Impedance Cardiography: Clinical Applications in Heart Failure

editorial

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John E. Strobeck, MD, PhD; Marc A. Silver, MD, Co-Editors in Chief

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Supplement to Congestive Heart Failure
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CME Questions
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 long-term hemodynamics. Current acute HF treatments can alter short-term and hemodynamic condition; chronic HF and improving a patient’s short-term management is aimed directly at stabilizing hemodynamic 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 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

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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.9–11 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>
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<th>Table 1. Impedance Cardiography Parameters</th>
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<tr>
<td><strong>PARAMETER</strong></td>
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<td>Stroke volume</td>
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<td>Cardiac output</td>
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<td>Cardiac index</td>
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<td>Systemic vascular resistance</td>
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<tr>
<td>Systemic vascular resistance index</td>
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<tr>
<td>Pre-ejection period</td>
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<tr>
<td>Left ventricular ejection time</td>
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<td>Systolic time ratio</td>
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<tr>
<td>Velocity index</td>
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<td>Acceleration index</td>
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<tr>
<td>Left cardiac work index</td>
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<td>Thoracic fluid content</td>
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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

Table II. Summary of Impedance Cardiography Applications in Heart Failure

<table>
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<tr>
<th>APPLICATION</th>
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<tr>
<td>Assessments and diagnostic</td>
<td>Establish baseline hemodynamics</td>
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<td>Trend changes to gauge level of hemodynamic decompensation</td>
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<td>Determine whether symptoms are due to hemodynamic deterioration</td>
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<td></td>
<td>Aid in differentiation of systolic vs. diastolic dysfunction</td>
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<td>Prognostic</td>
<td>Emergency department values predictive of length of stay and hospital charges</td>
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<td></td>
<td>Improvements associated with improving NYHA class, quality-of-life measures</td>
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<td></td>
<td>Abnormal values associated with mortality</td>
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<tr>
<td>Treatment</td>
<td>Determine stability for initiation and up-titration of β-blocker and ACE-inhibitor therapy</td>
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<tr>
<td></td>
<td>Assist in selection of drug agents and dosing</td>
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<td>Measure response to adjustments in therapy</td>
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<td>Determine need and optimal selection/dosing of IV therapy</td>
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<td></td>
<td>(dobutamine, milrinone, nesiritide)</td>
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<td></td>
<td>Optimize LVAD settings and wean patients from LVAD support</td>
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<tr>
<td></td>
<td>Determine optimal pacemaker settings in patients with AV sequential pacemakers</td>
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<tr>
<td></td>
<td>Detect hemodynamic changes due to compensation, medication, and diet compliance</td>
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<tr>
<td></td>
<td>Provide an adjunct to posttransplant myocardial biopsies</td>
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NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; LVAD = left ventricular assist device
Yung et al. (p. 7) validate 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. Springfield et al. (p. 14) 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 T (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...
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,15 hypertension,16 and atrioventricular sequential pacemakers.17 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.

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**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.
Comparison of Impedance Cardiography to Direct Fick and Thermodilution Cardiac Output Determination in Pulmonary Arterial Hypertension

Cardiac output (CO) is an important diagnostic and prognostic tool for patients with ventricular dysfunction. Pulmonary hypertension patients undergo invasive right heart catheterization to determine pulmonary vascular and cardiac hemodynamics. Thermodilution (TD) and direct Fick method are the most common methods of CO determination but are costly and may be associated with complications. The latest generation of impedance cardiography (ICG) provides noninvasive estimation of CO and is now validated. The purpose of this study was to compare ICG measurement of CO to TD and direct Fick in pulmonary hypertension patients. Thirty-nine enrolled patients were analyzed: 44% were male and average age was 50.8±17.4 years. Results for bias and precision of cardiac index were as follows: ICG vs. Fick (–0.13 L/min/m² and 0.92 L/min/m²), TD vs. Fick (0.10 L/min/m² and 0.41 L/min/m²), ICG vs. TD (respectively, with a 95% level of agreement between –0.72 and 0.92 L/min/m²; CO correlation of ICG vs. Fick, TD vs. Fick, and ICG vs. TD was 0.84, 0.89, and 0.80, respectively). ICG provides an accurate, useful, and cost-effective method for determining CO in pulmonary hypertension patients, and is a potential tool for following responses to therapeutic interventions.

Cardiac output (CO) measurement provides valuable diagnostic and prognostic information in the management of patients with left- and right-sided cardiac dysfunction. Pulmonary arterial hypertension (PAH), a condition characterized by elevation in the blood pressure of the pulmonary arteries of the lung, may result in right-sided heart failure and low CO. Untreated, the condition can be fatal. Despite the importance of CO in PAH, few studies have looked at the accuracy of current methods of CO measurements in this group of patients.

The purpose of this study was to compare the accuracy of impedance cardiography (ICG) to thermodilution (TD) and direct Fick in the measurement of CO and cardiac index (CI) in PAH patients.

Methods
The study protocol was approved by the Human Subjects Committee of the University of California, San Diego. Written informed consent was obtained for all patients. Patients who had been referred to the Pulmonary Vascular Program at the University of California San Diego Medical Center for evaluation of pulmonary hypertension were included in the study. All patients were considered clinically stable and the study was performed in the cardiac catheterization laboratory. Right heart catheterization was performed as part of the routine workup for the patients. A pulmonary artery catheter was placed via internal jugular vein in the usual manner, under fluoroscopic guidance. Exclusion criteria included age (<18 years), height (<4 ft or >7 ft 6 in), and severe obesity (>65% above ideal body weight).

All ICG CO (CO(ICG)) measurements were performed with the BioZ ICG monitor (CardioDynamics, San Diego, CA). CO(ICG) measurements were performed according to the manufacturer’s guidelines during the same period when CO by TD method (CO(TD)) was obtained by an independent cardiologist. Each CO(TD) was determined as a function of the area under the temperature–time curve, using a CO computer (Com II CO monitor, Baxter-Edwards, Deerfield, IL). As the cardiologist injected each fluid bolus (10 mL room temperature, 5% dextrose), to obtain a minimum of three CO(TD) values with <10% variation, the corresponding CO(ICG) values were recorded. Unlike the CO(TD) values, which were obtained usually at various times during the respiratory cycle, the CO(ICG) values were continually displayed and updated on the ICG monitor every 10 beats. In this manner, at least three pairs of CO measurements were obtained for each patient. The physician-determined acceptable CO(TD) measurements were averaged to obtain the final CO(TD) for each patient. The recorded CO(ICG) measurements corresponding to the accepted CO(TD) measurements were also averaged for each patient to obtain the final CO(ICG) for each patient. All recorded CO(ICG) measurements were used without any being either objectively or subjectively rejected.

Cardiac output measurements via the Fick method (CO(Fick)) were determined within 10 minutes of the paired CO(TD) and CO(ICG) measurements. A face mask was placed over the patient with a tight head strapping to ensure complete collection of expired gas. The system was...
checked periodically during the study for air leaks. Inhaled oxygen concentration was titrated at the beginning of the study with an oxygen blender to avoid hypoxia. Oxygen delivery was kept constant throughout, and stabilization of respiratory pattern was achieved by allowing a 5-minute rest period. Steady state was defined by a respiratory quotient between 0.65 and 0.9. Average steady state oxygen consumption was obtained using a portable indirect calorimetry monitor (Deltatrac, Datex Instrumentation, Helsinki, Finland). Briefly, it is an open system that analyzes the differential partial oxygen pressures (PO$_2$) of inhaled and exhaled gas using a paramagnetic oxygen sensor, and the gas flow is measured via a gas dilution system. To ensure accuracy, the system was calibrated before each study and the values were time-averaged over at least 5 minutes. Simultaneous arterial and mixed venous blood samples were then drawn for measurement of arterial oxygen saturation (SaO$_2$) and hemoglobin (Hgb) concentration. Arterial blood samples were obtained through either a radial or femoral arterial puncture, and the mixed venous blood samples were obtained from the distal port of the pulmonary artery catheter. Oxygen content was calculated using the equation:

\[ \text{Oxygen content} = 1.34 \times \text{Hgb} \times \text{SaO}_2 + 0.003 \times \text{PO}_2 \]

The CO$_{FICK}$ was then calculated by dividing the average oxygen consumption (VO$_2$) value with the difference between the concentration of arterial oxygen (CaO$_2$) and concentration of mixed venous oxygen content (CvO$_2$):

\[ \text{CO}_{FICK} = \text{VO}_2 / (\text{CaO}_2 - \text{CvO}_2) \]

All CO measurements were indexed by the patient’s body surface area and the following statistical analyses for comparing the average CO and CI for the three methods (CO/Cl$_{KGD}$, CO/Cl$_{TD}$, and CO/Cl$_{FICK}$) were performed: Pearson’s correlation, regression analysis, and Bland-Altman analysis for bias and precision. Bias is defined as the mean of all CO errors, and precision is defined as the standard deviation of CO errors. Age variables are expressed as mean ± standard deviation. Student paired t-test was used to determine statistical significance.

**Results**

Forty-two patients were enrolled in the study. Three were omitted from analysis, two due to the inability to obtain CO$_{KGD}$ and one due to the inability to obtain CO$_{FICK}$. No serious complication occurred during the study. Final analysis included 22 women and 17 men. Age was 50.8±17.4 years, range 18 to 80 years. All patients survived.

Etiology of pulmonary hypertension was due to primary pulmonary hypertension (nine patients, seven women and two men), chronic pulmonary thromboembolic disease (28 patients, 13 women and 15 men), idiopathic pulmonary hypertension (one female patient), and mixed connective tissue disease (one female patient). Tricuspid valve regurgitation was evident in all patients (nine mild, 19 mild-moderate to moderate, and 11 moderate-severe to severe). Patent foramen ovale was present in 14 patients.

The results for Pearson’s correlation, and Bland-Altman analysis for bias and precision (first standard deviation) for CO/Cl$_{KGD}$ and CO/Cl$_{TD}$ are listed in the Table. The results for Pearson’s correlation of CO ICG vs. Fick, TD vs. Fick, and ICG vs. TD were 0.84, 0.89, and 0.80, respectively.

**CO/Cl$_{TD}$ vs. CO/Cl$_{FICK}$ Comparison.** See Figure 3 for a scatterplot of the paired CO$_{TD}$ and CO$_{FICK}$ measurements. The results for Pearson’s correlation, and Bland-Altman analysis for bias and precision ± standard deviation for CO/Cl$_{TD}$ compared with CO/Cl$_{FICK}$ are listed in the Table. Bias and precision were 0.10 L/min/m$^2$ and 0.41 L/min/m$^2$, respectively, with a 95% level of agreement between –0.72 and 0.92 L/min/m$^2$ (Figure 4).

**CO/Cl$_{KGD}$ vs. CO/Cl$_{TD}$ Comparison.** Bias and precision were –0.43 L/min/m$^2$ and 0.53 L/min/m$^2$ respectively, with a 95% level of agreement between –0.149 and 0.63 L/min/m$^2$.

**Discussion**

The diagnosis and treatment of pulmonary hypertension often requires right heart catheterization procedures to assess pulmonary artery pressures, pulmonary vascular resistance, and CO. A truly continuous measurement of CO would be desirable to clinicians treating a variety of chronic and acute diseases, including pulmonary hypertension and heart failure. Through right heart catheterization, the TD method and Steward-Hamilton equation that utilizes temperature change over time has become the most common method of CO estimation in critically ill patients.$^4$-$^6$ However, no method of CO estimation is perfect, and multiple clinical limitations of the TD method exist.$^7$-$^{10}$ Technical issues can also affect the validity of TD, including computer calibration, catheter placement, rate of injection, temperature and volume of the injectate, timing of the injection during the respiratory cycle, and the position of the subject.$^{11}$

The direct Fick method of CO estimation utilizes oxygen uptake and the arteriovenous difference in oxygen content to estimate CO and is often considered the most accurate method. However, direct Fick can be time intensive and operator dependent due to the need to draw both
arterial and venous blood oxygen samples. TD has been compared with direct Fick in a variety of patient populations with generally good agreement. Of course, TD from the right heart catheterization allows only intermittent measures of CO. Changes in hemodynamics that occur in minutes or even hours in response to therapeutic interventions or disease progression cannot be monitored.

Noninvasive ICG uses eight sites on four adhesive sensors on the neck and chest to monitor impedance changes based on the introduction of a low amplitude alternating current to measure hemodynamic parameters such as CO and systemic vascular resistance. ICG was introduced as a concept to monitor hemodynamics in the 1940s and first commercialized in the 1960s. In the 1980s, Sramek and Bernstein put forward an improved ICG method, but signal processing limitations and invalid assumptions in CO algorithms produced inconsistent performance that did not compare well to TD or direct Fick methods. However, recent advancements with the latest generation of ICG devices have offered significant hope toward a new, noninvasive standard for hemodynamic monitoring. Recent trials with ICG have demonstrated acceptable intra-method reproducibility and inter-method comparison of accuracy with invasive methods.

A method to monitor CO less intermittently with invasive catheters was introduced by Yelderman. Often called continuous CO determination catheters, Haller et al. and Zollner et al. demonstrated that they do not really provide real-time monitoring of CO, with hemodynamic changes taking at least three and as long as 10 minutes to register fully. Although the accuracy of continuous CO catheters has been accepted clinically, differing opinions exist on the accuracy of the method compared with TD and direct Fick.

Some have suggested that the ability to monitor hemodynamics continuously would reduce workload of medical personnel, and that the increased surveillance may result in more frequent medical interventions of critically ill patients, possibly improving outcomes. A truly continuous method of hemodynamic monitoring would theoretically provide real-time determination of the effects of parenteral therapeutic agents, allowing titration of treatments based on patient-specific response. The ideal real-time monitor would also be noninvasive, and therefore reduce many of the clinical drawbacks surrounding the use of invasive hemodynamics monitoring, and provide a cost-effective method at the same time. Unfortunately, a validated tool to accomplish real-time monitoring of hemodynamics has been elusive.

In this study of spontaneously breathing, nonintubated pulmonary hypertension patients, ICG compared favorably in direct comparisons with the invasive methods (TD and direct Fick) and almost as well as the invasive methods compared with each other. ICG had greater bias and less precision and correlation when compared with TD and direct Fick, but there were no clinically significant differences between the accuracy of ICG and TD when compared with Fick, a result duplicated in another three-way comparison in heart failure patients. With the known limitations of TD, clinicians and researchers evaluating the accuracy of ICG may be advised to question whether differences between ICG and TD are due to the limitations of ICG, TD, or both methods.

ICG does not provide intracardiac pressures such as pulmonary artery or pulmonary artery wedge pressure, or the derivative pulmonary vascular resistance measure, but does provide measurement of fluid trending and myocardial contractility. Known limitations of ICG include severe aortic

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<td><strong>CI Bias [L/min/m²]</strong></td>
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**CO**=cardiac output; **CI**=cardiac index; **ICG**=impedance cardiography method; **Fick**=direct Fick method; **TD**=thermodilution method
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24. Ahmad F, Parvathaneni L, Silver MA. Utility and economic benefit of thoracic bioimped-

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tions, and Chantal C. Fletcher, MS, for her help in ensuring the accuracy of the equipment used in the study.

Figure 3. Scatterplot showing thermodilution (TD) vs. direct Fick method (Fick). CO=cardiac output

Figure 4. Bland-Altman analysis showing thermodilution vs. direct Fick method. CI=cardiac index

ICG vs. fick and TD to determine CO

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Comparison of Changes in Ejection Fraction to Changes in Impedance Cardiography Cardiac Index and Systolic Time Ratio

Ejection fraction (EF) is the most common measure of left ventricular function in patients with heart failure. However, serial measurements of EF are costly and not practical for guiding frequent management decisions. Impedance cardiography (ICG) provides noninvasive hemodynamic measures with proven validity. The purpose of this study was to assess how changes in ICG parameters compared with changes in EF in heart failure subjects enrolled in a comprehensive outpatient management program. Retrospective chart review identified 13 subjects with two sets of paired echocardiography and ICG measurements (before and after treatment in an outpatient heart failure clinic setting). Mean age was 69 ± 11 years, etiology was 54% ischemic heart disease, and mean New York Heart Association class was 2.5 ± 0.5. The mean time between pre- and posttreatment EF measurements was 198 ± 161 days. Changes in cardiac index and systolic time ratio by ICG were compared with changes in EF by echocardiography. From entry to final measurement, mean EF improved 9% ± 13%. Seven (54%) subjects had >5% improvement in EF; three (23%) had >5% decrease, and three had <5% change. Changes in ICG cardiac index and systolic time ratio were highly correlated with changes in EF (0.85, –0.73). ICG may be a practical, reliable, and cost-effective method of monitoring left ventricular function and guiding management decisions.

Heart failure (HF) is associated with diminished cardiac function and characterized by abnormal hemodynamic parameters. The most common descriptor of ventricular function in patients with HF is the ejection fraction (EF), which is obtained by imaging techniques including echocardiography. Echocardiography is time consuming and costly and EF measurement by this technique is moderately subjective. Therefore, frequent serial studies are not practical in the clinical management of patients with HF.

A simple and cost-effective noninvasive method of monitoring changes in ventricular function would be desirable in the clinical evaluation and management of patients with HF to identify and quantify decompensation or improvements due to pharmacologic or device-related interventions. Impedance cardiography (ICG) is a technology that is gaining acceptance in the evaluation and management of patients with HF. ICG utilizes the changes in thoracic impedance during the cardiac cycle to measure hemodynamic parameters with high reproducibility and strong correlation to invasive measures like thermodilution using a pulmonary artery catheter.2-4 ICG-measured systolic time intervals have been validated by comparison with reference methods like phonocardiography and have shown significant association with ventricular performance measured at a single point in time by echocardiography and radionuclide ventriculography.5-7

The purpose of this study was to determine how changes in ICG hemodynamic parameters compared with changes in EF in patients with chronic HF in a comprehensive outpatient program.

Methods

A retrospective chart review was performed for patients followed in the outpatient HF clinic at our institution between January 1, 2001, and August 31, 2003. Patients were eligible for inclusion in the study if they had two separate sets of paired EF and ICG measurements. A paired measurement was defined as an EF and ICG performed within 45 days of each other. EF was measured by standard echocardiography technique on physician order. The echocardiographic studies were performed and interpreted according to usual clinic protocols. If the echocardiography study produced a range for EF as opposed to a single number, the midpoint of that range was used as the EF for the measurement (i.e., 30%–35% = 32.5%). ICG recordings were obtained using commercially available equipment (BioZ ICG Monitor, CardioDynamics, San Diego, CA). No patients who met the paired EF and ICG measurements criteria were excluded.

EF, cardiac index (CI), and systolic time ratio (STR) data were entered into a database (Microsoft Excel, Microsoft Corp, Redmond, WA) and evaluated using the statistical analysis function.

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Continuous variables were expressed as mean ± standard deviation. Changes from initial paired measurements to final paired measurements were compared and plotted using a scatter plot format. Correlation coefficient was determined using Pearson’s method.

Results
Records from 73 patients followed in the HF clinic were reviewed for possible inclusion. Thirteen patients met the inclusion criteria, resulting in 26 paired measurements of EF and ICG parameters.

The mean age of the patients was 69±11 years. Eight patients were men (62%) and 12 (92%) were white. The etiology of HF was ischemic in seven patients (54%). Ten of 13 patients (77%) had entry EF ≤40%, suggesting primarily systolic dysfunction as the cause of their HF. The average interval between entry EF measurement and final measurement was 198±161 days, and average time between EF and its paired ICG measurements was 20±17 days. The Table shows the entry and final values for representative data elements for the patient group.

EF showed significant improvement (defined as a 5% increase in absolute terms) from entry to final measurement in seven patients (54%). Three patients (23%) had a significant worsening and three patients (23%) had no significant change in EF from entry to final measurement. Of the 10 patients with significant changes in EF (±5%), CI and STR each trended in the same direction as EF in eight patients (80%).

The change in CI as measured by ICG is plotted against change in EF in Figure 1. The correlation coefficient for changes in EF and changes in CI was 0.85. The change in STR from ICG data are plotted against change in EF in Figure 2. The correlation coefficient for the changes in EF and STR was −0.73.

Discussion
EF, the percentage of blood pumped with each heartbeat, is the most commonly cited measure of cardiac function and is routinely reported during an echocardiographic study. EF is used to characterize HF as the result of systolic or diastolic dysfunction and to stratify risk and guide therapy, such as the initiation of various medications. Serial echocardiographic studies are expensive and subject to inter- and intra-observer variation. These factors may limit the usefulness of echocardiography in guiding treatment decisions in patients with significant HF, particularly during short-term drug titration.

ICG measures of STR and CI are hemodynamic parameters that reflect cardiac pump function and contractility. CI is the amount of blood pumped by the heart in liters per minute, corrected for body surface area. Before the availability of ICG, CI could be measured only with a pulmonary artery

Table. Patient Characteristics at Entry and Final Measurements (N=13)

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ENTRY</th>
<th>FINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York Heart Association class</td>
<td>2.5±0.5</td>
<td>2.2±0.6*</td>
</tr>
<tr>
<td>No. taking a β-blocker [n [%]]</td>
<td>5 (39%)</td>
<td>13 (100%)*</td>
</tr>
<tr>
<td>No. taking an ACE inhibitor [n [%]]</td>
<td>6 (46%)</td>
<td>12 (92%)*</td>
</tr>
<tr>
<td>Ejection fraction [%]</td>
<td>29±13</td>
<td>37±11*</td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme; *p<0.01

Figure 1. Change in cardiac index (CI) vs. change in ejection fraction (EF)

Figure 2. Change in systolic time ratio (STR) vs. change in ejection fraction (EF)
catheter in the intensive care unit or catheterization laboratory and was not available in the office setting. STR, calculated as the ratio of the preejection period (time from onset of electrical systole to onset of mechanical systole) to left ventricular ejection time (duration of mechanical systole), negatively correlates with contractility and overall left ventricular performance.9

This study demonstrated strong correlations and directional agreement between changes in EF and changes in two ICG hemodynamic measures in patients undergoing treatment in an outpatient HF clinic. It is unclear whether the small differences that did exist occurred because of a change in ventricular function between the time of ICG and EF measurements, EF measurement variability, ICG measurement variability, or truly independent but converse measurements of cardiac function such as CI decreasing with EF increasing.

Because echocardiography evaluation is often prohibitive due to cost and reimbursement constraints, ICG measurements, which can be obtained easily and cost-effectively in an office setting, may serve as a valuable adjunct to and more cost-effective and appropriate means for day-to-day management of patients with HF. In addition to the HF clinic or cardiology setting, ICG is also easily available to general practitioners and internists and thus can help in the care of patients who do not have ready access to specialized cardiology clinics. ICG might help any practitioner recognize changes in a patient’s status more promptly, leading to treatment that could prevent clinical decompensation and hospital admission.

Published guidelines for the management of patients with HF stress the importance of β blockers and angiotensin-converting enzyme inhibitors for persons with systolic dysfunction. HF programs have demonstrated improvement via the use of these two medications that have been linked to improved functional class and prognosis.10 It is noted that patients in this study benefited from a significant increase in the use of these two classes of medications during the course of follow-up, and showed improvement in average EF and New York Heart Association functional class. The mechanisms of β blockers and angiotensin-converting enzyme inhibitor actions are likely due to both neurohormonal and hemodynamic factors. It is not established that the long-term benefits are related to short-term hemodynamic effects. However, in the day-to-day treatment decisions of using these medications, the hemodynamic considerations are clearly important and may limit the ability to initiate or up-titrate dosing regimens. The availability of accurate hemodynamic measures that correlate with EF measures of left ventricular function, such as the ICG-derived changes in CI and STR, can provide clinicians with valuable information with which to make management decisions.

The most significant limitations of this study are the small sample size and its retrospective design. In addition, the paired EF and ICG studies were not performed concurrently, raising the possibility that the patients may have had changes in hemodynamic status between the paired EF and ICG examinations. Added variability in EF measurements also likely occurred due to different technician operators and physician interpreters.

The strong correlation with changes in EF suggests that ICG may be a valuable and cost-effective tool for monitoring ventricular function in patients with HF due to decompensation or therapeutic intervention. Further study, including a larger series of patients enrolled in prospective fashion, is recommended.

REFERENCES

Utility of Impedance Cardiography to Determine Cardiac vs. Noncardiac Cause of Dyspnea in the Emergency Department

Determining the correct diagnosis of patients with dyspnea can be challenging. Early and accurate determination of the cause of dyspnea is vital in instituting timely and appropriate interventions. Hemodynamic parameters may aid in the evaluation of dyspnea, but are difficult to assess by physical exam. Impedance cardiography (ICG) is a newly validated method of determining hemodynamic parameters noninvasively. The purpose of this study was to determine the accuracy in differentiating cardiac from noncardiac causes of dyspnea utilizing ICG-derived hemodynamic parameters compared with that of emergency department (ED) physicians after initial history, physical, and laboratory tests. The final diagnosis, which was made retrospectively after review of the patient’s hospital record by a senior ED physician blinded to the ICG data, was compared with the treating ED physician’s and the ICG diagnoses. Thirty-eight patients who presented with dyspnea to a community ED were included in the study. There were significant differences in values of cardiac index by ICG (2.2 vs. 3.1; p<0.0001), systolic time ratio (0.52 vs. 0.37; p<0.01) and velocity index (32.9 vs. 42.7; p<0.01) between the cardiac and noncardiac groups, respectively. ICG measurements demonstrated greater sensitivity (92 vs. 83%), specificity (88 vs. 77%), and positive and negative predictive values (79 vs. 63% and 96 vs. 91%, respectively) compared with the ED physician in distinguishing cardiac from noncardiac cause of dyspnea. ICG can aid ED physicians in making more rapid and accurate determinations of cardiac vs. noncardiac cause of dyspnea. (CHF. 2004;10(2 suppl 2):14–16) ©2004 CHF, Inc.

Shortness of breath, or dyspnea, is the seventh most frequent cause of emergency department (ED) visits in the United States, accounting for more than 2.5 million visits per year. To identify the appropriate therapy for patients presenting with dyspnea, a determination must be made whether symptoms are due to a cardiac or noncardiac etiology. The evaluation of such patients is often challenging, especially when they have a history of both cardiac and pulmonary disease. Patients with cardiac disease may present with an altered hemodynamic state for which treatment needs to be targeted, but obtaining hemodynamic data via pulmonary artery catheterization is associated with cost and risk and is not standard care in the ED management of such patients. Studies have demonstrated that hemodynamic data cannot be reliably estimated by physician examination. Therefore, rapid and objective hemodynamic measurements in the ED may provide significant value in clinical decision making.

Impedance cardiography (ICG) is a validated, noninvasive method of determining hemodynamic parameters. Previous studies of ICG have demonstrated utility in the differential diagnosis of dyspnea, the prediction of hospital charges and length of stay, and the ability to change the real-time diagnosis and treatment decisions in dyspneic patients.

Methods Study Design. A prospective, blinded study was conducted to compare the ability of ICG hemodynamic measurements and ED physician diagnosis to determine cardiac or noncardiac cause of dyspnea.

Setting and Population. A convenience sample of patients presenting to the ED at a community hospital was enrolled. Patients were included if they met one or more of the following criteria: complaints of trouble breathing or shortness of breath, respiratory rate >20/min, or hypoxia (arterial oxygen concentration <90 on room air). Patients were excluded if they were <18 years of age, <3 ft 11 in or >7 ft 8 in tall, <66 lb or >341 lb, identified as trauma patients, unconscious or unable to speak, or pregnant.

Study Protocol. The Institutional Review Board approved the study protocol and informed consent was obtained for all study participants. All patients received a history and physical examination by an ED physician, as well as the following standard tests: electrolytes, kidney and liver function, complete blood count, electrocardiogram.

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chest radiograph, and arterial blood gas. When deemed medically necessary, an echocardiogram was performed.

The treating physician was blinded to noninvasive hemodynamic monitoring by ICG (BioZ ICG Monitor, CardioDynamics, San Diego, CA), which was collected on all patients. ICG utilizes four dual sensors on the neck and chest to apply a low amplitude, high frequency alternating electrical current to the patient’s thorax. Pulsatile changes in blood volume and velocity are measured as impedance changes and then applied to electrocardiogram and arterial blood pressure measurements to automatically calculate hemodynamic parameters such as cardiac output/cardiac index (CI), systemic vascular resistance index, and contractility and fluid indices.

The ED physician used the standard tests to diagnose the patient. A research assistant monitored patient enrollment, performed all ICG monitoring tests, and documented all data points.

Data Analysis. All data were entered into a spreadsheet (Microsoft Excel, Microsoft Corp, Redmond, WA). Following discharge from the hospital, each patient’s medical record was reviewed by a board-certified ED physician who was blinded to ICG results and not involved in the treatment of any study patients. Using all data recorded in the medical record, the reviewing physician determined a final hospital diagnosis, including whether the dyspnea was of cardiac or noncardiac origin.

ICG data were evaluated retrospectively and criteria for ICG-derived cardiac cause of dyspnea were defined as either a CI <2.4 or systolic time ratio (STR) >0.55 concurrent with a CI <3.0. For each patient, final diagnosis was compared with ICG-derived and ED physician diagnosis. Continuous variables are expressed as mean ± standard deviation. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results
Forty patients were enrolled in the study. Two were excluded due to an inability to obtain ICG data. No patients died during the course of the study. There were 16 men and 22 women included; the average age was 67.2±15.2 years. Twelve patients had a final diagnosis of cardiac cause of dyspnea, 26 had a noncardiac cause. Echocardiograms were deemed medically necessary in 24 patients, and results were provided in advance of ED physician diagnosis in 10 of these patients.

Patients with a cardiac cause of dyspnea had significantly (p<0.05) lower CI and velocity index, and higher STR and systemic vascular resistance index. A comparison of hemodynamic values of the cardiac and noncardiac groups is shown in Table I.

From the time of ED admission, chest radiographs were completed in 1 hour 22 minutes (±48) minutes, and ED physician diagnosis in 2 hours 57 minutes (±1 hour 14 minutes). Compared with the final diagnosis, the overall diagnostic accuracy by the ED physician was 79% (30/38) compared with 89% (34/38) for ICG. The ED physician diagnosed 10/12 patients correctly with a final diagnosis of cardiac cause, and 20/26 with noncardiac cause. ICG correctly diagnosed 11/12 patients with cardiac cause, and 20/26 with noncardiac cause. ICG demonstrated superior sensitivity, specificity, positive predictive values, and negative predictive values when compared with the ED physician in the final diagnosis of cardiac vs. noncardiac cause of dyspnea (Table II).

Discussion
Today’s ED environment challenges physicians to make decisions more quickly with greater reason to fear liability for

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Table I. Summary of Hemodynamic Statistics (N=38)*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>CARDIAC FINAL DX (n=12)</th>
<th>NONCARDIAC FINAL DX (n=26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI (mL/m²)</td>
<td>31.8 [25.3–38.4]</td>
<td>35.9 [32.9–38.9]</td>
<td>0.24</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.2 [1.9–2.5]</td>
<td>3.1 [2.9–3.3]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SVRI (dyne x s x cm⁵ x m²)</td>
<td>2742 [2066–3420]</td>
<td>2106 [1903–2309]</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VI (1/1000/s)</td>
<td>32.9 [25.9–39.9]</td>
<td>42.7 [38.4–47.1]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>STR</td>
<td>0.52 [0.37–0.68]</td>
<td>0.37 [0.33–0.41]</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

DX=diagnosis; SI=stroke index; CI=cardiac index; SVRI=systemic vascular resistance index; VI=velocity index; STR=systolic time ratio; *values are expressed as mean (95% confidence interval)

Table II. Summary Diagnosis Statistics (N=38)

<table>
<thead>
<tr>
<th>METHOD</th>
<th>SENSITIVITY (%)</th>
<th>SPECIFICITY (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG</td>
<td>92</td>
<td>88</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td>ED physician</td>
<td>83</td>
<td>77</td>
<td>63</td>
<td>91</td>
</tr>
</tbody>
</table>

Sensitivity=probability that a person with a true cardiac cause will test cardiac by the method; specificity=probability that a patient with a true noncardiac cause will test noncardiac by the method; PPV=positive predictive value, the probability that a person who tests cardiac is truly a cardiac cause; NPV=negative predictive value, the probability that a person who tests noncardiac is truly a noncardiac cause.
 mistakes. Even with the laboratory and diagnostic tests available to ED physicians today, an accurate initial determination of the underlying cause of emergent dyspnea remains challenging. Therefore, both the theoretical and practical benefits of a real-time monitor that would aid in the differential diagnosis and treatment of dyspnea are clear.

Our goal was to ascertain if ICG-derived hemodynamic data could be used to distinguish between cardiac and noncardiac causes of dyspnea in an adult population presenting to the ED. In this study, retrospective evaluation with ICG was able to accurately differentiate between cardiac- and noncardiac-related cause of dyspnea with greater sensitivity, specificity, and positive and negative predictive value compared with an ED physician using conventional methods.

In this study we independently evaluated ICG data and the treating ED physician’s diagnosis. However, in clinical practice ICG would not be utilized as a stand-alone test but by an ED physician in conjunction with other available laboratory and diagnostic tests. McCullough et al.14 reported that the accuracy of ED physicians in diagnosing cardiac vs. noncardiac cause of dyspnea was 74% in a study of 1586 patients. While our population was significantly smaller, the diagnostic accuracy of ED physicians was similar (79%). In the study by McCullough et al.,15 they also sought to determine if overall diagnostic accuracy could be improved by adding a screening test for B-type natriuretic peptide (BNP). The addition of BNP testing increased the overall diagnostic accuracy to 81.5%, but it was also concluded that BNP testing had little impact on medical decision making for patients who were already given a primary diagnosis of heart failure.

ICG information can be easily obtained by a nurse or cardiovascular technician in 3–5 minutes and does not require blood draw or time for laboratory analysis.15 This study did not compare ICG to BNP or evaluate the ability of ICG to change medical decision making. However, results from the Emergency Department Impedance Cardiography-aided Assessment Changes Therapy (ED-IMPACT) trial demonstrated that rapid provision of ICG hemodynamic information resulted in a change in treatment plan in 24% of dyspneic patients,12 while a similar study with BNP resulted in an 11% change.16 ICG measures have been shown to reliably reflect various aspects of cardiac function including blood flow (stroke volume and cardiac output), afterload (systemic vascular resistance), contractility (velocity index and STR), and changes in fluid status (thoracic fluid content). This information, available in real time, will likely allow a more targeted approach to correcting the hemodynamic abnormalities that may exist. In heart failure patients, for example, the ability to monitor cardiac output/CI or systemic vascular resistance in addition to blood pressure can identify vasoconstriction that would otherwise be unrecognized. In a dyspneic patient with normal blood pressure, low CI, and high systemic vascular resistance, an ED physician may be more likely to administer a vasodilating agent to treat the underlying hemodynamic cause of the symptoms, reducing afterload and improving cardiac output.

Data from the Acute Decompensated Heart Failure (ADHERE) registry demonstrate a clear mortality benefit in early administration of nitroglycerin or nesiritide in acute decompensated heart failure,17 and it is quite conceivable that ICG data could help increase the utilization of these two agents.

This study’s limitations include its small sample size and retrospective criteria for ICG diagnosis. A prospective trial with a larger set of subjects is needed to establish with greater confidence which hemodynamic parameters of ICG have the greatest value in assessing patients with dyspnea in the ED.

ICG can aid physicians in the differential diagnosis of dyspnea in a more accurate, timely, and cost-effective manner. This provides a sufficient rationale to consider ICG an important and emerging new tool in the diagnosis and treatment of dyspnea.

**References**


Evaluation of Impedance Cardiography as an Alternative to Pulmonary Artery Catheterization in Critically Ill Patients

Invasive pulmonary artery catheterization has historically been the method of choice for the evaluation of hemodynamic status. Impedance cardiography (ICG) is an accurate, noninvasive technique to obtain hemodynamic status information without the risk and cost associated with invasive methods. The purpose of this prospective, observational study was to determine whether the availability of ICG could decrease the need for placement of a pulmonary artery catheter in critically ill patients in coronary care units. After the need for hemodynamic data was determined, ICG parameters were provided to the attending physician who then decided whether pulmonary artery catheter insertion was still necessary. Of 107 subjects enrolled in the study, 14 (13%; 95% confidence interval, 7.3%–21.0%) were judged by the treating physicians to have indications for hemodynamic monitoring. In these subjects, the provision of ICG data allowed the physician to avoid placement of a pulmonary artery catheter in 10/14 patients (71%; 95% confidence interval, 41.9%–91.6%). When ICG was utilized, clinicians reported that the information was helpful in 10/10 patients (100%; 95% confidence interval, 74.1%–100.0%) and improved outcome in 6/10 patients (60%; 95% confidence interval, 26.2%–87.8%). ICG can replace the pulmonary artery catheter in coronary care unit patients, and clinicians utilizing ICG believe it aids medical decision making and improves patient outcomes.

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flutter, or frequent premature ventricular contractions (≥6/min).

Upon enrollment, the attending physician identified whether the patient needed hemodynamic monitoring via PAC. Once identified, ICG measurements were obtained in the supine position (BioZ ICG Monitor, Model 4110–101, CardioDynamics, San Diego, CA). The ICG method requires four sets of dual sensors, two sets attached at the base of the neck and two sets attached at the side of the patient's chest at the level of the xiphoid process in the mid-axillary line (Figure 1). The outer sensors transmit an alternating electrical current that is not felt by the patient; the inner sensors measure the changes in electrical impedance due to changes in the thoracic cavity. Changes in impedance are measured and used to calculate real-time hemodynamic parameters.

All ICG measurements were performed by nurses or technicians trained to use the device. A report listing the following ICG hemodynamic parameters was provided to the treating physician: stroke volume/stroke index, cardiac output/cardiac index, systemic vascular resistance/systemic vascular resistance index, and TFC.

Upon provision of the ICG data, the physician determined whether ICG could be used alone to provide hemodynamic information or if PAC insertion and monitoring were still required. If ICG information was sufficient, the physician documented its influence on patient care. When ICG was not used as the primary measurement for hemodynamics, the reason was documented.

Data are expressed in absolute and relative percent terms, and 95% confidence intervals were determined by a Monte Carlo simulation of 100,000 iterations.

Results
One hundred seven patients entering the CCU were screened for the need for invasive PAC placement and monitoring. The mean age was 71 years. Primary cardiac diagnosis was either decompensated HF or acute myocardial infarction. Some patients had a secondary diagnosis of pulmonary disease.

The study results with 95% confidence intervals are listed in Table I, and a flow diagram illustrating the decision-making process and results is shown in Figure 2. Of the 107 patients enrolled, 14 (13%) were initially judged as appropriate candidates for hemodynamic monitoring using a PAC. After the ICG data were made available to the treating physician, ICG was used in lieu of a PAC in 10 of 14 patients (71%). ICG data were rated as helpful in clinical decision making by the physician in all 10 of these cases (100%), and rated as helpful in improving the patient outcome in 6 of 10 patients (60%). In each of the four patients (29%) in whom PAC monitoring was still preferred after the provision of ICG data, the reason provided was unfamiliarity with ICG technology.

Discussion
There has been considerable debate about whether the benefits of PAC justify the risks associated with invasive monitoring. The central question is whether the hemodynamic information obtained by the PAC outweighs the potential for infection and other complications associated with an indwelling right heart catheter. Physicians who utilize PAC monitoring in patients hospitalized with HF maintain that the information is helpful in their disease management decisions for a particular patient. However, due to the lack of proven benefit of the PAC in prospective trials and the cost and risk associated with the procedure, many physicians treating hospitalized HF have reduced or eliminated their use of hemodynamic monitoring in such cases.

Although ICG does not provide pulmonary artery or pulmonary artery wedge (PAW) pressures, it does provide reliable and reproducible measures of cardiac index, stroke volume, systemic vascular resistance, and other hemodynamic parameters. In this study, ICG data allowed physicians to avoid performing PAC placement in 10 of the 14 patients in whom they originally deemed invasive monitoring necessary. Thus, 71% of patients who would otherwise have been subjected to the risks of right heart catheterization, including...
infection and pneumothorax, were managed successfully using only ICG. Others have suggested that ICG may offer enough similar information to reduce the need for a certain percentage of some invasive procedures, and have estimated that when ICG is utilized in place of PAC, cost savings are between $600 and $3088 per patient.\textsuperscript{26,27} As physicians become more comfortable with the use of ICG, it is likely that a significant portion of patients in CCUs will

<table>
<thead>
<tr>
<th>Table I. Study Results</th>
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</thead>
<tbody>
<tr>
<td><strong>VARIABLE</strong></td>
</tr>
<tr>
<td>Subjects enrolled</td>
</tr>
<tr>
<td>Need for PAC determined</td>
</tr>
<tr>
<td>ICG data used as primary HD data</td>
</tr>
<tr>
<td>PAC placed after ICG data</td>
</tr>
<tr>
<td>ICG rated as aiding decision making</td>
</tr>
<tr>
<td>ICG rated as helping improve patient outcome</td>
</tr>
</tbody>
</table>

CI=confidence interval; PAC=pulmonary artery catheter; ICG=impedance cardiography; HD=hemodynamic

<table>
<thead>
<tr>
<th>Table II. Projected Procedural Cost Savings With Impedance Cardiography (ICG)</th>
</tr>
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<tbody>
<tr>
<td><strong>ITEM</strong></td>
</tr>
<tr>
<td>PAC</td>
</tr>
<tr>
<td>Central venous catheter insertion kit</td>
</tr>
<tr>
<td>Pressure tubing</td>
</tr>
<tr>
<td>Premixed heparin drip</td>
</tr>
<tr>
<td>Trifurcated transducer monitor set</td>
</tr>
<tr>
<td>Co-set apparatus</td>
</tr>
<tr>
<td>Sterile gown, mask, gloves, drapes, and dressing</td>
</tr>
<tr>
<td>Medication for procedural sedation</td>
</tr>
<tr>
<td>Fluoroscopy procedure and interpretation</td>
</tr>
<tr>
<td>Additional ICU days cost ($1000/d)*</td>
</tr>
<tr>
<td>Nursing care time (site and catheter care) for 2 d (30 min/d × $30/h)</td>
</tr>
<tr>
<td>Physician insertion cost (CPT 93501)</td>
</tr>
<tr>
<td>ICG disposable/procedural cost</td>
</tr>
<tr>
<td>ICG technician time (5 min × $30.00/h) × 2 d</td>
</tr>
<tr>
<td>ICG physician professional interpretation (CPT 93701–26)</td>
</tr>
<tr>
<td>Total procedure cost</td>
</tr>
</tbody>
</table>

PAC=pulmonary artery catheterization; CPT=current procedural terminology; *days for typical, low, and high are derived from 25th, 50th, and 75th percentile differences between intensive care unit (ICU) bed days of PAC and non-PAC patients, from Connors AF, Peroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA. 1996;276(11):889–897. Adapted with permission from AACN Clin Issues. 1999;10(3):419–426.\textsuperscript{27}

<table>
<thead>
<tr>
<th>Table III. Projected Annualized Cost Savings by Percent Reduction and Pulmonary Artery Catheterization (PAC) Volume Per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO. OF PAC PROCEDURES PERFORMED PER MONTH</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>100</td>
</tr>
</tbody>
</table>

*Percentage of PAC procedures replaced with impedance cardiography

ICG as an alternative to PAC
ICG as an alternative to PAC

Significant portions of HF patients who are admitted to a hospital are not treated in a CCU or with hemodynamic parameters via the PAC. These patients may benefit from the use of ICG, which can easily be performed in an emergency department and subacute setting. The use of ICG in non-critical-care treatment may also result in significant cost savings, due to more targeted treatment of hemodynamic instability, effective titration of medications, and determination of patient stability for discharge.

In this study, the lack of PAW pressure did not appear to be a deterrent to utilizing ICG in place of PAC. Although isolated ICG measurements of TFC correlate poorly with PAW pressure, previous studies have shown that changing TFC levels can be utilized to monitor extravascular and intravascular volume changes. These studies have demonstrated sensitivity in monitoring changes in response to diuretic therapy as well as thoracentesis and pericardiocentesis.

One case report showed a similar relative reduction in TFC as with PAW pressure in response to treatment. Physicians rated ICG information as helpful in their decision-making process in all patients and believed it improved patient outcome in 60% of cases. Whether ICG actually influenced a change in intended treatment in these patients was not evaluated. However, a recent study in dyspneic patients demonstrated that ICG data changed the attending physician’s therapeutic plan a substantial 24% of the time.

These results suggest the potential for broad utilization of ICG technology, although there are certain limitations to this study. This was a small, behavioral study without defined end points to describe patient outcomes. There was no control group to compare patient care decision-making interventions based on the two different methods of hemodynamic monitoring and the findings are limited to the treatment of medical CCU patients.

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) is a multicenter, randomized controlled trial designed to test outcomes of PAC-guided therapy compared with that guided by clinical assessment alone in hospitalized HF patients. The BioImpedance cardioGraphy (BIG) substudy of ESCAPE will examine the diagnostic and prognostic role of ICG hemodynamic data collected in a blinded fashion. The data from ESCAPE and BIG will help define the future role of hemodynamic-guided therapy and ICG in the treatment of advanced HF.

The results of this study indicate that noninvasive hemodynamic parameters obtained by ICG can be used in a significant portion of patients who would otherwise require PAC placement. Clinicians using ICG believed the information was helpful in guiding therapeutic decisions and improving patient outcomes.

Figure 2. Flow chart of decision-making process and study results.

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>CCU patients with a potential need for HD monitoring (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physician determination of need for HD monitoring</td>
</tr>
<tr>
<td></td>
<td>HD monitoring required (n=14) (13%)</td>
</tr>
<tr>
<td></td>
<td>HD monitoring not required (n=93) (87%)</td>
</tr>
<tr>
<td></td>
<td>ICG data provided/physician determination of PAC requirement</td>
</tr>
<tr>
<td></td>
<td>PAC not required (n=10) (71%)</td>
</tr>
<tr>
<td></td>
<td>PAC required (n=4) (29%)</td>
</tr>
</tbody>
</table>

CCU=coronary care unit; HD=hemodynamic; PAC=pulmonary artery catheter; ICG=impedance cardiography.
REFERENCES


Association of Impedance Cardiography Parameters With Changes in Functional and Quality-of-Life Measures in Patients With Chronic Heart Failure

Assessment and prognosis of chronic heart failure is often difficult due to a lack of objective and easily obtainable parameters that accurately reflect disease status. This study was conducted to determine whether impedance cardiography (ICG) parameters were associated with changes in functional and quality-of-life measures in chronic heart failure patients. Retrospective chart review identified 64 patients (73% male, aged 73 ± 13 years) with paired ICG measurements followed for 180 ± 113 days. Outcome measures were changes in New York Heart Association class, 6-minute walk distance, patient visual analog scale score, and Minnesota Living with Heart Failure Questionnaire score. Measures of ICG, heart rate and blood pressure, left ventricular ejection fraction, and B-type natriuretic peptide levels were assessed for their association with outcome measures. From baseline to final evaluation, there were significant changes (p < 0.05) in New York Heart Association class (from 3.2 ± 0.5 to 3.0 ± 0.6), 6-minute walk distance (from 668 ± 380 m to 874 ± 390 m), patient visual analog scale score (from 49 ± 10 to 64 ± 20), Minnesota Living with Heart Failure Questionnaire score (from 54 ± 22 to 39 ± 22), and ICG parameters of stroke index (from 38 ± 9 to 41 ± 8), left ventricular ejection time (from 273 ± 42 to 291 ± 33), and systolic time ratio (from 0.56 ± 0.2 to 0.52 ± 0.2). Changes in multivariate ICG parameters were significantly correlated to changes in New York Heart Association class (R = 0.80), 6-minute walk distance (R = 0.94), patient visual analog scale score (R = 0.69), and Minnesota Living with Heart Failure Questionnaire score (R = 0.67). ICG provides objective data that reflects changes in chronic heart failure disease status and treatment effectiveness.


Methods

Subjects. Patients in this study were enrolled from a comprehensive outpatient HF program that included education, pharmacologic optimization, implantable device therapy, and behavior modification. Patients were treated by a single HF specialist with the goal of improving and extending life while decreasing need for hospitalization. Patient visits were scheduled as medically necessary. All patients with at least two visits at least 3 months apart and with paired ICG measurements were eligible for inclusion. Variables other than ICG were not always collected on visits when ICG measurements were performed, but the lack of availability of other variables did not exclude any patient from the study.

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E-mail: kvijay@azheart.com
Data Collection. All variables were obtained on physician order and were available to the treating physician. Functional measures included New York Heart Association (NYHA) classification and 6-minute walk distance (6MW) in meters. Additional patient-assessed qualitative measures included a quality-of-life assessment using a visual analog scale (VAS) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. Vital signs included heart rate (HR), systolic blood pressure, and diastolic blood pressure. Diagnostic testing of left ventricular ejection fraction (LVEF) was performed with transthoracic echocardiography. B-type natriuretic peptide (BNP) levels (BNP Triage, Biosite, San Diego, CA) and ICG noninvasive hemodynamic variables (BioZ ICG Monitor, CardioDynamics, San Diego, CA) were obtained. To obtain ICG parameters, patients were in a supine position and sensors were placed on both sides of the neck and lower thorax. After approximately 3 minutes, the measurements were recorded on the hemodynamic status report. All measures were repeated as necessary during subsequent visits to the clinic.

Database Creation and Statistical Analysis. A retrospective chart review was conducted for all enrolled patients. All available variables from the patient records were recorded in a database (MS Excel, Microsoft Corp, Redmond, WA) and analyzed with statistical analysis software (SAS, SAS Institute, Cary, NC). Measured variables were expressed as mean ± standard deviation. Individual variable differences from baseline to final were determined using the paired Student t test with significance at p<0.05. To compare changes in variables to each other, predictive measures were grouped in four categories: vital signs, LVEF, BNP, and ICG. Linear regression models were created to examine the association of the changes in predictive measures from baseline to final to changes in functional (NYHA, 6MW) or qualitative (VAS, MLHFQ) outcome measures. Each outcome measure was modeled with its baseline value as a covariate to evaluate the change in the predictive measure while adjusting for the initial value of the outcome measure. Univariate and multivariate models were created with quadratic fits to adjust for nonlinear relationships. The baseline for each end point was then fit and quadratic terms for the variable(s) in each series: vital signs, LVEF, BNP, and ICG. The baseline to final were determined using the paired Student t test with significance at p<0.05. To compare changes in variables to each other, predictive measures were grouped in four categories: vital signs, LVEF, BNP, and ICG. Linear regression models were created to examine the association of the changes in predictive measures from baseline to final to changes in functional (NYHA, 6MW) or qualitative (VAS, MLHFQ) outcome measures. Each outcome measure was modeled with its baseline value as a covariate to evaluate the change in the predictive measure while adjusting for the initial value of the outcome measure. Univariate and multivariate models were created with quadratic fits to adjust for nonlinear relationships. The baseline for each end point was then fit and quadratic terms for the variable(s) in each category grouping were added. The R² and adjusted R² for each model were calculated as indicators of the adequacy of the models. The p values were calculated using the Fisher exact test, with p<0.05 considered statistically significant.

| Table I. Baseline Clinical Characteristics (N=64) |
|-----------------|-----------------|-----------------|
| Age (years)     | 73.1±13         |
| Male gender (n [%]) | 47 (73)         |
| Ischemic heart disease (n [%]) | 48 (76)         |
| Mean NYHA class | 3.2±0.5         |
| LVEF [%]        | 25±10           |
| Creatinine [mg/dl] | 1.6±1.1        |

| Table II. Pharmacologic Treatment Changes |
|-----------------|-----------------|-----------------|
| PHARMACOLOGIC AGENT | BASELINE | N | % | N | % |
| ACE inhibitor   | 32            | 50 | 31 | 48 |  |  |
| ARB             | 13            | 20 | 11 | 17 |  |  |
| Digitalis       | 35            | 55 | 59 | 92 |  |  |
| Blocker         | 46            | 72 | 57 | 89 |  |  |
| Diuretic        | 52            | 81 | 59 | 92 |  |  |

NYHA=New York Heart Association class; LVEF=left ventricular ejection fraction

Results

Patient Characteristics. Sixty-four patients (73% male, aged 73.1±13 years) were enrolled in the study, with a mean observational time of 180±113 days. Baseline patient characteristics are summarized in Table I. NYHA class II accounted for five patients (8%), with 47 patients (73%) in class III, and 12 patients (19%) in class IV.

Treatment. Table II displays the changes in pharmacologic treatment. Compared with baseline and at final measurement, there were significantly more patients taking β-blockers (89% vs. 72%), diuretics (92% vs. 55%), and digitalis (92% vs. 72%). In addition, during the study period, 15 patients (23%) received biventricular pacemakers, 12 (19%) received automatic implantable cardioverter-defibrillators, and one (3%) received dual chamber pacemakers.

Hospitalizations and Deaths. Thirty-one patients (48%) were hospitalized during the study period, with 10 (16%) primarily for the exacerbation of HF. Eight patients (13%) died during the study, with five deaths specifically attributed to HF.

Frequency of Comparison Variables. In the 64 enrolled patients with paired ICG measurements, NYHA class data was available for 56 (88%), 6MW data for 39 (61%), VAS score data for 30 (47%), and MLHFQ score data for 44 (69%). Paired measurements of vital signs, LVEF, and BNP were available with NYHA data in 56, 35, and 36 patients, 6MW with 39, 24, and 28 patients, VAS with 30, 19, and 23 patients, and MLHFQ data in 44, 24, and 30 patients, respectively.

Baseline to Final Variable Changes. Significant group changes occurred in functional measures of NYHA class (from 3.2±0.5 to 3.0±0.6; p<0.01) and 6MW (from 667.7±380 m to 874.2±390 m; p<0.001) and qualitative measures of VAS (from 49±10 to 64±20; p<0.01) and MLHFQ score (54.4±22 to 39.3±22; p<0.0001). ICG measurement.
parameters showing significant change between paired measurements included stroke index (from 37.6±9 mL/m² to 40.9±8 mL/m²; p < 0.01), stroke volume (from 71.2±19 mL to 76.8±17 mL; p < 0.01), left ventricular ejection time (from 273±42 ms to 291±33 ms; p < 0.05), and systolic time ratio (from 0.56±0.2 to 0.52±0.2; p < 0.05). HR also changed significantly (from 72.7±13 to 67.4±9 bpm; p < 0.001). No significant changes occurred with BNP (from 568±338 pg/mL to 575.8±375 pg/mL; p = 0.47) or LVEF (from 25.5±12% to 29.5±13%; p = 0.11), although there were fewer baseline to end point measurements of LVEF (n = 37) and BNP (n = 42) than with ICG. ICG parameters of thoracic fluid content (from 33.9±7/kOhm to 32.4±7/kOhm; p = 0.13), acceleration index (from 82.7±34/100/s² to 88.6±37/100/s²; p = 0.14), and systemic vascular resistance index (from 2380±647 to 2267±684 dyne · s · cm⁻¹ · m²; p = 0.18) trended toward improvement, but changes were not statistically significant.

### Regression Analysis

Table III displays the full results of the univariate and multivariate regression analysis of predictor measures of vital signs, LVEF, BNP, and ICG to outcome measures of NYHA class (0.68, 0.59, 0.61, 0.80), 6MW (0.79, 0.73, 0.82, 0.94), VAS score (0.42, 0.22, 0.33, 0.69), and MLHFQ score (0.46, 0.47, 0.40, 0.67), respectively. Table IV displays the univariate ICG parameter association with outcome measures. The strongest univariate ICG parameter correlation with NYHA class was preejection period (R = 0.71), with 6MW were acceleration index and cardiac index (R = 0.76), with VAS was systemic vascular resistance index (R = 0.50), and with MLHFQ was cardiac index (R = 0.50).

### Discussion

Disease prognosis has always been, and will remain, of fundamental importance to physicians. In patients with HF, a more easily obtainable, objective evaluation of chronic HF status and prognosis would be of great value because it could increase awareness of pending decompensation and provide a feedback mechanism for short-term pharmacologic treatment decisions. This could allow more aggressive treatment strategies to prevent clinical decompensation. In clinical studies of HF, functional and quality-of-life measures such as NYHA class, 6MW, VAS score, and MLHFQ score have been used and well validated. However, these measures of clinical status and outcome are not consistently used in the management of HF in the vast majority of patients. Measurement of vital signs such as HR, systolic blood pressure, and diastolic blood pressure, and ventricular function with LVEF are performed more routinely in chronic HF patients, although the value of serial LVEF measurement has been debated.

In previous studies, ICG hemodynamic parameters have shown diagnostic value in determination of cardiac vs. noncardiac causes of emergent dyspnea, profiling of emergent HF vs. non-HF, and determination of systolic dysfunction vs. preserved systolic function. Prognostic value has been shown in advanced HF in profiling survivors vs. nonsurvivors and in association with need for hospitalization. ICG has demonstrated value in therapeutic management with pacemaker optimization, β blocker titration, and in documenting hemodynamic stability and improvement.

### Table III. Predictor Measure Association With Outcome Measures

<table>
<thead>
<tr>
<th>OUTCOME MEASURE</th>
<th>PREDICTOR MEASURE</th>
<th>R</th>
<th>R²</th>
<th>N</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>Vitals</td>
<td>0.68</td>
<td>0.46</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
<td>0.59</td>
<td>0.35</td>
<td>35</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td>0.61</td>
<td>0.37</td>
<td>36</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>ICG</td>
<td>0.80</td>
<td>0.64</td>
<td>55</td>
<td>0.0001</td>
</tr>
<tr>
<td>6MW</td>
<td>Vitals</td>
<td>0.79</td>
<td>0.63</td>
<td>39</td>
<td>0.0795</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
<td>0.73</td>
<td>0.55</td>
<td>24</td>
<td>0.4429</td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td>0.82</td>
<td>0.69</td>
<td>28</td>
<td>0.8425</td>
</tr>
<tr>
<td></td>
<td>ICG</td>
<td>0.94</td>
<td>0.89</td>
<td>39</td>
<td>0.0016</td>
</tr>
<tr>
<td>VAS</td>
<td>Vitals</td>
<td>0.42</td>
<td>0.17</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
<td>0.22</td>
<td>0.05</td>
<td>19</td>
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</tr>
<tr>
<td></td>
<td>BNP</td>
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<td>0.11</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>ICG</td>
<td>0.69</td>
<td>0.48</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLHFQ</td>
<td>Vitals</td>
<td>0.46</td>
<td>0.21</td>
<td>44</td>
<td>0.0333</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
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<td>24</td>
<td>0.0688</td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td>0.40</td>
<td>0.16</td>
<td>30</td>
<td>0.0401</td>
</tr>
<tr>
<td></td>
<td>ICG</td>
<td>0.67</td>
<td>0.45</td>
<td>44</td>
<td>0.0090</td>
</tr>
</tbody>
</table>

NYHA=New York Heart Association class; 6MW=6-minute walk test; VAS=visual analog scale score; MLHFQ=Minnesota Living with Heart Failure Questionnaire; Vitals=heart rate and blood pressure; LVEF=left ventricular ejection fraction; BNP=B-type natriuretic peptide; ICG=impedance cardiography.
with intravenous nesiritide administration.\textsuperscript{31,42} This evidence, along with familiarity of invasive hemodynamic parameters and positive anecdotal experiences with ICG, has prompted some comprehensive HF management programs to incorporate ICG measurements into their care pathways for both chronic and acute HF.\textsuperscript{43}

In our study, significant changes in pharmacologic and device therapy occurred from baseline to final measurement. These therapies were instituted because of their proven ability to improve outcomes, and in this population also resulted in the improvement in functional and qualitative measures. However, clinicians treating HF understand that patient response differs with each intervention—pharmacologic, device, or otherwise—which has created the need for more objective measures with which to evaluate therapeutic options.

The lack of a univariate change from baseline to final should not necessarily be taken as a lack of value of a measured variable. Some patients improved and others worsened during the study period. The comparison of changes in variables, therefore, provides a more useful framework for understanding their association to chronic HF status. Previous reports have demonstrated a link between NYHA and 6MW and invasive hemodynamics.\textsuperscript{44} In this study, we demonstrated significant ICG parameter changes from baseline to final, and univariate association with changes in functional measures (NYHA and 6MW) and quality-of-life measures (VAS score and MLHFQ score). Multivariate ICG models showed an even stronger correlation with these same measures, and were higher than multivariate vital signs and univariate LVEF and BNP.

It is unclear why different univariate ICG parameters showed the highest correlation in each outcome measure category. It may be because the parameters are measuring distinct HF characteristics and were related differently to each unique functional outcome measure. A change in one ICG parameter was not necessarily associated with a change in another, but because the multivariate association was significantly greater than the univariate association, we believe the collection of ICG parameters provides a more complete picture of HF status and should be evaluated as such.

Recently, measurements of BNP and N-terminal B-type natriuretic peptide (N-BNP) levels have emerged as an aid in the diagnosis of acute HF in the emergency department.\textsuperscript{45,46} Use of BNP in chronic HF is also expanding, but some have questioned the role of BNP or N-BNP levels in the medical decision-making process in such cases.\textsuperscript{47} The primary purpose of this study was not to evaluate BNP and BNP levels were collected in significantly fewer study subjects than with ICG. In this study population, BNP correlation was highest with changes in 6MW, although not statistically significant. Prior studies have demonstrated a BNP association with NYHA class.\textsuperscript{48,49} We demonstrated that BNP changes were significantly correlated with changes in NYHA class, similar to changes in vital signs and LVEF but lower than univariate and multivariate ICG. The variation of BNP levels in patients already diagnosed with chronic HF\textsuperscript{50} may be due in part to evaluating fewer study subjects or in the unclear determination of what constitutes a significant change in BNP, or in N-BNP level.\textsuperscript{51} We believe BNP and N-BNP do provide value in the treatment of chronic HF and acknowledge a need for refinement in sensitivity and specificity of these markers in diagnosis and prognosis of chronic HF. There is a need for development of specific interventions related to the change in levels of these neurohormonal markers.

While the use of BNP to guide medical decision making in HF is still evolving, the use of invasive monitoring of hemodynamics to aid in the reduction of filling pressures and afterload, with a resultant improvement in stroke volume and cardiac output, is more established.\textsuperscript{32} ICG provides non-invasive hemodynamic parameters, some of which may change as plasma neurohormone levels change.\textsuperscript{53} Serial

### Table IV. Univariate Impedance Cardiography Parameter Correlations With Outcome Measures (R values)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>NYHA (n=56)</th>
<th>6MW (n=39)</th>
<th>VAS (n=30)</th>
<th>MLHFQ (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td>0.65</td>
<td>0.74</td>
<td>0.37</td>
<td>0.49</td>
</tr>
<tr>
<td>CI</td>
<td>0.66</td>
<td>0.76</td>
<td>0.40</td>
<td>0.50</td>
</tr>
<tr>
<td>SVRI</td>
<td>0.61</td>
<td>0.70</td>
<td>0.50</td>
<td>0.39</td>
</tr>
<tr>
<td>PEP</td>
<td>0.71</td>
<td>0.68</td>
<td>0.19</td>
<td>0.41</td>
</tr>
<tr>
<td>LVET</td>
<td>0.66</td>
<td>0.71</td>
<td>0.22</td>
<td>0.45</td>
</tr>
<tr>
<td>STR</td>
<td>0.70</td>
<td>0.68</td>
<td>0.25</td>
<td>0.48</td>
</tr>
<tr>
<td>ACI</td>
<td>0.61</td>
<td>0.76</td>
<td>0.47</td>
<td>0.34</td>
</tr>
<tr>
<td>TFC</td>
<td>0.61</td>
<td>0.71</td>
<td>0.29</td>
<td>0.38</td>
</tr>
</tbody>
</table>

NYHA=New York Heart Association class; 6MW=6-minute walk test; VAS=visual analog scale; MLHFQ=Minnesota Living with Heart Failure Questionnaire; SI=stroke index; CI=cardiac index; SVRI=systemic vascular resistance index; PEP=preejection period; LVET=left ventricular ejection time; STR=systolic time ratio; ACI=acceleration index; TFC=thoracic fluid content.
invasive measurements of hemodynamic parameters have predicted cardiac death or transplantation, and it has been suggested that serial invasive measurements of hemodynamics offer a promising opportunity to monitor changes in chronic HF patients. Previous studies have demonstrated that HF specialists are more aggressive in treatment of chronic HF than cardiologists, and cardiologists more so than generalists. The low cost and time to acquire ICG measurements make the technology ideal for use in a community-based cardiologist’s or generalist’s office, in addition to the HF specialist setting. With greater access to objective measures of chronic HF status, perhaps nonspecialists could become more aggressive in their treatment and achieve better outcomes.

This study is primarily limited by its retrospective design and small number of subjects, although statistical significance was reached in a number of comparisons. In addition, the varying sample size between ICG, vital signs, LVFE, and BNP makes it difficult to conclude that one measurement is definitively superior to the others. The multivariate ICG model utilized more parameters than other models, allowing a greater opportunity for association. The treating physician’s knowledge of all variables when making treatment decisions may have created bias toward improving some variables over others.

This study compared ICG to commonly used outcome measures in HF research. Larger prospective trials such as the Prospective Evaluation of Decompensation by Impedance Cardiography Test will help determine which ICG parameters are associated with death or hospitalization, and will therefore further define ICG’s prognostic role in patients with chronic HF.

In our HF population, improvements in univariate and multivariate ICG parameters significantly correlated with changes in functional and QOL measures. ICG provides objective data that may reflect changes in disease status and treatment effectiveness, which may in turn lead to better treatment plans and outcomes.

Acknowledgment: The authors thank Gerard Smits, PhD, for providing statistical analysis and consulting on this project.

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55 De Maria AN, Raisinghani A. Comparative overview of cardiac output measurement methods: has impedance cardiography come of age? J Card Fail. 2000;6(2):40–47.
Use of Noninvasive Hemodynamics to Aid Decision Making in the Initiation and Titration of Neurohormonal Agents

Heart failure (HF) is characterized by both hemodynamic and neurohormonal abnormalities and manifests with symptoms such as peripheral edema, shortness of breath, fatigue, and weight gain. The progression of HF results from the activation of multiple neurohormonal regulatory processes, including an increase in sympathetic nervous system activity and activation of the renin-angiotensin-aldosterone system, endothelins, and natriuretic peptides. Angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic blockers, and nesiritide are pharmacologic agents for HF which have both short- and long-term neurohormonal and hemodynamic effects.

Hemodynamic factors can play prominently in clinical decision making, and knowledge of hemodynamics may be illuminating during initiation and up-titration of various HF medications. The concept of hemodynamic goal-directed therapy for HF has been shown to improve outcomes, and may be analogous to the use of hemodynamics and oxygen delivery in septic shock, where goal-directed therapy improved mortality in a randomized series of patients.

Initial and ongoing hemodynamic tolerance, as well as hemodynamic improvement associated with therapy, can now be noninvasively and reliably monitored with impedance cardiography (ICG). ICG provides the unique ability to continuously monitor a patient’s hemodynamic status without the requisite risks and cost of right heart catheterization and therefore extends the possibility of using hemodynamics on a much broader range of patients, including outpatients. ICG hemodynamic monitoring has been proposed as a valid option in HF treatment algorithms. Here we present three cases as practical examples in which clinicians used ICG hemodynamic information to help guide treatment of neurohormonal agents.

Case One: Nesiritide Therapy
A 58-year-old African-American woman was brought to the hospital emergency department (ED) by ambulance after becoming acutely short of breath at home. The patient could not list her routine medicines but it was determined that she had been prescribed a pill for diabetes, some type of blood pressure (BP) medicine, and a water pill after her most recent hospitalization. Upon questioning, she admitted that she had not taken her medicines in the past few days. In the ED, the patient was severely dyspneic with an oxygen saturation of 88% and extremely hypertensive to a BP of 198/122 mm Hg.

Upon examination, her heart rate was 113 bpm, and her respiratory rate was 32 BPM. She weighed 296 lb. Cardiac auscultation revealed a quiet, mid-systolic murmur and summation gallop; her lungs had diffuse rales, and she had mild pitting edema to the...
knees. The chest radiograph showed a large cardiac silhouette and prominent vascular markings with moderate interstitial edema; the electrocardiogram showed evidence of left ventricular hypertrophy. She was placed on ICG monitoring for hemodynamic assessment to aid in determining appropriate therapy.

The initial ICG data revealed cardiac output (CO) of 3.8 L/min and systemic vascular resistance (SVR) of 2854 dyne \( \times s \times cm^{-5} \). Both the hemodynamic and ED physician assessments were consistent with acute decompensated HF and pulmonary edema. The patient was given a bolus of nesiritide 2 \( \mu g/kg \) followed by a continuous infusion of 0.01 \( \mu g/kg/min \). Table I shows the clinical and hemodynamic findings at baseline and with intervention. During nesiritide treatment, respiratory rate decreased to 20 BPM, heart rate decreased to 88 bpm, BP decreased to 132/66 mm Hg, and SVR decreased to 1488 dyne \( \times s \times cm^{-5} \). Her CO rose significantly to 5.6 L/min. These objective changes in hemodynamic endpoints coincided with dramatic improvements in symptoms of dyspnea and orthopnea. Urine output of 1500 mL was documented over the next 2 hours. The patient was admitted to the observation unit for continued nesiritide treatment and reinstitution of oral medications guided by ICG. She was discharged after a 23-hour observation to follow up for further adjustment of her therapy for hypertension and HF.

**Discussion**

HF, by definition, is the inadequacy of the CO to meet the needs of the tissues under normal filling pressures. Reduced CO is paired with neurohormonal activation and is the hallmark of HF decompensation. This patient had clinical signs of elevated filling pressures and ICG data showed that she had a very low CO in relation to her body size. Her markedly elevated SVR was possibly the inciting factor for decompensation and caused by noncompliance with BP medications.

In acute HF with volume overload, the high preload and abnormally high filling pressures cause the symptoms of dyspnea and edema. Diuretic agents lower preload in such patients, helping congestive symptoms, but do not significantly decrease afterload and may not adequately improve cardiac output. BP is not a reliable indicator of CO, and a wide range of SVR values can exist at various BP levels. Nesiritide, with effects on afterload as well as preload, resulted in not only significant improvement in symptoms due to preload reduction but significant improvements in CO and SVR. Since each patient may respond uniquely, utilizing ICG to follow beat-by-beat changes in CO and SVR during therapy allows realtime titration of medications during observation. In this case, ICG demonstrated that the therapy was successful in restoring hemodynamic stability. Rapid improvement in ICG-measured hemodynamic parameters provided an early signal of patient response, which resulted in the early reduction in her nesiritide dosing with the prompt resumption of her oral medications. Sustained hemodynamic stability provided additional rationale for discharge rather than admission for further observation.

**Case Two: Titration of Carvedilol Therapy**

A 79-year-old white man, 6 ft tall and weighing 160 lb, was referred to an outpatient HF clinic with New York Heart Association (NYHA) class IV symptoms. He had been diagnosed with ischemic HF and mild mitral regurgitation; ejection fraction (EF) by echocardiogram was 27%. Serum creatinine was 2.42 mg/dL. His medication regimen upon entry into the clinic included enalapril 5 mg b.i.d., furosemide 20 mg q.d., and digoxin 0.125 mg q.d. Due to continued severe symptoms, he had recently been treated with IV milrinone 0.375 \( \mu g/kg/min \) and IV dopamine 2.5 \( \mu g/kg/min \) for 4 hours twice a week. In the clinic, ICG hemodynamic measurements were conducted as part of his initial evaluation. The hemodynamic parameters included heart rate of 57 bpm, BP of 159/58 mm Hg, cardiac index (CI) of 3.6 L/min/m², systemic vascular resistance index (SVRI) of 1904 dyne \( \times s \times cm^{-5} \times m² \), and thoracic fluid content (TFC) of 35.0 kOhm. TFC is a patient-specific measurement of thoracic impedance and reflects the fluid volume in the thorax, allowing for quantitative intrapatient fluid trending.

Using ICG guidance, carvedilol was initiated and increased in a stepwise fashion, ultimately achieving the targeted dose of carvedilol 25 mg b.i.d. with the discontinuation of inotropic medications. The patient had symptoms of fatigue during drug titration; however, the continued stability of ICG parameters helped the patient achieve the target dosage. Upon reaching the targeted dose of carvedilol, the patient had less fatigue and exertional dyspnea, and end organ perfusion was validated by a serum creatinine level decrease to 1.7 mg/dL. Table II provides a trend summary of the patient’s hemodynamic changes during carvedilol titration. The patient had no hospitalizations or ED visits during the up-titration period, and hemodynamics at the end of treatment were similar to the beginning but, importantly, were accomplished without the aid

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<th>Table I. Nesiritide Therapy</th>
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<td>PARAMETER</td>
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<td>Heart rate (bpm)</td>
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<td>Respiration rate (BPM)</td>
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<tr>
<td>SpO₂ (%)</td>
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<td>BP (mm Hg)</td>
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<td>CO (L/min)</td>
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<td>SVR (dyne × s × cm⁻⁵)</td>
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SpO₂=saturated oxygen by pulse oximetry; BP=blood pressure; CO=cardiac output; SVR=systemic vascular resistance.
of inotropic agents and their known negative effects on mortality.11 A subsequent echocardiogram was obtained and showed that his EF had increased to approximately 45%.

Discussion
Treatment with β blockers decreases the risk of worsening HF caused by prolonged activation of the sympathetic nervous system.12 Studies on carvedilol report a consistent reduction in death and hospitalization in patients with HF when taken in efficacious doses.13 Despite the overwhelming evidence for the benefit of carvedilol, there is a gap in treatment between those who can benefit and those who are actually treated with the drug.14 Patient response to β-blocker therapy differs and efforts to predict which patients will respond to the therapy are imprecise.15 Clinicians who struggle with β-blocker initiation and up-titration in HF are often concerned about whether a particular patient can hemodynamically tolerate the agent16 and are also lacking real-time quantitative tools to aid this assessment.

In this case example, monitoring and trending of the hemodynamic parameters provided by ICG assisted the clinicians in reaching the recommended therapeutic dose of carvedilol. This patient’s prior requirement of IV inotropic therapy with both milrinone and dopamine initially caused question as to whether he would tolerate increasing doses of carvedilol. The ICG indication of elevated SVRI also indicated a potential hemodynamic benefit from carvedilol’s additional α-blocking effects, and the subsequent SVRI reduction validated this perception. Serial ICG measurements allowed for the up-titration with greater confidence and success than might have been achieved without hemodynamic data. While the patient’s weight did not change appreciably, the significant rise in TFC during β blocker up-titration may provide some rationale for further augmentation of diuretic agents.

Case Three: Initiation of ACE Inhibitor Therapy
A 64-year-old white woman was referred to the HF clinic in May 2001. Her diagnosis was nonischemic cardiomyopathy and she was NYHA classification IIIb with an EF of 32.5% by multiple gated acquisition. Upon initial assessment, she had a score of 67 on the Minnesota Living with Heart Failure Questionnaire and was limited by severe dyspnea at 91 m on her 6-minute walk test. Her medications at clinic entry were digoxin 0.125 mg q.d., carvedilol 31.25 mg b.i.d., and furosemide 2, SVRI of 3228 dyne×s×cm⁻5×m⁻², respectively, and a decrease in TFC to 30.3/kOhm. Lisinopril was increased to 5 mg q.d. 2 weeks later, and the milrinone was reduced to a 6-hour infusion, 1 day a week. At a routine clinic visit about 3 weeks later, further up-titration of lisinopril was made to 5 mg in the morning and 2.5 mg in the afternoon. Milrinone was discontinued. NYHA class was improved to II and she was able to increase her distance on the 6-minute walk to 225.5 m.

One month later, lisinopril was prescribed at 5 mg b.i.d., and at her next visit the hemodynamic report indicated BP of 112/69 mm Hg; CI of 2.5 L/min/m²; SVRI of 2475 dyne×s×cm⁻5×m⁻²; and TFC of 28.4/kOhm. Her 6-minute walk distance increased to 343 m, which

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<th>Table III. Hemodynamics Changes With Addition and Up-Titration of ACE Inhibitor Therapy</th>
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<td>Heart rate (bpm)</td>
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<td>BP (mm Hg)</td>
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<td>CI (L/min/m²)</td>
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<td>SVRI (dyne × s × cm⁻5 × m⁻²)</td>
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<td>TFC (/kOhm)</td>
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<td>NYHA</td>
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<td>6-Minute walk test (m)</td>
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ACE=angiotensin-converting enzyme; BP=blood pressure; CI=cardiac index; SVRI=systemic vascular resistance index; TFC=thoracic fluid content; NYHA=New York Heart Association Class; ND=not determined.
corresponded with a Minnesota Living with Heart Failure Questionnaire score that improved to 22. A summary of the hemodynamic changes during the titration phase of the ACE inhibitor is listed in Table III. During this time, the patient had no hospitalizations or ED visits. One year following initial referral to the clinic her EF had increased to 42%.

**Discussion**

ACE inhibitors should be prescribed to all patients with HF who do not have contraindications. It is well known that ACE inhibitors are significantly underutilized,\(^1\) and many patients are treated with lower doses than those shown to be most beneficial in clinical trials.\(^2\) However, during titration of ACE inhibitors patients can develop symptoms of dizziness and hypotension, or require hospitalization. Concerns over side effects can often prevent clinicians from initiating or up-titrating the drug, so knowledge of hemodynamics before increasing drug dose during titration may help physicians identify patients with hemodynamic need and tolerance for higher doses.\(^3\) In this specific case study, ICG findings of persistently elevated SVRI helped the clinicians increase the ACE inhibitor in a stepwise fashion. Of significance is the fact that the patient was already at a maximum dose of carvedilol when the ACE inhibitor was reinitiated. The case also demonstrates an initial improvement in SVRI may be transient, and that continued surveillance may lead to the need for continued up-titration of the ACE inhibitor. The decreased afterload from initial to final was at least in part responsible for the patient’s demonstrated improvement in EF from 30% to 42%. The patient’s functional status improved, as shown by her increased walking distance on the 6-minute test. Importantly, she did not experience any untoward symptoms or require hospitalization.

There is debate over the most appropriate dosing of ACE inhibitors for individual patients.\(^4\) Comparison of group characteristics, as is the case in most clinical trials, often tells us little about a specific patient’s optimal ACE inhibitor dose. Because BP itself can be a poor guide to hemodynamic status, ICG-measured SVRI may be a more valuable parameter for determining which patients will benefit from higher doses of ACE inhibitors. In this case, both CI and SVRI provided important information that aided in optimal dose titration and tissue perfusion leading to improved functional status and quality of life.

**Conclusion**

Although HF is both a hemodynamic and neurohumoral disorder, it is the hemodynamic effects of various medications that are readily measurable and that can limit therapy during drug titration. ICG provides accurate noninvasive hemodynamic information that can guide physicians during neurohumoral agent therapy in both chronic and acutely decompensated HF. These three cases demonstrate that ICG can be a valuable tool to aid decision making by clinicians caring for HF patients.

### REFERENCES

CME Questions

INSTRUCTIONS FOR COMPLETING THIS FORM: Read the papers and answer all the true/false questions that follow. Please select the one best answer for each and place your selection on the answer grid. YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION and return the form within 6 months of the papers’ publication to receive credit. Letters of credit will be mailed to participants bimurally.

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OBJECTIVE AND TARGET AUDIENCE: All health care providers eligible to claim AMA PRA Category 1 CME credits can submit questions for this activity. At the conclusion of this activity, participants should be able to: 1) summarize the important points discussed in the papers reviewed; 2) identify patients to whom the papers are relevant; 3) modify management practices as new information is learned; and 4) identify deficiencies in their knowledge base.

Strobeck and Silver (pages 1–6)
1. Heart failure has been defined as cardiac output not sufficient to meet the body’s demands.
2. Hemodynamic profiling in four quadrants created by wet vs. dry and cold vs. warm determinations is a new concept in heart failure.
3. Use of impedance cardiography (ICG) to quantify changes in perfusion (wet vs. cold) and congestion (wet vs. dry) has the potential to improve assessment and aid therapeutic decisions.

Yung, Fedullo, Kinninger, et al. (pages 7–10)
4. The accuracy of ICG cardiac output values vs. direct Fick method is similar to thermodilution vs. direct Fick in pulmonary hypertension patients.
5. ICG can provide measures of systemic vascular resistance, but not pulmonary vascular resistance.

Parrott, Burnham, Quale, et al. (pages 11–13)
6. ICG can replace the diagnostic echocardiogram in the determination of systolic and preserved systolic function.
7. Changes in ICG measures of cardiac index and systolic time ratio correlated with changes in ejection fraction in heart failure patients in a comprehensive heart failure management program.
8. Use of ICG may allow physicians to determine ventricular function between echocardiogram measurements to aid patient assessment and therapeutic options.

Springfield, Sebat, Johnson, et al. (pages 14–16)
9. In this study, multiple ICG parameters were significantly different in patients with a cardiac etiology of dyspnea vs. a noncardiac cause of dyspnea.
10. When compared with emergency department evaluations of dyspnea, ICG-based diagnoses of dyspnea had superior sensitivity, specificity, positive predictive value, and negative predictive value.
11. ICG-based diagnosis of dyspnea is expected to replace physician diagnosis of dyspnea in clinical practice.

Silver, Cianci, Brennan, et al. (pages 17–21)
12. Use of the pulmonary artery catheter is correlated with strong improvements in heart failure outcomes in randomized controlled trials.
13. ICG is a noninvasive method of hemodynamic measurement that can provide many of the same data parameters as pulmonary artery catheterization, but without the requisite risks and costs.
14. Use of ICG in patients who were candidates for pulmonary artery catheterization caused the treating physician to change the decision to place a pulmonary artery catheter more than 50% of the time.

Vijayaraghavan, Crum, Cherukuri, et al. (pages 22–27)
15. The visual analog scale and the Minnesota Living with Heart Failure Questionnaire are quality-of-life measures used in the assessment of persons with heart failure.
16. Changes in ICG parameters were not significantly associated with changes in quality-of-life measures or functional measures of heart failure.
17. Changes in ejection fraction, B-natriuretic peptide levels, and vital signs did not correlate as highly as ICG compared functional and quality-of-life measures, but the number of comparisons were fewer than with ICG.

Summers, Parrott, Quale, et al. (pages 28–31)
18. Nesiritide is a pharmacologic agent with both hemodynamic and neurohormonal effects.
19. Angiotensin-converting enzyme inhibitors and β-blockers are often underutilized in heart failure patients.
20. ICG can help determine hemodynamic tolerance and hemodynamic response to an angiotensin-converting enzyme inhibitor or a β blocker.

CME Answers are available on the Congestive Heart Failure page at www.lejacq.com

32 CME questions
CME Answer Grid

|   | T | F |   | T | F |   | T | F |   | T | F |   | T | F |
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| 1 |   |   | 6 |   |   | 11|   |   | 16|   |   |   |   |
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CME Evaluation

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<th>Agree</th>
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<tr>
<td>1. My knowledge was enhanced by this activity.</td>
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<td>2. The activity helped to clarify issues specific to heart failure patients.</td>
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<td>3. The information obtained from this exercise will have an impact on my care of patients.</td>
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<td>4. The format of the exercise was useful.</td>
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