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 0.46 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. (CHF. 2004;10(2 suppl 2):7–10) ©2004 CHF, Inc.

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 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 (COICG) measurements were performed with the BioZ ICG monitor (CardioDynamics, San Diego, CA). COICG measurements were performed according to the manufacturer’s guidelines during the same period when CO by TD method (COTD) was obtained by an independent cardiologist. Each COTD 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 COTD values with <10% variation, the corresponding COICG values were recorded. Unlike the COTD values, which were obtained usually at various times during the respiratory cycle, the COICG 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 COTD measurements were averaged to obtain the final COTD for each patient. The recorded COICG measurements corresponding to the accepted COTD measurements were also averaged for each patient to obtain the final COICG for each patient. All recorded COICG measurements were used without any being either objectively or subjectively rejected.

Cardiac output measurements via the Fick method (COFick) were determined within 10 minutes of the paired COTD and COICG 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 (PO₂) 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 (SaO₂) 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 (VO₂) value with the difference between the concentration of arterial oxygen (CaO₂) and concentration of mixed venous oxygen content (CvO₂):

\[ \text{CO}_\text{FICK} = \frac{\text{VO}_2}{\text{CaO}_2 - \text{CvO}_2} \]

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/CI_FICK, CO/CI_ICG, and CO/CI_TD) 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_ICG, and one due to the inability to obtain CO_TD. 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/CI_FICK as compared with CO/CI_ICG and CO/CI_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/CI_TD vs. CO/CI_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/CI_TD compared with CO/CI_FICK are listed in the Table. Bias and precision were 0.10 L/min/m² and 0.41 L/min/m², respectively, with a 95% level of agreement between –0.72 and 0.92 L/min/m² (Figure 4).

**CO/CI_ICG vs. CO/CI_TD Comparison.**

Bias and precision were –0.43 L/min/m² and 0.53 L/min/m² respectively, with a 95% level of agreement between –0.1.49 and 0.63 L/min/m².

**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 Stewart-Hamilton equation that utilizes temperature change over time has become the most common method of CO estimation in critically ill patients. However, no method of CO estimation is perfect, and multiple clinical limitations of the TD method exist. 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.

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
tor hemodynamics in the 1940s and was introduced as a concept to monitor hemodynamic parameters such as CO and systemic vascular resistance. ICG is a method to measure blood flow and cardiac output based on the introduction of a low frequency alternating current to measure electrical impedance changes in the arterial and venous blood oxygen samples. It is generally good agreement. Of course, the accuracy of ICG may be advised to question whether differences between ICG and TD are due to the limitations of ICG or the derivative pulmonary vascular resistance measure, but does provide measurement of fluid trending and myocardial contractility. Known limitations of ICG include severe aortic dynamic 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 than when compared with 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

<table>
<thead>
<tr>
<th>Table. Intermethod Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>ICG vs. Fick</td>
</tr>
<tr>
<td>TD vs. Fick</td>
</tr>
<tr>
<td>ICG vs. TD</td>
</tr>
</tbody>
</table>

CO = cardiac output; CI = cardiac index; ICG = impedance cardiography method; Fick = direct Fick method; TD = thermodilution method.

**Figure 1.** Scatterplot showing impedance cardiography (ICG) vs. direct Fick method (Fick). CO = cardiac output.

**Figure 2.** Bland-Altman analysis showing impedance cardiography vs. direct Fick method. CI = cardiac index.

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 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 hemodynamics 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 than when compared with 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


Kirk U. Knowlton, MD for his help in performing all the cardiac catheterizations, and Chantal C. Fletcher, MS, for her help in ensuring the accuracy of the equipment used in the study.

Acknowledgment: The authors thank Kirk U. Knowlton, MD, for his help in performing all the cardiac catheterizations, and Chantal C. Fletcher, MS, for her help in ensuring the accuracy of the equipment used in the study.