Comparative Overview of Cardiac Output Measurement Methods: Has Impedance Cardiography Come of Age?

Cardiac output, usually expressed as liters of blood ejected by the left ventricle per minute, is a fundamental measure of the adequacy of myocardial function to meet the perfusion needs of tissue at any time. Decreases in cardiac output over time (when cardiac output is measured under similar conditions) may signal myocardial functional deterioration and the onset or progression of heart failure. Conversely, improvements in cardiac output may indicate a positive response to medical therapy. However, most methods for evaluating cardiac output are technically demanding, require specialized training and specialized environments for measurement, and are costly. Therefore, most measurement techniques are impractical for routine evaluation of disease progression and/or response to treatment in the prevention and/or management of heart failure. This paper provides a comparative overview of commonly employed cardiac output measurement strategies with emphasis on developments in impedance cardiography which suggest that impedance cardiography has the potential to make routine assessment and trending of cardiac output a viable alternative to assist in the management of both chronically and acutely ill patients, including those with heart failure.

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Manuscript received December 17, 1999; accepted January 24, 2000

Heart failure—the inability of the heart to provide sufficient cardiac output (CO) to meet tissue perfusion needs at an acceptable filling pressure—is indisputably a major health care concern at the turn of the millennium. The incidence of chronic heart failure has increased as treatment for previously fatal ischemic, structural, and inflammatory cardiovascular conditions has improved and as the bulk of the population ages. Concomitantly, the proportion of the health care economy spent on the diagnosis, treatment, and chronic management of heart failure has increased dramatically, demanding even greater efforts to respond to this health care problem. Although specific work is being directed toward identifying the structural changes at the cellular level (e.g., myocyte apoptosis), mechanisms, and optimal treatment modalities for heart failure, the major clinical thrust currently consists of developing a comprehensive program of disease management. Such programs include: 1) control of medical conditions that predispose to heart failure; 2) recognition of early stages of heart failure and/or changes in ventricular function that may signal deterioration; and 3) intervention to retard disease progression.

The state of knowledge and technology related to evaluating events at the cellular level, which are associated with heart failure, are in their infancy. Therefore, current efforts primarily are directed at the clinical level. The contemporary focus of disease management is shifting from symptom management to evaluating hemodynamic performance including CO, left ventricular volumes, and ejection fraction. Objective, accurate, reproducible, and easy to obtain measurements of physiological parameters which are indicators of hemodynamic function, are essential for managing both predisposing conditions and heart failure itself.

CO, typically expressed as the liters of blood ejected into systemic circulation from the left ventricle per minute, is a primary standard for estimating the adequacy of myocardial pump function and the need for therapeutic intervention. Traditionally, measurement of CO has been achieved invasively with balloon

floatation catheters, a procedure involving some risk of complications and discomfort. Invasive techniques for CO determination are complex, require special training, and often are costly to perform, which discourages routine use of CO in clinical practice. This is particularly so in the outpatient setting, which is the site of a major portion of the care and disease management for heart failure. This paper provides a comparative overview of several widely used methods for determining CO, and focuses on an evaluation of one newer technology, impedance cardiography (ICG), that appears to meet the criteria of safety, simplicity, reproducibility, and cost effectiveness for estimating, monitoring, and trending CO in outpatient, as well as inpatient settings.

Comparative Overview of Methods for Evaluating Cardiac Output

A variety of methods for evaluating CO exist, including invasive Fick or indicator dilution methods, cardiac ultrasound done noninvasively by transthoracic Doppler echocardiography or semi-invasively as transesophageal echocardiography (TEE), and noninvasive ICG technologies. The Fick and indicator dilution methods, such as thermal dilution require right heart catheterization (RHC), typically performed by using a balloon flotation Swan-Ganz catheter. The catheter is inserted through the subclavian or jugular veins and advanced through the right atrium and ventricle and the pulmonic valve until the catheter tip is located in the pulmonary artery. Although a Swan-Ganz catheter may be safely left in place for hemodynamic monitoring and/or the rapid administration/delivery of medication to critically ill patients, the potential for complications and system malfunction increases with time.

Direct Fick Cardiac Output. The Fick oxygen consumption method for calculating CO is based on the principle that the total uptake of a substance by an organ is the product of the amount of blood flowing through the organ and the difference between the arterial and venous (AV_{dif}) concentrations of that substance. When the uptake is known, then the flow can be calculated. For direct Fick CO determinations, the amount of oxygen extracted in the respiratory cycle is measured from inspired and expired gas as the "total oxygen consumption." During the period of time when the oxygen consumption is being measured, a sample of mixed venous blood is withdrawn from the pulmonary artery and, simultaneously, an arterial blood sample is withdrawn from any arterial line. Arterial and venous blood oxygen contents are determined and the arterial-venous oxygen (AVO_2) difference is calculated. The total oxygen consumption (in mL/min X 100) is divided by AVO_2 difference to yield CO in mL/min; the results are divided by 1000 to yield CO in L/min.

Accurate CO derived via the direct Fick method is dependent upon the patient being in a steady hemodynamic and metabolic state, stable respiratory rate, heart rate, oxygen consumption, and respiratory exchange ratio. As the AVO_2 difference narrows, small errors in either the collection or analysis of respired gases or blood samples increase the probability of large variations in the CO estimate. Thus, direct Fick CO is more accurate in low output than in high output states. Direct Fick CO determinations are time consuming, require multiple personnel meticulously carrying out the technique in specialized environments, and produce a one time only measure of CO. Therefore, use of direct Fick CO (although considered the "true" gold standard against which other methods are evaluated) is usually confined to the cardiac catheterization lab and research settings.

Indirect Fick Cardiac Output. Like the direct Fick method, the indirect Fick CO determination uses a sample of mixed venous blood drawn from the pulmonary artery. However, rather than using direct measurement of total oxygen consumption and arterial blood oxygen, the indirect Fick uses pulse oximetry devices to derive the arterial oxygen content. The arterial-venous oxygen difference ($AVO_{2\ dif}$) is calculated using a weighting factor (1.36) times the hemoglobin times the arterial oxygen saturation minus the venous oxygen saturation. The cardiac index (CI) is derived using the formula 130 divided by the AVO_{2dif} times 10; the CO is calculated as the CI times the body surface area (BSA). Like the direct Fick calculations, small errors in either the collection or analysis of the mixed venous blood sample, errors in the hemoglobin levels, unreliability of the oximetry device or errors in calculating BSA will affect the CO accuracy. However, because the indirect Fick procedure is less cumbersome than direct Fick procedure, the indirect Fick can be performed at the patient's bedside by specially trained personnel and can be used serially.

Indicator Dilution Methods for Calculating Cardiac Output. Indictor dilution methods, such as dye dilution and thermal dilution, are also based on the Fick principle. However, rather than measuring oxygen content, dye dilution methods use a

known quantity and concentration of nontoxic, indocyanine green dye injected into the pulmonary artery. The blood/dye solution is sampled at a constant rate from a systemic artery (such as the brachial, radial, or femoral artery). The concentration of the dye is measured over time by a densitometer that records a dye concentration curve over time. The amount of dye injected is divided by the area under the curve to yield a CO measure. Like the direct Fick, this method is cumbersome and requires extreme precision as well as several highly trained personnel. Further, the dye is photosensitive and unstable over time mandating quick use after preparation. Like the direct Fick, the dye dilution method provides a one time CO measure and is usually performed only in research settings. Based upon the above, dye dilution CO measurements are rarely used in clinical practice.

Thermodilution (TD) CO is an indicator dilution method using an iced or room temperature solution of normal saline or 5% dextrose in water (D5W) of known temperature as the indicator. The temperature of the injectate is equivalent to the "concentration" of the indicator. The patient's baseline core temperature is recorded via a thermistor bead located in the tip of the pulmonary artery catheter (PAC), which floats freely in the pulmonary artery. A known amount (5–10 cc) of the "colder than the temperature of the blood" fluid indicator is injected as a bolus into the right atrial chamber through the proximal port of a multichannel PAC. The thermistor at the tip of the PAC records the temperature change in the pulmonary artery on a time/temperature curve. The area under the curve is inversely proportional to the CO. The area is calculated and the CO measurement is digitally displayed on the CO computer. The temperature/time curves are inspected for adequacy and the procedure is repeated. Typically, because biological variations lead to an average difference of between 5%–20% in individual TD CO curves, the TD CO is based on an average of at least three individual measures taken in the same time period that are within 10% of each other.[1] If more than three injectates are required to obtain three measures within the 10% limit, the high and low values are usually discarded and the other values are averaged. TD CO can be performed at the patient's bedside by one person. TD CO has become the most widely used clinical method for repeated measurements and, in many studies, it is used as the gold standard against which other measures are evaluated. However, high and low output states, intracardiac shunts, dysrhythmias, and valvular regurgitation affect TD CO measurement and should be considered as possible exclusion criteria. Because TD CO is an invasive procedure, it must be performed by trained personnel in a laboratory or critical care setting.

Continuous Cardiac Output. Like TD CO, continuous cardiac output (CCO) is an indicator dilution method requiring RHC (or PAC). But, rather than using and sensing temperature changes resulting from the injection of a cold injectate, CCO technology involves the use of heat. The CCO pulmonary artery catheter is equipped with a thermal coil, which is positioned in the right ventricle and intermittently heats the surrounding blood. The temperature change in the blood ejected from the right ventricle is sensed by a thermistor located in the tip of the CCO PAC, which floats freely in the pulmonary artery. Like the other invasive methods previously described, CCO monitoring is an invasive procedure requiring specialized training and a specialized environment for insertion; subsequent monitoring must be done in a critical care unit or cath lab. In comparison to Fick and indicator dilution methods, CCO has a lower risk of measurement error secondary to inadequate technique. CCO provides serial (rather than one time only) measures of CO, which can be trended.

Echocardiography. Echocardiography is a noninvasive technology that uses ultrasound waves to produce dynamic recordings of cardiac anatomy and blood flow through the heart and great vessels and thereby, is capable of measuring stroke volume. Cardiac ultrasound can provide the basis for stroke volume determination from either 2-D images alone, or in combination with Doppler flow velocity recordings. Echo recordings are dependent upon unimpeded transmission of the ultrasound beam into the heart and great vessels, and do not yield technically adequate data in all patients. As a tomographic technique, some measurement imprecision exists. The actual acquisition of the data requires a skilled operator and meticulous measurement procedures. Accordingly, although echocardiography can provide repeatable, portable, noninvasive measurements of stroke volume and CO, it is not routinely applied for this purpose clinically at the present time.

Assessment of Cardiac Output by 2-D Echocardiography. Because 2-D echocardiography enables visualization of the entire left ventricle (LV) perimeter in multiple planes, it is well suited for the measurement of cardiac chamber volumes and ejection fraction.[2–5] Obviously, stroke volume can be readily derived from such measures as the difference between end diastolic and end systolic volumes. Numerous algorithms have been applied to calculate LV

volumes by echocardiography. Currently, the most commonly used algorithm to calculate LV volumes is based upon the Simpson rule, which derives measurements by dividing the LV by parallel planes into a number of small segments (usually referred to as disks) and then summating the area of the individual disks. This approach has the advantage of making no assumptions about the geometry of the ventricle. The optimal correlations between 2-D echo and other techniques have been achieved with a modification of the Simpson rule that separately quantifies the volume of the apex as an ellipsoid.[5–10]

Regardless of the methodologic approach used, accurate calculations of LV volumes by echocardiography require attention to detail and are critically dependent upon high quality images to delineate the endocardium and image the entire LV perimeter. As a rule, echocardiographic estimates of LV volumes underestimate those calculated by other techniques and are most accurate in the absence of significant alterations of LV size and contraction. End systolic measurements are more accurate than those made at end diastole, probably due to superior endocardial definition. Nevertheless, echocardiographic calculations of LV volumes have generally yielded correlation coefficients in excess of 0.75 as compared with radionuclide angiography, cineangiography, and autopsy studies, regardless of the algorithm employed.[2–10] Of importance, calculation of LV volumes generally yields values with a standard error of estimate that renders these measurements suitable for clinical decision making in the care of most patients.

Doppler Assessment of Cardiac Output. Although measurements of LV volumes and ejection fraction can be obtained by 2-D echocardiography, Doppler interrogation provides a complementary noninvasive assessment of systolic function. One of the most important applications of Doppler is in the calculation of stroke volume.[11] Stated simply, the flow volume through any orifice can be calculated as the product of the cross sectional area and velocity. Cross sectional area measurements can be obtained from echocardiographic images, while Doppler can provide velocity values. As the annulus of the aortic valve is nearly circular, its cross sectional area can be estimated from a measurement of diameter, as $\pi(\text{diameter}/2)^2$. The pulsed wave Doppler envelope also can be recorded at the same level. The mean flow velocity through the orifice is calculated by integrating velocity over time (i.e., by measuring the area under the Doppler curve). This velocity time integral, often called the stroke distance, is then multiplied by the cross sectional area at the level of the Doppler interrogation to obtain the stroke volume.[11–14] The product of the stroke volume and heart rate then yields CO. Theoretically, stroke volume can be calculated at any valve annulus.[14–18]

Calculation of stroke volume by the Doppler method involves a number of assumptions. The orifice must be circular and constant in size, and the flow velocity must be uniform throughout the cross sectional area. Because the measurement of annular radius is squared in the computation of area, it is the most important source of error of Doppler stroke volume analysis. In addition, the angle between the flow and the interrogating beam must be $<20°$. Despite the uncertainty of these assumptions, Doppler derived measurements of CO and stroke volume have shown a good correlation with TD, Fick, and the angiographic calculations, though the correlation is not perfect.[11–15,19]

Cardiac Output Estimates Using Transesophageal Echocardiography. TEE uses ultrasonic waves transmitted from and recorded by a transducer mounted on a flexible gastroscopic device, which is passed into the esophagus. TEE overcomes problems associated with impaired transmission of the sound beam into the heart and great vessels. This semi-invasive procedure requires the patient to be fasting for six hours and usually to undergo conscious sedation. While complications to this procedure are rare, it requires extensive training to perform. Thus, while it is possible to perform TEE on outpatients, it is neither practical, cost effective, nor desirable for obtaining repeated measures of CO over time.

Impedance Cardiography Cardiac Output. ICG, the application of thoracic electrical bioimpedance (TEB) technology (a form of electrical impedance plethysmography) for the evaluation of cardiac function estimates CO by measuring changes in TEB over time during the cardiac cycle. Sensor pads are placed on the root of the neck and the thorax. A safe, imperceptible, low voltage, high amplitude, alternating current is introduced through the outermost sensors and the voltage is sensed through the innermost sensors. The difference between the voltage that is introduced and that which is sensed indicates the amount of resistance (impedance) the electrical current encounters (or in the converse, the level of conductivity of the matter through which the current is passed). Electrical current seeks the path of least resistance. Blood, specifically plasma, is the most highly conductive (least resistant) media in the thorax. Resistance (impedance) to electrical current in the thorax changes in relation to the amount of

blood in the aorta; as the blood volume increases during systole, conductivity increases and resistance (impedance) decreases. ICG measures and records these changes in resistance (impedance) over time as a volume wave form similar to an arterial pressure waveform. ICG also records the electrical activity in the myocardium as a nondiagnostic ECG. Using proprietary algorithms, values are calculated or derived for heart rate, stroke volume, CO, and estimates of contractility and workload and are both displayed on a monitor screen and stored in the computer memory.

ICG is the easiest method currently available for determining CO. Because the procedures for obtaining ICG data are simple (require <5 minutes) as well as noninvasive, extensive specialty training is not needed; the procedures can be learned and performed in any setting by health care technicians, patients, or even lay persons who have been oriented to the technology. A closer examination of the technology and its accuracy and reproducibility in estimating CO follows.

ICG Technology

How It Works. ICG—the application of TEB technology for the assessment of cardiac function—is based on Ohm's law, which states that resistance (impedance or Z) to alternating current flow is inversely proportional to voltage (U) when the current (I) remains constant ($Z=U/I$).[20] Changes in impedance (delta Z or dZ) over changes in time (delta t or dt), when current is held constant, reflect a change in the properties of the conducting medium (inherent resistance, length, or cross sectional area).[20–22] If two of the three properties (e.g., the length and cross sectional area) of the conducting medium are held constant, then any change in impedance can be attributed to the third property (e.g., inherent resistance).

ICG works by: 1) introducing a low energy, high frequency alternating current (I) of a specific frequency and amplitude, which is held constant through the thorax; 2) measuring the voltage drop (U); and 3) calculating the impedance (Z) to the flow of energy. Because the thorax is composed of both conductive (intracellular, extracellular, and interstitial fluid and blood) as well as less conductive or nonconductive substances (bone and air), the thorax is a good conductor of energy. Baseline impedance (Z_0), the amount of impedance/conductivity of all of the conductive matter in the thorax, is measured. Changes in impedance over changes in time are calculated (dZ/dt) and displayed numerically and graphically as a waveform to reflect the dynamic state of fluid (the most conductive medium) in the thorax. Because blood is a highly conductive medium and the aorta is highly distensible, changes in thoracic impedance reflect changes in the pulsatile volume of blood flow through the aorta in response to electrical and mechanical events in the myocardium.[20,21,23–25] The stroke volume is derived from the impedance waveform and the ECG using specific algorithms. CO is calculated as heart rate times stroke volume. Continuous, beat to beat, monitoring of stroke volume and CO is recorded using digital signal processing and proprietary algorithms.

How It Evolved. ICG was introduced in the late 1930s;[26] however, systematic study of TEB technology was delayed until the late 1960s when the National Aeronautics Space Administration (NASA) considered it for use in monitoring astronauts during the Apollo manned flight into space.[27,28] Early testing of TEB ICG produced satisfactory results on healthy humans in hemodynamic equilibrium, although it consistently overestimated CO. However, when used for monitoring critically ill patients, the accuracy, precision, and reproducibility of ICG measures was inconsistent, at best. The state of the science and art of TEB was not sufficiently developed to determine whether these inconsistencies were a result of technology deficiencies or physiological phenomena (pathological processes and compensatory mechanisms) peculiar to the state of critical illness. As a result, ICG fell into disfavor or was not accepted clinically.

Subsequent developments in computer technology, TEB technology, and scientific knowledge about physiology and compensatory mechanisms in relation to postural change, exercise, neurohormonal activation, and critical illness have reopened interest in TEB ICG for hemodynamic monitoring in the last decade. An enhancement of TEB technology and its applications was facilitated by the advances in microcomputers, the use of digital signal processing, high speed numeric processing applications, and improved software and algorithms for calculating hemodynamic parameters from the impedance wave form and ECG (manufacturer's specifications for BioZ.com™ CardioDynamics International Corporation, San Diego, CA).[29] More recent studies[30,31] using the newer technology are demonstrating improved reliability and reproducibility of ICG monitoring in a variety of conditions from lower negative pressure environments to stable heart failure. Thus, it is possible to use TEB ICG to monitor hemodynamic activity continuously, to record and trend serial measurements, and to electronically mark events for docu-

menting changes in relation to postural changes, fluid load, loss or shift, work load demand, and, most importantly, acute responses to treatment interventions in a variety of states of health and illness. Because the equipment is portable and the technology is noninvasive, TEB ICG measures can be obtained in any inpatient or outpatient setting, including the physician's office or the patient's home. Clearly, however, utilization of TEB ICG is dependent upon the accuracy and reproducibility of the CO measures.

Accuracy and Reproducibility of Cardiac Output Measurement Strategies

Measurement of any clinical phenomenon must both be accurate and reproducible before it is used to facilitate clinical decision making about treatment modifications. First, there must be evidence that the method actually measures what it is designed to measure. Accuracy (or validity) is evaluated by comparing the new measure(s) to an existing, known to be accurate, and reproducible standard, usually by a test of linear relationship. Obviously, such validation is critically dependent upon the accuracy of the gold standard. However, a test of linear relationship only indicates that two measures vary together; as one changes there is a corresponding change in the other. Although determining whether or not the two measures vary together is a fundamental step in assessing accuracy and establishing utility, the strength of the relationship does not indicate the "goodness of fit" or extent of agreement between the two measures. The level of agreement, an indication of how well the value obtained for one variable matches or corresponds with the value obtained for the other variable, is critical in establishing accuracy. The multivariate coefficient of determination (R^2) statistic provides one estimate of goodness of fit and indicates the extent to which variability in one measure accounts for variability in the other measure. Two other important aspects of agreement are bias (the extent to which the new measure under or overestimates the gold standard) and precision (the range of new measure's values that encompasses 95% of the values obtained). The smaller the bias and the narrower the range between the upper and lower limits (standard deviation [SD] of the mean differences), the greater the equivalence (or agreement) of the two measurement methods.[32] Tables I and II and the following section present an overview of the results of recent tests of accuracy, and precision of ICG compared to commonly employed clinical measures of CO: thermodilution (TD), Fick, and Doppler echocardiography.[31,33–61]

Fuller[62] completed a metaanalysis of studies assessing the validity of impedance CO measurements, which were based on the earlier technology; all studies reported correlations. He reported that impedance CO showed a good correlation with TD CO (bivariate correlation coefficient [r]=0.82), with dye dilution CO (r=0.83), and with Fick CO (r=0.80), but only a moderate agreement with radionuclear angiography (r=0.65). Studies with critically ill patients had lower correlations than studies done with noncritically ill patients. More recently, Raaijmakers et al[63] reported a metaanalysis of 112 impedance validation studies published between 1968–1997, one-third of which involved cardiac patients. Because they found that there was no normal distribution of correlation coefficients among these studies, they performed a Fisher's Z_f transformation to the data and generated a pooled r^2 statistic and the 95% confidence interval (CI) for the r^2 rather than reporting the r values. They found an overall correlation of r^2=0.67 (CI=0.64–0.71), which is equivalent to r= approximately 0.8. Further analysis revealed two factors influencing the strength of the correlation: the reference method and subject characteristics (including health status and weight). It should be noted that although these authors carried out an extensive literature search, their reports were based on the findings of studies using ICG technologies in their earlier stages of development.

Tables I and II demonstrate that ICG CO measures are clearly related to CO measured by other accepted methods. Importantly, as reported by Fuller[62] and Raaijmakers et al[63] and illustrated in these tables, it can be seen that selection of the "gold" standard criterion is critical to interpreting the findings. When measured against itself, the direct Fick method has been reported to have approximately a 6%–10% margin of error even when the oxygen consumption method is carefully performed. This could result in up to ±0.6L/min difference in a CO that is approximately 6 L/min, which would mean that the "true" CO is anywhere between 5.4–6.6 L/min. The reproducibility of TD CO measures derived from the average of three measures, is approximately 5% under optimal conditions. (It should be noted that using an averaged measurement as a sole measurement reduces the variability as an effect of regression toward the mean.) A 5% difference would be a difference of approximately ±0.3 L/min for a CO reading of 6.0 L/min, which would mean that the "true" mean CO is between 5.7–6.3 L/min. If the standard used has variability itself, then the degree of difficulty in establishing the bias and accuracy of the new measure increases and the results are suspect. One

TABLE I. IMPEDANCE CARDIOGRAPHY CARDIAC OUTPUT VALIDATION STUDIES

PUBLISHED PAPERS

AUTHOR JOURNAL (YEAR)	SAMPLE	SYSTEM	COMPARISON	BIAS (PRECISION)	r VALUE
Belardenelli Am J Cardiol (1996)	N=25 CAD patients (ischemic HF=A; no HF=B) Exercise lab	NCCOM3-R7S S/B Formula	CO TD-TEB Fick-TEB	Rest $A_{TD\text{-}TEB}$=–0.70 (-0.10,+0.66) $B_{TD\text{-}TEB}$=-0.04 (-0.37,+0.44) $A_{Fick\text{-}TEB}$=-0.30 (-1.20,+ 0.70) $B_{Fick\text{-}TEB}$ Exercise $A_{TD\text{-}TEB}$ $B_{TD\text{-}TEB}$ $A_{Fick\text{-}TEB}$ $B_{Fick\text{-}TEB}$	Rest $A_{TD\text{-}TEB}$ r=0.94 $B_{TD\text{-}TEB}$ r=0.98 $A_{Fick\text{-}TEB}$ r=0.85 $B_{Fick\text{-}TEB}$ r=0.95 Exercise $A_{TD\text{-}TEB}$ r=0.90 $B_{TD\text{-}TEB}$ r=0.90 $A_{Fick\text{-}TEB}$ r=0.93 $B_{Fick\text{-}TEB}$ r=0.89
Bishop Acad Emerg Med (1996)	N=54 gunshot wound patients; N=24 with thoracic injury and thoracostomy ED, OR, PAR, SICU 254 pairs of data	Renaissance/ Wang	CI TD-TEB	-0.011 (±1.1) -0.018 (±1.4)	r=0.79 r=0.71
Burchell Crit Care Med (1997)	N=21 SICU patients 202 pairs of data		CO Fick-TEB	0.49 (±1.01)	
Castor Br J Anaesth (1994)	N=10 patients on IPPV 131 pairs of data	NCCOM3-R7	CO TD-TEB DU-TEB During IPPV During apnea Spontaneous ventilation	During IPPV TD-TEB=+1.4% DU-TEB=-16% During apnea TD-TEB=-2.2% DU-TEB=-18.7% Spontaneous ventilation TD-TEB=-2.1% DU-TEB=-32.4%	
Cybulski J Physiol Pharmacol (1993)	N=9 healthy adults (10 heart cycles each)	?	SV Doppler-TEB		r=0.69
DeMey Br J Clin Pharmacol (1993)	N=10 healthy men rest, IV isoprenaline, IV phenylephrine	NCCOM3	SV "Standard ICG"–NCCOM	30.3 mL (15.5–45.2 mL)	
Doering Crit Care Med (1995)	N=34 cardiac surgical patients	NCCOM3-R7	TD-TEB	Pre-op + 0.16 (±0.60) Post-op 0.02–0.21 (1.06–1.72)	Pre-op r=0.88 Post-op r=0.046–0.227
Kinderman Pacing Clin Electrophysiol (1997)	N=53 patients pacemaker optimization	?	SV Doppler-TEB		ATP r=0.66 AVP r=0.53
Patterson Biol Psychol (1993)	N=26 healthy males	?	SV Cardio green dye-TEB		% change in SV r=0.16–0.42
Perrino J Cardiothorac Vasc Anesth (1994)	N= 50 patients Noncardiac surgical	NCCOM3-R7	TD-TEB	-0.41 (1.6 to–2.4)	r=0.84

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PUBLISHED PAPERS					
AUTHOR JOURNAL (YEAR)	SAMPLE	SYSTEM	COMPARISON	BIAS (PRECISION)	r VALUE
Pickett Am J Cardiol (1992)	N=43 patients 201 pairs of data	ICG system by HDC Co, Mesa, AZ	CO TD-Kubicek equation TD_{mean} - Kub_{mean} TD-Sramek equation TD_{mean} Sam_{mean}		TD_{ind} -TD_{mean} r=0.92 TD_{ind} - Kub_{ind} r=0.75 TD_{mean} - Kub_{ind} r=0.86 TD_{ind} - Sam_{ind} r=0.66 TD_{mean} - Sam_{ind} r=0.66
Sageman Crit Care Med (1993)	N=50 patients undergoing CABG	NCCOM3-R7	TD-TEB	Overall 0.33 (±3.14) Obese -0.16 (±3.56) No Ventilator 00.75 (±1.68)	Overall r=0.24 Obese r=0.000 No Ventilator r=0.45
Shoemaker Clin Investig (1994)	N=68 critically ill patients 842 pairs of data	Renaissance	CO TD-TEB	-0.013 (±1.4)	r=0.86
Shoemaker Acad Emerg Med (1996)	N=60 critically ill patients - ED 224 pairs of data	Renaissance	TD-TEB	CI0.61 (±0.50)	r=0.81
Shoemaker Chest (1998)	N=680 patients 2192 pairs of data	Renaissance	CI TD-TEB	-0.124 (±0.75)	r=0.85
Thangathurai J Cardiothorac Vasc Anesth (1997)	N=23 adults undergoing extensive ablative oncology surgery	Renaissance	CO TD-TEB	-0.1 (±0.8)	r=0.93
van der Meer Int Care Med (1996)	N=20 mechanically ventilated patients	?	CO TD-Sramek equation TD-Sramek- Bernstein equation TD-Kubicek equation TD adjusted Kubicek equation	LS electrode configuration & SB equation 0.15 (±0.96) SC electrode configuration & aK equation 0.19 (±1.19)	LS & SB equation r=0.86 SC & AK equation r=0.79
van der Meer ACTA Anaesthesiol Scand (1997)	N=37 mechanically ventilated patients Subgroup of normal body weight N=25	IPG-104 impedance Mini-Lab (RJL Systems, Detroit & Equip Medical, Maassluis, The Netherlands)	CO TD-TEB Sramek-Bernstein equation	N=37 -0.06 (±1.25) N=25 0.09(±0.96)	N=37 r=0.60 N=25 r=0.85

Author Journal (Year)	Sample	System	Comparison	Bias (Precision)	r Value
Weiss Am J Emerg Med (1995)	N=15 non-critically ill patients 51 pairs of data N=13 MICU patients 49 pairs of data	NCCOM3-R7	TD-TEB	Cath lab 0.231 (±2.19) MICU 0.031 (±2.33)	Cath lab r=0.69 MICU r=0.81
Woltjer Br J Anaesthesia (1996)	N=37 patients 24–36 hours post cardiac surgery	IPG-104 impedance Mini-Lab (RJL Systems, Detroit & Sanofi Sante, Maassluis, the Netherlands)	SV TD- Sramek- Bernstein equation TD-Kubicek equation Sramek- Bernstein equation- Kubicek equation		LS electrode configuration & K equation r=0.69 LS & SB equation r=0.64 SC SC electrode configuration & K equation r=0.90 SC & SB sequation r=0.73
Woltjer Am Heart J (1997)	N=19 stable heart cath patients (without aortic valve disorder)	IPG-104 impedance Mini-Lab (RJL systems, Detroit & Equip Medikey, Gouda, the Netherlands)	SV TD-TEB Kubicek equation	1.8 (±28.8)	r=0.88
World QJ Med (1996)	1) N=21 ICU patients needing RHC (TD-TEB) 2) N=50 patients undergoing general anesthesia (DOP–TEB)	NCCOM3-R7	TD-TEB (1) Doppler- TEB (2)	(1) -0.14 (±1.6) (2) 0.48 (±2.9)	
Young Brit J Anaesthe (1993)	N=19 septic patients	NCCOM3-R6	CI TD-TEB	1.69	r=0.36
Yakimets Heart-Lung (1995)	1) n=17 elective angio patients (Fick-Teb) 2) N=28 heart surgery patients (TD-TEB)	NCCOM3-R7	CO FICK-TEB TD-TEB	Fick-TEB Rest -1.050 (±1.529) Fick-TEB Exercise -1.505 (±2.214) TD-TEB Immediate post OHS -0.425 (±1.325) TD-TEB 2–3 hours post OHS -0.358 (±1.235)	Fick-TEB Rest r=0.684 Fick-TEB Exercise r=0.219 TD-TEB Immediate post OHS r=0.547 TD-TEB 2–3 hours post OHS r=0.505

TABLE II. SELECTED CARDIAC OUTPUT VALIDATION STUDIES USING REFINED IMPEDANCE CARDIOGRAPHY TECHNOLOGY PUBLISHED IN PROCEEDINGS OF SCIENTIFIC SYMPOSIA

Studies Presented at Scientific Symposia						
Author	Symposium (Year)	Sample	System	Comparison	Bias (Precision)	r value
Greenberg	Heart Failure Society of America (Sept 1999) (CHF, 2000)	N=62 stable heart failure outpatients	BioZ®	CO & SV TEB-TEB (intraday and one week interval)		CO interday r=0.86–0.90 SV inter-day r=0.84–0.86
Raisinghani	AM Col of Cardiol (Apr, 1998)	N=191 patients ICU, Cath lab, OR (CABG)	BioZ®	CO TD-TEB	-0.13 (±1.15)	CABG r=0.78 Overall r=0.73
Sageman	Am Heart Assoc (Nov, 1999)	N=20 post CABG ICU patients	BioZ®	CI TD-TEB	-0.07 (±0.2)	r=0.95
Verhoeve	Heart Failure Society of America (Sept, 1998)	N=96 adults enrolled in cardiac rehabilitation program	BioZ®	CI & SI TEB-TEB (one week interval)		CI intraday r=0.959 SI intraday r=0.967 SI interday r=0.860
Yung	Am Thoracic Soc (Chest,1999)	N=33 patients Cath lab	BioZ®	CI Fick-TD Fick-TEB TD-TEB	Fick-TD 0.09 (±0.43) Fick-TEB -0.14 (±0.44) TD-TEB -0.23 (±0.55)	Fick-TD r=0.89 Fick-TEB r=0.85 TD-TEB r=0.80
Zeigler	Am Coll of Chest Phys (Nov. 1999) (Chest, 1999)	N=52 ICU patients 100 pairs of data	BioZ®	CO TD-TEB	0.446 (±1.243)	r=0.89

can never be assured that observed differences are a result of measurement error of the standard or in the new method. However, just such analyses are most often used to accept or to reject new technology. The question, "How good is good enough to accept a new technology?" remains unanswered based on these commonly relied upon criteria. Of greater relevance, perhaps, is whether the new technology provides an index of LV function, which is of value in assessing disease severity, prognosis, or therapy. In this regard, TEB ICG offers the potential for significant application in congestive heart failure.

Summary and Conclusions

A number of methods exist for measuring CO as an index of myocardial function in clinical settings. Each technique has advantages and disadvantages, including patient safety/risks, extensiveness of training needed to perform the measurements, the type of environment needed to safely perform them, and their appropriateness for repeated or serial measures that can be trended over time to evaluate disease progression and response to treatment. The reproducibility and accuracy of the methods are also of critical importance. However, it is clear that there is no perfect gold standard for measuring CO. The best effort produces an estimate. Chaos theory teaches that the greater the number of estimates (or high speed snapshots), the greater the likelihood of obtaining a "true" image of the phenomenon and being able to observe the pattern and organization of that phenomenon. Thus, serial measures that can be taken over time and trended are most likely to capture the "true" state of myocardial function. ICG is a technology that permits cost effective, serial esti-

mates of CO at low risk to the patient. Technological developments are improving the reproducibility, accuracy, and precision of ICG CO. Given the absence of a precise gold standard, perhaps it is more important to determine whether new technology can be used as an independent parameter to provide more, better, and/or more clinically significant data than can be obtained through unaided clinical observation. An important question, then, is not the extent to which ICG CO measures correspond with other measures, all of which are of limited accuracy, but rather, the extent to which the technology can be used to trend clinically significant data at low risk and lower cost. Such studies are on the horizon, and will likely define the role of ICG in the management of congestive heart failure.

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