

Bench to Bedside: Electrophysiologic and Clinical Principles of Noninvasive Hemodynamic Monitoring Using Impedance Cardiography

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Abstract

The evaluation of the hemodynamic state of the severely ill patient is a common problem in emergency medicine. While conventional vital signs offer some insight into delineating the circulatory pathophysiology, it is often impossible to determine the true clinical state from an analysis of blood pressure and heart rate alone. Cardiac output measurements by thermodilution have been the criterion standard for the evaluation of hemodynamics. However, this technology is invasive, expensive, time-consuming, and impractical for most emergency department environments. Impedance cardiography (ICG) is a noninvasive method of obtaining continuous measurements of hemodynamic data such as cardiac output that requires little technical expertise. ICG technology was first developed by NASA in the 1960s and is

based on the idea that the human thorax is electrically a nonhomogeneous, bulk conductor. Variation in the impedance to flow of a high-frequency, low-magnitude alternating current across the thorax results in the generation of a measured waveform from which stroke volume can be calculated by a modification of the pulse contour method. To adequately judge the possible role of this technology in the practice of emergency medicine, it is important to have a sufficient understanding of the basic scientific principles involved as well as the clinical validity and limitations of the technique. **Key words:** hemodynamics; monitoring; impedance cardiography. *ACADEMIC EMERGENCY MEDICINE* 2003; 10:669–680.

Emergency departments (EDs) continue to see patients of greater acuity in increasingly crowded hospitals. To provide adequate and protracted care for these potentially critically ill patients, emergency physicians are frequently utilizing the traditional tools of the intensivists for diagnosis, monitoring, and treatment.¹ Because of the challenging environment in the ED, noninvasive technologies such as ultrasound, pulse oximetry, and external cardiac pacers are often used in preference to invasive techniques to assess and support the hemodynamic system.

The most important function of the circulation is to provide transport of oxygen and substrates to and from the tissues.² The primary goal of hemodynamic

monitoring is to determine the adequacy of this oxygen delivery. Since oxygen transport is a direct function of the perfusion pressure, arterial oxygen content, and cardiac output, these physiologic parameters are called “vital signs.” While determination of blood pressure, heart rate, respiratory rate, and oxygen saturation is readily available in most clinical settings, assessment of the true hemodynamic state from an analysis of these measurements alone is difficult.² For example, cardiac output is considered the single most important driving force in the circulation. Invasive Swan Ganz monitoring is usually impractical and possibly risky as a part of routine practice in the ED, but the need to know the state of central hemodynamics can be critical to appropriate emergency decision making and resuscitation. Recently, noninvasive techniques have been developed to assess cardiac output. The purpose of this article is to describe the principles and clinical development of noninvasive techniques to assess cardiac output in the ED.

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TECHNIQUES OF CARDIAC OUTPUT DETERMINATION

Before Swan's use of invasive pulmonary artery catheters paved the way for the development of the thermodilution technique, many investigators had explored noninvasive or minimally invasive methods

to estimate cardiac output. Most of these methods used modifications of the “pulse contour method,” first used practically by Hamilton and Remington.³ In this procedure, the area under the curve of the arterial pressure waveform is used to estimate stroke volume and cardiac output. While the techniques developed using this method had surprisingly accurate results, the technology required to measure the pulse pressure waveform was cumbersome and not clinically practical in most circumstances.

The convergence of escalating concerns over the safety of invasive hemodynamic monitoring and the recent developments in microprocessors and signal analysis technology has culminated in a renewed interest in some of the noninvasive monitoring methods. One noninvasive technology that has gained considerable interest in emergency medicine is the application of the technique of thoracic electrical bioimpedance (TEB) to the clinical practice of impedance cardiography (ICG). ICG holds the promise of rapid and continuous measurements of cardiac output and central fluid volume that require little technical expertise. However, to adequately judge the integrity of this new technology, it is important to have a sufficient understanding of the basic scientific principles involved, the validity and limitations of the technique, and the possible role of the method in the practice of emergency medicine.

ELECTROPHYSIOLOGIC PRINCIPLES AND THEORY OF STROKE VOLUME DETERMINATION

Ohm's Law states that the flow of an electrical current (I) is equal to a voltage drop (E) between the two ends of a circuit divided by the resistance or impedance (Z) to current flow.⁴

$$I = E/Z \quad \text{or} \quad Z = E/I$$

If the current remains constant, then changes in voltage across the circuit are equal to changes in the impedance to current flow. Furthermore, if the impedance (Z) is dependent upon the cross-sectional area (A), the length (L), and resistivity (ρ) of the conducting material, then changes in Z can be related to changes in volume (V) of the conductor by the expression:

$$Z = \rho(L/A) \quad \text{or} \quad Z = \rho(L^2/V)$$

In this equation, $V = A \cdot L$ and resistivity (where ρ is a constant specific to the composition of the material) is measured in Ω cm. This supposition is the fundamental principle behind the concept of ICG.

In the early part of the twentieth century, Hoebbers, Cole, and others were examining the conductance of biological tissues with development of the Cole-Cole principle.^{4,5} In the Cole-Cole analysis, the human body is treated as both a cylinder and an insulator with cell membranes surrounding small conductors consisting of intracellular fluid and embedded in a larger conductor of extracellular fluid. This creates a parallel circuit that has both resistance and capacitance.

In 1940, a landmark article by Nyboer introduced the use of the bioimpedance technique to study changes in volume in a tissue.⁶ Nyboer extended this concept to examine periodic changes in blood volume and flow in extremities via the technique of impedance plethysmography. This technique records a proportional impedance response to volumetric changes in the arm and uses the following equation to relate the impedance change (ΔZ) and the base impedance Z_0 to the change in volume (ΔV):

$$\Delta V = \rho(L^2/Z_0^2)\Delta Z$$

Differentiating this equation with regard to time (t) varying pulsatile changes in volume, Nyboer derived the expression:

$$\Delta V(t) = \rho(L^2/Z^2)\Delta Z(t)$$

Building on the seminal work of Nyboer, Kubicek and others investigated the possibility of measuring total blood flow within the aorta (representing cardiac output) by examining impedance changes across the thoracic cavity under the influence of a constant-magnitude, high-frequency measurement current and coined the term “thoracic electrical bioimpedance” (TEB).^{4,7,8} In his original model, Kubicek used the simple assumption of the thorax as a cylinder of cross-sectional area (A) and length (L) that would serve as an electrically nonhomogeneous bulk conductor of some constant injected current circuit. The human thorax is composed of mostly muscle, lung, fat, skin, bone, and air; all of which have very high resistivity ($R = 200\text{--}5,000 \Omega$ cm).⁹ By contrast, blood, with its electrolyte-rich fluid base, has a very low resistivity (plasma: $R = 65 \Omega$ cm; whole blood: $R = 130 \Omega$ cm), though it composes a much smaller portion of the total volume of the thorax ($\sim 15\%$). However, since electrical currents tend to take the path of least resistance, it can be postulated that the majority of the current flowing through the thorax would travel up the blood-filled aorta and vena cava since they would serve as natural conduits (Figure 1). Kubicek then considered that the changes in impedance observed to occur within this thorax conductor would also reflect changes in the volume within the great vessels.

Using information derived from the changing impedance during the cardiac cycle (time-dependent

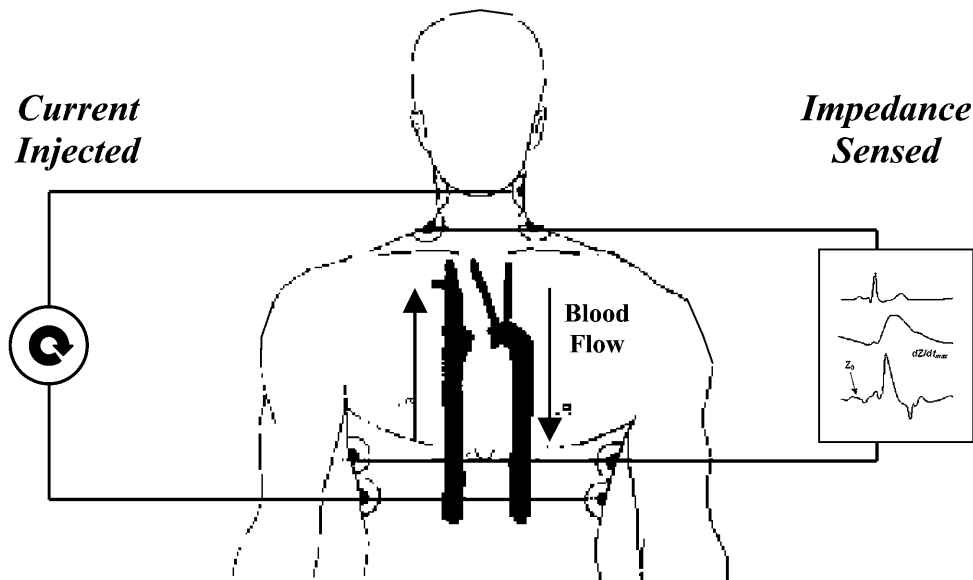


Figure 1. Tetrapolar system of electrodes, separating the current pathway from the sensing pathway. After injection of electricity by way of the outer electrodes, the impedance to flow of the current through the thorax along the path of least resistance (i.e., the great vessels) is sensed by way of the inner electrodes.

waveform), Kubicek estimated the stroke volume in a method similar to the pulse contour method (Figure 2). However, the signal artifact produced by respiration prevented accurate assessment of ejection times and measurements of the magnitude of the change in impedance attributable to the change in blood in the thoracic aorta during systole. This limitation was overcome by utilizing the maximum of the first derivative $(\delta Z/\delta t)_{\max}$ of the thoracic impedance waveform. The peak volume change within the aorta during systole would occur during peak current flow

(PF) and can be determined from the Nyboer relationship when there is a peak change in impedance:

$$PF = \rho(L^2/Z_0^2)(\delta Z/\delta t)_{\max}$$

Since the area under the arterial pulse pressure waveform accurately reflects stroke volume, this area can be estimated if the peak pressure change dP/dt_{\max} is multiplied by the total ejection time.^{3,7} The equation for peak flow can then be transformed into the Kubicek expression:

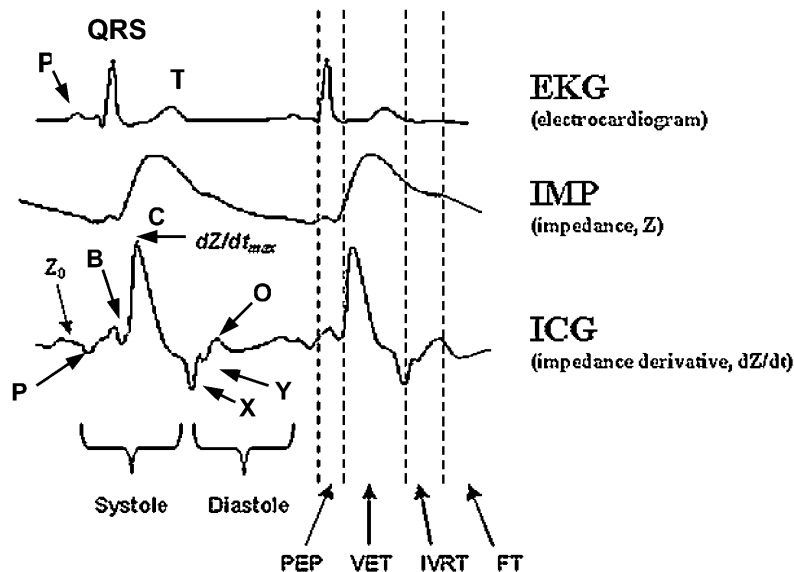


Figure 2. Waveforms Z_0 : baseline impedance; A: atrial wave; B: aortic valve opening; C: maximum aortic flow (dZ/dt_{\max}); X: aortic valve closing; Y: pulmonic valve closing; O: mitral valve opening; PEP: pre-ejection period; VET: ventricular ejection time; IVRT: isovolumic relaxation time; FT: ventricular filling time.

$$\Delta V = SV = \rho(L^2/Z_0^2)(\delta Z/\delta t)_{\max} \text{VET}$$

where VET is the ventricular ejection time as determined from the impedance waveform.

Underlying Assumptions. The Kubicek equation incorporates several assumptions.^{4,7-9} The primary supposition is that the change in thoracic impedance seen is due primarily to increases in the aortic volume. This supposition has been challenged by investigators who assert that changes in hematocrit, reorientation of the erythrocytes as blood begins to flow, and the arterial run-off of blood out of the thorax during the course of systole all may effect the changes in the Z values observed. While it is important to know the possible limits of any technology used in diagnosis, none of the problems associated with the Kubicek assumptions appear to significantly limit the usefulness of the method, and values for stroke volume obtained by ICG correlate well with other techniques, as is discussed below. However, considerable effort has been made to eliminate some of the assumptions of the Kubicek model and to create a more accurate equation.

Sramek revised the model from that of a cylinder to that of a truncated cone, which is closer to the actual electrical field distribution in the thorax.^{7,8} The physical volume of this cone was estimated to be about one third of the volume of the cylinder model, and the equation for stroke volume was again revised to become:

$$SV = (L^3/4.2)(\delta Z/\delta t)_{\max} \text{VET}/Z_0$$

Finally, Sramek determined that the average distance (L) is 17% of the total body height (H) of the individual, thereby eliminating the need for length measurements. Since cardiac output is usually directly proportional to the body size, this assumption seemed reasonable, and the Sramek equation became:

$$SV = ((0.17H)^3/4.2)(\delta Z/\delta t)_{\max} \text{VET}/Z_0$$

where $0.17 \cdot H^3/4.2$ is sometimes defined as the volume of electrically participating thoracic tissue (VEPT). Bernstein further modified this equation by normalizing to an ideal body weight by a factor δ .^{5,8,9} The modified Sramek (Sramek-Bernstein) equation then became:

$$SV = \delta(\text{VEPT})(\delta Z/\delta t)_{\max} \text{VET}/Z_0$$

There has been some controversy regarding the proper model and equation to use. There are very little data comparing the results of head-to-head measurements made by the different equations when compared with traditional invasive techniques. Intuitively, the Sramek-Bernstein model should be more accurate, although this has not always been found to be true when applied practically. While most commercially available devices use a modified Kubicek

equation, some devices on the market allow the user a choice in equations. Regardless of which equation or model used, a reasonable estimation of the stroke volume can be ascertained if we are able to determine the two important variables of $\delta Z/\delta t_{\max}$ and VET.

THE PHYSIOLOGIC ORIGINS OF THE IMPEDANCE SIGNAL AND WAVEFORM

In ICG, the patient interfaces with the transducer through a series of disposable surface electrodes providing the connection for measurements of current flowing in a direction parallel to the spine.^{7,9} Most modern ICG devices use a tetrapolar system of electrodes, separating the current pathway from the sensing pathway by at least 5 centimeters (Figure 1). One set of the external surface electrodes, placed on the upper abdomen and upper neck, is the source and sink of a constant high-frequency, very-low-magnitude current that provides coverage of the thorax with a homogeneous electrical field. Typical frequencies and amplitudes used in ICG range from 50 kHz to 100 kHz at 0.2 mA to 5 mA. The voltage is sensed by the two pairs of electrodes placed at the beginning of the thorax (the line of the root of the neck) and the end of the thorax (the level of diaphragm—the xiphoid process level). These sensing electrodes also detect the electrocardiogram (ECG) signal. In order to eliminate the skin-to-electrode impedance, highly conductive pre-gelled electrodes are often used. The “Z” electrical resistance (impedance) of the thorax to this measurement current is indirectly proportional to the content of fluid in the thoracic cavity. As blood is pumped out of the heart and into the aorta during the cardiac cycle, the volume of this fluid in the thoracic conduit and, therefore, the impedance to flow of the current change dramatically with time. ICG technology converts the time-varying measurement of the Z electrical resistance of the thorax into waveform from which a variety of parameters related to different physiological events are derived.

The important parameters required to compute stroke volume and cardiac output are dZ/dt and VET. While the ECG depicts the electrical events of the heart, the ICG waveform is a fingerprint of the mechanical events of cardiac contraction. When used in conjunction, the timing landmarks on the ECG and dZ/dt signals enable measurement of $(dZ/dt)_{\max}$ and the systolic time intervals such as the VET and the pre-ejection period (PEP) and an overall analysis of other cardiac electromechanical activities. Some ICG instruments use waveform ensembles averaging over a burst of 20–30 seconds to improve the accuracy of the signal and to eliminate noise. Others have used sophisticated algorithms that examine a time-frequency power analysis for the determination of critical points. The standard points of the impedance waveform are: “A,” beginning of electromechanical systole; “B,” opening of aortic valve; “C,” maximal

mechanical contraction (dZ/dt_{\max}); "X," closing of aortic valve; "Y," closing of the pulmonic valve; and "O," mitral valve opening (Figure 2).

$\delta Z/\delta T_{\max}$

The concept of the maximum of the first derivative ($\delta Z/\delta t$)_{max} of the thoracic impedance waveform stemmed from the observation that the simple recording of the general impedance waveform and ECG reveals a signal that is variable in its baseline and form. This impedance is composed of three components that vary over the cardiac cycle:

$$Z(t) = Z_0 + Z_R(t) + Z_H(t)$$

The Z_0 is the baseline impedance of all the thoracic tissues, fluid, and air, with an average normal value in man of around 25 Ω . As Z_0 does not change acutely with time, $Z_R(t)$ (respiration) and $Z_H(t)$ (hemodynamic) jointly determine the impedance waveform changes. The respiratory component $Z_R(t)$ typically induces a change of about 1 Ω . The hemodynamic component is in the range of 0.1 to 0.2 Ω , which is only 0.3–0.5% of the total thoracic impedance. $\delta Z/\delta t_{\max}$ was initially measured directly from the slope of the simple impedance waveform. However, this method proved to be too variable for routine clinical use. The first derivative of these impedance changes with respect to time ($\delta Z/\delta t$) were found to eliminate much of the variations in the baseline due to respirations and largely reflects $Z_H(t)$ changes only. This is explained by the fact that $Z_H(t)$ has a much higher frequency than $Z_R(t)$ (average heart rate of 70 beats/min, compared with a normal respiratory rate of 14 breaths/min). Using this derivative methodology, it has been determined that almost all of the impedance changes were derived from changes in the systemic thoracic aorta alone.^{4,5,7,9} Therefore, the rate of cardiovascular TEB changes (dZ/dt) (i.e., the first derivative of impedance) is an image of the aortic blood flow and its maximum value, $(dZ/dt)_{\max}$, is proportional to the aortic blood peak flow.

PEP AND VET

The systolic time interval (STI) begins at the point of the electrical initiation of ventricular contraction and ends with the ejection of blood from the ventricles and closure of the aortic valve. The STI is composed of a PEP and a VET.

$$STI = PEP + VET$$

The PEP is the period of electromechanical delay or the time interval of isovolumic contraction of the ventricles and the VET is the time from the opening of the aortic valve until its closure at the end of systole. The VET is a major component of the equations used

to calculate stroke volume and must be accurately estimated from the impedance waveform. Since the ECG and impedance waveform are on the same time scale, they can be aligned to determine the opening and closing times of the aortic valve (Figure 2).

The electrical initiation of contraction (Q point) is readily determined as the point marking the beginning of the QRS in the ECG signal obtained from the ICG electrodes. When there is a sharp demarcation in the beginning of the systolic drop in impedance (C-wave), it is easy to determine the B point marking the end of the PEP and the beginning of the VET. However, this point can be difficult to ascertain if there is a noisy signal or prominent atrial wave (A-wave). Sometimes there is a notchpoint at the end of the atrial wave that allows objective determination of the B point. Computer algorithms have also been developed to analyze the $\delta Z/\delta t$ slope and detect any change in the curvature that could represent the B notchpoint.^{4,5,7} Some investigators choose to use the point on the $\delta Z/\delta t$ downslope that coincides with the end-diastolic baseline of the impedance waveform. The end of the VET (X point) is also easily noted in most impedance tracings and is one of the advantages to using the derivative of the Z tracing as the basis for signal processing. This apex marks the point of aortic valve closure and the beginning of the shift to the diastolic phase of the cardiac cycle. It also coincides with the incisura of the aortic pulse contour.

The PEP can range from 40 to 120 msec (avg. 100 msec), while the VET typically ranges from 200 to 350 msec (avg. 300 msec). The ratio is thought to reflect a measure of ventricular contractility, although these time intervals can be affected by several hemodynamic factors, including heart rate and blood pressure. Most correlative studies have found excellent agreement of the impedance-derived systolic time intervals with those measured by both invasive and noninvasive techniques, and very few critics ever question the ability of ICG as a method for determining cardiac time intervals.

PHYSIOLOGIC CORRELATES OF OTHER LANDMARKS OF THE IMPEDANCE WAVEFORM

Other important landmarks of the impedance waveform include the A-, C-, and O-waves (Figure 2).

A-wave. The A-wave of the impedance cardiogram is the small negative deflection from baseline that occurs during the PEP and before the opening of the aortic valve and is strongly correlated with atrial contraction.^{4,5,7}

C-wave. The C-wave is the major upward deflection in impedance seen during systolic phase of the

cardiac cycle that peaks at the point of $\delta Z/\delta t_{\max}$.^{4,5,7} It is first deflection from baseline after the A-wave and begins with the B point and ends with the X point. Because the $\delta Z/\delta t_{\max}$ and VET are defined by the shape, depth, and duration of the C-wave, the majority of research in correlating physiologic events has focused on this portion of the impedance waveform. The aortic pulse pressure wave is responsible for most of the form of the C-wave, and the $\delta Z/\delta t_{\max}$ of the C-wave is correlated with the peak aortic blood flow.

O-wave. The O-wave is defined by the diastolic portion of the cardiac cycle and peaks at the point of mitral valve opening (O point).^{4,5,7} The filling of the vena cava and pulmonary vein during the early phase of diastole results in the up-slope of the impedance signal until the opening of the tricuspid and mitral valves, beginning the ventricular filling. During the terminal portion of the O-wave, there is an increase in the impedance signal and a return to baseline at the end of diastole (Z point) as the venous system empties into the heart. This waveform is important in that very few techniques in clinical medicine are able to tell us much about the events of diastole, cardiac filling, or venous return.

EVOLUTION INTO A CLINICAL METHODOLOGY

The discovery of the bioelectric principles, the derivation of the theory behind the stroke volume estimations, and the practical methods applied to the measurements of the waveforms so far described represent only a small part in the development of ICG as a technology. Over the past 40 years, a stepwise progression of innovations has culminated in a clinical methodology for noninvasive cardiac output determination. The concept of TEB or impedance cardiography as a means of monitoring cardiac output in astronauts⁹ led to the development of the Minnesota impedance cardiograph (MIC). The MIC is an electronic system for measuring impedance changes across the thorax that would reflect cardiac function and blood flow from the heart's left ventricle into the aorta. Space-qualified miniaturized impedance units based on the MIC technology were introduced to service aboard Space Shuttle flight STS-8 in 1983. It was after this high-profile introduction that the technology became commercially available and the methodology of ICG has since undergone numerous transformations. However, the evolution of ICG as a practical clinical methodology is far from complete and literally hundreds of investigators around the world have made incremental contributions to this young field. It is also quite evident that the development of the technology is far from optimal and some failures have resulted in skepticism among

clinicians who tried to utilize some of the early forms of ICG devices. Many of the limitations of ICG are also the constraints in our own technical skills in signal analysis and data processing, as well as our understanding of the clinical meaning of many aspects of the impedance waveform. Along with development of the technique, many researchers have contributed to the validation of the method and defined its applications in clinical medicine. In fact, a simple Medline search reveals that there are more than 1,000 articles that have some reference to impedance cardiography.

HEMODYNAMIC PARAMETERS MEASURED

Stroke Volume/Cardiac Output. The noninvasive determination of stroke volume and cardiac output can have important implications for the diagnosis and management of a number of clinical conditions often seen in the practice of emergency medicine. Stroke volume is determined from the magnitude of the changes in the electrical conductance of the current as it traverses the thorax by way of the aorta. When combined with heart rate, this measure provides a continuous estimate of cardiac output.^{4,9} From the cardiac output measure, parameters such as total peripheral resistance, aortic compliance, and other hemodynamic constants can be estimated.

Central Fluid Volume. Central fluid volume status can be extremely difficult to assess in the critically ill patient. Most methods for measuring blood and extracellular fluid volumes are highly invasive, logistically cumbersome, or difficult to interpret. Baseline impedance of the thoracic cavity (Z_0) and its inverse, thoracic fluid volume index (TFVI), are strongly correlated with thoracic intravascular fluid volumes, and are found to change significantly in the presence of acute pulmonary edema.¹⁰ This index provides a noninvasive and continuous measure of the central fluid status and can be used to monitor the effects of treatments or as a diagnostic adjunct when the underlying pathophysiologic state is uncertain.^{4,10}

Cardiac Time Intervals. Different points and deflections within the impedance waveform have been correlated with many of the intervals within the cardiac cycle.^{4,5} It is simple to ascertain both the systolic and diastolic time intervals by ICG and use these measures to make clinical determinations of pathophysiologic mechanisms.^{11,12} The PEP is the isovolumic contraction interval beginning with the initiation of the QRS complex at point Q and ending with the start of mechanical systole as marked by the initial deflection of the systolic waveform. The left ventricular ejection time (LVET) begins at the end of the PEP and ends at the closure of the aortic valve when ejection ends as determined by the dZ/dt

waveform. Diastolic time intervals are found to coincide with the second deflection of the ICG waveform. The X to O period represents the IVRT (a measure of diastolic function and active ventricular relaxation), which begins with the aortic valve closure and ends at the point of the maximum second deflection. The beginning of the QRS complex on the ECG (Q) and the start of the primary ICG waveform mark the end of diastole.

Contractility/Ejection Fraction. Along with cardiac output determination, the impedance waveform can be used to evaluate cardiac contractility. The maximum rate of the second derivative of impedance, $(d^2Z/dt^2)_{\max}$, is a reflection of the maximum acceleration of aortic blood flow, and is a measure of the inotropic state in a manner similar to the way dP/dt has been used previously. This parameter is usually normalized to the baseline impedance and is called the "acceleration index."⁷ Other similar contractility indices (Heather Index = $dZ/dt_{\max}/QZ1$, where dZ/dt_{\max} is the maximum deflection of the initial waveform and QZ1 is the time from the beginning of the Q wave to peak dZ/dt , and Minnesota Index) are also based on the dZ/dt_{\max} .⁹

The PEP/LVET ratio was first used by Weissler about 40 years ago to noninvasively calculate the cardiac ejection fraction (EF), but the method was seldom used because of the technical difficulties associated with measuring these time intervals.¹³ However, ICG is known to accurately measure cardiac time intervals, and Capan et al. have validated a similar method for calculating EF using ICG measurements.¹⁴

Additional Parameters. Several additional hemodynamic parameters such as total peripheral resistance, aortic compliance, and pulmonary capillary wedge pressures have been estimated or calculated from the impedance waveform.^{9,15} An analysis of typical waveforms may also be used in the diagnosis of such pathologic states as mitral regurgitation and idiopathic hypertrophic subaortic stenosis (IHSS).¹⁶ This "reading of the waveform" is an area of ICG that has great diagnostic potential for defining the total electromechanical events of the heart and the conjoining circulation.

VALIDATION OF THE TECHNIQUE

In order for ICG to be a useful modality in the ED setting, it is important that clinicians have confidence in the measurements obtained. There are currently more than 200 studies in the literature correlating ICG determinations of cardiac output with some invasive criterion standard measurements. While most of the evidence is positive, not all of the studies show good correlations. However, several comprehensive meta-

analyses of this literature have found overall correlations (r) ranging from 0.82 to 0.93.^{17,18} Our review of the literature of comparisons of ICG findings with measurements using a variety of criterion standard techniques in humans is outlined in Table 1. When these studies are merged using the advanced methodology of Hunter and Schmidt for directly combining correlation coefficients, there is generally good overall agreement, although a few individual studies did report poor concurrence.¹⁹ Most notable is the correlation of the ICG measures with the settings of a left ventricular assist device. Though thermodilution measurement of cardiac output is considered to be the clinical "gold standard," the technical problems and variability often found with this method make comparisons with ICG by the Bland-Altman method more reasonable.²⁰ Using this statistical method, there has been very good agreement between ICG and thermodilution techniques.²¹

In a recent large multicenter study, the ICG provided stable signals and reliable cardiac output estimations even under extenuating emergency conditions.²¹ In this study there were 2,081 simultaneous bioimpedance and thermodilution cardiac output measurements in 860 critically ill patients from the ED, operating room (OR), and intensive care unit (ICU). The correlation coefficient, r , was 0.85; the precision and bias were $-0.124 + 0.75 \text{ L/min/m}^2$. No instances of spurious impedance values that would have led to incorrect or harmful therapy were observed.²¹

When conditions interfere with accuracy, they could be identified by reductions in the baseline impedance (Z_0) $<15 \Omega$ and by the height of the impedance waveform $<0.3 \Omega$. Using these values as criteria in a prospective evaluation of 213 data pairs in 46

TABLE 1. Comparison of the Cumulative Correlation Coefficients (Weighted Average and Meta-analytic) from a Variety of Studies (201 Studies) Using Different Criterion Standards

Methods*	Average r	Meta-analytic	No. of Measurements
Overall	0.81	0.94	16,803
Thermodilution	0.81	0.95	10,959
Direct Fick	0.79	0.95	587
Indirect Fick	0.80	0.90	541
Doppler	0.61	0.86	284
Dye-dilution	0.81	0.93	902
Ventriculography	0.72	0.81	295
Echocardiography	0.69	0.92	281
Isotope dilution	0.88	0.88	41
Integrated flow	0.83	0.83	49
Pulsatile flow	0.76	0.76	17
LVAD	0.89	0.89	30
MRI	0.92	0.98	20
EM flow probe	0.84	0.88	2,807

*LVAD = left ventricular assist device; MRI = magnetic resonance imaging; EM = electromagnetic.

patients, the correlation coefficient, r , was 0.93; bias and precision were -0.14 ± 0.54 L/min/m². The average difference between thermodilution and impedance measurements was $9.8\% \pm 6.7\%$ and was similar to the differences between successive thermodilution measurements ($9.4\% \pm 6.2\%$) under similar conditions. This is also consistent with previous studies where thermodilution decreased an average of 15% with expiration and increased 12%–15% with inspiration.²¹ The correlations of ICG versus thermodilution cardiac output were also equivalent to those of pulse oximetry when compared with the standard blood gas analysis performed in the same clinical series.²¹

In the study, noninvasive monitoring favorably compared with invasive thermodilution catheter monitoring in postoperative patients and patients with blunt trauma, gunshot wounds, head injuries, sepsis, strokes, drug overdose, hypertensive crises, acute myocardial infarction, and acute gastrointestinal bleeding. Of note, there was appreciable disparity in the presence of severe pulmonary edema, advanced adult respiratory distress syndrome, congestive heart failure, and late-stage septic shock with capillary leak. However, the comparison was considered sufficiently accurate to be useful clinically for making therapeutic decisions in more than 90% of all the acutely ill patients. Moreover, the continuous online displays of the data allow calculation of net cumulative deficits or excesses.

It is important to know whether the accuracy of ICG varies with the clinical condition or particular disease state. When average correlations from the literature are compared according to patient types (Table 2), there are some notable differences. While the average values from these studies are reasonable in most cases, the ranges can be broad from study to study.

This finding may represent unique problems in these groups of patients or may only be a function of differences in the specific technology used or operator dependency.

It could be argued that absolute accuracy for the cardiac output values is not as essential as are the direction and patterns of changes in hemorrhagic, traumatic, septic, and postoperative shock, because pre-injury or pre-illness baseline values are rarely available and there are considerable variations in optimal therapeutic goals. Often the emergency physician needs to know only whether the cardiac output is high, low, or normal. Nevertheless, the trends of ICG-derived cardiac output changes closely track the changes in cardiac output by the thermodilution method.²¹ More study is needed to further define the clinical value of the ICG measurements and their role in decision analysis in patients in the ED, especially those in profound shock or organ failure.

CLINICAL APPLICATIONS IN EMERGENCY MEDICINE

Differentiating the Hemodynamic State. The emergency physician is often faced with the difficult task of evaluating the undifferentiated patient within a very narrow window of time. The ICG technology can be used in the acute setting as a diagnostic adjunct when the primary hemodynamic state is uncertain. Distinguishing high- from low-flow states is important in the differentiation of diverse forms of shock. Conditions such as sepsis, dehydration, cardiac failure, and neurogenic shock can present with hypotension without other distinctive characteristics. Likewise, acute dyspnea may arise from a variety of decidedly different hemodynamic and pulmonary etiologies.

TABLE 2. Comparison of the Cumulative Correlation Coefficients (Weighted Average) of Impedance Cardiography Measurements with a Criterion Standard in a Variety of Clinical Conditions: Possible Problems that Would Result in Inaccurate Cardiac Output Estimation

Type of Patient*	Average Correlation (Range)	Possible Problems in Cardiac Output Estimation
Healthy	0.81 (0.50–0.98)	Hyperdynamic/overestimates
Pediatric/neonatal	0.83 (0.28–0.97)	Lower current/underestimates
Intubated	0.84 (0.1–0.98)	Noise/variable estimates
Obstetric	0.81 (0.28–0.97)	Anatomic landmarks/underestimates
Elder	0.95 (single study)	Atherosclerosis/underestimates
Obese	0.76 (0.58–0.94)	Conduction/underestimates
CHF	0.83 (0.63–0.99)	Lung edema/underestimates
CAD/AMI	0.79 (0.22–0.95)	Weak pulse/underestimates
Sepsis	0.56 (0.36–0.75)	Runoff/underestimates
Hemorrhagic shock	0.88 (0.84–0.98)	Low flow/underestimates
COPD	0.92 (single study)	Conduction/overestimates
GSW	0.72 (single study)	Noise/variable estimates
Chest tubes	0.35 (single study)	Noise/variable estimates
Animals	0.86 (0.41–0.98)	Anatomic landmarks/underestimates

*CHF = congestive heart failure; CAD/AMI = coronary artery disease/acute myocardial infarction; COPD = chronic obstructive pulmonary disease; GSW = gunshot wound.

Studies conducted within the emergency setting have demonstrated the usefulness of ICG as a diagnostic adjunct in these challenging clinical situations.^{10,21,22} A more complex analysis of the underlying circulatory mechanisms involved may be especially helpful when the pathophysiologic derangements are due to some toxicologic agent or unusual medical condition (e.g., thyrotoxicosis, heart transplant rejection, pacemaker malfunction).^{23,24} In general, the ICG measurement can be used to put the findings of the traditional vital signs into a more complete systems-analysis perspective.²⁵

Clinical Monitoring. Evaluating and monitoring patients for hemodynamic stability are an important part of the practice of emergency medicine. Optimizing oxygen delivery by monitoring hemodynamic parameters helps to direct therapy and guide resuscitation. Unfortunately, heart rate is frequently undependable as a critical gauge. Similarly, blood pressure changes tend to be a late indicator of circulatory instability. Studies in trauma patients have demonstrated the utility of ICG measurements for the early identification of patients with hemorrhage or shock.^{26,27} In fact, as little as 450 mL of blood loss may be detected by changes in the baseline impedance.²⁸ ICG technology allows for continuous beat-to-beat monitoring of the stroke volume and cardiac output so that early trends and small changes can be readily recognized. Monitoring these changes in cardiac output has also been used in the ED to assess the efficacy of treatment regimens in patients with congestive heart failure and to direct inotropic and fluid therapy in shock.

OUTCOMES STUDIES

Many studies have shown that using physiological endpoints to guide resuscitation beyond the usual clinical algorithms improves patient outcomes and survival.^{21,29–36} Invasive hemodynamic parameters obtained by pulmonary artery (PA) catheterization, and other methods to define survivors' patterns, have been reported to provide criteria for therapeutic goals in critically ill patients.^{25,29,32,33} When noninvasive hemodynamic measurements have been used in the ED to guide early shock management, there is a significant impact on the progression to organ failure and mortality.^{33,34} Similar measurements and calculated endpoints derived from ICG monitoring have been used to improve management, outcomes, and survival in patients with shock, congestive heart failure, and hypertension.^{21,33,35}

In one study, blunt trauma patients had an ICG monitor placed shortly after arrival to the ED. The monitor accurately revealed episodes of low cardiac index and decreased tissue perfusion that was found to occur more often in nonsurvivors.³¹ The application

of the noninvasive monitor early in the resuscitation of blunt trauma patients also proved to be useful in determining the cardiac output and predicting survival. In other trials, noninvasive ICG monitoring provided information that accurately identified episodes of decreased cardiac output in critically ill patients.^{26,33} The decrease in cardiac index was significantly greater in the nonsurvivors compared with the survivors. Thus, measuring and optimizing the cardiac index and other physiologic endpoints (e.g., oxygen delivery) in the early stages with ICG appear to improve outcomes in critically ill ED patients. Several recent resuscitation studies have demonstrated superior outcomes when early goal-directed therapy and advanced hemodynamic monitoring are used. This may prove to be a general principle for optimal care regardless of the technology utilized.^{30,34–36}

IMPEDANCE CARDIOGRAPHY AS A RESEARCH TOOL

As a research tool, ICG has been used to gather information in clinical studies that would be either unethical or extremely difficult to perform by invasive means.^{16,37} When investigating hemodynamics by invasive means, there is always some distortion of the variables being measured. The dynamics of cardiovascular functioning are certainly altered when the chest is opened to insert an electromagnetic flow probe. Noninvasive techniques allow the investigator to observe the circulation in its natural, untouched state.

Clinical research in the ED of critically ill patients is often difficult due to the inability to measure objective hemodynamic endpoints. ICG provides a noninvasive potential tool to assess these endpoints.

OPTIMAL BIOIMPEDANCE TECHNOLOGY

In the ED setting, the optimum ICG technology should be portable, easy to apply, and stable in noisy environments. A variety of manufacturers have now designed very compact instruments that are mounted on rolling stands. If the technology evolves to become a regular module in some of the standard fixed monitoring systems, then portability will become less of an issue. The number of lead placements required varies depending on the instrument used. This is due to the different methods of signal analysis. In the emergency setting, the fewer the leads that are necessary, the easier the system will be to apply and use on a routine basis. Some systems require the placement of four leads, though it is important to be sure that they have good signal integrity and Food and Drug Administration (FDA) licensing with this limitation. Most of the commercial systems require special electrode pads to be used for adequate signal detection. These can also logistically add to the

complexity of operation and inherent cost of using the system. Some systems use standard ECG pads that greatly simplify application at the same time the routine rhythm monitors are attached. The algorithms and methods of signal analysis are proprietary and are the main technical differences between the various instruments. The time-frequency analysis method is considered very stable, but requires more leads. Many of the instruments use an ensemble averaging technique that can eliminate most of the sporadic noise. It is important to compare the documented signal-to-noise ratios between the different instruments before making a choice. If the technology has been used successfully during stress testing, then it will probably function well in the ED environment. Just as with the ECG and pulse oximetry waveforms, it is essential to visualize a good signal before trusting the digital values obtained. The ability to examine the waveform in detail will be especially important to the more experienced user when looking for some of the nuances in the reading.

LIMITATIONS OF IMPEDANCE CARDIOGRAPHY

There are a number of limitations that should be noted when ICG measurements are used. Some of these restrictions are technical and some are purely clinical. While the experienced cardiographer can often work around these factors, in some cases the ICG test is simply unusable and more invasive techniques must be used.

Stroke Volume Calculations. The small discrepancies in measurements found between the different mathematical models presented above have led some to conclude that the equations are not interchangeable, and the results of studies performed with differing methodologies should not be compared.^{4,7,8,16} In fact, there is not a consensus on a model for calculating stroke volume. As more mainstream companies and researchers begin to explore this technology, it is likely that an entirely new and more accurate equation and model will be derived. It may be that the new methodology will come in the form of a complex computer model and simulation or may involve a tomographic perspective. In any case, the application must remain simple with limited electrode applications to win widespread clinical acceptance, particularly as a monitoring device.

ECG Signal Abnormalities. From a signal analysis perspective, additional difficulties arise when there is no clear ECG waveform to monitor, or when the signal of the QRS is aberrant, of low voltage, or contaminated with noise. In the typical ECG, the maximum signal for QRS occurs in the lead II plane, and it has been suggested by some that this is the lead that

should be used to determine the beginning of the systolic time interval (STI). Regardless of the lead choice, it is usually best to define a lead that has a positive deflection for the R-wave. Pacemakers sometimes skew the signaling of the initiation of electrical propagation within the ventricles, especially if the mechanisms involve atrial pacing or dual chamber ventricular pacing. This is also true for patients who have bundle branch blocks, abnormal P-wave morphology, dextrocardia, or any mechanism that prevents accurate determination of the initiation of the QRS. Several of the devices currently available commercially allow the experienced user to reposition the demarcation of the beginning of the STI based upon the appearance of the ECG/QRS waveform. In addition, advanced computer algorithms have greatly improved the identification of some of these crucial points.^{4,9,16}

Movement Artifacts. In almost all monitoring and imaging techniques, motion, anxiety, restlessness, shivering, agitation, and hyperventilation may interfere with measurements and increase physiologic responses. Factors preventing good electrode-to-skin contact (sweating, oils, severe obesity) may also limit the accuracy of signal detection.^{9,16}

Low Impedance Values. When Z_0 and dZ/dt values are lower than 15Ω and 0.3Ω , respectively, impedance estimates are observed to track and trend thermodilution values, but are not regarded as sufficiently reliable to be taken at face value. This is a major limitation of the method. However, it is less important in emergency conditions to have the same accuracy required in stable ICU conditions, since the patient's own baseline measurements are often unknown and optimal values for each patient may vary with comorbid conditions. In practice, 15% differences between invasive and noninvasive cardiac output estimations would be acceptable, when >50% changes from the normal range are present. Thermodilution also has appreciable inaccuracies in both high and low cardiac output ranges and under many of the same circumstances that limit ICG measurements. Direct Fick VO_2 measurements, the physiologist's criterion standard, are often precluded by the non-steady states of emergency conditions where monitoring is most often needed. Regardless of this limitation, it has been shown that ICG is very accurate for detecting changing hemodynamic status, which is most often what is needed by emergency physicians.

Excessive Thoracic Fluid States. Increased lung fluids that permit electrical signals to bypass aortic flow during cardiac systole may have erroneous values due to low signal-to-noise ratios.^{7,9} Appreciable differences between ICG and thermodilution measurements were seen in patients with pleural

effusions, severe congestive heart failure, severe pneumonia, hemothorax, and open thoracotomy with metal retractors. In each of these conditions, the electrical field distortions produced by electrolyte-fluid abnormalities allowed the electrical signal to bypass aortic blood flow, which is the source of impedance changes.

Tachydysrhythmias. Finally, there is a group of clinical conditions such as late stage cirrhosis, hyperdynamic states, tachycardia, and cardiac dysrhythmias in which cardiac output measurements by bioimpedance method underestimate the thermodilution values.^{9,16} In heart rates over 140 beats/min, the percentage of total aortic blood flow occurring in systole is appreciably less than that occurring with normal heart rates, and there may be distortion in the $\delta Z/\delta t$ signals that is presumed to be due to an exponential decay of the conductivity change in decelerating flow. This effect has not been widely reported, though some commercial vendors set upper limits on the heart rates for use of their impedance devices.

Absolute Limitations. In general, ICG should not be used for patients with severely abnormal cardiac or thoracic anatomy and is of little value in monitoring patients in cardiac arrest or during cardiac compressions.

FUTURE OF IMPEDANCE CARDIOGRAPHY IN EMERGENCY MEDICINE: THE "6TH" VITAL SIGN?

The evaluation of the hemodynamic state of the severely ill patient is a common problem in emergency medicine. The conventional simplistic equations relating cardiac output, heart rate, blood pressure, and peripheral resistance may not be helpful in determining the complex interrelationship of physical hydrodynamics present within the human circulation. While the typical "vital signs" offer some insight into delineating the circulatory pathophysiology, it is often impossible to determine the true clinical state from an analysis of blood pressure and heart rate alone.^{2,22} Recently, oxygen saturation by pulse oximetry has emerged as a fifth vital sign that has helped in determining the severity of the patient's condition.³⁸ Cardiac output is the hallmark of the circulation's ability to deliver oxygen and nutrients to the vital organs and often is considered the "unknown vital sign." The noninvasive technique of ICG has allowed emergency physicians to rapidly obtain information concerning the cardiac output of the acutely ill patient. However, the technology has noted limitations. Developments in methods of data acquisition and signal analysis should advance the clinical potential of this tool.

The ED is the primary entry point into medical care for many acutely ill patients, and this initial period provides a crucial opportunity for the early assessment and rapid therapeutic interventions that may affect outcome. Shock is easily diagnosed in late stages when therapy is ineffective, but early diagnosis is difficult due to imprecise signs and subjective symptoms. ICG-based monitoring provides objective circulatory criteria that could replace clinical guesswork with physiologic endpoints related to outcome. The simplicity and noninvasive nature of the ICG measurements could make cardiac output the "sixth" vital sign for the evaluation of the emergency patient.¹⁶

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