97 l/min. Bias calculations ranged between -0.072 and 0.104 l/min. Precision (2 SD) calculations ranged between 0.873 and 1.228 l/min for 95% confidence intervals. Pearson’s correlation ranged from 0.919 to 0.938. Conclusions: Cardiac output measured with the new device correlates well with the thermodilution measurements of cardiac output during and immediately following coronary artery bypass grafting. The overall agreement between the two methods was good. The new device is an accurate non-invasive method of measuring cardiac output during coronary artery bypass grafting. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Cardiac output; Cardiac surgery; Thermodilution; Electrical bioimpedance; Bioresistance; Hemodynamics

1. Introduction

Hemodynamic monitoring continues to be an integral part of peri- and postoperative care for patients undergoing cardiac surgery. Cardiac output (CO) is an important parameter in these measurements. To date, the clinical tool used to measure CO is the Swan–Ganz catheter using a thermodilution technique. However, the procedure is invasive, expensive, and may lead to complications [1,2].

A number of attempts have been made to determine CO in a non-invasive manner [3–6]. Using thoracic electrical bioimpedance techniques (TEB), moderate success has been achieved in some clinical settings [3,4,6–8]. The technique has been unsuccessful when applied to patients undergoing cardiac surgery [9–11]. A new non-invasive cardiac system device has been developed to utilize whole body bioresistance in a semi-empirical formula to determine the CO. Accuracy of the CO measurement using this device was established comparing thermodilution CO (ThCO) for patients undergoing right and left heart catheterization [12]. The purpose of this investigation was to compare the
new technology for measuring cardiac output with thermodilution measured CO in patients undergoing coronary artery bypass grafting (CABG).

2. Patients and methods

2.1. Patients

Thirty-one patients undergoing elective, primary CABG were prospectively studied; 15 at Wolfson Medical Center and 16 at Johns Hopkins University School of Medicine. Patients with aortic valve insufficiency, mitral and tricuspid regurgitation or cardiac shunt were not included. The CABG was similar in both hospitals. All patients underwent a median sternotomy. Cardiopulmonary bypass was established using an aortic and single venous cannula. Diastolic arrest was achieved with cold sanguineous potassium cardioplegia in both antegrade and retrograde fashion. The internal mammary artery was used to graft the left anterior coronary artery (LAD) in all cases, and saphenous vein grafts were used to bypass the other obstructed vessels. Proximal anastomoses were performed using a partial occlusion technique in both antegrade and retrograde fashion. The interval from induction of anesthesia to sternotomy was 10 min, after creation of a pericardial pocket (T3), ten min after induction of anesthesia but before incision (T1), after sternotomy (T2), and 16 at Johns Hopkins University School of Medicine. There were no atrial flutter or atrial fibrillation.

2.2. Protocol

The study protocol was approved by Edith Wolfson and Johns Hopkins Institutional Review Boards. For each patient demographic and clinical data was tabulated. In each patient, CO measurements were taken at five different time intervals during the procedure; after induction of anesthesia but before incision (T1), after sternotomy (T2), after creation of a pericardial pocket (T3), ten min after weaning from bypass (T4), and immediately after arrival in the intensive care unit (T5).

At each time interval, three adequate thermodilution measurements were made. All measurements were made at end expiration during the respiratory cycle. Thirty-one patients underwent 155 thermodilution CO measurements. Nineteen measurements were excluded because of 10% variation between the measurements. Simultaneously, three bioresistance measurements were taken at each interval, and their average was considered the bioresistance CO measurement.

Each bioresistance measurement took 20 s. Since these measurements were continuous, there was no time between measurements such that to achieve an average bioresistance CO measurement took 1 min.

2.3. Thermodilution method

At both hospitals seven French true size thermodilution catheters (Baxter Healthcare, Irvine, CA) were inserted in the operating room after induction of anesthesia. The proper location of the thermodilution catheter was confirmed by hemodynamic measurements and by postoperative chest roentgenograms. The pulmonary artery catheter was connected to a thermodilution cardiac output monitor (‘Horizon 2000’, Mennen Medical, Israel was used at Wolfson Medical Center, and 7010 Series Marquette, Madison, WI at Johns Hopkins Institutions). Ten milliliters of room temperature 5% dextrose solution was injected manually at end-expiration by an experienced anesthesiologist who was unaware of the bioresistance CO results.

2.4. Whole body resistance method

NICaS® 2001, a non-invasive cardiac system device (NICaS® 2001, Teledyne-NIM, LLC, North Andover, MA, 510K, certificat number K942227), was utilized for measuring bioresistance CO. Two proprietary designed, NICaS® disposable electrodes (510K, certificat number K972002) were applied to each wrist, and were then connected to the non-invasive cardiac system device. The system passed an AC current 30 kHz and 1.4 mA through the whole body. It then measured the resistive portion of the bioimpedance. Since the electrodes were placed on the distal aspect of the extremities, the current passed through all major arteries and veins of the systemic circulation. As such, the system measured the bioresistance of the systemic circulation and allowed calculation of the stroke volume.

In 1992, Tsoglin and Frinerman and developed a new semi-empirical formula for calculating the stroke volume (SV) [13]:

$$SV = \frac{HCT_{corr} \times k_{el} \times K_{weight} \times IB \times HCT_{corr} + \Delta R}{R} \times \frac{\alpha + \beta}{\beta}$$

where $k_{el}$ is a coefficient related to blood electrolytes, $K_{weight}$ is a ratio of a patient’s weight to ideal weight, $IB$ is the index balance equal to the ratio of the measured extracellular fluid volume (as measured from the baseline impedance) to the expected extracellular fluid volume, $HCT_{corr}$ is a hematocrit correction factor proportional to measured hematocrit, $K_{sex,age}$ is a coefficient depending upon a patient’s sex and age, $H$ is a patient’s height, $\Delta R$ is the incremental change of the resistive portion of the bioimpedance, $R$ is the baseline whole body bioresistance and $\alpha + \beta/\beta$ is the ratio of the sum of the systole time plus diastole time divided by the diastole time derived from the first structure of the varying portion of the bioresistance.

Using whole body resistance measurements and the above formula, $SV$ was calculated and converted to $CO$.

2.4.1. Statistical analysis

The correlation between methods at each time point was evaluated by Pearson’s correlation coefficient and simple linear regression. The degree of agreement between methods at each time point was evaluated by calculation of the bias (mean between-method difference) and precision (mean bias ±2 SD) [14].
**Table 1**

Patient demographic and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Wolfson Medical Center</th>
<th>Johns Hopkins Medical Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (N)</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Females (N)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>63.26 ± 9.94</td>
<td>64.2 ± 9.37</td>
</tr>
<tr>
<td>Minimum age (years)</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Maximum age (years)</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Average weight (kg)</td>
<td>73.13 ± 14.74</td>
<td>87.14 ± 13.29</td>
</tr>
<tr>
<td>Minimum weight (kg)</td>
<td>42</td>
<td>59</td>
</tr>
<tr>
<td>Maximum weight (kg)</td>
<td>102</td>
<td>108</td>
</tr>
<tr>
<td>Average height (cm)</td>
<td>166.3 ± 10.4</td>
<td>176.92 ± 8.96</td>
</tr>
<tr>
<td>Minimum height (cm)</td>
<td>140</td>
<td>160</td>
</tr>
<tr>
<td>Maximum height (cm)</td>
<td>183</td>
<td>185</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>26.8 ± 0.77</td>
<td>25.56 ± 0.403</td>
</tr>
<tr>
<td>Number of vessels bypassed</td>
<td>3.33 ± 0.96</td>
<td>2.55 ± 0.73</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>46.67</td>
<td>18.75</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>53.33</td>
<td>56.25</td>
</tr>
</tbody>
</table>

*Lowest temperature during the operation.

3. Results

Thirty-one patients were evaluated in the study. Demographic and clinical data are shown in Table 1. The agreement between the average CO measured by bioresistance versus thermodilution is shown in Table 2. The plot of the regression analysis and difference versus mean for all measurements at all times in the 31 patients is shown in Fig. 1a,b. There was good correlation between ThCO and nCO ranges of cardiac output during all phases of CABG and the immediate postoperative period.

4. Discussion

The initial attempt to obtain CO by measuring the stroke volume (SV) through thoracic electrical bioimpedance (TEB) was performed by Kubicek [15] at the National Aeronautics Space Agency (NASA) where he introduced the equation that became the basis for bioimpedance cardiology:

$$SV = \rho \left( \frac{dZ}{dr} \right) \times \left( \frac{(L^2T)}{Z_0} \right)$$

where SV is related to the resistivity of blood (\(\rho\)), \(dZ/dr\) is the first peak of the derivative of the bioimpedance curve, \(L\) is the distance between the electrodes, \(Z_0\) is the mean time averaged thoracic bioimpedance and \(T\) is the ventricular ejection fraction.

The equation was modified by Bernstein [16] to:

$$SV = VEPT \times \left( \frac{dZ}{dr} / Z_0 \right)$$

where VEPT is a coefficient that represents the volume of electrically participating tissue. Using this equation, limited clinical success has been achieved in determining CO using bioimpedance techniques. Correlation to thermodilution techniques have been achieved in healthy volunteers, patients undergoing operations without cardiopulmonary bypass, patients undergoing procedures in the cardiac catheterization laboratory, and small numbers of intensive care unit patients [3,4,7,17–20].

This equation has been problematic due to difficulties in accurately computing VEPT, and its application becomes impractical in a patient undergoing rapid hemodynamic changes. Furthermore, determination of VEPT is dependent upon the accurate placement of electrodes, which is not always possible during open heart surgery. In addition, this equation still depends upon the first derivative of the bioimpedance curve, which is a rapidly fluctuating factor. As a result, attempts to correlate bioimpedance CO in the patient with thermodilution techniques during CABG have been unsuccessful [9,10].

In addition to practical problems, there is a conceptual problem in applying TEB to measure stroke volume. TEB measurements of the bioimpedance includes both systemic and pulmonary circulations. The two circulations cannot be separated by measurements and variation in proportion of these circulation will lead to inaccurate measurements of SV [21,22]. This will not happen in whole body bioresistance measurements where the systemic circulation dominates the measurement and reflect LV SV.

The physiological and physical basis of bioimpedance has been studied by many authors [23–25]. However, the variation between different tissues and their complex structures make it difficult to model their electrical behavior. In terms of bioresistance, the body may be divided into the ‘blood compartment’ and ‘tissue compartment’. In the

**Table 2**

Agreement of CO by NICaS and thermodilution measurements (n = 31)

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean ThCO</th>
<th>Mean nCO</th>
<th>RR²</th>
<th>Regression slope²</th>
<th>SEE</th>
<th>y intercept</th>
<th>Bias (mean between-method difference) (l/min)</th>
<th>Precision mean ± 2 SD (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After anesthesia</td>
<td>4.19</td>
<td>4.19</td>
<td>0.93/0.86</td>
<td>1.128</td>
<td>0.328</td>
<td>–0.529</td>
<td>0.0086</td>
<td>–1.113–1.131</td>
</tr>
<tr>
<td>After sternotomy</td>
<td>4.14</td>
<td>4.12</td>
<td>0.92/0.85</td>
<td>0.898</td>
<td>0.185</td>
<td>0.404</td>
<td>–0.019</td>
<td>–0.863–0.823</td>
</tr>
<tr>
<td>After pericardiotomy</td>
<td>4.14</td>
<td>4.24</td>
<td>0.93/0.86</td>
<td>0.915</td>
<td>0.326</td>
<td>0.456</td>
<td>0.104</td>
<td>–0.105–1.223</td>
</tr>
<tr>
<td>Immediately after bypass</td>
<td>5.06</td>
<td>4.97</td>
<td>0.92/0.85</td>
<td>0.967</td>
<td>0.367</td>
<td>0.324</td>
<td>–0.0083</td>
<td>–1.234–1.138</td>
</tr>
<tr>
<td>ICU admission</td>
<td>4.71</td>
<td>4.62</td>
<td>0.94/0.88</td>
<td>0.891</td>
<td>0.306</td>
<td>0.424</td>
<td>–0.072</td>
<td>–1.156–1.012</td>
</tr>
</tbody>
</table>

SEE, standard error of the estimate; ICU, intensive care unit.

*\(y\), cardiac output by NICaS 2001 bioimpedance; \(x\), cardiac output by thermodilution.

146 of 158.
‘blood compartment’, conductivity is high and therefore a current introduced into the body will travel primarily in this compartment. The resistance changes in this compartment as the blood volume varies in the great arteries due to pulsatile flow. In the ‘tissue compartment’, there is less significant current flow and constant resistance. In each individual, the resistance in the ‘tissue compartment’ is determined by the patient’s height, lean body weight (muscle) to fat ratio, sex, age, body build, extracellular fluid volume, and electrolytes. In the ‘blood compartment’, the

![Graph](image)

Fig. 1. (a) Linear regression analysis comparing bioresistance measured cardiac output with thermodilution cardiac output for all averaged measurements in the study. (b) Mean difference between bioresistance measured cardiac output and thermodilution cardiac output for all averaged measurements in the study.
improved the ability to calculate
measure
require that the operation stop for the 20–30 s required to
licated while the
sensitive to movement so that the patient cannot be manipu-
measure
impossible using previous techniques.

dynamics are changing rapidly. Such a correlation would be

dern of the patients’ volume status, temperature, blood electrolytes and hemody-

The new methodology showed good correlation between
thermodilution and bioresistance CO during all phases of
CABG and the immediate postoperative period in two inde-

tications allow for the accurate calculation of the sys-
temic bioresistance with which accurate LV SV can be
calculated.

The method utilized in this study has been proven accu-
rates undergoing catheterization [12]. It was also
shown to be accurate in a pilot study in patients under-
CABG [26]. Compared with previous attempts to
 correlate bioresistance with SV, the equation has major
advantages.

1. The equation does not depend on rapidly fluct ating
time derivatives of bioimpedance.

2. The equation uses empirically derived coeffici nts that
are obtained from laboratory values and simultaneously
measured bioimpedance values instead of the artifi ial
and diffic u to approximate VEPT.

3. The precise placement of the electrodes is not a critical
factor.

4. The NICaS® electrode arrangement is optimal to mea-
sure the left ventricular SV.

5. The respiration has almost no effect on the NICaS® CO
measurements in real time.

The new methodology showed good correlation between
thermodilution and bioresistance CO during all phases of
CABG and the immediate postoperative period in two inde-
hospital populations. Correlation was good in all
ranges, including low cardiac output. This fact is important
since patients undergoing CABG frequently have low car-
diac output. This was even true in the immediate post car-
diopulmonary bypass period where changes in the patients’
volume status, temperature, blood electrolytes and hemody-

The new device has certain limitations. First, it cannot
measure CO while using diathermy. Second, the device is
sensitive to movement so that the patient cannot be manipu-
ulated while the CO is being measured. These two factors
require that the operation stop for the 20–30 s required to
measure CO. Finally, the device measures SV and multiplies
it by heart rate to measure CO. Arrythmias in which the
heart rate varies signific ntly will result in a non-represen-
tative measurement of CO.

In summary, a new device using a semi-empirical equa-
tion relating SV to changes in the resistive portion of the
patients’ bioresistance has been developed. Information
about specific patient data, blood components and body
habitus inserted into the analytical software has signific ntly
improved the ability to calculate SV from the bioresistance
data. The device allows accurate, easy to obtain, non-inva-
sive CO during cardiac surgery. Within the above stated
limitations, we have confir ed the validity of the new biore-
sistance methodology in 31 patients who underwent CABG.
Bioresistance measured cardiac output correlated well with
Th.CO during the CABG procedure and the immediate post-
operative period.

Acknowledgements

This paper was prepared in consultation with Diklah
Geva who prepared the statistical calculations, and with
the technical assistance of Sally Esakov.

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EVALUATION AND MANAGEMENT OF THE ELDERLY HOMEBOUND PATIENT WITH CONGESTIVE HEART FAILURE
C. Gresham Bayne MD

BACKGROUND: The frail elderly patient population is characterized not only by age demographics, but by the inadequacy of the office-based medical model to meet their needs when they can no longer reach the physician’s office on a regular basis. In addition, we are often called to see the new patient with presenting symptoms of heart failure precipitated by one of many proximate causes.

Congestive Heart Failure (CHF) is the leading cause for hospitalization after the age of 65. There are one million admissions for CHF annually with 80% of the patients over 65 years of age. CHF is the most costly DRG in the United States with annual costs exceeding $10 billion. The incidence and prevalence of CHF are rising in the population with prevalence doubling each decade after age 45. The one year survival for Class III and IV CHF elder patients is still only about 60%. The best objector predictor for survival has been the cardiothoracic ratio on standard chest Xray.

There is a close and perhaps causative relationship between hypertension and CHF in the elderly due to the complex neurohormonal reflexes involved (see below). As people age the cardiovascular system normally increases its electrical impedance, has lowered beta-adrenergic responsiveness, alters its myocardial energy metabolism, with the heart usually showing impaired diastolic relaxation and compliance. The net effect is a marked reduction in the cardiovascular reserve.

PRECIPITATING EVENTS:
These precipitating events must be evaluated first, before the patient’s failure can be addressed. The most common of these is the failure to take their medications due to financial, social, or cognitive problems. Despite the medication failure, the benefit might be afforded us to switch them to the more acceptable geriatric approach to congestive heart failure than has often been the case in the past. Briefly stated, the philosophy of treatment has changed dramatically in past years from a diuretic-based ramp-up to the primary use of ACE inhibitors and other afterload reducers. This modern approach will be discussed more fully later.

Other precipitating factors common to our population include anemia, hyperthyroidism, infection, new onset arrhythmias such as atrial fibrillation, change in diet, silent myocardial infarction, worsening valvular disease, inappropriate use of the sodium-retaining NSAIDS, and environmental changes such as increased ambient humidity or temperature, and stress. Obviously, these historical and clinical factors must be evaluated in perspective.

The absence of a readily available medical records and EKG/Xray documentation mandates the use of appropriate technology when patients present with symptoms suggestive of failure. Even in non-acute settings, the ability to have local physicians copy
and send forward medical records is so remote, it should not be anticipated that a chart is forthcoming. In fact, many of the patients will be well-served by an entirely new approach to their clinical symptoms, especially those on multiple medications. Obviously, precipitating causes should be addressed before redirecting the primary interest in care to the failure itself.

PHYSIOLOGY REVIEW:

The function of the heart is to pump arterialized blood forward under sufficient pressure to meet the peripheral tissue metabolic needs. Given adequate oxygenation and a normal hemoglobin, the cardiac output, defined as the pulse times the stroke volume, should pump enough blood to prevent angina (ischemia to the heart), cold knee caps (ischemia to the skin), oliguria or azotemia (ischemia to the kidney) and confusion (ischemia to the brain). Thus, a quick iSTAT and pulse oximetry is required to rule out azotemia, hypoxemia, and a metabolic acidosis demonstrated by the base deficit. Even a venous sample with a normal base excess is adequate to prove the absence of a low perfusion state.

NOTE that the above definition of inadequate cardiac output (CO) did NOT mention the blood pressure at all! In fact, the only time hypotension is an emergency for bedbound patients is when the diastolic pressure is below 60 mmHg and the patient experiences angina or failure symptoms. Since coronary arterial blood flow is 85% during diastole, the aortic root pressure is critical in determining myocardial perfusion. Thus, in the emergency room, some patients in shock with angina find that dopamine is the best analgesic!

To evaluate the failing heart, one needs to think in terms of myocardial efficiency, NOT blood pressure. Efficiency of the heart is measure in terms of Oxygen Demand by the heart as balanced against the Stroke Work Index. We will first address the Oxygen Demand, which is determined by five factors, of which only three are clinically relevant: the pulse, the mean arterial pressure and the wall tension index (as measured by the CXR assessment of cardiomegaly). Myocardial oxygen demand is linearly increased as the pulse increases over 100, dramatically increased by mean arterial pressure (usually estimated by a value one-third the distance between the diastolic and systolic pressures), and increases despite the same cardiac output with increases in the left ventricular end-diastolic volume (cardiomegaly).

Thus, the patient with a pulse of 110, a blood pressure of 140/100 and cardiomegaly on CXR is demanding much more oxygen for their heart than a patient of normal heart size and vital signs. When the presenting symptoms include angina, the approach to failure is first to treat the increased demand by using nitrates or nifedipine to lower the MAP, slow the pulse, and vasodilate the coronary arteries. Once stabilized, the failure may be addressed.
Stroke Work Index (SWI) is a complicated clinical measurement requiring the use of a pulmonary arterial catheter, but can be thought of in clinical terms quite simply. Remember, the heart does not have to create higher than normal pressures to increase its cardiac output (CO) if the peripheral vascular resistance (PVR) is reduced. The SWI is calculated basically by multiplying the cardiac output times the PVR. The human heart is a very efficient flow generator, but a very inefficient pressure generator. Thus, oxygen demand to increase cardiac output is efficiently handled, but requirements for hypertension are disastrous. It is important to note that the failing heart may, due to its inefficiencies and maladaptive neurohumoral reflexes, simply increase the blood pressure without generating much increase in the CO. Thus, hypertension is the enemy of both ischemic heart disease and congestive heart failure.

The physiological changes in the elderly which occur in the chronic state of heart failure are numerous and complex. They include:

1. Increased renin levels, which increases the conversion of Angiotension I to Angiotension II, the most potent vasoconstrictor known
2. Increased renin levels promoting the kidney to increase aldosterone leading to increased retention of sodium and water
3. Increased adrenergic background tone by the adrenal cortex with elevated circulating norepinephrine levels and inappropriate hypertension
4. Decreased levels of adenyl cyclase leading to decreased levels of cyclic AMP which can lead to lower protein kinase, calcium entry levels and calcium re-uptake by the myofibrils

The net result is a chronic “fight or flight” background level of physiologic stress which ultimately leads to cardiac failure. I think of my elderly patients as on an endogenous catecholamine drip producing more hypertension than forward flow. Since it is unlikely that the patient will ever be “normal,” it is useful to think in terms of therapy to maximize forward blood flow at the lowest physiologic cost.

TREATMENT PRINCIPLES:

To maximize the cardiac output, we typically intervene with the three major forces we can easily effect with medication: Preload, Contractility, and Afterload.

Preload: The hypovolemic patient may be in shock or hypotensive simply because of fluid depletion. This is often easily discerned by the history, physical and iSTAT testing, but often problematic in the bedbound, demented patient. The hypervolemic patient is often much harder to evaluate, since chronic rales, interstial lung disease, emphysematous changes, obesity, patient intolerance to the exam, may all affect our confidence level. Therefore, some simple in-home testing may be useful. The CXR showing cardiomegaly is strong support for a chronic hypervolemic state and elevated left ventricular filling pressures. The presence of LVH or left ventricular strain pattern in the EKG (R waves in V5 and V6 add up to more that 25mv) is often associated with overload.
A final test, done only in the normotensive or hypertensive patient, is the so-called “Chatterjee” test when one monitors the pulse before and after a single dose of sublingual nitroglycerine. Since NTG predictably lowers the pulmonary capillary wedge pressure (PCWP) (left ventricular filling pressure), the hypervolemic patient will NOT have a tachycardic change in pulse with NTG. The normal or hypovolemic patient will increase their pulse by 10% or more. Thus, the absence of tachycardia in response to NTG is de facto evidence of increase PCWP and indicates the need for (temporary) diuresis.

The use of nitrates alone to control preload and subsequent CHF symptoms is complicated by the tolerance that all patients develop for the longer acting versions. The use of nitrates in the elderly is most often useful on the acute housecall when the patient has suddenly decompensated and has hypertension in addition to the symptoms of CHF. One must be cautious in the home when using nitrates to be able to place the patient in recumbency before administration, as the “nitrate syncope” syndrome is much more likely in our patients.

The use of diuretics has been the mainstay of treatment for both hypertension and failure for some forty years, despite the fact that diuretics have yet to be shown in controlled prospective clinical trials to increase survival rates. Currently, some 35-40% of all seniors over the age of 65 are taking a diuretic in some form. However, cumulative studies are now overwhelming in their condemnation of the indiscriminate application of either loop or thiazide diuretics due to the following known side effects:

1. 60% of all toxic drug reactions are due to diuretics in the elderly
2. diuretics are the most common drug reaction requiring hospitalization
3. both types cause increased serum cholesterol, although subsequent cardiac disease is unproven
4. both cause increased uric acid levels with subsequent tophaceous gout
5. both cause glucose intolerance in Type 2 prone patients, and the instigation of Type 2 diabetes is NOT reversible by stopping the diuretic (bumex less than lasix)
6. both cause deafness, even in chronic oral dosing regimes (bumex less than lasix)
7. both cause decreased calcium absorption and worsen osteoporosis (loop worse than thiazides)
8. both cause behavioral risks with incontinence in the female, urinary retention in the male
9. both can lead to hyperkalemia in the elderly as well as hypokalemia
10. both can cause severe hyponatremia in the elderly

Thus, the use of diuretics is now considered second or third line therapy, after more contemporary treatment for both hypertension and/or failure has failed.

Contractility: The state of inotropy of the heart in failure patients is compromised by many of the maladaptive neurohormonal changes discussed above as well as the loss of cardiac tissue from current ischemic heart disease and past infarcts. Unfortunately, the
use of phosphodiesterase inhibitors in the elderly to increase inotropy has been clinically unsuccessful and the use of adrenergic agents such as dopamine and dolbutamine requires monitoring and infusion therapy along with the hassles of an intravenous. Early studies on NY Stage IV CHF patients on home dobutrex drips have prolonged life but at a significant cost on the quality of life.

What we have learned in the ICU from the two adrenergic agents in most common use today is important. Whereas, dopamine causes a more potent increase in inotropy and blood pressure, it has little or no effect on PCWP, increases ventricular irritability, and requires much more care. Dolbutamine, on the other hand, not only has less toxicity at the same cardiac output, but lowers the PCWP dramatically, thereby restoring the normal cardiac anatomy and reducing myocardial oxygen demand.

To reduce the oxygen demand of the heart, the eighties and early nineties saw an increase in the use of beta blockers even in failure patients. Unfortunately, the use of beta blockers to control hypertension in the elderly involves much more toxicity, and (other than post MI) has shown to increase mortality due to side effects, including an increase in cholesterol for all age groups.

The use of digoxin remains controversial in patients without the need for rate control in atrial fibrillation. Although digoxin is the oldest and most proven inotropic agent, and the only one which does so while decreasing the wall tension index (cardiomegaly), its toxicity and need for periodic serum measurements makes it of much more problematic in the demented, homebound elderly CHF patient. A NEJM study in 1997 on Class II or III CHF patients showed no change in mortality with digoxin therapy in addition to ACE inhibition (see below), but a significant improvement in functional status and decrease in hospital days. Most patients with an ejection fraction of over 45% will do well on digoxin alone for control of symptoms of CHF. Obviously, the ability to measure directly an improvement in cardiac output with digitalis would allow better patient selection in the future.

Suffice to say, patients with cardiomegaly and/or a S3 gallop should have a trial on digoxin alone before using multiple drug regimes. Finally, no one argues about the use of digoxin to control rapid ventricular response in the patient with atrial fibrillation.

Afterload: If the SWI can be reduced by reducing the MAP, one might be able to both increase the forward flow of blood (CO) as well as decrease the myocardial oxygen demand. This would be the best of both worlds! Indeed, we now know that peripheral vasodilatation has less morbidity and better survival rates with better functional status than conventional beta blocker/diuretic regimes. The geriatric meetings are replete with studies confirming the observation that the ACE inhibitors by themselves can often control hypertension and should be used for patients with risk of CHF (such as LVH or cardiomegaly on CXR), and especially diabetics even when they are asymptomatic.
By using ACE inhibition at lower doses beginning at night, one can often avoid orthostatic hypotension and preserve the peripheral vasomotor reflexes so important to prevent side effects. Many patients can be converted from 2-4 older medications (digoxin, lasix, KCL, tenormin) to a single dose of benzapril 10 mg hs. Titrating the benzapril up to 80 mg daily may control the blood pressure while relieving the symptoms of failure as well. The therapeutic effects must be evaluated by the patient’s subjective reports of exercise tolerance or orthopnea, as well as objective weights. If CHF is to be controlled on ACE inhibitors alone, the patient will lose weight on it.

In addition, the Cooperative North Scandinavian Enalapril Survival Study showed that ACE inhibition improves symptoms and exercise tolerance, while affording significant survival benefits among patient with severe CHF. These agents not only decrease afterload, but preload as well, and deter activation of the neuroendocrine system leading to reduced risk of hypertensive episodes, stress reduction, less fluid retention, and perhaps less arrhythmogenicity.

Before reverting back to the diuretics which some patients simply must have, adding a calcium channel blocker in angina patients or alpha receptor blockade may be useful to improve inotropy by increasing coronary blood flow and further decreasing the peripheral vascular resistance. In addition, the newer calcium-channel blockers such as amlodipine have been shown to increase end-diastolic ventricular relaxation, promoting ventricular filling and increasing stroke volume at the same filling pressures. Once the afterload is under control, the SWI is decreased enough to usually require no further therapy requirements for heart failure. Of course, if you cannot know the cardiac output, you cannot calculate afterload, so using BP as a surrogate if fraught with undertreatment biases. Should further therapy be required, a diuretic may be cautiously introduced since their effect is additive to both ACE inhibition and calcium channel blockade.

What has been lacking in both the critical care and outpatient arenas is an ability to know the systemic vascular resistance. Thus, we are still basing our clinical decisions on non-physiological parameters: i.e., mean arterial pressure. Although MAP may be a useful guideline for stroke prevention, many patients with borderline /low cardiac outputs have normotension while their SVR is markedly elevated. We cannot know this without measurement of the cardiac output, which heretofore has been invasive and expensive with the pulmonary arterial catheter. The advent of non-invasive, inexpensive cardiac impedance studies in the outpatient and other settings has opened up a dramatic opportunity to not only titrate therapies toward maximum lowering of the SVR to improve cardiac output, but also to titrate therapies both acutely and chronically toward the best cardiac efficiency factors, since impedance can track the pre-ejection period and minimize isovolumetric contraction time.

The Use of Cardiac Impedance in the Home-Bound Patient

Background: For over twenty-five years it has been possible to provide a non-invasive monitoring system capable of measuring the trends in cardiac output, stroke volume,
ejection fraction and total intra-thoracic fluid. Since the chest is essentially a box containing a variable amount of non-conducting air in the lungs and airways, and a variable amount of salt water in tissue and blood, measuring the resistance to the flow of electricity through the chest should correlate to fluctuations in air and/or fluid.

In fact, this measurement, known as impedance, can easily be measured across the chest by a series of paired electrodes placed on the neck and lateral chest wall. The static values measured on an insensitive scale correlate to Total Fluid Content or TFC of the chest and will change over time with things like pleural effusions, extravascular lung water, and congestive heart failure. Using a very sensitive scale, one can see alterations in impedance conforming to the pumping action of the heart during each systole. Since the heart pumps blood out of the chest once the aortic valve opens, the velocity of this pumping action can be calculated from the first derivative of impedance or $dZ/dT$. The peak value of $dZ/dT$ correlates closely with the stroke volume (SV) of each heartbeat. Since the cardiac output is easily calculated by multiplying the SV time heart rate, one can watch online as therapies affect the cardiac output.

In the 1960’s impedance research was done primarily in Israel where engineers were best in signal acquisition technology or Russia, where cognitive strengths were focused on complex algorithms to reduce the signal noise from motion or respiratory artifact. Recently, a combination of these talents has come together to produce an FDA-approved non-invasive, whole-body impedance measurement which has the distinct advantage of not having to undress female patients (electrodes are placed on two extremities). There continues to be controversy over which is “best,” trans-thoracic or whole body impedance. In addition, there remains argument over which proprietary algorithm should be used. Proponents of the Sramek Equation believe selecting the single best systole for detailed examination and reporting is superior to averaging data from many systolic waveforms during a one minute sample (for example) analyzed by the Kubicek Equation.

The second derivative of impedance varies with the acceleration of the blood as it exits the left ventricle and correlates closely with the inotropic state of the heart. Since electrodes can easily sense the EKG tracing of a patient, one can pinpoint the R wave and measure the time between the initiation of systole and the time when the aortic valve opens, sensed as the onset of the acceleration of blood or the second derivative of impedance. This period is called the PEP or Pre-Injection Period, a time when the heart is maximally consuming oxygen during systole, but doing no useful work, since no bloodflow has yet occurred in the aorta. The longer the PEP, the more inefficient the heart is for any given cardiac output. Examples of clinical conditions which prolong the opening of the aortic valve or PEP are hypertension, myocardial dyskinesis, ventricular aneurysm, and aortic stenosis. Finding the maximum cardiac output for the minimum PEP has now become routine in setting time intervals for two channel pacemakers.

Since the closing of the aortic valve is also marked by an abrupt deceleration of blood flow in the aorta, one can use impedance to mark the closure of the aortic valve. Thus, the LVET, or Left Ventricular Ejection Time, when the left ventricle is actually pumping...
blood, can now be tracked with non-invasive monitoring. More importantly, it turns out that clinical studies of patients with heart disease, including mitral valve disease and atrial fibrillation, have shown an extremely close inverse correlation of the left ventricular ejection fraction and the PEP/LVET ratio.

Clinical Significance in the Home Bound Patient:

Many patients over the age of 80 are not only homebound, but extremely demented and frail. Not only do they have a high prevalence of congestive heart failure, the number one cause of death in the elderly, but they cannot get to the cardiologist for appropriate studies. Even if they could, they cannot tolerate a treadmill or other means of evaluating their heart. For those that can make it to the cardiologist's office, Medicare policy limits payment for the gold standard of doppler ultrasound to annual usage in most cases. Thus, the reality is that the homebound patient is usually not followed objectively in the management of their cardiac function during therapeutic changes directed at blood pressure or congestive heart failure.

It is clear now that afterload and CHF control are critical to maximizing both the lifespan and the functional status of these patients. Unfortunately, we have not had access to objective measurements for any of our therapies in the home. For instance, it is generally agreed that ACE inhibition therapy should be maximized to a physiologic endpoint, but daily weights, clinical exam, and pulse oximetry are late findings and too non-specific with too many covariables to give us confidence.

The use of cardiac impedance as a non-invasive static and dynamic monitoring system to document cardiac function in the home represents a break-through technology allowing us to pursue better quality of care for these patients. Using the principle of transthoracic bioimpedance, intensivists and surgeons have known for over a decade that cardiac output and ejection fractions can be monitored with as much reliability as thermodilution Swan-Ganz catheter measurements. Not only is the data correlated with direct Fick measurements as well as thermodilution, the bioimpedance measurements show less inter-operator variability and higher reproducibility for trend analysis with a given patient.

In summary, the use of FDA-approved portable bioimpedance devices (paid by Medicare at about $40/test), such as the (www.cardiodynamics.com), the HemoSapiens (www.hemosapiens.com) or NIMedical (www.ni-medical.com) offers another step forward in low-cost, comprehensive testing and monitoring of patients outside of the hospital environment: whether in the home, the outpatient clinic, or the physician’s office. It is likely that the ease of use and higher physiological parameters measured will make this monitoring a mainstay for both future cardiologists and housecall physicians, although the high capital costs of machines and low per-test reimbursement have limited growth in the fee-for-service sector.
Examples of theoretical usage of non-invasive measurement of trans-thoracic impedance in the homebound patient:

1. Evaluation of the new patient in heart failure
2. Weaning CHF patients off their high-dose beta-blockers and calcium channel/diuretic therapies
3. Titrating to the maximum dose of ACEI/ARB consistent with renal impairment
4. Monitoring diuretic therapies in the bedbound patient or others that cannot be weighed
5. Adjustment of pacemaker rate settings for maximum cardiac output in marginal patients
6. Titrate hypertensive therapies to the point of maximum cardiac efficiency
7. Evaluate the patient with frequent PVCs, AF or other arrhythmia affecting output
8. Evaluate starting or stopping of digoxin therapy
9. Safety in rapid rehydration or transfusion therapy at home
10. Monitoring the terminal patient remotely to aid the family in planning, etc.
11. Monitoring patient compliance with dietary restrictions or fluid hydration overnight
12. Use in pharmacologic stress test for IHD evaluations in the bedbound patient
13. Monitoring of pleural effusions over time or during thoracentesis
14. Screening for CHF in patients with poor histories and weakness
15. Evaluate Cyclosporine or EPO-induced hypertension
16. Short term stabilization of the patient in pulmonary edema