Anesthesiology Research and Practice

# Hemodynamic Monitoring Today

Guest Editors: Maurizio Cecconi, Jamal A. Alhashemi, Maxime Cannesson, and Christoph K. Hofer

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# Editorial Board

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*Editorial*

# Hemodynamic Monitoring Today

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Hemodynamic monitoring has been part of the routine management of intensive care patients and high risk surgical patients since the advent of the pulmonary artery catheter (PAC) more than thirty years ago. The growing availability of new less invasive devices over the past decades has now made it possible to monitor cardiac output (CO) more often in the operating room, as well as in new clinical settings such as the emergency department.

In this special issue papers have been arranged that discuss different aspects of hemodynamic monitoring, from technical issues to new clinical applications.

The first paper titled "*Perioperative intravascular fluid assessment and monitoring: a narrative review of established and emerging techniques*" is a review on perioperative intravascular fluid assessment and monitoring. How cardiovascular physiology can be monitored is explained, and different technologies are presented.

The second paper titled "*Cardiac output assessed by invasive and minimally invasive techniques*" is a review on all available technologies to monitor CO. The authors start from the PAC and carry on to present the more recent less invasive devices. The review covers technical aspects as well as clinical validation and use.

The third paper titled "*The effect of a hyperdynamic circulation on tissue Doppler values: a simulation in young adults during exercise*" presents research done on healthy individuals undergoing strenuous exercise, using left ventricular tissue Doppler velocity (TDI), giving us new data on the use of TDI in hyperdynamic circulation.

The fourth paper titled "*The effect of airway pressure release ventilation on pulmonary catheter readings: specifically pulmonary capillary wedge pressure in a swine model*" investigates the effect of the airway pressure release ventilation (APRV) on the PAC readings in an animal model. This paper gives new insights into the heart-lung interaction when using this new mode of ventilation.

In the fifth paper titled "*Clinical applications of heart rate variability in the triage and assessment of traumatically injured patients*" heart rate variability (HRV) is explored. HRV represents a way of looking at the function of autonomic nervous system during stress conditions and has been studied in different areas as a predictor of morbidity and mortality. In this paper the authors focus on the use of HRV in trauma patients.

The sixth paper titled "*Recommendations for haemodynamic and neurological monitoring in repair of acute type A aortic dissection*" gives a perspective on how hemodynamic monitoring should be used in conjunction with other clinical strategies. In this review the authors describe how hemodynamic monitoring can be combined with neurological monitoring in order to optimize the circulation guaranteeing adequate cerebral blood flow.

The seventh paper titled "*Assessing the left ventricular systolic function at the bedside: the role of transpulmonary thermodilution-derived indices*" is a review on the use of transpulmonary thermodilution to measure CO and other derived variables. The authors focus on how these variables

can be used to assess the left ventricular function in different clinical situations.

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*Review Article*

# Perioperative Intravascular Fluid Assessment and Monitoring: A Narrative Review of Established and Emerging Techniques

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Accurate assessments of intravascular fluid status are an essential part of perioperative care and necessary in the management of the hemodynamically unstable patient. Goal-directed fluid management can facilitate resuscitation of the hypovolemic patient, reduce the risk of fluid overload, reduce the risk of the injudicious use of vasopressors and inotropes, and improve clinical outcomes. In this paper, we discuss the strengths and limitations of a spectrum of noninvasive and invasive techniques for assessing and monitoring intravascular volume status and fluid responsiveness in the perioperative and critically ill patient.

## 1. Introduction

The ability to assess intravascular volume is an essential part of perioperative care and the management of perioperative hemodynamic instability. Insufficient intravascular volume can result in decreased oxygen delivery to tissues and organ dysfunction, while fluid overload states can contribute to the development of edema and organ dysfunction, including respiratory failure. The injudicious use of vasopressors and inotropes in the hypovolemic patient can be hazardous and increase the risk of a poor outcome.

Two concepts are relevant to assessments of fluid status in perioperative and critical care. *Euvolemia* describes a state of normal body fluid volume that allows adequate filling of the cardiac chambers and, in turn, makes it possible for the heart to produce a cardiac output that can meet the organism oxygen demand. In the setting of euvolemia, neither diuresis nor fluid administration is necessary. *Fluid responsiveness* describes the ability of the heart to respond to filling volume variations, modifying its stroke volume and consequently the cardiac output. From a patient management perspective, fluid responsiveness determines the extent to which circulatory homeostasis can be maintained with fluids alone versus the need for inotropes or vasopressors. An understanding of both concepts derives from the Frank-Starling relationship describing the changes in cardiac stroke volume in response to changes in cardiac preload. The ascending portion of the Frank-Starling curve will correspond to the fluid responsive phase of resuscitation, as seen with an increase in the cardiac output. Once the left ventricle reaches the plateau phase of the curve, fluid administration will not improve the cardiac output any further; it may lead to the adverse effects related to fluid overloading, such as hydrostatic pulmonary edema.

In a broad sense, if euvolemia is the goal of fluid use in resuscitation, then fluid responsiveness reflects the process of working toward establishing euvolemia. In evaluating the various techniques for analyzing fluid status, it is helpful to contrast their utility in predicting fluid responsiveness versus euvolemia and to consider how these relative strengths and weaknesses may be paired with different clinical situations to yield accurate and meaningful information. Methods of interpreting intravascular volume range from clinical assessments such as inspection of veins and passive leg raising, to more invasive methods such as central venous and pulmonary artery catheterization, to newer technically

intensive methods such as echocardiography and analysis of flow parameters.

## 2. Assessment of Fluid Status by Physical Examination

Only extremes of body water can be predicted by clinical examination. Tachycardia and hypotension and loss of skin turgor are associated with frank hypovolemia in unanaesthetized adults, while tenting of skin and sunken eyes and fontanels can be found in infants. The ability to detect hypervolemia is more dependent upon cardiac pathology where smaller grades of fluid excess can produce findings such as rales, a third heart sound, oxygen desaturation, jugular vein distension, and peripheral edema. In operative patients, experienced clinicians can often predict hypovolemia from the clinical situation. Fluid deficits resulting from a patient's *nil per os* (NPO) status and use of inhalational agents and positive pressure ventilation early in a case are usually indicative of relative hypovolemia, and anesthesiologists typically respond by increasing the volume of infused fluids. Blood loss and release of inflammatory mediators can also reduce blood volume, preload, and vascular tone in latter phases of an operation, when, again, additional boluses would likely be given with careful assessment of the blood pressure response.

Depending on patient position and access, examination of neck veins and passive leg raising test can yield useful information. The *passive leg raising test* (PLR) delivers a reversible endogenous fluid challenge by increasing venous return resulting from elevating the legs to 45 degrees in a supine patient and evaluating its effect on blood pressure and heart rate. One simple described way to perform PLR is by using the pivotal motion of the bed to transfer a 45 degree recumbent patient into a horizontal position with supine trunk and elevated legs [1]. This technique recruits the splanchnic blood in addition to the blood from lower extremities, in contrast to simply elevating legs in a supine patient. PLR test has shown good correspondence with other derived indices to predict fluid responsiveness in patients with sepsis and pancreatitis [2] and has been specifically evaluated with transthoracic echo [3] and esophageal Doppler [4] in mechanically ventilated patients. Most operative situations will preclude the use of PLR and likely prompt the clinician to assess the response to a fluid bolus. However, in evaluating patients postoperatively, this simple technique may be useful.

## 3. Invasive Pressure Monitoring

*3.1. Central Venous Pressure (CVP).* CVP is the measurement of pressures within the thorax in the superior vena cava (SVC) and serves as a reasonable surrogate for the corresponding right atrial pressures. CVP is the most widely used technique for measuring intravascular volume in critically ill patients [5].

The CVP pressure tracing consists of three positive waves (a, c, and v) and two negative waves (x and y). The CVP is specifically measured at the "z" point of the CVP tracing which corresponds to the leading edge of the c wave (Figure 1). At this part of the cardiac cycle, the catheter tip is in continuity with the ventricle and hence affords the best estimate of cardiac preload [6]. As with the measurement of jugular venous distension, the reference point for measurement of the CVP is the midaxillary line in the fifth intercostals space. Numerical recordings of CVP are measured at end expiration, a time in the respiratory cycle where the opposing forces of lung elasticity and chest recoil are balanced and exert the least pressure on the central and pulmonary vasculature. In patients with forcible expiration, the true CVP may be better represented by a value at the start of expiration [6]. Failure to attend to these basic principles will lead to erroneous data with little reproducibility across multiple users and time points.

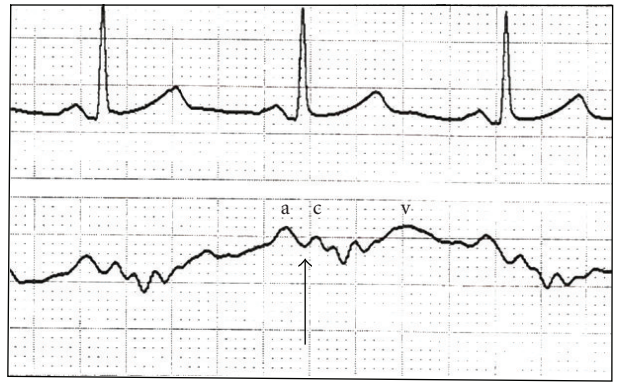


Figure 1: A typical CVP waveform (lower tracing) and accompanying electrocardiogram (upper). The a, c, and v waves are shown, along with the z point (arrow), indicating the appropriate time in the cardiac cycle for CVP measurement. All analyses need to occur at end expiration.

In our experience, single point estimates of CVP are of limited clinical value unless they are low (<5 mm Hg) and confirm an existing suspicion for hypovolemia. Trends and their correspondence to clinical evidence of organ function and perfusion help to create a more meaningful picture of fluid needs and euvolemia. The standard for testing volume responsiveness is to give a fluid challenge. This involves giving fluids to increase the CVP by 2 mm Hg and then determining whether it increased the CO [7]. In a study of 83 ICU patients, Magder and Bafaqeeh showed that patients who were able to increase the CVP by 2 mm Hg after receiving a bolus of approximately 500 mL of isotonic crystalloids over 10–30 minutes had a cardiac index increase of 300 mL/min/$m^2$. The two important findings of the study were that only 4.5% of the patients with a CVP more than 10 mm Hg responded to a fluid challenge, also of the patients who had increase in CO, 42% had a simultaneous increase in blood pressure. Therefore, the two conclusions from the study were that patients with a CVP of more than 10 mm Hg were poor responders to volume infusion and that 10 mm Hg may represent euvolemia in most individuals. Second, blood pressure increase was not a good indicator of cardiac response to a fluid challenge [8].

The Society of Critical Care Medicine's Surviving Sepsis protocol recommends to fluid resuscitate a septic patient to a target CVP goal of 8–12 mm Hg and 12–15 mm Hg in a mechanically ventilated patient [9]. Though these recommendations are part of a sepsis care bundle that has been shown to improve survival, the CVP should not be interpreted in isolation, but rather in conjunction with the cardiac output. Depending on where the patient is on the Frank Starling curve, some patients may be adequately resuscitated at a CVP of 6-7 mm Hg, while others may still be hypovolemic at 10 mm Hg.

The discussion above applies to use of jugular and subclavian veins. If these sites are not available, femoral vein line pressures have been shown to be a good substitute for CVP. In various studies in spontaneously breathing and ventilated patients, inferior vena cava pressures have been shown to be around 0.5 mm Hg lower than the SVC pressures on average and rarely more than 3 mm Hg different [10]. Though the readings have been shown to be reliable in patients receiving mechanical ventilation and high positive end expiratory pressure, the same rule cannot be applied to patients with raised intra-abdominal pressures, as encountered during laparoscopy.

A healthy person can have a CVP less than zero in upright position and still have an adequate CO and be euvolemic. Conversely, CVP can be high in a patient with poor ventricular function and low cardiac output or with a good ventricular function and volume overload [6]. As illustrated by these common scenarios, values derived from pressure readings are most useful when used in conjunction with a dynamic clinical response such as blood pressure or urine output, or some measure of cardiac output. Echocardiography, analysis of venous oxyhemoglobin saturation, and immediate changes in blood pressure have all been used in this regard.

Another distinct advantage of central venous catheterization is the ability to obtain simultaneous measurements of pressure or pressure change and central venous saturations ($ScvO_2$) with a single device. $ScvO_2$ values of more than 70% are consistent with an adequate cardiac output and perfusion status, although this relationship is true only with adequate hemoglobin levels and stable oxygen requirements ($VO_2$) of the body. The early goal-directed therapy for severe sepsis and septic shock has $ScvO_2$ monitoring as an integral part of the resuscitation goals [11]. Intermittent blood sampling and catheters with special sensors are equally efficacious means of measuring $ScvO_2$.

*3.2. Pulmonary Artery Catheters (PACs) and Pulmonary Artery Occlusion (Wedge) Pressures.* Aberrations in right heart compliance and pulmonary vascular resistance as may arise from cardiac and lung pathology can drastically alter the relationship between CVP and left heart preload. Pulmonary artery catheterization has therefore remained an attractive option to measure both right and left heart and pulmonary artery pressures in critically ill patients with such underlying pathology. The monitor is based on a balloon-tipped catheter that "floats" through the right atrium and ventricle and into the pulmonary artery as it is advanced. When "wedged" in one of the proximal branches of the pulmonary artery (PA), the catheter is in continuity with the left ventricle. With some minor gradients in between structures, as long as the catheter is the West Zone III of the lung and no mitral valve pathology is present, the following relationship exists.

*3.3. Wedge Pressure ∝ Left Atrial Pressure ∝ Left Ventricular End-Diastolic Pressure (LVEDP).* When pulmonary vascular resistance is not elevated, the PA diastolic pressure approximates the pulmonary artery wedge pressure (PAWP) and provides a useful estimate of LVEDP without having to advance and wedge the catheter.

Pulmonary artery catheters can also be used to measure mixed venous saturations and CO via the Fick principle by analysis of blood aspirated from the catheter's distal port. Typically, most CO measurements are made by electronic analysis of a thermal wash-out curve of fluid of a known temperature detected proximally at the point of injection and distally at a thermistor located 4 cm from the catheter tip. Continuous measurement of CO is accomplished with catheters containing an additional thermal filament and a computation module. The latter system requires occasional set-up time and calibration. Data from either of these catheters can be used to derive right ventricular ejection fraction (REF) and right ventricular end-diastolic volume (RVEDV). Thus, in addition to titration of fluids, the impact of inotropes, vasoconstrictors, and other interventions can be measured and followed. Low REF has been found to be helpful in identifying myocardial depression and as a marker of poor prognosis in septic patients [12]. In cardiac surgery patients, REF and RVEDV may be helpful in early detection of impaired right ventricular function secondary to right coronary artery stenosis [13].

As with the CVP, PAWP measurements are dependent on myocardial compliance. Multiple studies on ICU patients have shown that PAWP in acute illness correlates poorly or inconsistently with left ventricular end-diastolic volume (LVEDV) [14–17]. Comparisons of PAWP and right RVEDV index found the latter to correlate more reliably with changes in cardiac index (CI) [18, 19]. Though RVEDV by PAC has been found to be consistent with different methods of measurement, such as ventriculography [20] and angiography [21, 22], other investigators have found the data less convincing [23, 24]. De Simone et al. compared 3D echocardiography data with PAC-derived RVEDV and found no significant correlation between the two [25].

For most of the past three decades, use of the PAC was based on the uncontested assumption that targeted improvement of physiologic parameters to supranormal endpoints is a desirable strategy. This approach began in the early 1970s when Shoemaker and colleagues described a pattern of higher ventricular performance, oxygen delivery, and oxygen consumption which predicted survival in trauma patients [26]. Subsequent studies in surgical patients seemed to confirm the survival benefit of using the PAC to facilitate increasings CO and oxygen delivery [27, 28]. In high-risk surgical patients, a significant reduction in mortality (4% versus 30%) followed early implementation of

a protocol attempting to reach supranormal cardiac indices ($CI \geq 4.5\,L/min/m^2$), [29]). A similar reduction in mortality (5.7% versus 22%) was seen in high-risk surgical patients randomized to a protocol where an oxygen delivery index of greater than 600 $mL/min/m^2$ was achieved by dopexamine infusion [30], and a later study of trauma patients demonstrated a decrease in mortality from 37% to 18% with a similar protocol of PAC-facilitated endpoints [31].

Using the PAC to facilitate increased oxygen delivery in medical and surgical ICU patients was the next natural step. However, therapy designed to achieve such supranormal values had no effect in one study where therapy was targeted to achieve a supranormal CI and normal $SvO_2$ [32], did not improve outcome in patients randomized to receive an $O_2$ delivery index of $\geq 600\,mL/min/m^2$ in another [33], did not improve outcomes in septic patients where supranormal indices of $DO_2$ and $VO_2$ were attempted [34], and, finally, decreased survival in a study using the PAC to guide supranormal hemodynamics [35]. In the studies above, use of the PAC was intertwined with a specific protocol for achieving key therapeutic endpoints, thus seeming to negate the value of the technology, when the flaw may have been the endpoint the technology was used to achieve. A more recent generation of controlled studies comparing pulmonary artery and CVP catheters with less stringent, and in some cases clinician-generated endpoints, have again shown no benefit of the catheter *per se* in high-risk surgical patients [36], patients with shock and sepsis [37], and adult patients with the acute respiratory distress syndrome (ARDS) [38]. In the Canadian study of surgical patients, the PAC was associated with a higher incidence of nonfatal pulmonary embolism[36].

Use of PACs has fallen over the last ten years due to the factors cited above, as well as due to higher complication rates [39], frequent misinterpretation of PAC data [40], and relative success with CVP-based methods for resuscitation in septic shock [11]. The American Society of Anesthesiologist Practice Guidelines recommend PAC for high-risk surgical patients only [41].

At present no study has demonstrated a positive association between PAC use for fluid management and survival [42]. Many of the randomized studies allowed physician exclusion of patients thought to benefit from the monitoring system, such as patients with heart failure and pulmonary hypertension where fluid management is only one of a handful of variables under active scrutiny and manipulation. Such use is likely to be highly individualized and unlikely to conform to a set protocol or study design that will allow a definitive statement of benefit. It is therefore prudent to be aware of the capabilities of the PAC and maintain an open mind about its potential value when a fuller physiologic picture may be necessary to make decisions regarding fluid responsiveness and volume status.

## 4. Cardiorespiratory Interactions and Dynamic Analysis of Fluid Status

Cardiac output and blood pressure interact with the respiratory system in a predictable manner according to the relationships indicated in Table 1. With positive pressure ventilation, venous return to the left ventricle is augmented, causing a rise in cardiac output and blood pressure during early inspiration. Later, the decrease in RV preload caused by positive intrathoracic pressure causes a drop in LV preload and systemic blood pressure [42]. Compared to the static hemodynamic parameters (CVP, PAWP), which are measured at one point in the cardiac cycle, dynamic parameters have been shown to be more accurate in assessment of intravascular volume and fluid responsiveness.

Table 1: Cardiorespiratory interactions used to predict volume responsiveness are listed. RV: right ventricle; LV: left ventricle.

| Mode of inspiration | RV preload | RV postload | LV preload | LV postload |
|---|---|---|---|---|
| Spontaneous | ⇑ | ⇓ | ⇓ | ⇑ |
| Controlled | ⇓ | ⇑ | ⇑ | ⇓ |

It is well recognized that pulsus paradoxus, or an inspiratory fall in systolic blood pressure by more than 10 mm Hg, is seen in critically ill patients with hypovolemia. With hypovolemia, the myocardium is at the steep portion of the Frank-Starling curve, so any minor variation in the preload with inspiration or expiration can cause appreciable changes in CO and blood pressure. Some rather direct and accurate inferences regarding intravascular volume can be made from analysis of arterial pressure waveforms and Doppler analysis of aortic blood flow. Ironically, while positive pressure ventilation is used, the accuracy of pressure-based measures of fluid responsiveness such as CVP is highly debated, while flow-based measurements achieve their highest accuracy. Indices of intravascular fluid and preload assessment derived from positive pressure ventilator-induced arterial blood pressure changes include systolic pressure variability, the respiratory systolic variation test, stroke volume variability, and respiratory changes in arterial pulse pressure.

*4.1. Systolic Pressure Variability (SPV).* The range of blood pressure (difference between maximal and minimal systolic BP) during a single positive pressure breath is defined as SPV. The baseline systolic pressure is taken using a short apneic period. SPV has 2 components, delta up and delta down, corresponding to the difference between the baseline and the peak amplitude during early expiration and at end inspiration, respectively. SPV refers to the sum of delta up and delta down or the total amplitude variation (Figure 2).

Beside intravascular volume status, SPV and its two components can be affected by a multitude of factors which include arrhythmias, chest wall and lung compliance, abdominal pressure, method of ventilation (spontaneous or mechanical), and myocardial function [43–46]. All these factors remaining stable, variations in SPV will reflect changes in intravascular volume. With a normal myocardium functioning at the steep portion of the Frank Starling Curve, SPV is mainly due to delta down component, with a decrease in ventricular filling with positive pressure ventilation [44].

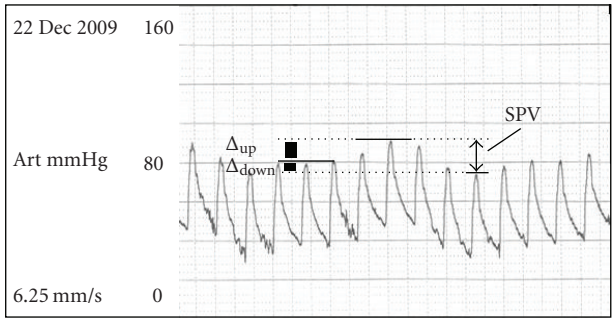


Figure 2: Arterial line tracings showing systolic pressure variation during the respiratory cycle. The pressure at end expiration defines baseline systolic pressure. SPV has two components, delta up and delta down, corresponding to systolic pressure waves reading at peak amplitude of early inspiration (the upward component or delta up) and at end inspiration (the downward component or delta down). The total amplitude variation or the sum of delta up and delta down is thus the SPV, shown with the arrow on the right of the diagram.

On the other hand, SPV is comprised of a delta up component in a patient with a failing myocardium, which is preload insensitive but responsive to afterload reduction with positive pressure ventilation [47]. The increase in pressure surrounding the heart decreases transmural pressure during systole (and hence afterload), thereby improving the ejection fraction. No exact values of SPV for determination of hypovolemia have been established. In a study by Rooke, SPV less than 5 mm Hg and delta down component less than 2 mm Hg showed absence of hypovolemia [48].

Other methods of analyzing fluid responsiveness from respiration-induced changes in arterial pulse waves have been described and validated. The r*espiratory systolic variation test* uses the slope obtained by the minimal systolic BP during a ventilator maneuver involving four successive incremental positive pressure breaths [49]. Greater negative slope was found to correlate with increasing amounts of hemorrhage [50]. *Respiratory change in arterial pulse pressure (DPp)* is defined as the difference in pulse pressure of the highest (Ppmax) and lowest magnitude (Ppmin) over several respiratory cycles, divided by the mean of the 2 values, expressed as a percentage. In one study, a DPp of 13% differentiated fluid responders from nonresponders [51]. *Stroke volume variability* is an index that is based on beat-to-beat variability in the arterial pulse during the respiratory cycle [52].

While all of these parameters can be measured manually via printouts from raw arterial pressure waves, a number of commercial systems discussed below provide automated analysis and trending along with means of measuring cardiac output. The PiCCO system (PULSION Medical Systems AG, Munich, Germany) derives volumetric parameters from arterial waveforms via a set of algorithms termed pulse contour analysis. The latter method, first described by Wesseling et al., computes the end-diastolic to end-systolic change in pressure over systemic vascular resistance (SVR) [53]. The beat-to-beat change in the shape of the arterial pressure waveform reflects the changes in the impedance of the aorta. Absolute values of aortic impedance and SVR obtained by thermodilution (using the same monitor) are necessary for calibration of the monitor; from this, values of stroke volume, cardiac output, and vascular resistance are derived. Thus, pulse contour is able to convert pressure-based signals such as pulse pressure and pulse pressure variability into analogous volume-based signals. Validation studies with the PAC showed that pulse contour analysis was able to track increases in stroke volume accurately in volume responsive postcardiac surgery patients [54, 55]. Likewise, through use of SVV as a gauge of volume responsiveness, investigators were able to predict intraoperative fluid requirements for obese patients undergoing bariatric surgery [56].

In principle, the monitor could indicate fluid responsiveness via pulse variability with mechanical ventilation as a stand-alone monitor, but, with calibration, an additional wealth of information is available. Unlike the PAC, the injectate signal is collected at one of the large arteries outside of the thorax (femoral, axillary, or brachial) and thus measures transpulmonary blood flow. Mathematical analysis of the transpulmonary dilution curve can be carried out further to derive actual fluid compartments within the thorax. Two of the derived parameters, extravascular lung water (EVLW) and global end-diastolic volume (GEDV), are of particular interest. Both GEDV and the related intrathoracic blood volume (ITBV) are volumetric preload parameters in contrast to the more commonly used pressure-derived parameters from CVP and PACs. Changes in GEDV have correlated better with changes in stroke volume than with changes in CVP [57]. The ability to measure extravascular lung water carries the hope of being able to differentiate and follow problems such as pulmonary edema and ARDS [58], the latter with a positive survival associated with which excess fluid use could be avoided [38, 59]. An observational study of septic patients by Martin demonstrated a better survival in those with lower EVLW [60]. Further, fluid therapy algorithms guided by GEDV and EVLW rather than clinical assessment can lead to faster resolution of pulmonary edema, shortened requirement for vasopressors, mechanical ventilation, and thereby ICU stays [61, 62].

An investigation of postoperative cardiac surgery patients showed that CO derived by PAC and transpulmonary method is clinically comparable [63]. The advantage of transpulmonary thermodilution over the PAC is that it does not require insertion into a pulmonary artery (reduce risk of arrhythmias and pulmonary artery rupture), though it does require a CVC and an arterial catheter and their attendant complications. Artifactual increases in CO introduced by tricuspid regurgitation in PAC use would not be present with use of transpulmonary blood flow measurement. Inability to measure mixed venous oxygen saturations can be partially compensated by trending central venous saturations via a CVC.

Similar measurements using transpulmonary lithium dilution and detection by an ion selective electrode are the basis of another commercial system providing continuous

CO and pulse wave analysis, the PulseCO (LiDCO Ltd, London, UK) [64]. The concentration-time curve for lithium ion calibration is read out on an attachment appended to the tubing on an existing artery after injecting from any intravenous line. The analytic algorithm is different from pulse contour in a few fundamental ways. The resulting "pulse power" computation is not sensitive to changes in pulse pressure amplitude found in distal arteries and is not affected by under- or over-dampening of arterial pressure transducers [65]. With these corrections built into the computational scheme, the LiDCO does not require a central arterial line. The less invasive nature of this system may also present advantages in certain patient populations such as those with limited central access or severe arterial disease. Despite these advantages, the LIDCO system does not give data such as GEDV and ITBV, and calibration measurements are limited by a desire to minimize lithium exposures (the number is, however, not defined by the manufacturer). The accuracy of the system is also low on patients on therapeutic lithium [65]. A more recent iteration of the LiDCO, the "LiDCO rapid," uses a software-based nomogram to estimate stroke volume without the need for lithium calibration. Accuracy of the latter has been shown to differ from thermodilution-based cardiac output measurements in cardiac surgery patient; the thought being that the recalibration may be required in such dynamic situations where the arterial compliance fluctuates widely through the course of a case (i.e., pre- versus post-cardiopulmonary bypass) [66]. Pulse wave analysis systems including both LiDCO and PiCCO have been used in combination with passive leg raising to accurately predict fluid responsiveness [67].

Another recently introduced system called FloTrac/Vigileo (Edward Lifesciences, Irvine, Calif) has also been designed to function without external calibration. Instead individual demographic data (height, weight, age, and sex) are used with arterial waveform analysis to calculate CO, the principle being that SV is proportional to pulse pressure (PP). In addition, the FloTrac can also calculate SVV, and if a central venous catheter is present, SVR and central venous saturation can be obtained. Like the LiDCO rapid, the FloTrac features ease of use and requires only an arterial catheter [68]. A study comparing PiCCO with FloTrac found FloTrac/Vigileo (2nd generation software) to be as accurate as the PiCCO in predicting fluid responsiveness using SVV, although the threshold value of SVV for the FloTrac/Vigileo was lower (9.6%) than for the PiCCO (12.1%) [69]. A meta-analysis found FloTrac in acceptable agreement with CO derived with thermodilution techniques. However, the authors concluded that, in patients with rapid hemodynamic changes, hyperdynamic circulation, aortic regurgitation and intraaortic balloon pump counterpulsation, its use was questionable [68].

Pressure Recording Analytical Method (PRAM) (MostCare device, Vytech, Padu, Italy) is another device that estimates CO from the area under the arterial pressure wave. No external calibration is required as with FloTrac. A study in hemodynamically stable children comparing Doppler echocardiography found PRAM reliable, though more validation studies are required [70].

## 5. Echocardiography

From its initial use in outpatient settings in 1970s, echocardiography has found its place in all inpatient settings, ranging from the operating rooms to the intensive care unit (ICU). Different modalities of ultrasound include transthoracic echo being most noninvasive and portable, while the more invasive nature of esophageal Doppler and transesophageal echo is well tolerated in anesthetized patients. Nevertheless, all echographic techniques spare the patient the complications related to vascular access and indwelling devices. Also, in contrast to the PAC which is dependent on pressure measurements to make volume determinations, echocardiography relies on direct visualization of the cardiac anatomy and flow dynamics. Moreover, in patients where causes of circulatory failure overlap, echocardiography provides the ability to evaluate structural abnormalities (pericardial tamponade), contractility (ejection fraction), besides assessment of intravascular volume.

*5.1. Transthoracic Echo (TTE).* Improved image quality with portable study echo machines in the last decade has made TTE a popular tool for intravascular fluid assessment in the ICU. More recently, its use has been advocated in the perioperative settings due to its ability to provide quick, noninvasive functional and fluid assessment. Right heart preload can be reliably obtained by direct measurement of the inferior vena cava diameter (IVC) variations with respiration (Figure 3) and also by right and left ventricular end-diastolic volumes. One study showed that a 50% decrease in IVC diameter (caval index), seen by subcostal views with spontaneous breathing, correlated with an RA pressure of less than 10 mm Hg (mean SD 6 ± 5), as measured by CVP measurements [71]. Recent study in emergency department settings found caval index measurement a useful noninvasive tool for initial determination of CVP [72].

In mechanically ventilated patients, IVC variations with respiration (Delta DIVC) of 12% differentiated patients who responded with increased CO to a fluid bolus from nonresponders [73]. In another study with mechanically ventilated septic patients, the CVP and the IVC diameter increase on inspiration (distensibility index (dIVC)) was measured before and after a gelatin fluid challenge of 7 mL/kg. Response was measured as an increase in CI of 15% or more. dIVC greater than 18% predicted fluid responsiveness with a sensitivity and specificity of Ninety percent. CVP, on the other hand, correlated poorly with CI ($r = 0.17$, $P = .45$) and dIVC [74]. In spite of difficulty in visualizing IVC in postabdominal surgeries and obese patients, TTE provides a quick, noninvasive and reliable method of volume status of the patient.

*5.2. Transesophageal Echocardiography (TEE).* Besides cardiac anesthesia, TEE is now used routinely in other complex and long surgeries (e.g., liver transplant), especially among patients with known cardiac pathology. In our operating rooms, the quick availability of TEE machines makes this

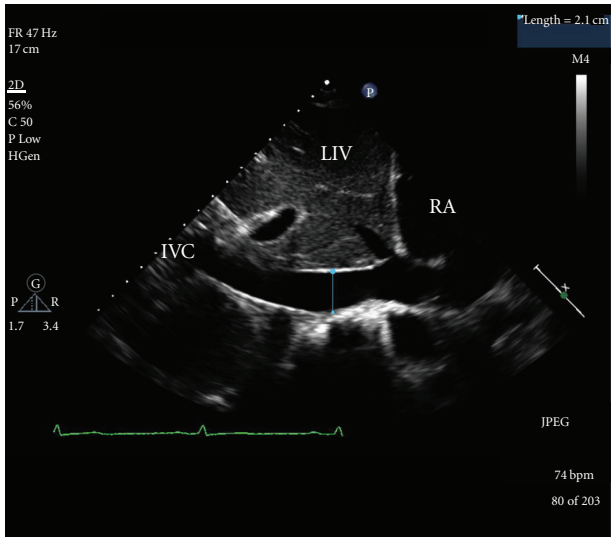


Figure 3: A subcostal view of the cavoatrial junction and adjacent structures. RA: right atrium; IVC: inferior vena cava; LIV: liver.

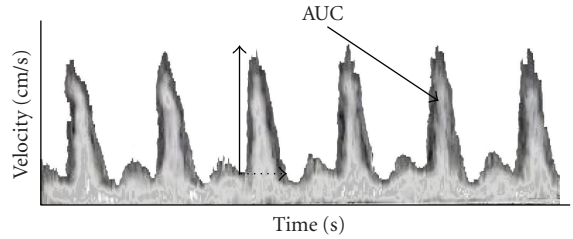


Figure 4: Esophageal Doppler tracings from descending aorta blood flow. Flow time and peak velocity are indicated by dashed and vertical arrows, respectively. Parameters derived from the latter measurements include corrected flow time (FTc), acceleration, and stroke distance. The area under the curve (AUC) is equivalent to stroke distance, the length traveled by an erythrocyte during a single cardiac cycle. Assuming that the flow is via a cylindrical path, the stroke volume (SV) is the product of aortic cross-sectional area and the stroke distance. Aortic blood flow is calculated from the product of heart rate and calculated SV and is not exactly equal to true cardiac output, as approximately 10% of total cardiac output is diverted to subclavian and cerebral arteries upstream to where flow is measured.

a first-line diagnostic modality for experienced users when unexpected hemodynamic instability is encountered.

For general use, the main focus is on intravascular volume status assessment and overall cardiac function. In the ICU, TEE is recommended when diagnostic information cannot be adequately obtained by TTE [75]. Limitations of TEE include the lack of availability of trained personal and equipment, the requirement of adequate sedation or intubation, and the impracticality for continuous postoperative use. Also, TEE is an invasive procedure and contraindicated in patients with esophageal strictures and malformation.

As with TTE for IVC measurements to determine preload, TEE can be used to measure SVC collapsibility. Volume expansion was found to decrease SVC collapse, decrease RV stroke volume variation, and increase CI in a study in 22 mechanically ventilated ARDS patients with septic shock [76]. A collapsibility index of 36% was found to predict an 11% increase in CI following a fluid bolus in a separate study [77].

Both TTE and TEE allow visual estimation of ventricular volume. Ninety percent of the stroke volume is obtained by ventricular shortening in the short axis [78]. Therefore, measurement of the LV end-diastolic area using mid-transgastric short axis view by TEE can give a reliable estimate of LV end diastolic volume [79]. In practice, a qualitative assessment of LVEDA provides a quicker and quite reliable assessment, as Leung and Levine report that systolic cavity obliteration is 100% sensitive in detecting hypovolemia [80]. Fluid challenge in these cases can be followed by serial echo views of ventricular filling and correlation with the CVP. On the other hand, distended left ventricle with decreased EF would indicate minimal benefit from a fluid challenge. Additionally, a distended right ventricle and empty left ventricle may indicate right ventricular failure possibly from acute pulmonary embolism or pulmonary vascular disease.

*5.3. Esophageal Doppler Monitoring (EDM).* Using the Doppler principle to calculate blood flow velocity in the aorta, EDM can be used to provide minimally invasive continuous CO monitoring. EDM comprises of a small, thin, flexible probe with a Doppler transducer at the tip, inserted 35 cm into the esophagus, and has a tolerability similar to a nasogastric tube [81]. A continuous Doppler beam is used to generate flow velocity profile by analyzing reflected ultrasound waves from the moving red blood cells. Figure 4 shows a flow-time tracing generated by EDM. Flow time is defined as the time needed by the left ventricle to eject the SV and is represented on the waveform from the start of the upstroke to its return to baseline. As flow time is also dependant on the heart rate, "corrected flow time" or FTc analogous to QTc in the electrocardiogram (ECG) is used in flow calculations. Area under the flow time curve is called the stroke distance. Combining with cross-sectional area can give the stroke volume. The cross-sectional area of the descending aorta can be obtained using nomograms (based on patients' height and weight) or measured directly with the M-mode by the EDM. Correction factor of 1.4 is used to adjust for blood lost to the coronaries and upper body circulation [81]. Additional analysis of flow velocity profile (peak velocity and upslope) can be used to evaluate left ventricular sensitivity to afterload and contractility.

While nearly emerging devices for fluid management have sought to first establish themselves as similar to the "gold standard" PAC, the initial studies of EDM are relatively unique in their attempt to associate a positive clinical outcome with device use. In postsurgical patients, hypovolemia is a notorious cause of splanchnic hypoperfusion, prolonged hospital stays, and even increased mortality in moderate- to high-risk surgical patients [82–84]. With the use of a fluid management protocol built around using the continuous CO and FTc parameters of EDM monitoring, investigators were

able to reduce the time to bowel motility, decrease the time to solid food intake, and shorten hospital stay [82, 85].

An analogous method for evaluation of cardiac output is based on estimation of blood flow via analysis of *electrical bioimpedance*. With electrical velocimetry (EV), all measurements are made via four ECG electrodes applied along one side of the patient's body. A small amplitude alternating current is applied to one pair of electrodes, while the other detects the change in electrical signal through the cardiac cycle. When blood moves forward through the ascending aorta during ventricular ejection, red cells tend to align more along the body's long axis, and create less impedance of electrical signals traveling along the same vector. Thus, from analysis of the electrical signal during the cardiac cycle, velocity and flow time parameters are generated and used to calculate stroke volume and cardiac output.

Comparisons between EV and thermodilution cardiac output measurements show a good level of agreement over a wide range of outputs in adult cardiac surgery patients and critically ill adults [86, 87]. An excellent correlation ($r = 0.97$) was found between EV and cardiac output measurements made by the Fick method (using direct measurements of $VO_2$) in children with congenital heart disease, and EV measurements correlated well with Doppler measurements made via transesophageal echo in cardiac surgery patients [88, 89].

Limitations to EDM use are similar to TEE. In addition, severe aortic regurgitation, severe lung disease, altered thoracic blood flow, and presence of intra-ortic balloon pump can alter accuracy of EDM [81].

## 6. Conclusion

Resuscitation of the hypotensive patient in the perioperative setting can be challenging. Accurate and timely assessment of fluid status and fluid responsiveness are cornerstones in the management of the hypotensive patient. Both hypovolemia and hypervolemia can be harmful. Goal-directed fluid management can result in the appropriate use of fluids, vasopressors, and inotropes, resulting in improved patient outcomes. Invasive, noninvasive, static, and dynamic monitoring methods have strengths and limitations. Continual monitoring of unstable patients through the resuscitation period utilizing a combination of techniques can improve the utility of hemodynamic information, improve the accuracy of assessments of volume status, and improve patient outcomes.

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*Review Article*

# Cardiac Output Assessed by Invasive and Minimally Invasive Techniques

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Cardiac output (CO) measurement has long been considered essential to the assessment and guidance of therapeutic decisions in critically ill patients and for patients undergoing certain high-risk surgeries. Despite controversies, complications and inherent errors in measurement, pulmonary artery catheter (PAC) continuous and intermittent bolus techniques of CO measurement continue to be the gold standard. Newer techniques provide less invasive alternatives; however, currently available monitors are unable to provide central circulation pressures or true mixed venous saturations. Esophageal Doppler and pulse contour monitors can predict fluid responsiveness and have been shown to decrease postoperative morbidity. Many minimally invasive techniques continue to suffer from decreased accuracy and reliability under periods of hemodynamic instability, and so few have reached the level of interchangeability with the PAC.

## 1. Cardiac Output Assessed by Invasive and Minimally Invasive Techniques

Cardiac output (CO) measurement has long been considered essential to the assessment and guidance of therapeutic decisions in critically ill patients, by providing an indirect indication of systemic oxygen delivery and global tissue perfusion. Perioperatively, CO monitoring has become virtually routine for certain high-risk patients and in major surgeries, where large fluid shifts are expected.

## 2. History

The technique was first described in 1870 by Adolf Fick [1], who computed an animal's CO by utilizing oxygen concentrations in arterial and venous blood samples, where CO is equal to oxygen consumption ($VO_2$), divided by arterial oxygen content ($CaO_2$) minus mixed venous oxygen content ($CvO_2$) [2, 3]:

$$\mathrm{CO} = \frac{\mathrm{VO_2}}{(\mathrm{CaO_2} - \mathrm{CvO_2}) \times 10}. \tag{1}$$

Pulmonary artery catheterization was first performed experimentally in dogs by Grehant and Quinquaud in 1886, but the technique would not become available to humans for another fifty years [4].

Indicator-dilution techniques later developed. In 1897, Stewart described experiments pioneering the indicator-dilution principle, when he injected sodium chloride into the central circulation of animals and measured its subsequent concentration in the femoral artery [5]. Hamilton modified this principle to account for the varying concentrations of diluted injectate over time in human circulation, developing a time concentration curve to reflect this phenomenon [2]. CO was shown to equal the quantity of indicator dye (indocyanine green) injected, divided by the area under the dilution curve measured downstream, today known as the Stewart-Hamilton equation [5]:

$$\mathrm{Flow} = \frac{C_0 V_0}{\int c(t)\mathrm{d}t}, \tag{2}$$

where $C_0$ denotes initial injectate concentration and $V_0$ represents initial injectate volume. The denominator represents the concentration of diluted injectate over time, thus the area under the dilution curve.

Based on the same concept as indicator-dilution methods, Fegler introduced thermodilution (TD) in 1954 by injecting a cold solution as an indicator and measuring changes

in blood temperature detected distally [6]. In 1970, Swan et al. developed what they termed a "flow-directed balloon-tipped" multiple lumen catheter, the pulmonary artery catheter (PAC) [7]. The introduction of the PAC enabled physicians to measure CO by TD both at the bedside and intraoperatively. Forty years later, this method is still considered the clinical gold standard for CO measurement, secondary to its extensive utilization in a variety of clinical settings.

## 3. Intermittent Bolus Pulmonary Artery Thermodilution

The TD technique is founded on the law of conservation of energy [9]. A known amount of cold solution is injected through the proximal port of a PAC into the right atrium, and this solution is detected distally by a thermistor several centimeters from the end of PAC. The change in blood temperature detected causes a change in the thermistor resistance, allowing for the calculation of the area under the TD curve. CO is determined from a modified Stewart-Hamilton equation [10, 11]:

$$\mathrm{CO} = \frac{\mathrm{VI} * (\mathrm{TB} - \mathrm{TI}) * K1 * K2}{\int \Delta \mathrm{TB}\,(t)\mathrm{d}t}, \tag{3}$$

where VI is injectate volume, TB is blood temperature, TI is injectate temperature, $K1$ is a density factor: (specific heat (injectate) $\times$ specific gravity (injectate))/(specific heat (blood) $\times$ specific gravity (blood)), and $K2$ is a computation constant accounting for heat exchange in transit, injection rate, and catheter dead space. The denominator, change of blood temperature as a function of time, reflects the area under the TD curve (Figure 1) [6].

## 4. Reliability of Thermodilution

Despite being considered the gold standard technique for CO measurement, the reproducibility of TD technique has been heavily scrutinized and, to our knowledge, no data on the subject has been published in the last 20 years. Studies continue to quote statistical significance as demonstrated by Stetz et al. in 1982 [12], where the accuracy of TD was compared to that of Fick and dye-dilution methods. The conclusion was that all three methods are "of equal merit." The intrinsic reproducibility of TD measurements was also analyzed, with the conclusion being that there must be a minimal difference of 12–15% between three serial CO determinations, to suggest clinical significance [12]. The inherent error of TD measurement, has subsequently been quoted in this manner.

*4.1. Sources of Error.* Accurate CO estimation can only be made if several assumptions are true. The amount of cold injectate must remain constant between the injection and detection sites. There must be complete mixing of blood and injectate and no fluctuations in baseline blood temperature during measurement [9]. Sources of error may be considered to be technical or intrinsic to certain physiologic states.

Technical errors can be due to loss of indicator before, during, or after injection, variability of temperature and volume of injectate, and thermistor malfunction. Although TD was first performed with 10 mL of iced 5% dextrose water, most studies over time have demonstrated no difference in accuracy when iced or room-temperature injectate was used [2, 10, 13]. When using an iced indicator, rewarming of injectate prior to administration and heat transfer during transit can both result in an overestimation of CO. When the volume of indicator injected is less than the assumed amount, an overestimation of CO can occur. Recommended volumes are 10 mL for adults and 0.15 mL/kg for children [6]. A clot over the catheter tip or contact with a vessel wall due to a wedged catheter can insulate the thermistor and result in spurious measurements. An injection time of 4 seconds or less with steady pressure has been recommended to prevent a delayed upstroke of the TD curve. Coiling of the catheter may change the distance from the injection site to the tip and also introduce error [6].

Both physiologic and pathologic states can lead to inaccurate CO measurements. Fluctuations in baseline pulmonary artery temperature occur with cardiac and respiratory oscillations. Rewarming in the initial minutes after cardiac bypass results in a transient decrease in core body temperature as heat distributes to the periphery. Measurements taken at this time can significantly underestimate the true CO [14]. Simultaneous rapid intravenous infusions have also been shown to alter computed CO [2].

It should be emphasized that TD with a PAC measures right ventricular outflow and not systemic CO. Intracardiac shunts can, therefore, lead to inaccurate measurements. In patients with left-to-right shunts, early recirculation of injection results in a subsequent distortion of the downward slope of the TD curve [15]. In the presence of right-to-left shunts, a portion of the indicator will bypass the thermistor, resulting in an overestimation of CO. Both pulmonary and tricuspid valve insufficiencies can likewise lead to unreliable CO determinations. The recirculation of indicator across incompetent valves can overestimate or underestimate CO, depending on the severity of the regurgitation and the underlying systemic CO [2].

Spontaneous and mechanical ventilation both alter right ventricular output throughout the respiratory cycle more so than left ventricular outflow. Studies evaluating the effects of the mechanical ventilatory cycle on TD measurements reveal inspiratory decreases in right ventricular ejection fraction and subsequent increases in right ventricular end systolic volumes [16]. A fall in left-sided CO, however, is largely prevented by the increase in right ventricular end diastolic volume. These findings explain the greater ventilatory modulation of right ventricular volumes. In the past, measurements taken at the end of expiration were thought to produce the greatest reproducibility. On the contrary, it is argued that more reliable estimations of mean TD CO should be taken from three to four serial CO measurements at different phases of the cycle [6]. Some authors recommend at least eight measurements taken randomly at different times during the ventilatory cycle [16].

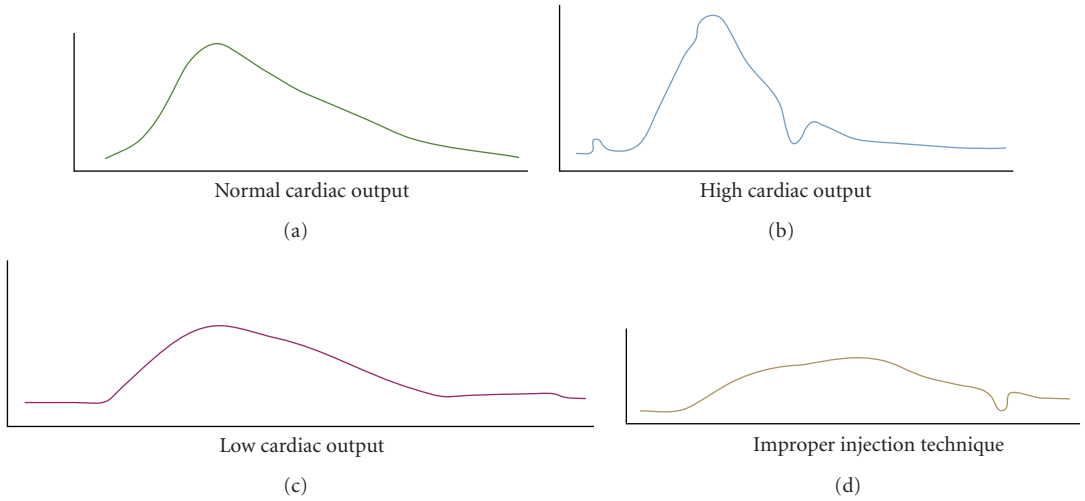


Figure 1: Thermodilution cardiac output curves. Used with permission from [8].

## 5. Continuous Pulmonary Artery Thermodilution

Applying the same principles of TD, newer technologies applied to PACs allow continuous CO measurements. By utilizing an electric filament incorporated into the right ventricular portion of the PAC, blood flowing through the right heart is heated intermittently, approximately 15 to 25 cm proximal to the PAC tip. The resulting thermal signal is measured by a thermistor at the catheter tip. CO measurements by continuous TD have been shown to generally correlate well with intermittent bolus measurement [2]. These catheters provide a continuous trend of CO, decrease operator workload, and possibly reduce infection risk associated with bolus technique. However, since the values displayed are updated every 30 to 60 seconds, what is reflected is the average value for CO measured over the previous 5–15 minutes [9]. Leibowitz and Oropello [17] studied average in vivo time delays associated with sudden changes in CO of critically ill patients. The mean in vivo response times were reported to be 9.3, 10.5, and 11.8 minutes for a 50, 75, and 90% response, respectively [17]. Due to these inherent time delays, many clinicians argue these continuous monitors should be considered a "continual" rather than continuous real-time monitor [15]. These catheters may therefore be less optimal in detecting and measuring abrupt CO changes, but could be a more accurate representation of global CO.

*5.1. Controversies Regarding Use.* In the early 1980's, studies demonstrated improved outcomes with both perioperative and intensive care utilization of pulmonary artery catheterization [17]. However, in 1987, Gore et al. [18] published a study showing that mortality from myocardial infarction actually increased with PAC use. Although this investigation was merely a case-control, chart review study without retrospective risk adjustment, the article led to an editorial calling for a "moratorium" on PAC use [19].

Studies using the PAC to optimize cardiac index, mixed venous oxygen saturation (Sv02), and oxygen delivery have failed to show any reduction in morbidity and mortality of critically ill patients. In the large multicenter, SUPPORT study, a propensity score using multivariable logistic regression, looked at the association between right heart catheterization and specific outcomes. Investigators revealed an increase in 30-day mortality in patients with PACs [20]. The National Heart, Lung, and Blood Institute (NHLBI) and Food and Drug Administration (FDA) have published a consensus statement advocating for RCTs with the PAC in patients with congestive heart failure (CHF), acute respiratory distress syndrome (ARDS), sepsis, and septic shock, as well as low-risk coronary artery bypass graft surgery (CABG) [21].

*5.2. Evidence from Randomized Controlled Trials.* In 2003, the Canadian Critical Care Clinical Trials Group reported the largest RCT to date, comparing goal-directed therapy using a PAC versus standard care with a central venous catheter (CVC) [22]. There were no differences in hospital mortality, median length of stay (LOS), or one-year survival rates, despite an increased use of inotropic agents, vasodilators, antihypertensives, and erythrocyte and colloid transfusions in the PAC group. PAC-related adverse events occurred in 1.5% of patients versus 0.7% related to central venous catheter use alone [22].

In 2005, the PAC-Man study, a RCT done in United Kingdom ICUs, also failed to show evidence of benefit or harm with PAC management [23]. The LOS in the ICU and hospital and days of organ support required were similar in patients managed with and without a PAC. There was a 10% (46 in 486) incidence of direct complications due to PAC use, the most frequent being hematoma formation, arterial puncture, and arrhythmias. This study, similar to Sandham et al. [22], refuted the claim of increased mortality associated with catheter use. Other studies utilizing a PAC in patients with severe sepsis, septic shock, and/or ARDS failed to show a change in mortality rate [24–26]. In 2006, low-risk patients undergoing off-pump, beating-heart surgery showed no difference in operative mortality or outcome variables between patients with or without PACs [27].

The ESCAPE trial, funded by the NHLBI, evaluated the effectiveness of PACs guiding therapy in patients with severe CHF [28]. The use of the PAC had no effect on the primary endpoint of days alive out of hospital; however, a trend for "greater functional improvement after therapy guided by the PAC" was reported [28]. A concurrent PAC registry was established for hospitalized heart failure patients with a PAC who were not randomized to the trial. The study has been criticized for excluding patients with a higher disease severity and mortality risk [29]. In addition, no treatment protocol or proven therapy was directed towards PAC use [30]. Due to a lack of goal-directed therapy, both groups of patients likely received similar interventions.

A RCT conducted by the NHLBI Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network in 2006 compared treatment of acute lung injury in patients managed with PACs versus CVCs [25]. There were no statistical differences in mortality in the first 60 days before discharge home, ventilator free days, or LOS in ICU. The PAC group received more red blood cell transfusions and had approximately twice as many catheter-related complications, most commonly arrhythmias.

Why is it that, despite such detailed hemodynamic information, PACs fail to improve patient outcomes? One suggestion is that the lack of goal-directed therapy tailored towards PAC use has prevented us from altering morbidity and mortality. Pulmonary artery catheterization should be seen as a diagnostic tool and not mistaken to be therapeutic [31].

## 6. Minimally and Noninvasive Techniques

Although TD may be considered the gold standard for CO measurement, its use is limited, mainly because of the associated risks of pulmonary artery catheterization (arrhythmias, valvular lesions, infection, pulmonary emboli, pulmonary infarction, and pulmonary artery rupture). Additional costs are also significant. The ideal technique for CO measurement is minimally or noninvasive, is continuous, does not require calibration, and is accurate, reproducible, and reliable during various physiologic states [32]. A multitude of new technologies for CO measurement have been developed and are now available for clinical use (Table 1).

*6.1. Methods of Comparison.* Studies of reliability, accuracy, and precision of newer methods of CO measurement generally involve a comparison with more established techniques, such as TD. In the past, correlation and regression analysis was used, however, Bland-Altman analysis has become the preferred method of statistical analysis for determining level of agreement. The difference between comparative measurement is plotted (the bias) against the mean values of each pair of readings. The standard deviation (SD) of each bias measurement is calculated and 95% confidence limits drawn ($\mu \pm 2$SD). The latter is the limits of agreement, upon which a determination of precision is based [33].

L. A. H. Critchley and J. A. J. H. Critchley [33] performed a meta-analysis and found wide variations in the presentation of statistical data for comparison studies. They advocated that studies present the mean CO ($\mu$), the bias, the limits of agreement (95% C.I.), and the percentage error ($\pm 2\text{SD}/\mu$) and concluded that acceptance of a new technique should rely on limits of agreement of up to $\pm 30\%$. They point out that the Bland-Altman method does not compensate for the magnitude of the measurements and the size of the error and suggest that percentage error be calculated for each set of data as opposed to calculating it one time from the averaged data.

## 7. Pulse Power Analysis

Pulse power analysis is based on the theory that fluctuations of blood pressure about the mean are directly related to the stroke volume (SV) ejected into the arterial system [34]. Accuracy of measurement is complicated by several factors.

(i) Nonlinear compliance of the arterial wall. Decreased aortic compliance occurs at higher than at lower blood pressures (BPs).

(ii) Wave reflection, since pulse pressure detected in a peripheral artery is a composite of the pressure wave from ejection from the heart and the reflected pressure wave from the distal arterial tree. Changes in systemic vascular resistance (SVR) affect the reflected wave augmentation of the arterial pressure. The size of the reflected waves is also found to vary with the sampling site proximity to the central circulation and patient age.

(iii) Damping of the transducer system.

(iv) Aortic systolic outflow. Filling is pulsatile; however, outflow tends to be continuous [34].

The LiDCO method of pulse power analysis utilizes a proprietary autocorrelation algorithm (PulseCO (LiDCO, Cambridge, UK)) which addresses the factors mentioned above. The assumption made is that, following calibration and correction for compliance, there is conservation of mass/power and so a linear relationship exists between net power and net flow. Autocorrelation allows for the determination of the beat period as well as the net power change across the whole beat from the stroke volume. As a result, the effect of reflected waves is negated. Since the method is time based, the effects of arterial damping are minimized. Apart from extreme conditions, the pulse power tends to remain the same regardless of the degree of damping [34].

The LiDCO plus (Cambridge, UK) system is coupled to a lithium dilution system, a technique first described by Linton et al. [35] in 1993. Either central or peripheral venous access may be used in addition to a peripheral arterial line, to which a disposable lithium sensitive sensor is attached. The sensor membrane contains an ionophore which is selectively permeable to lithium [36]. The membrane voltage is related to the plasma lithium concentration using the Nernst equation. The voltage is amplified and digitalized for analysis. Sodium supplies the baseline voltage in the absence of lithium.

Table 1: Comparison of minimally invasive cardiac output monitoring techniques (CI: cardiac index, HR: heart rate, and ECG: electrocardiogram).

| Technique | Advantages | Additional variables | Invasiveness | Limitations |
|---|---|---|---|---|
| LiDCO plus | Continuous CO measurement | SV | Arterial line | Requires good fidelity of arterial waveform |
| | Useful in goal-directed therapy | SVV | Peripheral or central venous line | Calibration affected by neuromuscular blockers |
| | | | | Contraindicated in lithium therapy |
| | | | | Requires transpulmonary lithium dilution calibration |
| PiCCO plus | Continuous CO measurement | GEDV | Arterial line | Requires good fidelity of arterial waveform |
| | | EVLV | | Requires transpulmonary thermodilution calibration |
| | | SVV | | |
| | | PPV | | |
| FloTrac/Vigileo | Continuous CO measurement | SVV | Arterial line | Requires good fidelity of arterial waveform |
| | No calibration required | | | |
| NICO | Ease of use | Shunt | Endotracheal intubation | Affected by changes in dead space or V/Q matching |
| | | Ventilatory variables | Valid only with $PaCO_2 > 30$ mmHg | |
| Bioimpedance | Noninvasive | | Cutaneous electrodes | Affected by electrical noise, movement |
| | Continuous CO measurement | | | Electrode contact affected by temperature and humidity |
| | | | | Requires hemodynamic stability |
| | | | | Not useful in dysrhythmias |
| Bioreactance | Noninvasive Continuous CO measurement | | Cutaneous electrodes | |
| ECOM | | SV | Endotracheal intubation | Coronary blood flow not recorded |
| | | CI | | Electrocautery produces interference |
| | | SVR | | No fully validated human studies |
| | | HR, ECG | | |
| Ultrasound dilution | Measures flow in ECMO and hemodialysis circuits | | Arterial line | Fluid overload with saline injection in sensitive patients |
| | | | Central venous catheterization | Errors from indicator loss in inadequate lung perfusion |
| | | | | Errors in the presence of septal defects |
| TEE | Used to evaluate cardiac anatomy and function, preload, and myocardial ischemia | SV | Esophageal probe | Mainly used perioperatively |
| Esophageal Doppler | Useful in goal-directed therapy | SV | Esophageal probe | Measures only descending aortic flow |
| | | | | Assumptions about aortic size may be erroneous |

The LiDCO plus monitor requires CO calibration with lithium dilution once every eight hours according to the manufacturer. It has been suggested, however, based on recent data, that repeat calibration should take place during major hemodynamic changes [37]. Cecconi et al. [38] concluded that, for good precision, three lithium dilution measurements should be performed. During calibration, isotonic lithium chloride (150 mM) is given intravenously (0.02 to 0.04 mmol/kg). CO is derived from the dose and the area under the concentration-time curve. Since lithium is only distributed in the plasma fraction of blood, for the determination of CO, blood flow is determined by dividing plasma flow by 1-packed cell volume, assessed on the basis of hemoglobin/33 [2].

The accuracy of the Pulse CO algorithm may be compromised under the following circumstances:

(i) aortic valve regurgitation,

(ii) post-aortic reconstruction,

(iii) intra-aortic balloon pump,

(iv) highly damped peripheral arterial lines,

(v) severe peripheral arterial vasoconstriction,

(vi) inaccurate sodium and hemoglobin measurements,

(vii) arrhythmias,

(viii) intra- or extracardiac shunts.

In addition, each 1 g/dL difference in hemoglobin artifactually results in a 4% change in the CO measurement [39].

Lithium therapy is a contraindication to the use of LiDCO, as overestimation of CO occurs with elevated background levels. Some nondepolarizing muscle relaxants contain high levels of quaternary ammonium residues, causing the electrode to drift. Recalibration is recommended prior to injection of the drugs or after the peak concentration has fallen. Bolus dosing is also recommended if nondepolarizing muscle relaxant use cannot be avoided.

The safety of lithium use has been well established. Since lithium does not occur naturally in plasma, does not bind to plasma or tissue proteins, and is not lost in passage through the pulmonary circulation, tiny doses may be used. Levels achieved are <1% of therapeutic levels used during treatment of mania with lithium carbonate [36].

For the newer LiDCO rapid (Cambridge, UK), lithium dilution has been replaced with a nomogram which has been derived from in vivo data, to estimate CO. The system features simplicity and ease of use. It was designed to provide reliable hemodynamic trends, which would be useful for goal-directed fluid therapy. In a clinical setting where absolute values for SV and SVR are required, a calibrated, system is warranted [40].

*7.1. Validation Studies.* Investigators studying small patient populations under different clinical settings and with different reference standards have reported variable findings regarding the accuracy of the LiDCO system. While some have suggested acceptable accuracy [41–44], others have found unacceptable accuracy compared to PAC-derived CO [45, 46].

Linton et al. [35] studied 9 patients immediately after-cardiac-surgery and reported good correlation ($r = 0.89$) and a bias 0.3 (0.5) L/min between LiDCO and intermittent bolus pulmonary artery TD (PATD). Costa et al. [47] reported agreement between LiDCO and intermittent PATD in 23 after-liver-transplant patients exhibiting the typical hyperdynamic circulation; the reported bias and 95% limit of agreement for the PAC versus $\text{PulseCO}_{\text{Li}}$ were 0.29 L/min ($r = 0.85$) with a percentage error of 16.8%.

The validity of the device has also been studied in pediatric patients. Kim et al. [48] reported good correlation ($r = 0.94$) with PATD in 20 children (age range 2.5–15.5 years) undergoing cardiac catheterization. In smaller children (<20 kg), a separate analysis still showed good correlation (0.89). Linton et al. [49] compared the device against transpulmonary TD in 20 pediatric patients (age range 5 days–9 years) and also reported good accuracy ($r = 0.96$).

Yamashita et al. [46] compared bolus PATD with the PulseCO, calibrated with CO by the TD method in patients during cardiac-surgery. They found poor correlation ($r =$ 0.49–0.55) and large bias (0.3–0.76), concluding that the methods were not interchangeable. In an observational study of 8 after-cardiac-surgery patients, McCoy et al. [45] compared continuous cardiac index monitoring (CCI) with LiDCO, using a peripheral iv line for indicator delivery. The investigators found minimal bias (−0.01) but wide 95% limits of agreement with respect to the mean, suggestive of clinically significant differences.

In a randomized controlled trial, Pearse et al. [50] used LiDCO to guide goal-directed therapy (GDT) in high-risk surgical patients. The outcome was fewer complications and shorter length of hospital stay in the GDT group.

Costa et al. [51] carried out comparisons between the LiDCO rapid and intermittent and continuous PATD in 10 after-liver-transplant patients. Their preliminary data showed that, the LiDCO rapid provided acceptable readings, with percentage errors of 26 and 30%, respectively, compared with intermittent and continuous PATD.

Multiple studies are ongoing using the LiDCO rapid to gauge fluid responsiveness and guide fluid management. [52–54]. The LiDCO rapid is also currently being used in a large government-supported multicenter trial currently underway in the UK, OPTIMISE, aimed at improving surgical outcomes by optimizing cardiovascular management [55].

## 8. Pulse Contour Analysis

Pulse contour analysis for CO measurement is based on the hypothesis that the area under the curve of the systolic part of the arterial pressure waveform is proportional to the SV [56]. Wesseling et al. [57] developed the first successful algorithms in the 1970's, which continuously analyze the pressure waveform from an arterial line. The area under the systolic portion of the arterial pulse wave (measured from the end of diastole to the end of the ejection phase) divided by the aortic impedance gives a measure of the stroke volume, which multiplied by the heart rate gives the cardiac output.

*8.1. The PiCCO System.* The PiCCO system (PULSION Medical Systems) is the first pulse contour device to be introduced into clinical practice [4, 56]. In 2007, the PiCCO2 replaced the PiCCO.

External manual calibration of the system is performed via transpulmonary TD every eight hours, or up to hourly during periods of hemodynamic instability [58, 59]. Blood temperature changes from a thermo-indicator solution injected via a CVC are detected by a thermistor-tipped catheter, typically placed in the femoral artery. Alternatively, the radial, axillary, or brachial artery may be used; however, longer catheters are required to adequately assess the aortic pressure wave signal from more distal sites. Although accuracy of the transpulmonary TD technique may be affected by the longer transit time, errors due to airway pressure variation are eliminated. The calibration is repeated three to five times to obtain a calibration factor for calculation of continuous CO, intrathoracic blood volume (ITBV), and extravascular lung water (EVLW).

Global end-diastolic volume (GEDV) is also measured and, together with ITBV, is representative of cardiac preload and EVLW. EVLW, comprising intracellular, interstitial, and intra-alveolar water, is measured intermittently using transpulmonary TD as a means of quantifying pulmonary edema [60]. Systolic pressure variation and stroke volume variation (SVV) provide information about volume status in mechanically ventilated patients [32].

*8.2. Limitations.* The accuracy of analysis is influenced by vascular compliance, aortic impedance, and peripheral arterial resistance. Second generations of the system software address issues related to differences in individual patients' aortic compliance and now analyze the shape of the waveform and the pulsatile systolic area [61].

Results may be altered secondary to technical problems such as air bubbles in the system, clotting of the catheter, and inadequate indicator. Problems with analysis are also seen with severe arrhythmias, raised EVLW (requiring more indicator), aortic aneurysm (causes ITBV and GEDV to be overestimated), severe valve insufficiency (CO is correct, but preload is overestimated), and rapidly changing body temperature. Recirculation of thermo-indicator may occur in patients with intracardiac shunts and in pediatric patients with open ductus Botalli [60].

*8.3. Validation Studies.* The pulse contour analysis method has largely been found to correlate well against pulmonary artery thermodilution (PATD) in numerous studies under varying conditions, including coronary artery bypass grafting (CABG) [62–65]. Some bias should be recognized, however, since TD is required for calibration [66]. Other investigators have reported large discrepancies between the two techniques. Halvorsen et al. [67] reported unacceptably large discrepancies with the PATD during off-pump CABG. For lung transplantation, good correlation was found between PiCCO and TD [68]. Significant errors during periods of hemodynamic instability, with the need for repeated recalibration has been reported [69]. In burn patients, good correlation during low to normal CO was reported; however, greater discrepancy was seen at high cardiac indices [70].

## 9. FloTrac/Vigileo

The FloTrac Vigileo (Edwards Lifesciences, LLC, Irvine Calif, USA) is another pulse contour device, which was first introduced in April, 2005 [4]. The device provides continuous CO measurement from a proprietary FloTrac sensor attached to a standard peripheral arterial catheter, which is connected to the Vigileo monitor. Calculations of SVR and SVV are also displayed. A significant feature of the system is that, unlike PiCCO and Pulse CO, external calibration is not required as the algorithm performs its own calibration using patient demographics and waveform analysis [4]. Notably, no central venous line is required.

The FloTrac algorithm integrates multiple characteristics of the arterial pressure waveform with patient specific demographic data. Parameters include heart rate (HR), the standard deviation of the arterial pressure, a scale factor proportional to vascular and peripheral resistance combined over the arterial pressure waveform (mean, standard deviation, skewness and kurtosis), pressure-dependent Windkessel, compliance and body surface area [71]. The standard deviation of pulse pressures sampled over 20 seconds is correlated with a predicted SV based on demographic data (age, gender, height, and weight) and extrasystoles and other minor artifacts are eliminated via a beat-detection algorithm [37]. Impedance is also determined from the demographic data. Vascular compliance and resistance are derived from arterial waveform analysis [56].

Second generation versions (1.07 or later) undergo calibration every minute, with improved CO measurement compared with earlier versions [37]. The third generation device, with its Dynamic Tone Technology, is purported to use additional physiologic variables, with automatic adjustment for changes in vascular tone [72]. The third generation is undergoing investigations during hemodynamic instability, such as sepsis and acute circulatory failure [73]. When used in conjunction with a central venous pressure catheter, systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) may be calculated [71].

*9.1. Limitations.* Since the calculations depend on the fidelity of the waveform, good arterial signal quality is critical to accuracy of CO measurement. Unreliable measurements are seen in the presence of arrhythmias and during intra-aortic balloon pump use. Although any arterial site may be cannulated, Compton et al. [74] found errors introduced when different sites had mean arterial pressure (MAP) differences of 5 mmHg or more. Mayer et al. [75] reported the percentage error for the FloTrac/Vigileo in obese patients, with their altered arterial compliance, to be slightly higher than that in nonobese when compared with pulmonary artery TD.

*9.2. Validation Studies.* Although some investigators have reported that the FloTrac appears to be reliable in several situations, its reliability is questioned in hemodynamically unstable patients [74, 76]. Manecke and Auger [77] found satisfactory correlation with PATD for clinical use in after-cardiac-surgery patients, and in a multicenter trial, McGee et al. reported the FloTrac to be comparable to PATD in critically ill patients [78].

Biancofiore et al. [79] found limited accuracy in patients with low SVR who were undergoing liver surgery. Similarly, Matthieu et al. [80] and Krejci et al. [81] found poor agreement in liver-transplant patients with low SVR compared with PATD. Hamm et al. [71] compared the device with instantaneous readings from a pulmonary artery catheter in nine patients undergoing CABG and concluded that the two were not clinically equivalent. Sakka et al. concluded that transpulmonary TD was more accurate than with FloTrac in septic patients [82].

The manufacturer reports that the system's third generation algorithm (software version 3.02) has broadened its database to include more patients with hyperdynamic conditions and is undergoing investigation [72]. Mayer et al. [83] found only moderate correlation with PATD (overall

percentage error of 46%) in patients undergoing CABG with software version 1.03; however, they later reported percentage errors of 28.3% and 20.7% intraoperatively and ICU, respectively, when studying the 1.1 software version in a similar patient population [84].

Further studies are warranted to validate the device's reliability under varying physiologic states. Hofer et al. [85] compared the device with the PiCCO to determine how well fluid responsiveness could be predicted using SVV and found similar accuracy. Suehiro and Okutani [86] concluded that SVV as measured by the FloTrac system was able to predict fluid responsiveness in patients on one lung ventilation. High risk patients undergoing major abdominal surgery who received goal-directed fluid therapy using the FloTrac/Vigileo device (software version 1.14) were found to have fewer complications and decreased hospital LOS [87].

## 10. The NICO System: Fick's Principle Using Carbon Dioxide

The NICO system (Novametrix Medical Systems, Wallingford, Conn, USA), first introduced in 1999 [4], uses the differential Fick partial rebreathing technique to measure CO in intubated, sedated, mechanically ventilated patients.

Fick's principle, using $CO_2$ as an indicator, is rewritten as follows:

$$\mathrm{CO} = \frac{\mathrm{VCO_2}}{\mathrm{Cv_{CO_2}} - \mathrm{Ca_{CO_2}}}, \tag{4}$$

where $VCO_2$ is elimination of $Ca_{CO_2}$ and $Cv_{CO_2}$ is arterial and venous $CO_2$ content, respectively.

$Ca_{CO_2}$ may be calculated from the $PaCO_2$ or estimated from the end-tidal $CO_2$. Diffusion abnormalities limit the accuracy of estimation [32]. $VCO_2$ is calculated from the dif ference between inspired and expired $CO_2$ content. $Cv_{CO_2}$ is estimated by using a partial rebreathing technique.

A proprietary disposable rebreathing loop is attached to the ventilator circuit, in addition to a mainstream infrared $CO_2$ sensor, a fixed orifice differential pressure pneumotachometer, and a rebreathing valve. Every three minutes, partial rebreathing is initiated by opening the rebreathing valve, which adds 150 mL of dead space to the circuit. The difference between normal and rebreathing ratios are used to calculate pulmonary blood flow [4, 88]. Shunt correction is carried out using Nunn's isoshunt curves, a series of curves that describe the relationship between $PaO_2$ and $FiO_2$ for different levels of intrapulmonary shunt. Shunt is determined by using the $PaO_2$ and $FiO_2$.

The intubated patients must be able to tolerate the brief period of rebreathing. Ventilator settings may need adjustment due to the at least 35 mL of increased dead space introduced.

*10.1. Limitations.* The normal difference between mixed venous and arterial $CO_2$ tension is approximately 6 mmHg. Any increase, due, for example, to increased dead space, would lead to changes in the calculated CO too. The $PaCO_2$ and $PvCO_2$ relationship is only valid when the $PaCO_2$ is more than 30 mmHg and when the $CO_2$-Hgb dissociation curve is linear. Hyperventilation to a $PaCO_2 < 30$ mmHg would lead to inaccuracies in CO measurement. Since only nonshunted blood is measured, the shunt fraction must be estimated for an accurate measure of CO. The shunt fraction is estimated using the shunt equation:

$$\frac{Q_s}{Q_T} = \frac{\mathrm{CcO_2} - \mathrm{CaO_2}}{\mathrm{Cc_{O_2}} - \mathrm{CvO_2}} \tag{5}$$

where $CaO_2$, $CvO_2$, and $CaO_2$ are the end-capillary, venous, and arterial oxygen content. To measure these noninvasively, Nunn's isoshunt plots are used.

*10.2. Validation Studies.* Variable results have been published using this technique, with many studies involving patients with varied degrees of intrapulmonary shunt in settings from cardiac-surgery or in hemodynamically unstable ICU patients [32]. Moderate agreement during thoracic surgery was found compared with pulmonary artery TD [89].

Kotake et al. [90] found improved correlation with TD with newer software versions compared with previous studies in patients undergoing abdominal aortic aneurysm repair [91]; however, they concluded that the technology still has not reached the level of interchangeability. In a small study of patients undergoing hip replacement, NICO was compared to TD and a slight underestimation was found, with a small degree of bias. For off-pump CABG patients, investigators concluded that NICO reliably and more rapidly measured CO compared with TD. The authors reported the tendency to underestimation perioperatively, but overestimation in the postoperative period. The limits of agreement were reported to be larger intraoperatively than postoperatively [92]. Similar values were obtained from NICO and PATD for patients before undergoing cardiopulmonary bypass (CPB); however, after separation, NICO tended to underestimate CO [93]. Other investigators comparing NICO and TD for major surgery or the ICU found that NICO slightly underestimated CO compared to TD [94]. Following CABG, NICO had insufficient agreement with TD, as opposed to pulse contour [95]. NICO was found to underestimate CO compared with TD in ICU patients after cardiac-surgery and found least suitable where CO was high [96]. Poor agreement was reported in a similar patient group [97]. Decreased correlation has been reported in the setting of high CO, decreased minute ventilation, increased intrapulmonary shunt, or severe chest trauma [32]. Rocco et al. [98] reported bias of $-2.3$ L/min when $Q_s/Q_p$ exceeded 35%.

## 11. Thoracic Bioimpedance

Thoracic bioimpedance (TEB) is the least invasive of the CO monitors. The technology was first developed by Kubicek et al. [99] in the 1960's, with the initial testing being carried out on astronauts [100]. The basis for its use was later pioneered by Lababidi et al. [101] in 1970, with subsequent improvements carried out over the following decades, based on animal and human research. The technique finally became

popularized based on studies by Shoemaker et al. in the 1990's [100, 102].

The underlying theory is that the thorax is a cylinder perfused with fluid (blood) which has a specific resistivity. Bioimpedance is the electrical resistance to a high-frequency low-amplitude current transmitted from electrodes placed on the upper and lower thorax [32]. Typically, six electrodes are placed—two on either side of the neck and four in the lower thorax. Current transmitted from the outermost surface electrodes is sensed by the innermost set of surface electrodes. The impedance ($Z_o$) is calculated from the voltage changes, which are indirectly proportional to the volume of fluid in the thorax, such that increased fluid results in lower TEB [103]. Blood flow from the aorta is primarily responsible for the change in impedance. Stroke volume is estimated based on the formula

$$\mathrm{SV} = \frac{\rho(L^2)}{(Z_\Phi^2)} \cdot \left[\mathrm{VET}_x \frac{(d_z)}{(dt_{\max})}\right], \tag{6}$$

where $\rho$ is the resistivity of blood (ohm-cm), $L$ is the distance between electrodes (cm), $Z_\Phi$ is the mean thoracic impedance between electrodes (ohm), VET is the ventricular ejection time (sec), and $(d_z/d_t)_{\max}$ is the maximum negative slope of the bioimpedance signal (ohm/sec) [89]. Several hemodynamic parameters may be calculated using HR and noninvasive blood pressure, together with the SV [103].

*11.1. Limitations.* TEB is affected by a number of factors [32]:

(i) changes in tissue fluid volume,

(ii) respiration-induced changes in the volume of pulmonary and venous ("noise" must be filtered out from the desired changes in volumetric blood flow of the aorta),

(iii) changes in electrode contact or position,

(iv) arrhythmias—the VET is determined using the interval between QRS complexes,

(v) acute changes in tissue water, for example, pulmonary or chest wall edema or pleural effusions,

(vi) noise from electrocautery, mechanical ventilation and surgical manipulation,

(vii) changes in myocardial contractility, for example, from anesthetic drugs or ischemia.

*11.2. Validation Studies.* Several investigators found that TEB compared favorably with PATD in varying settings including during cardiac catheterization, surgical patients, and emergency room patients [102, 104–108]. Van De Water et al. [109] found the TEB compared favorably with TD in post cardiac surgical patients. Kööbi et al. [110], using whole-body impedance cardiography in CABG patients, reported excellent repeatability which allowed for continuous monitoring. Spiess et al. [111] used BioZ (SonoSite Inc, Bothell, Wash,USA) intraoperatively for patients undergoing CABG and found that the technique initially compared well with TD, but, immediately postoperatively, the Bland-Altman analysis was not as robust. Of note, good correlation was seen during opening of the chest. Spinale et al. [112] used TEB for post-CABG patients and found good correlation with TD but poor correlation in patients who developed severe tachycardia and frequent arrhythmias.

Several investigators have found poor reliability and poor correlation with PATD in after-cardiac-surgery, the critically ill and the elderly [113–115]. In a meta-analysis performed by Rotcajg et al. [116], the conclusion was that TEB might be useful for trend analysis but not diagnostic interpretation. Correlation appeared to be better with repeated measurement designs. Atherosclerotic changes in the aorta of elderly patients reduces the Windkessel effect and contributes to increased inaccuracy [114].

TEB appears unlikely to become a routine monitor of CO for anesthesia or critical care unless further refinements in signal processing occur.

## 12. Thoracic Bioreactance

Thoracic bioreactance technology developed as a refinement of TEB. Bioreactance analyses beat-to-beat changes in the phase of electrical voltage signal relative to the applied current signal across the thorax. Changes in intrathoracic volume produce variations in electrical capacitive and inductive properties (bioreactance). The techniques for detecting relative phase shifts are powerful and less affected by noise and external interference [115]. Thoracic bioreactance technology is commercially available as the NICOM system (Cheetah Medical Inc., Indianapolis, Ind, USA). Two dual-electrode stickers are placed on either side of the thorax—one electrode is used to inject the sine-wave high-frequency (75 kHz) current into the body and the other is used by the voltage input amplifier [115]. The final measurement is determined by averaging the 2 signals.

*12.1. Validation Studies.* Several validation studies of thoracic bioreactance have been conducted, using continuous PATD as the reference continuous technique. Investigators report good correlation between the two methods ($r$ = 0.64–0.9) and minimal bias [115–117]. Comparisons are limited by differences in intrinsic variability of measurements of PATD and differences in the time responsiveness of the 2 modalities. In addition, PATD only measures right ventricular output, excluding the bronchial circulation. For this reason, Rotcajg et al. [116] considered 20% bias and precision as acceptable.

Smaller studies comparing NICOM with PICCO and Vigileo devices report similar capabilities between the devices [116, 118].

*12.2. Limitations.* The assumption that the area under the flow pulse is proportional to the product of peak flow and VET may not be valid under periods of low flow, and readings may have decreased accuracy [115].

## 13. Endotracheal Cardiac Output Monitor

The endotracheal cardiac output monitor (ECOM; ConMed, Irvine, Calif, USA) measures CO using impedance

plethysmography. The ascending aorta lies in close proximity to the trachea. Using the principle of bioimpedance, a low frequency current of 2 mA and 200 kHz is delivered from electrodes attached to a standard endotracheal tube (ETT) [119].

The ECOM 6 3D endotracheal tube (ETT) is a standard ETT to which are attached three orthogonal pairs of sensing electrodes on the cuff. Current is delivered between an electrode on the shaft of ETT and the number three electrode on the balloon. The sensing electrodes on the cuff detect the change in impedance secondary to aortic blood flow. The three-dimensional array allows for up to twelve combinations of electrodes which may be used for measurement of flow. This compensates for positional and anatomical differences between the cuff and aorta [119].

A proprietary algorithm calculates SV based on impedance changes. Increased blood flow in the aorta leads to decreased impedance. Apart from CO, also displayed are HR, ECG waveforms, SV, CI, and SVR [120].

*13.1. Limitations.* Coronary blood flow, which represents about 4-5% of CO is not recorded. Electrocautery produces interference.

*13.2. Validation Studies.* The technology is not yet fully validated in humans. A porcine study found excellent correlation when compared with transit time flow probes [120]. A study in cardiac-surgery patients reported poor correlation with TD, wide limits of agreement and a large percentage error [121].

## 14. Ultrasound Dilution

Ultrasound dilution (UD) is a minimally invasive technique, first introduced in 1995, and widely used in hemodialysis and in extracorporeal membrane oxygenation (ECMO) to measure shunt flow, vascular access recirculation and CO [122]. The technique uses isotonic saline as an indicator to measure hemodynamic variables.

The underlying principle is that blood ultrasound velocity is a function of total blood protein concentration, temperature and plasma average ion concentration. The injection of isotonic saline results in decreased blood ultrasound velocity, from which dilution curves can be produced [123]. The setup involves a disposable tubing, which is used to create an extracorporeal loop between existing peripheral arterial and central venous catheters. The arteriovenous loop is primed with heparinized saline. A roller pump circulates blood from the artery to the vein. Two reusable sensors are clamped onto the arterial venous limbs of the loop. These sensors measure the changes in blood ultrasound velocity and blood flow following a bolus of saline injected into the venous side. The CO calculation is based on the Stewart-Hamilton principle [123].

*14.1. Validation Studies.* Relatively few studies investigating the technology have been undertaken thus far. Galstyan et al. [122] compared CO and blood volumes using UD and PiCCO technology in adult ICU patients and concluded that the two were equivalent and interchangeable in that patient population. PiCCO blood volumes were significantly higher. The technology appears to be able to be used in different patient population groups. Krivitski et al. [123] performed in vitro studies to confirm the ability of UD technology to measure small flows and volumes in pediatric patients and neonates. Tsutsui et al. [124] found good correlation with TD in patients undergoing abdominal surgery.

## 15. Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is widely used in the perioperative setting for evaluating cardiac anatomy and function. Doppler techniques for the measurement of CO are most commonly based on Simpson's rule. Early operators made determinations using the pulmonary artery, which only reflects right ventricular CO. Two-dimensional echocardiography determined the cross-sectional area of the PA, which was multiplied by the integral of the instantaneous flow velocity, determined by pulsed wave Doppler in the plane of the cross section [125]. A drawback is difficulty visualizing the PA in a significant number of patients because it may be obscured by the left main stem bronchus.

The validated frequently used technique developed by Perrino et al. [126] determines the cross-sectional area of the left ventricular outflow tract ($CSA_{LVOT}$) in a mid-esophageal aortic long axis view. Planimetry is used to measure the area of the aortic valve. To measure aortic blood flow, the probe is positioned in a transgastric short-axis view of the left ventricle at the mid-papillary level. The image array is rotated approximately 120° to produce imaging of the LVOT and ascending aorta lying parallel to the ultrasound beam. Continuous-wave Doppler is used to measure aortic blood flow velocities at the level of the aortic valve. Doppler CO is calculated as a product of the velocity time integral, $CSA_{LVOT}$, and HR [127]. Another method described uses the transgastric, apical view to assess aortic blood flow. The ultrasound beam is oriented almost parallel to the aortic valve blood flow. Probe positioning for this view is technically challenging [61].

## 16. Esophageal Doppler

Esophageal Doppler (ED) utilizes a flexible probe, approximately the size of a nasogastric tube, at the tip of which is a transducer (4 MHz continuous or 5 MHz pulsed wave). The probe may be left in place for days to weeks in intubated, sedated, mechanically ventilated patients. When advanced to the mid-thoracic level, ideally between the 5th and 6th thoracic vertebrae, the device is parallel to and thus able to measure blood flow velocity in the descending aorta [128]. It is assumed that the aorta is a cylinder and flow is calculated by multiplying the cross-sectional area ($CS_a$) by the velocity ($V_f$). Since velocity changes with pulsatility of flow, $V_f$ is described as the area under the curve of a velocity-time graph [32]. The area is calculated as the integral of the velocity curve over time ($dV/dt$) from the start to the end of aortic

blood flow ($T_0$ and $T_1$, resp.). This area, known as the stroke distance, is the distance travelled by the blood during systole (cm). This value is multiplied by the $CSA_a$. The aortic area may be derived either from published nomograms or direct measurement [32]:

$$CO = HR \times SV. \quad (7)$$

SV changes can be used to guide fluid administration. ED also has the capability of determining the corrected time flow (FTc), which is the systolic flow time corrected for an HR of 60/min. This value, which represents the time from the beginning of the aortic waveform upstroke to its return to baseline, is used as a measure of cardiac preload. Good correlation with other techniques, such as pulmonary artery occlusion pressure, along with improved outcomes has been reported [129–132].

*16.1. Limitations.* Only descending aortic blood flow, which represents about 70% of total flow, is measured, and so a correction factor ($K$-factor) must be added to compensate for the blood flow to aortic arch vessels. This flow ratio may vary with metabolic activity, between different organs and during hemodynamic instability, and the validity is questionable outside of young healthy patients [32]. An inconstant proportion of blood flow to the descending aorta may also occur in the setting of aortic coarctation, aortic cross clamp, and pregnancy. Turbulence due to thoracic aneurysms, aortic balloon pump, aortic valve disease interfere with the validity of results [133].

$CSA_a$ changes with variations in pulse pressure, vascular tone, aortic compliance, volume status, or catecholamine use. Direct measurement produces greater accuracy [32]. In 76 patients with acute circulatory failure, measurements of aortic blood flow before and after a fluid bolus revealed an underestimation of the response to the fluid bolus in a significant number of patients if readings were based on an estimated unchanged $CSA_a$ as opposed to directly measured aortic velocity and $CSA_a$ [134]. Proper probe position is essential to accuracy of determination of $V_f$. The Doppler beam must be within 20° of axial flow to obtain good measurement.

With respect to fluid management, interpretation of FTc may be complicated by its inverse relationship with SVR. In conditions of elevated SVR, such as heart failure or excessive vasopressor use, FTc is reduced and may prompt fluid administration. Other conditions, such as pericardial tamponade or mitral stenosis, where there is limited cardiac filling will produce a decreased FTc and again prompt further fluid administration in a scenario where the patient may already have optimal cardiac filling based on the starling curve. SV has thus been argued to be a preferable variable to monitor fluid status [135, 136].

*16.2. Validation Studies.* Multiple studies have compared the validity of ED for measurement of CO against PATD under varying conditions [129, 137–139]. Dark and Singer [139] published a meta-analysis of eleven studies in critically ill patients, finding a pooled median bias of 0.19 L/min (range: −0.69–2.0 L/min) for CO. Boulnois and Pechoux [140] reported the pooled limits of agreement for 3 studies including 90 patients under a range of flow states to be −2.21 to 2.33 L/min. Laupland and Bands [133], in a meta-analysis of 25 studies, concluded that ED was reliable, responsive to changes, was showed good agreement with low bias, however, the wide limits of agreement raised concerns about precision. The two techniques are therefore not thought to be interchangeable; however, ED may be used to track changes [137].

Improved patient outcome has been demonstrated by a number of investigators when ED is used in goal-directed fluid therapy. Sinclair et al. [132] reported ED-guided fluid loading resulted in greater improvements in SV and CO with fluid administration in study patients, as well as faster recovery and decreased LOS than in controls. Venn et al. [141] similarly reported reduced hypotension and faster recovery for ED-monitored patients undergoing femoral fracture repair, compared with controls who received central venous pressure monitoring. In patients having major elective surgery, Gan et al. [142] reported earlier return to bowel function and decreased incidence of postoperative nausea and vomiting. Mythen and Webb [131] found a decreased incidence of gut mucosal perfusion (measured by gastric tonometry), major complications, and decreased hospital and ICU stay in cardiac-surgery patients who received goal-directed colloid therapy guided by ED compared with standard management. Wakeling et al. [143] randomized 128 patients receiving colorectal surgery to fluid management with guided with ED or central venous pressure monitoring. Decreased hospital LOS and faster gut recovery were seen in the ED-guided group. Noblett et al. [144] reported shorter hospital stay and decreased morbidity in patients undergoing colorectal resection who received ED-guided fluid management. Additionally, the intervention group had lower levels of interleukin 6, which may be a reflection of improved bowel perfusion. Conway et al. [145] reported improved hemodynamics in patients having major bowel surgery and fewer ICU admissions. In trauma patients, ED-guided fluid therapy resulted in decreased blood lactate levels, reduced infectious complications and decreased hospital and ICU LOS [146]. A nurse delivered ED-guided fluid protocol in patients after-cardiac-surgery resulted in shortened hospital LOS [147].

## 17. Conclusion

Despite controversies, complications, and inherent errors in measurement, intermittent bolus PATD CO measurement continues to be the gold standard. Newer techniques provide less invasive alternatives and will be increasingly adopted over time; however, the currently available monitors are still unable to provide central circulation pressures or true mixed venous saturations and cannot replace the PAC [32]. Many minimally invasive techniques continue to suffer from decreased accuracy and reliability under periods of hemodynamic instability, and so few have reached the level of interchangeability with the PAC. Esophageal Doppler and pulse

contour monitors have the advantage of being able to predict fluid responsiveness. Their use in GDT has already been shown to decrease postoperative morbidity, and the use of these technologies is anticipated to continue to lead to greater improvement in outcomes [32].

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*Research Article*

# The Effect of a Hyperdynamic Circulation on Tissue Doppler Values: A Simulation in Young Adults during Exercise

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Left ventricular tissue Doppler imaging (TDI) velocities are used to monitor systolic and diastolic function, but it is not known how these may change in a hyperdynamic circulation, as often occurs in anesthesia and critical care medicine. Twenty-six healthy young volunteers were recruited and left ventricular systolic and diastolic tissue Doppler velocities measured at rest, light exercise, strenuous exercise, and recovery (10 minutes after exercise). At rest, TDI velocities significantly decreased from base to apex ($P < .001$). Within basal, mid, and apical sections, systolic and diastolic peak velocities differed between segments ($P < .05$), except for systolic middle ($P = .094$) and late diastolic apical velocities ($P = .257$). Basal septal velocities differed from basal lateral, for systolic ($P = .041$) but not diastolic peak values. Inferobasal radial values differed from basal lateral values for both systolic and diastolic velocities ($P < .05$). Both systolic and diastolic TDI velocities increased significantly in all segments in a proportionate manner with a hyperdynamic circulation.

## 1. Introduction

Tissue Doppler imaging is commonly used to assess diastolic function, and for the assessment of left atrial pressure. These measurements are most commonly applied to outpatients under resting conditions. The normal values reported in outpatients may not apply during acute changes in hemodynamic state, which occurs frequently in intensive care patients or those undergoing anesthesia. Assessment of left ventricular systolic and diastolic function during exercise using tissue Doppler imaging (TDI) has been used to detect underlying pathology, such as ischemic heart disease [1].

It is important to determine whether left ventricular systolic and diastolic tissue Doppler velocity values are similar in all segments in young healthy adults in order to identify if values from different segments can be used interchangeably. Exercise induces a hyperdynamic circulation, and TDI values may alter from resting conditions. Such changes assessed in normal young adults may be indicative of changes that should be expected in pathological hyperdynamic circulation states, with the premise that an absence of predicted change could indicate pathology.

The aim of the study was to assess changes in left ventricular systolic and diastolic tissue Doppler velocities during a hyperdynamic circulation, in normal healthy subjects under resting and exercise conditions.

## 2. Materials and Methods

*2.1. Subjects.* Twenty-six healthy volunteers, between the ages of 18 to 22 years, were recruited. Written, informed consent was obtained. This study was approved by The University of Melbourne Human Research Ethics Committee in accordance with the Code of Practice of the National Health and Medical Research Council of Australia.

The study was conducted in the Human Laboratory of the Cardiovascular Therapeutics Unit, Department of Pharmacology, University of Melbourne.

Table 1: Subject demographics and hemodynamic variables.

| | Rest | Light exercise | Heavy exercise | Recovery | $P$ |
|---|---|---|---|---|---|
| Heart rate | 69.8 ± 10.5 | 120.0 ± 9.9 | 141.0 ± 13.0 | 93.3 ± 9.5 | <.001 |
| Systolic blood pressure (mm Mg) | 123.4 ± 14.7 | 157.0 ± 18.8 | 146.4 ± 19.8 | 116.4 ± 8.4 | <.001 |
| Diastolic blood pressure (mm Hg) | 66.5 ± 9.3 | 68.7 ± 11.7 | 68.3 ± 10.9 | 62.3 ± 10.2 | .043 |

Values are mean ± standard deviation; $P$ values are determined using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction for the comparison of values from baseline to recovery.

*2.2. Echocardiography.* All recordings were performed with a SonoSiteMicroMaxx (Sonosite Australia, NSW, Australia) echocardiography machine with a 2.5 MHz phased array transducer. A comprehensive transthoracic study was first performed to exclude any unexpected pathology. Subjects were in the lateral decubitus position and simultaneously monitored with an electrocardiogram (ECG).

Echocardiography images were digitally recorded and analysed offline using Prosolv Cardiovascular Analyser (Vision Software, QLD, Australia). Each measurement was the average of 3 consecutive beats from 2 observers.

Demographic data, heart rate, and blood pressure were recorded prior to echocardiography. The heart segments were imaged from apical views; the radial TDI from the parasternal short axis view, and M-Mode assessment of left ventricular function, was performed from the parasternal long axis view.

Recordings were made at the end of each condition. Exercise recordings were measured at apical basal septal and lateral views and parasternal short axis inferobasal view.

For postexercise recordings TDI recordings were performed for basal septal and basal lateral segments and the inferobasal (radial) segment, in order to minimise the risk of changes in circulatory parameters during the period of recording.

*2.3. Exercise Protocol.* Exercise was performed by running on a treadmill.

Recordings were performed at 4 time periods.

(i) Baseline—resting phase.

(ii) Low-intensity exercise—running on a treadmill for 2 minutes or until reaching a heart rate of 100–120 beats·min$^{-1}$.

(iii) Heavy-level exercise—running on a treadmill for 5 minutes or until reaching a heart rate of greater than 140 beats·min$^{-1}$.

(iv) Recovery—10 minutes after heavy exercise.

Heart rate and blood pressure were monitored with each condition.

*2.4. Statistics.* Data are presented as mean ± standard deviation. Values from baseline to exercise were analysed by repeated measures ANOVA for within-subject difference with Greenhouse-Geisser correction for multisample asphericity. Statistical significance was defined as $P < .05$. Graphs were constructed using GraphPad Prism 5.0., and analyses were performed using SPSS version 14.0.

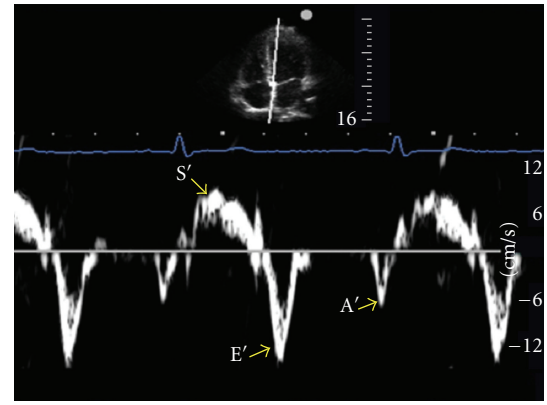


Figure 1: Spectral tissue Doppler tracing for the apical 4-chamber transthoracic window, showing the cursor position on the septal basal segment. The transducer is placed at the apex of the heart and angled towards the head.

Interobserver variability analysis was done using the Bland and Altman 95% limits of agreement method [2]. The mean is the average of two observers. Mean difference is the difference of means between two observers expressed as a positive value. The "limits of agreement" was defined as two standard deviations of the difference and expressed as a percentage of the average value of the mean difference. An acceptable limit of agreement is ±30% [3].

## 3. Results

Twenty-nine volunteers were enrolled and 3 were withdrawn because of inadequate imaging or inability to complete the exercise protocol. Twenty-six subjects were included in the study. There were 11 males and 15 females, with a mean age of 19.8 ± 1.5 years (18–22), height of 169.7 ± 7.2 cm (157–186), and weight of 64.6 ± 10.2 kg (50–104). Hemodynamic variables during the exercise protocol are summarised in Table 1. All subjects were found to have a normal left ventricular mass (mean mass 119.4 g ± 6.8). Ejection fraction calculated using Teichholz formula was 53.5 ± 0.8%.

*3.1. Resting Values.* Within each ventricular wall, velocities decreased significantly from basal to apical segments ($P < .001$) (Figure 1 and Table 2). There was no significant difference in radial TDI for the inferobasal or anterobasal segments.

Table 2: Resting tissue Doppler velocities of segments.

| Segment | Annulus | Basal | Middle | Apical | Apical cap | $P$ |
|---|---|---|---|---|---|---|
| *Lateral* | | | | | | |
| S′ | 10.4 ± 0.4 | 9.6 ± 0.5 | 8.7 ± 0.5 | 6.5 ± 0.3 | 6.7 ± 0.5 | .002 |
| E′ | 17.9 ± 0.4 | 16.5 ± 0.5 | 14.2 ± 0.7 | 8.7 ± 0.5 | 5.6 ± 0.4 | <.001 |
| A′ | 6.5 ± 0.4 | 5.4 ± 0.3 | 4.7 ± 0.2 | 3.8 ± 0.2 | 3.6 ± 0.3 | <.001 |
| *Septal* | | | | | | |
| S′ | | 8.7 ± 0.3 | 7.1 ± 0.3 | 5.4 ± 0.3 | | <.001 |
| E′ | | 14.4 ± 0.4 | 11.7 ± 0.4 | 7.5 ± 0.5 | | <.001 |
| A′ | | 6.4 ± 0.4 | 5.0 ± 0.3 | 3.8 ± 0.2 | | <.001 |
| *Inferolateral* | | | | | | |
| S′ | | 8.8 ± 0.3 | 7.5 ± 0.4 | 6.1 ± 0.4 | | <.001 |
| E′ | | 14.2 ± 0.7 | 12.0 ± 0.6 | 7.8 ± 0.7 | | <.001 |
| A′ | | 5.9 ± 0.3 | 4.8 ± 0.4 | 4.3 ± .2 | | <.001 |
| *Anteroseptal* | | | | | | |
| S′ | | 10.7 ± 0.2 | 8.9 ± 0.3 | 7.1 ± 0.4 | | <.001 |
| E′ | | 19.1 ± 0.5 | 15.0 ± 0.5 | 9.6 ± 0.4 | | <.001 |
| A′ | | 6.6 ± 0.3 | 5.4 ± 0.3 | 4.1 ± 0.2 | | <.001 |
| *Anterior* | | | | | | |
| S′ | | 9.6 ± 0.3 | 8.1 ± 0.4 | 6.5 ± 0.3 | | <.001 |
| E′ | | 16.1 ± 0.4 | 13.0 ± 0.4 | 7.7 ± 0.4 | | <.001 |
| A′ | | 5.2 ± 0.3 | 4.2 ± 0.2 | 3.8 ± 0.2 | | <.001 |
| *Inferior* | | | | | | |
| S′ | | 10.6 ± 0.3 | 9.3 ± 1.1 | 6.4 ± 0.2 | | <.001 |
| E′ | | 18.1 ± 0.5 | 13.6 ± 0.6 | 8.8 ± 0.5 | | <.001 |
| A′ | | 7.3 ± 0.5 | 5.5 ± 0.3 | 4.2 ± 0.2 | | <.001 |
| *Inferobasal* | | | | | | |
| S′ | | 6.8 ± 0.4 | | | | |
| E′ | | 12.0 ± 0.9 | | | | |
| A′ | | 4.5 ± 0.3 | | | | |
| *Anterobasal* | | | | | | |
| S′ | | 6.3 ± 0.4 | | | | |
| E′ | | 7.4 ± 0.6 | | | | |
| A′ | | 3.8 ± 0.2 | | | | |

Values are mean ± standard deviation. All velocities are in $cm \cdot sec^{-1}$; S′: peak systolic velocity; E′: peak early diastolic velocity; A′: peak late diastolic velocity. $P$ values are determined using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction for the comparison of values from basal to apical segments.

Within the base, middle, and apical sections of the heart, velocities were significantly different between segments for both systolic and diastolic measurements ($P < .05$), with the exception of middle section systolic velocities ($P = .094$) and the apical late diastolic velocities ($P = .257$) (Figure 2). There was no difference in diastolic TDI velocities for septal basal and lateral basal segments, but there was a small but significant difference in systolic velocities ($P = .041$). For radial TDI measurements, the inferobasal segment velocities were significantly lower than the anterobasal segment (systolic ($P < .001$), early diastolic ($P < .001$), and late diastolic velocities ($P = .009$)).

*3.2. Exercise Values.* Tissue Doppler velocities changed significantly, proportionate to exercise effort, in all segments studied during the exercise and recovery (all comparisons $P < .001$) (Figure 3 and Table 3).

*3.3. Interobservor Variability.* Interobservor variability data for echocardiography measurements are summarised in Table 4. All variables were within accepted limits of agreement of ±30% [3].

## 4. Discussion

Our study showed that tissue Doppler velocities are not uniform across different myocardial segments, either within wall (base to apex) or between basal, middle, or apical sections. The highest systolic and diastolic velocities occur in the basal segments and decrease significantly from base to apex. During exercise all tissue Doppler values increased proportionate to effort and reduced with recovery (Figure 4).

Our results may have implications for critically ill patients, particularly those with hyperdynamic circulations. Apical views are at times difficult to acquire in supine

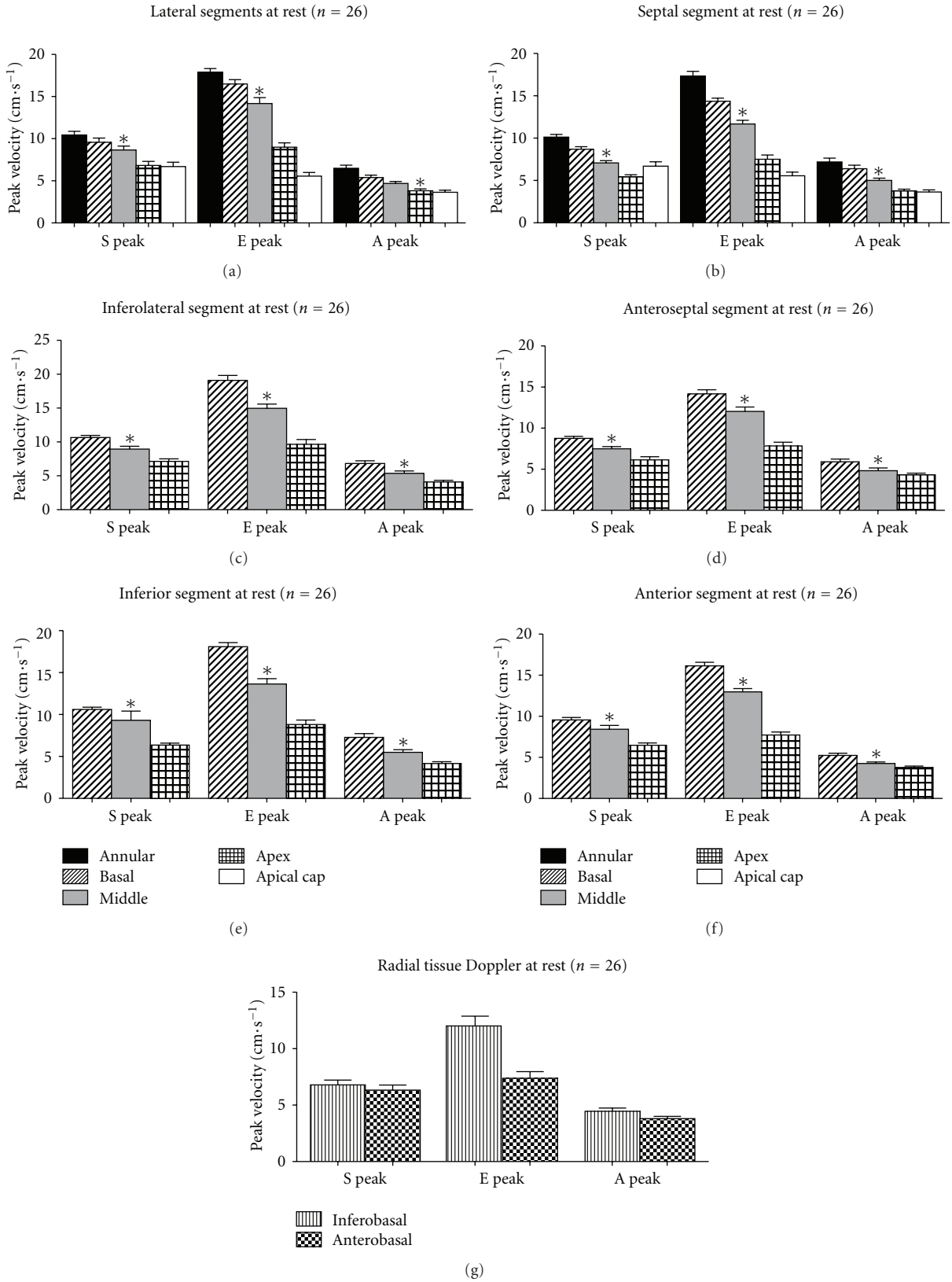


FIGURE 2: Resting Tissue Doppler velocities for each ventricular wall ((a)–(f)) and for radial measurements of the inferobasal and anterobasal segments (g). S: systolic velocity; E: early diastolic velocity; A: late diastolic velocity; Error bars are standard error of the mean. $^*P < .001$. $P$ values are determined for the comparison of values from basal to apical segments using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction.

Table 3: Changes in tissue Doppler velocities during exercise.

| Segment | Baseline | Light exercise | Heavy exercise | Recovery | *P* |
|---|---|---|---|---|---|
| *Lateral* | | | | | |
| S′ | 9.6 ± 2.3 | 19.1 ± 4.6 | 25.8 ± 5.5 | 10.7 ± 2.7 | <.001 |
| E′ | 16.5 ± 2.4 | 22.3 ± 3.7 | 25.1 ± 4.7 | 11.7 ± 3.8 | <.001 |
| A′ | 5.4 ± 1.5 | 12.7 ± 2.9 | 19.0 ± 3.0 | 5.8 ± 2.7 | <.001 |
| *Septal* | | | | | |
| S′ | 8.7 ± 1.6 | 15.7 ± 3.5 | 22.0 ± 4.2 | 9.4 ± 1.6 | <.001 |
| E′ | 14.4 ± 1.9 | 18.1 ± 4.9 | 22.8 ± 5.6 | 11.7 ± 4.0 | <.001 |
| A′ | 6.4 ± 2.2 | 10.2 ± 2.8 | 16.5 ± 2.9 | 6.8 ± 2.7 | <.001 |
| *Inferobasal* | | | | | |
| S′ | 6.8 ± 3.0 | 15.0 ± 3.0 | 19.7 ± 4.1 | 9.3 ± 2.3 | <.001 |
| E′ | 12.0 ± 4.5 | 15.8 ± 4.2 | 20.3 ± 5.8 | 11.5 ± 3.6 | <.001 |
| A′ | 4.5 ± 2.1 | 9.6 ± 2.1 | 15.4 ± 2.7 | 7.0 ± 2.9 | <.001 |

All velocities are in $cm \cdot sec^{-1}$; S′: peak systolic velocity; E′: peak early diastolic velocity; A′: peak late diastolic velocity. *P* values are determined using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction for the comparison of values from baseline to recovery.

Table 4: Interobserver variability.

| | Mean | Mean difference | Limits of agreement (±2SD) (%) |
|---|---|---|---|
| LV EDV (mL) | 84.5 | 7.2 | 4.5 (5.3) |
| LV ESV (mL) | 40.5 | 4.3 | 2.4 (6.0) |
| EF (%) | 53.5 | 1.2 | 2.3 (4.3) |
| Left Atrial area ($cm^2$) | 14.4 | 0.4 | 0.6 (4.3) |
| Interventricularseptal thickness (cm) | 0.8 | 0.0 | 0.1 (7.7) |
| Posterior wall thickness (cm) | 0.8 | 0.1 | 0.0 (5.5) |
| LV internal dimension (diastole) (cm) | 4.3 | 0.4 | 0.2 (4.2) |
| LV mass (g) | 119.4 | 7.3 | 16.3 (13.7) |
| *Tissue Doppler imaging velocities* | | | |
| S′ | 8.3 | 0.3 | 0.3 (3.1) |
| E′ | 12.8 | 0.1 | 0.2 (1.4) |
| A′ | 5.3 | 0.2 | 0.1 (2.1) |

All velocities are in $cm \cdot s^{-1}$; S′: peak systolic velocity; E′: peak early diastolic velocity; A′: peak late diastolic velocity; mean: average of two observers; Mean difference: difference of means between two observers expressed as a positive value. Limits of agreement: two standard deviations of the difference as a percentage of the average value of the mean difference. Percentage (%) is relative to the mean.

ventilated patients; images that can be obtained may be foreshortened, or more apically placed segments may be the only segments visible. Values between segments differ and should not be considered equivalent when diagnosing systolic or diastolic abnormality. Secondly, our data shows that values *should increase* in a hyperdynamic circulation, indicating that even "normal" values may represent pathology during hyperdynamic circulation conditions. However, we urge caution in directly translating these findings to the critically ill, where the disease process may produce very different haemodynamic conditions to the exercising young adult.

The most commonly used segments in clinical practice are the septal basal and lateral basal segments. The diastolic velocities were equivalent, and thought the systolic values differed, the difference was small and not clinically important. This may not be the case, however, when there is regional disease in the basal myocardium. Cardim et al. [4], however, found that tissue Doppler velocities were higher in the lateral and inferior basal segments than in the septal and lateral segments for both systolic and diastolic function. The systolic and diastolic velocities in our study were higher than those reported in [4–6]. This could be due to the younger age of our cohort, and TDI values have been reported to decrease with age [6]. Lateral wall diastolic TDI values are reported to be higher than septal velocities, which was consistent with the trend observed in this study.

There was a significant difference between the velocities in segments within the base, middle, and apex of the heart wall with exception to the systolic middle and late diastolic apical velocities. Therefore, using velocities interchangeably between segments is not possible. Greaves and Alam found similar results [5, 7], reporting that the septal segment velocities were lower than the anterior, lateral, and inferior sites

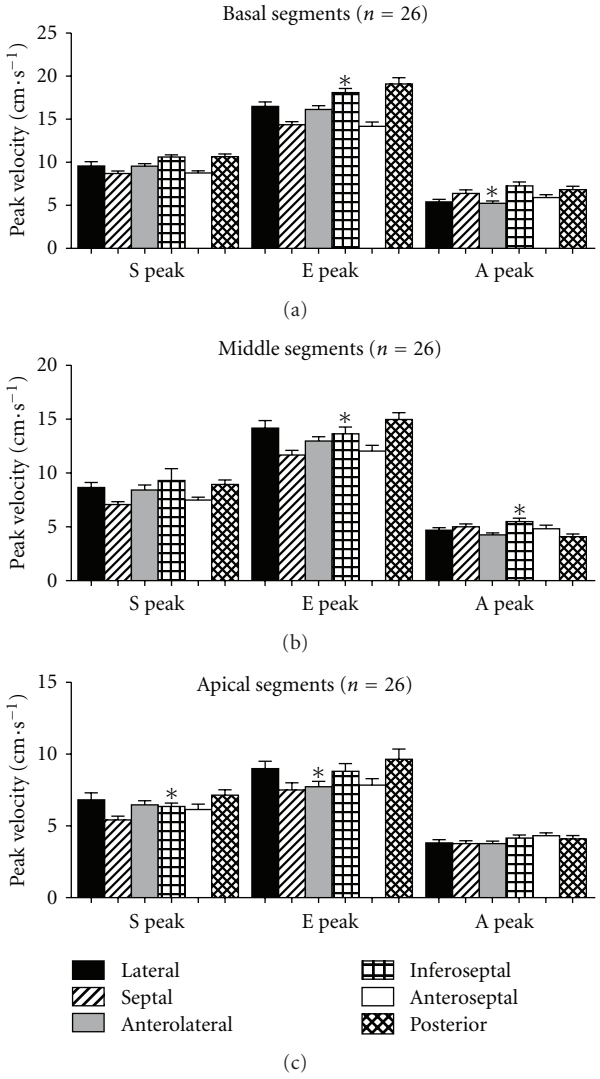


Figure 3: Resting tissue Doppler velocities for basal (a), middle (b), and apical (c) sections. S: systolic velocity; E: early diastolic velocity; A: late diastolic velocity; Error bars are standard error of the mean. $^*P < .001$. $P$ values are determined for the comparison of values from basal to apical segments using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction.

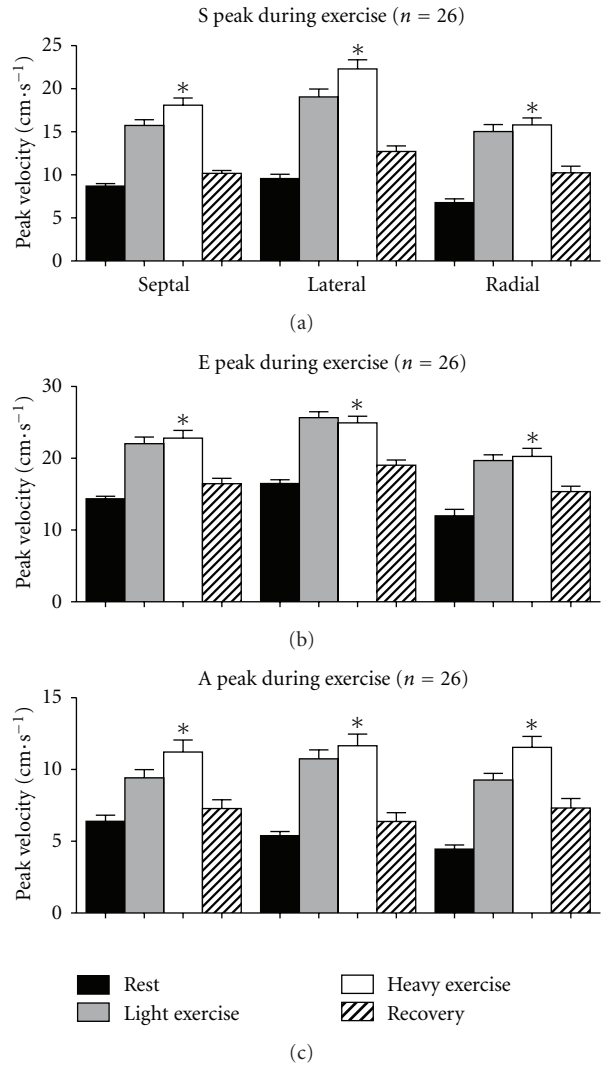


Figure 4: Tissue Doppler values during exercise for systolic (a), early diastolic (b), and late diastolic velocities (c). Septal is septal basal segment, lateral is the lateral basal segment, and radial is the inferobasal segment measured in the short axis. $^*P < .001$. $P$ values are determined for the comparison of values from basal to apical segments using repeated measures ANOVA for within subject difference with Greenhouse-Geisser correction.

and attributed this to "the presence of ample longitudinally orientated fibres in these parts of the left ventricle." Lateral systolic and diastolic velocities were found to be greater than septal systolic and diastolic velocities. Therefore the ventricular walls have a physiological heterogeneity and the velocities cannot be used interchangeably. Cardim described that the difference between the two segments occurred due to the "sandwich" position of the septum in between ventricles, the septum having a greater physiological stress than the lateral segments, the septalcytoarchitecture being rich in circumferential fibres, the degrees of interstitial fibrosis, and the proportion of myocyte/adrenergic receptors in comparison to the lateral wall [4]. Our study found significant differences between the lateral and inferior segments for both systolic and diastolic velocities. Radial values were lower than longitudinal values. It is therefore not possible to use radial tissue Doppler velocities as a substitute for longitudinal velocities. Greaves found radial values were lower than longitudinal [5].

During exercise, values for systolic and diastolic tissue Doppler imaging measurements increased proportionate to effort and reduced during recovery. There was a significant increase in all velocities in all segments at different degrees of exercise. Wilkenshoff looked at regional systolic velocity in 20 normal subjects during bicycle ergometry and found the velocities to increase during exercise [8].

Studies on left ventricular response during exercise have shown an increase in left ventricular ejection fraction [9–11]. There is an early increase in the ejection fraction and a tendency to decrease the ejection fraction as peak exercise

is approached. The changes in tissue Doppler velocities in our studies reflect a similar effect, though the subjects were not exercised to maximal effort.

Stress echocardiography can be useful in investigating ischaemia and help increase our understanding of the physiological effects of ischaemia. Tissue Doppler imaging gives a quantitative and regional measure and is beneficial in measuring these changes. Exercise induced abnormalities of left ventricular function have high sensitivity and specificity for ischaemia (>90%) [10]. A decrease in regional wall motion and left ventricular ejection fraction is considered a diagnostic hallmark of exercise induced myocardial ischaemia [10]. This indicates the location of an abnormality. An increase in TDI velocities with exercise is an expected response, and it is possible that an absence of increase, or decreased velocities could indicate regional pathology. More research in patients with known ischaemic disease is required to answer this question.

The primary limitation is that we used exercise to simulate a hyperdynamic circulation. Healthy young adults were enrolled so that systolic and diastolic function would not be affected by possible medical comorbidities. Apical velocities were difficult to measure. Our study found that signal quality was reduced in the apical images, which could have contributed to lower recorded velocities in the apex, as well as differences in fibre alignment, and the angle dependence of Doppler imaging, which is enhanced in the apical region [12]. Echocardiographic studies during exercise are difficult to interpret due to the greater expansion of the lungs and higher respiratory frequency during exercise causing a reduction in the acoustic windows in most individuals [10]. It is considered optimal to acquire images in subjects in an upright position during exercise, but this is difficult. In our study, we obtained images in the supine left decubitus position immediately after exercise. Bougault has shown that left ventricular systolic and diastolic tissue Doppler imaging velocities are reproducible during exercise [13]. Further research is required in a sick cohort of patients to evaluate the impact of our findings.

## 5. Conclusion

Tissue Doppler velocities decrease from base to apex. There was a difference in velocities within the basal, middle, and apical segments. During hyperdynamic circulation velocities increase proportionate to effort and reduce with recovery.

## Authors' Contribution

All authors participated in the design, analysis, and manuscript preparation. Data acquisition and offline analysis was performed by N. Ruizhi and A. Huynh.

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*Research Article*

# The Effect of Airway Pressure Release Ventilation on Pulmonary Catheter Readings: Specifically Pulmonary Capillary Wedge Pressure in a Swine Model

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*Background*. Airway pressure release ventilation (APRV) is a mode of mechanical ventilation that theoretically believed to improve cardiac output by lowering right atrial pressure. However, hemodynamic parameters have never been formally assessed. *Methods*. Seven healthy swine were intubated and sedated. A baseline assessment of conventional ventilation (assist control) and positive end-expiratory pressure (PEEP) of 5 cm $H_2O$ was initiated. Ventilator mode was changed to APRV with incremental elevations of CPAP-high from 10 to 35 cm $H_2O$. After a 3-to-5-minute stabilization period, measurements of hemodynamic parameters (PCWP, LAP, and CVP) were recorded at each level of APRV pressure settings. *Results*. Increasing CPAP caused increased PCWP and LAP measurements above their baseline values. Mean PCWP and LAP were linearly related (LAP = 0.66*PCWP + 4.5 cm $H_2O$, $R^2 = 0.674$, and $P < .001$) over a wide range of high and low CPAP values during APRV. With return to conventional ventilation, PCWP and LAP returned to their baseline values. *Conclusion*. PCWP is an accurate measurement of LAP during APRV over variable levels of CPAP. However, PCWP and LAP may not be accurate measurements of volume when CPAP is utilized.

## 1. Background

The effects of positive pressure ventilation on hemodynamic parameters are known to be complex. They are determined by an integral relationship betweenvascular resistance and intrathoracic pressure [1, 2].

Positive pressure ventilation increases intrathoracic pressure (ITP), which increases right atrial (RA) pressure, leading to a decrease in venous return. Subsequently, this decreased right ventricle (RV) filling decreases left ventricle (LV) preload and allows for greater LV contraction with decreased energy expenditure. In patients who are volume overloaded, this could be beneficial. However, in hypovolemic patients, this may induce cardiovascular insufficiency [2, 3]. Therefore, knowledge of the volume status of mechanically ventilated patients is essential. On critically ill patients, pulmonary artery catheters (PACs) can be used for hemodynamic monitoring. Pulmonary capillary wedge pressure is reflective of left atrial pressure (LAP). Left atrial pressure is reflective of left ventricular end-diastolic pressure (LVEDP), which is a measure of preload, and preload is an estimation of volume. These relationships hold true when cardiac compliance is constant and pulmonary capillary pressure is greater than alveolar pressure [4].

Other effects of positive pressure ventilation can be less beneficial. For example, juxtacardiac ITP due to hyperexpanding lungs can decrease left ventricular diastolic compliance and subsequently impair LV contractility [2]. In some studies, this has been associated with decreased cardiac output [5]. Also, positive end expiratory pressure (PEEP) can induce regional hyperinflation, which compresses alveolar vessels and increases pulmonary vascular resistance (PVR), which can potentially lead to RV failure, or cor pulmonale [2].

Despite these hemodynamic effects, mechanical ventilation improves pulmonary gas exchange and restores

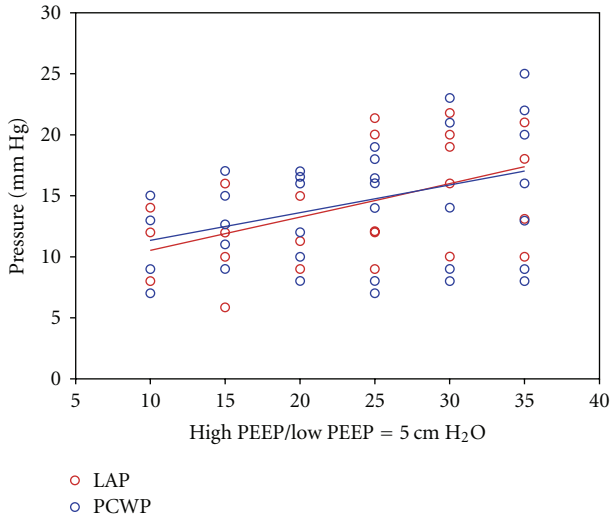


Figure 1: Illustration of variability in LAP and PCWP as high PEEP is increases with constant low PEEP of 5 cm $H_2O$.

arterial blood acid-base balance. There are many modes of mechanical respiratory support but airway pressure release ventilation (APRV) has offered clinical advantages for ventilator management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in comparison to conventional mechanical ventilation [6, 7]. APRV is a method of ventilation that uses continuous airway pressure in time-released cyclical fashion that was first described in 1987 [8]. This mode of ventilation is theoretically known for improved ventilation-perfusion matching through improved alveolar recruitment, leading to improved airway exchange. Many advantages of this mode have been described, such as: lower airway pressures, lower minute ventilation, minimal adverse effects on cardiocirculatory function, ability to spontaneously breathe throughout the entire ventilatory cycle, decrease of sedation use, and near elimination of neuromuscular blockade [6, 7, 9]. In addition, APRV is theoretically believed to improve cardiac output by lowering the right atrial pressure and improving preload due to decrease of pleural pressures and increase in abdominal pressure [9].

The relationship between LAP and PCWP has not been formally assessed with APRV. In this study, we compare PCWP with LAP in a swine model while APRV mode of ventilation is used to establish the reliability of this measurement in estimating volume.

## 2. Method

Seven 30–45 kg male swine were sedated with propofol to facilitate tracheal intubation and instrumentation. However, muscle relaxants were not given to the animals so they were able to ventilate spontaneously. A pressure transducer was placed down the endotracheal tube and used to monitor mean airway pressure (Paw). Right and left femoral arterial and venous accesses were obtained to monitor mean arterial pressure (MAP) and central venous pressure (CVP), respectively. Then, a Medtronic 8 French transseptal sheath was introduced through atrial septum and connected to pressure transducer to continuously record LAP. Finally, pulmonary artery catheter was advanced until distal tip was placed into the pulmonary artery, radio-graphically below the level of the left atria, for measurement of PCWP at the end of expiration. All connections to the pressure transducer were zeroed and measurements confirmed. The pressure transducer was zeroed at the level of the atria prior to obtaining measurements. The animals were placed on conventional ventilation (assisted control) with tidal volume 6cc/kg and PEEP of 5 cm $H_2O$. Mean PCWP and LAP were recorded as baseline values. APRV protocol initiated with changing CPAP-high from 10 to 35 cm $H_2O$ and CPAP-low varied from 5 to 30 cm $H_2O$ in 5 unit increments with a ratio of $T_{High}$ to $T_{Low}$ of 4 : 1. Hemodynamic parameters were recorded for 30 seconds after each APRV pressure change following a period of stabilization that ranged from 3 to 5 minutes. Linear regression analysis (Sigma Stat version 3.1) was employed to assess changes in mean PCWP and mean LAP with increases in high PEEP and at constant low PEEP (5 cm $H_2O$). The relationship between mean PCWP (mmHg) and LAP (mmHg) was assessed by regression analysis for each animal to assess individual variability and all animals pooled with ARPV. $P$ values <.05 were considered significant.

## 3. Results

With increasing levels of CPAP during APRV, mean PCWP and LAP increased in response to increasing airway pressure. Mean PCWP and LAP of the group were linearly related (LAP = 0.66*PCWP + 4.5 cm $H_2O$, $R^2 = 0.674$, and $P <$ .001) over a wide range of high and low CPAP during ARPV (Figure 1). The slope of this regression line differed with each individual animal (Figure 2). A Bland-Altman analysis also demonstrates agreement between mean PCWP and LAP over a 95% confidence interval (CI).

## 4. Discussion

To our knowledge, this is the first study to evaluate changes in cardiovascular parameters during increasing levels of CPAP with APRV mode of ventilation. The linear relationship between PCWP and LAP, conferred by two methods of agreement, demonstrates how PCWP is an accurate assessment of LAP with APRV mode of ventilation over CPAP ranges of 10 to 35 cm $H_2O$. The individualized relationship between these values for each animal likely represents the unique cardiac and pulmonary compliance of each animal.

This experimental swine model also demonstrates that increasing levels of CPAP transpire to elevations of PCWP and LAP from baseline values. Since no interventions in volume were made during this assessment and these values returned to baseline when convention ventilation was restored, this suggests that the temporary elevation in these pressures was not caused by permanent volume change but by temporary pressure change (Figure 3). Also, when evaluating pressure changes during periods of $T_{High}$ and

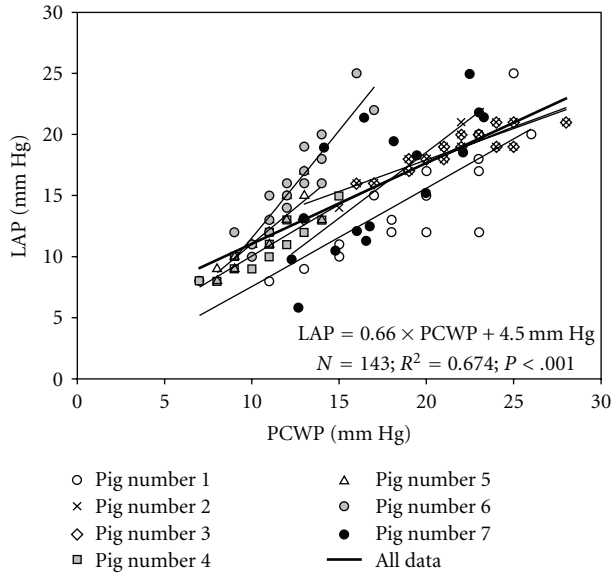


Figure 2: Regression data comparing left atrial pressure (LAP) to pulmonary capillary wedge pressure (PCWP).

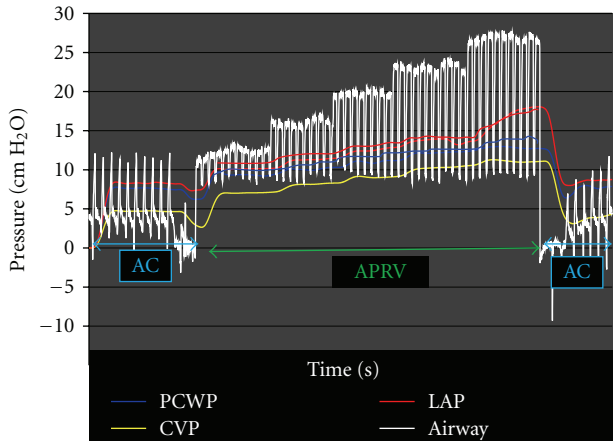


Figure 3: Representation of changes in PCWP and LAP in the same swine model as modes of ventilation change from AC to APRV and back to AC with return of both PCWP and LAP to baseline.

$T_{Low}$, there were no change in the readings of either PCWP or LAP and they remained elevated without drop to baseline.

There were several limitations to this study. First, the swine used had healthy, compliant lungs. APRV is normally used in patients with injured, less compliant lungs. One could argue that compliant lungs would be able to expand further with greater levels of PEEP and increase intrathoracic affects on cardiac compliance. Second, CPAP in APRV is commonly set to levels beyond the 35 cm $H_2O$ maximum used in this study. Therefore, it is unclear how greater CPAP would affect hemodynamic monitoring. Also, without monitoring ITP, we were unable to comment on how this variable affects hemodynamic monitoring. This limitation was due to the fact that attempts at placement of ITP in training models lead to pneumothoraces and attempts at placement were aborted in study model. Despite these limitations, the waveform tracings clearly demonstrate how increased positive pressure increases hemodynamic parameters without any changes in volume status. Future studies with animal models mimicking ARDS are planned to address these limitations and define the change in cardiac output and left ventricular chamber size with APRV.

## 5. Conclusion

PCWP accurately reflects LAP during APRV with increasing CPAP. However, PCWP and LAP may not be accurate estimates of volume. The poor correlation of PCWP to left ventricular end-diastolic volume in patients with elevated PEEP is a well-investigated finding under conventional modes of ventilation and appears to hold true with APRV. Whether this disparity is secondary to the hypothetical influences of ITP or cardiopulmonary compliance has yet to be demonstrated.

## Abbreviations

ALI: Acute lung injury
ARDS: Acute respiratory distress syndrome
APRV: Airway pressure release ventilation
CVP: Central venous pressure
CPAP: Continuous positive airway pressure
ITP: Increases in intrathoracic pressure
LAP: Left atrial pressure
LV: Left ventricle
LVEDP: Left ventricular end-diastolic pressure
MAP: Mean arterial pressure
PAC: Pulmonary artery catheters
PEEP: Positive end-expiratory pressure
PCWP: Pulmonary capillary wedge pressure
RA: Right atrial
RV Right ventricle
RVR: Right ventricular resistance.

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*Review Article*

# Clinical Applications of Heart Rate Variability in the Triage and Assessment of Traumatically Injured Patients

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Heart rate variability (HRV) is a method of physiologic assessment which uses fluctuations in the RR intervals to evaluate modulation of the heart rate by the autonomic nervous system (ANS). Decreased variability has been studied as a marker of increased pathology and a predictor of morbidity and mortality in multiple medical disciplines. HRV is potentially useful in trauma as a tool for prehospital triage, initial patient assessment, and continuous monitoring of critically injured patients. However, several technical limitations and a lack of standardized values have inhibited its clinical implementation in trauma. The purpose of this paper is to describe the three analytical methods (time domain, frequency domain, and entropy) and specific clinical populations that have been evaluated in trauma patients and to identify key issues regarding HRV that must be explored if it is to be widely adopted for the assessment of trauma patients.

## 1. Introduction

Heart rate variability (HRV) is defined by the fluctuating time between normal sinus beats (RR intervals) [1] and indicates modulation of the heart rate by the autonomic nervous system (ANS) [2]. Afferent inputs from sensory and baroreceptors within the heart and great vessels, respiratory changes, vasomotor regulation, the thermoregulatory system, and alterations in endocrine function determine ANS influence on the heart [1].

In 1997, a consensus panel issued a set of guidelines regarding the measurement and interpretation of HRV [3]. Changes in HRV are now an accepted method of assessing autonomic dysfunction in patients in several pathologic states, with and without structural heart disease. In the 14 years since that report, there have been major technological advances and hundreds of publications in various patient populations, but there has been no comprehensive review specifically directed at trauma. This paper attempts to fill that gap.

It is now well established that absence of HRV is an early predictor of brain death [4, 5] and that low HRV correlates with increased mortality and morbidity after trauma [6–13]. Abnormal HRV is associated with increased intracranial pressure and decreased cerebral perfusion pressure [5, 9, 10, 14, 15]. Recently, it was suggested that HRV is a "new vital sign" and could be used as a trauma triage tool [7, 8, 11, 16, 17]. However, the mechanisms responsible for these associations are not clearly established, and no specific therapy is currently available to treat patients with abnormal HRV. Furthermore, there is no consensus on exactly how to measure HRV. Typically, it is quantified using at least one of three analysis domains: time, frequency, or entropy. Despite its enormous potential for assessment and triage, HRV has not been widely adopted in trauma patients. This paper will attempt to address the reasons for this and explore the major advances in various analytical techniques since the initial consensus report on HRV was issued in 1997.

## 2. Methods

*2.1. Literature Search and Retrieval.* The U.S. National Library of Medicine (Pubmed) Database was queried from January 1997 to August 2010 using the following keywords alone or in combination: "heart rate variability," "trauma,"

Table 1: Definitions of time-domain metrics of heart rate variability.

| Variable | Abbreviation | Description |
|---|---|---|
| Standard deviation of normal-normal RR intervals (NN) | SDNN | Measures the standard deviation of RRI for an entire measurement [3] |
| Standard deviation of average NN interval | SDANN | Measures the standard deviation of RRIs for short segments of ECG (usually 5 minutes) [3] |
| Root mean squared successive difference | RMSSD | Calculation of the square root of the mean squared differences in successive RRIs [3] |
| Proportion of successive NN intervals >50 ms | pNN50 | Number of the number of interval differences of successive NN intervals >50 ms divided by total number of NN intervals [3] |
| Integer heart rate variability/heart rate volatility | HRVi | Calculation of the standard deviation of the integer heart rate for 5-minute increments [11, 15, 19–21] |
| Cardiac volatility-related dysfunction/cardiac uncoupling | CVRD | Percentage of time per 24-hour period that HRVi falls within a critically low range (0–0.5 or 0.3–0.6 bpm) [6, 12, 22] |

"volatility," "complexity," "entropy," "heart period variability," "autonomic," "physiology," "high frequency," "low frequency," "time domain," "frequency domain," "nonlinear dynamics," and "triage." Results of the electronic searches were supplemented by recommendation of peers and by reading reference lists of included studies.

*2.2. Inclusion/Exclusion Criteria.* Cohort studies, case control studies, and case series in the English language in adult or pediatric trauma patients were included in this paper. Studies not performed in human trauma patients or case reports were excluded.

## 3. Time Domain

*3.1. Overview.* This method subjects the integer heart rate or the R-R interval to basic statistical analysis (Table 1). Calculations which utilize interbeat (RR) intervals are taken from data sampled at a high rate (>100 Hz). Those derived from the integer HR are sampled less frequently (0.25–1 Hz). All time-domain variables provide information regarding global autonomic function but differ in whether they provide information on short-term variability (SDNN, RMSSD, and pNN50) or long-term variability (SDANN, HRVi) [3, 18].

*3.2. Clinical Applications in Trauma*

*3.2.1. Prehospital.* In 2009, King et al. evaluated ECG data from 75 patients transported by helicopter to a level 1 trauma center to test if HRV could prospectively identify patients who would most benefit from urgent intervention. They reported that SDNN was a more accurate predictor of the presence of major injury and the need for life-saving operation than heart rate, systolic blood pressure (SBP), Glasgow Coma Scale (GCS), or paramedic judgment [16], but real-time data were not available.

*3.2.2. ICU.* In 2004, Grogan et al. published a report on the Signal Interpretation and Monitoring (SIMON) project, a system implemented at Vanderbilt in 1998 for the continuous capture of physiologic data in patients admitted to the trauma ICU. They noted that heart rate volatility (which would later be referred to as integer HRV) and cardiac volatility-related dysfunction (later to be called uncoupling) during the first 24 hours of hospitalization were accurate independent predictors of morbidity and mortality, outperforming traditional vital signs [19]. Since its inception, published reports using data from this system have shown that HRVi and coupling predict mortality with as little as 12 hours of data [11, 20]. Increased uncoupling has been correlated with diminished physiologic reserve (defined as acidosis, coagulopathy, and hemorrhage severity), infection, multiple-organ system failure (MOSF), adrenal insufficiency, traumatic brain injury (TBI), and mortality [6, 11, 12, 20, 22]. These patients are particularly of interest, since they are at risk for multiple conditions associated with autonomic dysfunction such as sepsis, MOSF, adrenal insufficiency, as well as the frequent need for sedation and mechanical ventilation. A 2007 study by Proctor et al. showed that in patients assessed in either the ICU or the resuscitation bay, SDNN and RMSSD were correlated with the presence of TBI on computed tomography (CT) scan of the head as well as mortality [23].

*3.3. Limitations.* There are several drawbacks specific to time-domain analysis. Although data acquired using the SIMON system is available continuously, HRVi and uncoupling are only capable of predicting outcome after data has been acquired for 12 or 24 hours, respectively. SDNN and RMSSD are both depressed by increases in heart rate [18], which suggests the possibility that decreases in these variables with morbidity and mortality are due to tachycardia in severely injured patients. However, these associations have not been shown when the mean heart rate is examined in these studies, suggesting that decreased time-domain variability is not solely a response to tachycardia. Time-domain analysis is also unable to distinguish between distinct biological signals [18], and more sophisticated measures such as frequency analysis are able to distinguish the effects

Table 2: Definitions of frequency-domain metrics of heart rate variability.

| Variable | Abbreviation | Description | Interpretation |
|---|---|---|---|
| Total power | TP | Total power of periodic oscillations in the ECG signal—represents total RR interval spectral power | Global measure of autonomic function [3] |
| High frequency power | HF | Power spectral density of high-frequency oscillations (0.15–0.4 Hz) | Function of respiratory rhythms under vagal (parasympathetic) regulation [18, 24, 31] |
| Low frequency power | LF | Power spectral density of low-frequency oscillations (0.04–0.15 Hz) | Baroreceptor reflex-related modulation of cardiac pacemaker activity via sympathetic and parasympathetic stimulation [4, 18, 31] |
| Very low frequency power | VLF | Power spectral density at very-low-frequency oscillations (<0.04 Hz) | Associated with vasomotor, thermal, and humoral regulation via sympathetic nerve activity [24, 31] |
| Low/high frequency ratio | LF/HF | Ratio of low-frequency power to high-frequency power | Represents ratio of sympathetic to parasympathetic nerve activity [31] |

of different ANS components on regulation of the heart rate.

## 4. Frequency Domain

*4.1. Overview.* This method involves analysis of the oscillations of RR intervals over time. Data are recorded at high frequency (>125 Hz) and the recording audited for ectopic beats and electrical artifact prior to analysis [24]. The digitized ECG tracing is analyzed such that the entire wave form is represented as the sum of periodic sine waves of different frequencies (Table 2) adjusted with respect to amplitude and phase so that the final sum replicates the original data [24]. This is done using mathematical processes such as continuous wavelet transformation (CWT), fast Fourier transform (FFT), and complex demodulation (CDM). The various energies that contribute to the heart rate impulse are grouped into three different peak levels, based upon their location on the power spectrum. Each peak corresponds with a different component of the ANS.

*4.2. Clinical Applications in Trauma*

*4.2.1. Prehospital.* In 2006, Cooke et al. demonstrated that an increase in the HF/LF ratio was associated with increased mortality in a series of 42 patients transported by helicopter to a trauma center [7]. In a similar study evaluating the prehospital ECG data of 31 patients in 2009, Batchinsky et al. showed that HF amplitude (HFA) distinguished survivors from nonsurvivors with a data set as small as 100 beats [25]. HFA, an assessment of the amplitude of the oscillations in the HF range derived via CDM, was found to be a reliable predictor despite reductions in data set length or changes in patient status during the recording. This makes it a practical solution for the prehospital trauma setting where the average length of recording may be as little as one minute or 100 beats in length and the patient's condition is dynamic [25].

*4.2.2. TBI.* The majority of the research on HRV in the frequency domain in trauma has focused on TBI patients. Goldstein et al. published several reports in children demonstrating suppression of LF and HF in association with brain death, decreased GCS, severity of neurologic injury, and poor outcome [4, 26]. Other studies in children have demonstrated that decreases in LF/HF are correlated with increases in intracranial pressure (ICP) greater than 30 mmHg, decreases in cerebral perfusion pressures (CPP) below 40 mmHg, and increased mortality [5]. Multiple subsequent studies in adults with TBI have shown that decreases in LF, HF, LF/HF, and total power (TP) are associated with brain death, increased mortality, decreased CPP, increased ICP, and poor outcome [10, 27–29]. Patient with decreased frequency-domain values in the postinjury period exhibited a prolonged duration of rehabilitation and neurologic recovery [30]. Regardless of the age group studied, frequency-domain variables have been proven to be indicative of severity and accurate predictors of outcome in TBI patients.

*4.3. Limitations.* Frequency-domain analysis is more sensitive to artifact or ectopy than the statistical time-domain methods. Since it is not feasible to screen patients for ectopy prior to monitoring in a trauma setting and ectopy has been shown to be common in healthy volunteers and trauma patients [32], this would appear to limit the utility of this method in the prehospital triage of trauma patients. Assumptions of stationarity and periodicity must be fulfilled, meaning that the overall condition of the patient must not change during the recording and the signal must be comprised of oscillations [18]. Long-term recordings of frequency-domain variables are not as useful, since the detailed information given about specific ANS components is obscured when recordings are averaged over long periods [3].

## 5. Entropy Domain

*5.1. Overview.* This method analyzes overall disorder or randomness in the ECG signal. It encompasses numerous methods which are summarized in Table 3. Nonlinear dynamic methods can be applied to the R-to-R interval to assess the complex variability present within the signal

Table 3: Definitions of entropy metrics of heart rate variability.

| Variable | Abbreviation | Description | Interpretation |
|---|---|---|---|
| Approximate entropy | ApEn | Measures the amount of irregularity in the RRI signal [40, 41] | Lower value reflects less complex signal |
| Sample entropy | SampEn | | |
| Multiscale entropy | MSE | The sum of sample entropies [37] | |
| Similarity of distributions | SOD | The probability of similar RRI signal amplitude distributions as a function of time [33] | Higher SOD reflects more similarity and less complex regulation |
| Point correlation dimension | PD2i | Measures time-dependent changes in the degrees of freedom of a data set [33] | Lower value signifies loss of regulatory complexity |
| Fractal dimension by dispersion analysis | FDDA | Determines the fractal organization of the signal; measures self-similarity in the signal structure [41] | Lower value implies lower complexity of signal regulation |
| Fractal dimension by curve lengths | FDCL | | |
| Detrended fluctuations analysis | DFA | Determines fractal-like correlation properties and uncovers short- and long-range correlations within the signal [42] | Distinguishes between fluctuations generated by complex systems and those arising from external stimuli |
| Signal stationarity | StatAv | Assesses whether the mean and SD of the signal change during time in each data set [8] | Lower value reflects a more stationary signal |
| Symbol dynamics entropy | SymDyn | Measures the probability of certain patterns within the RRI time series [33] | Lower value implies a more predictable signal with less complex regulation |
| Percentage of forbidden words | FW | | |
| Symbol distribution entropy | DisnEn | | |

[33]. All measures of entropy are a global representation of autonomic nervous system functioning and complexity. The entropy methods quantify the probability of a repetitive pattern in the RR interval. If the next pattern can be predicted from the previous section, the signal is considered low in entropy and is therefore less complex [34]. The most commonly used variables are approximate entropy (ApEn) and sample entropy (SampEn), which are a reflection of the amount of irregularity in the R-to-R interval. Calculation of entropy can be accomplished with the use of proprietary software such as WinCPRS software (Absolute Aliens Oy, Turku, Finland) [13, 35, 36] and MATLAB 5.3 (the MathWorks, USA) [37] or by importing integer HR data into a publically available algorithm derived by Costa et al. at http://www.physionet.org/ [38, 39].

### 5.2. Clinical Applications in Trauma

*5.2.1. Prehospital.* The first study with use of heart rate complexity in trauma in the prehospital setting originated at the Army Institute for Surgical Research [8]. A total of 117 patients were screened in the prehospital setting for ectopy-free, 800 beat ECG segments, but only 31 patients met criteria. The data showed that prehospital loss of RR interval complexity as measured by ApEn, SampEn, FDDA, and DFA distinguished survivors from nonsurvivors. ApEn outperformed traditional vital signs such as heart rate and blood pressure and was an independent predictor of in-hospital mortality [8]. In a follow-up study published two years later, the same cohort of patients was re-examined using slightly different methodology. They found that SampEn was consistently associated with mortality down to a data set size of 200 beats and was the only independent predictor of mortality [25]. These data suggested that SampEn may still be useful as an overall reflection of complexity in settings where longer sections of ECG cannot be obtained.

The same group conducted another study in the prehospital setting with regard to life saving interventions (LSI). LSI was defined as endotracheal intubation, cardiopulmonary resuscitation, cricothyroidotomy, and needle decompression. Complexity measures (ApEn, SampEn, FDDA, and DFA) were all lower in those patients who required LSI. SOD was higher in those patients, which is also consistent with decreased complexity. Because SampEn is relatively unaffected by a decrease in number of beats or RRIs, down to a data set of 200 beats, it may be more useful for emergency triage situations where only short segments of ECG data are available [43]. In 2010, Rickards et al. examined the use of HRV in identifying need for LSI in prehospital patients with normal initial vital signs. Out of multiple time-, frequency-, and entropy-domain variables evaluated only FDCL was associated with the need for LSI on multivariate analysis [17]. Before widespread application in the prehospital setting can be adopted, meaningful real-time interpretation of short interval data must be available.

Table 4: Heart rate variability analysis techniques and their uses in trauma.

| Technique | Description | Metrics | Evidence of changes in trauma | Population |
|---|---|---|---|---|
| Time domain | Estimation of variability using statistics and measures of central tendency [3] | HRVi | ↓ predicts mortality, ICH, adrenal insufficiency [11, 15, 19–22, 36] | ICU |
| | | Uncoupling | ↑ reflects acidosis, coagulopathy, MOSF, AI, severe TBI, ↑ ICP, predicts mortality [6, 9, 12, 22] | ICU |
| | | SDNN | ↓ predicts TBI, mortality, acidosis, LSI [16, 23] | Prehospital<br>ER<br>ICU |
| | | RMSSD | ↓ reflects TBI, hemorrhage, mortality [23, 28, 47] | ER<br>ICU |
| Frequency domain | Calculation of power (amplitude) of contributing frequencies to an underlying signal [18] | TP | ↓ reflects ↑ICP, TBI, prolonged neurologic recovery, need for LSI, mortality, brain death [10, 28, 43] | ICU<br>Outpatient |
| | | LF | ↓ reflects ↑ICP, TBI, hemorrhage, need for LSI, mortality, brain; ↑ reflects ↑CI, HR, MAP death [4, 10, 27, 28, 37, 43, 48, 49]. | ER<br>ICU |
| | | HF | ↓ reflects trauma, ↑ICP, need for LSI, hemorrhage, brain death, and mortality [10, 37, 43, 47, 50, 51] | Prehospital |
| | | LF/HF | ↑ reflects ↑ICP, ↓CPP; ↓ reflects brain death, mortality, hemorrhage, ↓GCS, poor neurologic outcome [5, 7, 10, 27, 48, 51] | Prehospital<br>ICU |
| Entropy | Measurement of overall disorder, randomness, or irregularity of a physiologic signal [18] | MSE | ↓ predicts mortality [13, 35, 36, 45] | ICU |
| | | ApEn | ↓ reflects trauma, burn, hemorrhage, brain death, and ↑ICP, MOSF, predicts mortality; ↑ reflects resuscitation [8, 14, 25, 29, 34, 37, 52] | Prehospital |
| | | SampEn | ↓ reflects trauma, mortality, burn, and hemorrhage; ↑ reflects resuscitation; predicts LSI [8, 25, 43] | Prehospital |
| | | FDCL | ↓ reflects hemorrhage; ↑ reflects resuscitation; ↓ predicts LSI [17] | Prehospital |
| | | FDDA | ↓ reflects need for LSI, hemorrhage, mortality [8, 25, 43] | Prehospital |
| | | DFA | ↓ reflects mortality; predicts LSI [8, 25, 43] | Prehospital |
| | | SOD | ↑ reflects need for LSI, mortality [8, 25, 43] | Prehospital |
| | | StatAv | ↓ reflects mortality [25] | Prehospital |

HRVi: integer heart rate variability; ICH: intracranial hypertension; MOSF: multiple-organ system failure; AI: adrenal insufficiency; TBI: traumatic brain injury; SDNN: standard deviation of normal-normal RR Intervals (NN); RMSSD: root mean squared successive difference; LSI: life-saving intervention; ICP: intracranial pressure; TP: total power; LF: low-frequency oscillations power spectral density; HR: heart rate; CI: cardiac index; MAP: mean arterial pressure; HF: high-frequency oscillations power spectral density; LF/HF: low-to-high-power spectral density ratio; MSE: multiscale entropy; ApEn: approximate entropy; SampEn: sample entropy; SymDyn: symbol dynamics entropy; DisnEn: symbol distribution entropy; FDCL: fractional dimension by curve length; FDDA: fractional dimension by dispersion analysis; DFA: detrended fluctuations analysis; SOD: similarity of distributions; StatAv: signal stationarity; PS2i: point correlation dimension.

*5.2.2. ICU.* Intensivists have traditionally relied on sampling markers of hemodynamic and physiologic status at a single time point and can only compare these values with those collected at other discrete time points [44]. Because heart rate complexity data reflects overall balance of autonomic outflow, responsiveness, and neuroendocrine mechanisms, there is tremendous potential for the use in the care for critically ill patients [45]. Whereas other measures of HRV have correlated with multiple disease states including sepsis [46], multiorgan system dysfunction [29], and adrenal insufficiency [22], entropy has not been studied until recently.

Batchinsky et al. found that entropy, as measured by ApEn and SampEn, was lower in burn patients within 8 hours of admission to the intensive care unit [34]. Decreased ApEn has also been associated with mortality in acute TBI [37]. Norris et al. have investigated another measure of complexity in the intensive care unit, multiple-scale entropy (MSE). They found that MSE was significantly lower in nonsurvivors and was predictive of mortality using as little as 3 hours of heart rate data [36]. MSE measured within the first 24 hours was able to identify trauma patients at risk of in-hospital death [13]. Subsequent studies have correlated decreased MSE and beta-adrenergic receptor polymorphisms with increased mortality [35] and have shown that MSE predicts mortality independent of probability of survival based on location and mechanism of injury [45].

*5.3. Limitations.* Despite the overwhelming evidence of associations between heart rate complexity and numerous clinical outcomes, measurement and interpretation have limitations. A major constraint for clinical use is the fact that data needs to be analyzed off line with the use of proprietary software or algorithms. At this point, there is no way to conduct real-time evaluation of complexity data, and nearly all of the studies have been done retrospectively. In addition, analysis of ECG data requires that they be free of ectopy. If ectopic beats are encountered in a data set, the data must either be excluded, or the beat must be replaced via linear interpolation [33, 36]. The removal of patients with ectopic beats from analysis can introduce selection bias into the sample [3].

## 6. Summary

There are at least 23 different variables using the 3 different methods of analysis that reflect HRV (Table 4), each with strengths and weaknesses. Decreases in HRV in trauma patients indicate significant injury or pathology and accurately predict morbidity and mortality. However, there are multiple challenges which must be overcome before HRV can become a routine monitoring and triage tool in trauma. The key issues for future investigations are

(1) how to implement HRV in the triage of civilian and military trauma,

(2) guidelines for the monitoring and assessment of trauma patients using HRV,

(3) development of normal values and thresholds for treatment,

(4) target values for resuscitation.

If HRV is to be a useful tool, real-time, simplified variability data must be made available to medics and physicians. Multiple wireless vital signs monitoring technologies are currently in development, several of which are able to provide continuous measurements of variability. Future trials integrating these devices into the triage and treatment of trauma patients will determine the clinical utility of HRV.

## Acknowledgments

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*Review Article*

# Recommendations for Haemodynamic and Neurological Monitoring in Repair of Acute Type A Aortic Dissection

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During treatment of acute type A aortic dissection there is potential for both pre- and intra-operative malperfusion. There are a number of monitoring strategies that may allow for earlier detection of potentially catastrophic malperfusion (particularly cerebral malperfusion) phenomena available for the anaesthetist and surgeon. This review article sets out to discuss the benefits of the current standard monitoring techniques available as well as desirable/experimental techniques which may serve as adjuncts in the monitoring of these complex patients.

## 1. Introduction

This review encompasses our opinions and recommendations regarding haemodynamic and neurological monitoring during the conduct of acute type A dissection repair (ATAAD) and centre around the detection and avoidance of intraoperative malperfusion. The review covers the conduct of operation and monitoring that is relevant for most institutions that are not major tertiary aortic centres. We have not considered pharmacological and anaesthetic techniques of management of the dissection patient as this topic is beyond the remit of this review.

The pragmatic Stanford classification of aortic dissection assigns the descriptor type A to those dissections involving the ascending aorta (which in the majority of cases require emergency surgical repair) while type B categorises those dissections not involving the ascending aorta (which are often initially managed medically). ATAAD incorporates types I and II of the DeBakey classification (type I ascending and distal aorta and type II ascending aorta only) while Stanford type B dissections, which arise usually distal to the origin of the left subclavian artery are analogous to DeBakey-type III lesions (Figure 1). Within the type A category, the DeBakey-type I dissection can be regarded as more sinister than type II because of the increased propensity for malperfusion phenomena and patency of a residual false lumen after any surgical repair. ATAAD is highly lethal when managed conservatively. Historically, mortality has been approximated at 1-2% per hour following symptom onset with up to 90% mortality within 30 days [1–3]. This excessive mortality is due to intrapericardial rupture with tamponade, acute severe aortic regurgitation with heart failure secondary to acute left ventricular volume overload, malperfusion of the coronary, central nervous or visceral circulation, and rupture beyond the pericardium.

Despite excellent results from individual surgeons and expert centres [6, 7] and advances in anaesthetic, perfusion, and surgical techniques [8], in general, operative outcomes for ATAAD have remained static with mortality rates from large databases that perhaps better reflect "real-world" practice still around 15–30% [2, 9–13]. Despite this, emergency operative repair converts a 90% mortality into a 70% survival chance and as such currently remains the gold standard of care.

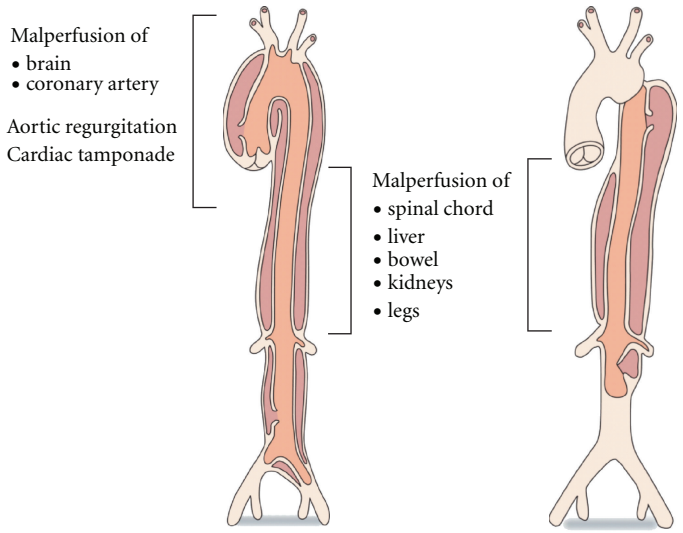


Figure 1: Subtypes and complications of aortic dissection, (a) type A and (b) type B aortic dissections. Type A encompasses Debakey I (ascending aorta only and therefore less potential for malperfusion phenomena) and II and type B Debakey III classifications. Reproduced with permission from Golledge and Eagle [4].

## 2. Aims of Surgery

The aim of surgical intervention for ATAAD is to manage the potentially fatal complications associated with it. These are

(i) intrapericardial rupture and tamponade,

(ii) malperfusion phenomena (coronary, neurological, and visceral),

(iii) acute aortic valve regurgitation.

These aims are achieved by replacement of the ascending aorta (including the aortic root if required) with resuspension/replacement of the aortic valve and excision of the proximal entry tear if possible and obliteration of the distal false lumen.

## 3. The Propensity for Malperfusion: The Crux of Haemodynamic Monitoring

Malperfusion may be defined as a compromise of flow within the aorta or its branch vessels which may lead to end-organ ischaemia (Figure 2). The predominant aetiology relates to pressurisation of the false lumen without a reentry tear. The pressurised false lumen then partially or completely obstructs true luminal flow, jeopardising end-organ perfusion. Usually, this is a dynamic phenomenon. This means that during ventricular systole, preferential false luminal perfusion via a large entry tear occurs and the true lumen collapses leading to malperfusion. Although, pressurisation abates during diastole, end-organ perfusion is still compromised. Other types of malperfusion phenomena may occur with a fixed or static obstruction occurring when the larger false lumen is thrombosed. In other circumstances, thrombosis in low-flow dissected arteries

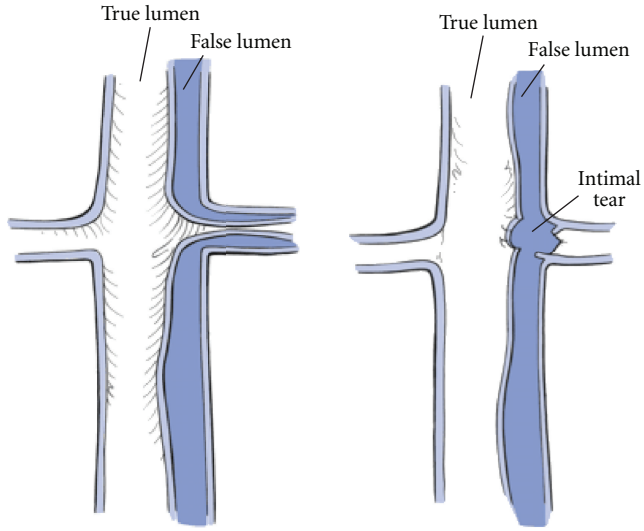


Figure 2: Malperfusion phenomena associated with acute type A dissection, (a) malperfusion is secondary to true lumen compression by the false lumen and (b) occlusion of the branch vessel by extension of the false lumen. Reproduced with permission from Reece et al. [5].

may itself lead to thrombosis while in others complete transection of the intima may lead to intussusception into a vessel with compromise of flow. It is important to differentiate between radiological and clinical malperfusion. Radiological malperfusion is more common and represents apparent embarrassment of flow to branch vessels. However, the prognostic relevance of malperfusion is determined by evidence of end-organ ischaemia and its clinical effects. Therefore, while some embarrassment of innominate artery

flow may be detected on computerised tomography, it is only when this is accompanied by clinically apparent neurological sequelae that patient outcome is affected.

The DeBakey classification adds additional information of relevance to malperfusion in ATAAD. A DeBakey-type II dissection, restricted to the ascending aorta may cause coronary, cerebral and right upper limb malperfusion but by definition, in the absence of aortic luminal compromise, should not contribute to more distal malperfusion phenomena. In contrast, a DeBakey-type I dissection that extends beyond the aortic arch has the additional potential to generate more distal malperfusion phenomena including the left upper limb, spinal cord, viscera and kidneys, and lower limbs.

## 4. When Does Malperfusion Occur?

*4.1. Presurgery Malperfusion.* Malperfusion phenomena may already exist prior to surgery and the timing of their management before, during or after aortic repair is a matter of great debate [14–16]. Moreover, the known presence of malperfusion will affect monitoring strategy. In the International Registry of Aortic Dissection (IRAD) database patients presenting with clinically detectable pulse deficits (carotid or peripheral) have been demonstrated to have a worse prognosis. Pulse deficit has been shown to be an independent predictor of in-hospital mortality, and mortality rate increases with the number of pulse deficits detected [17].

Malperfusion phenomena may worsen during anaesthesia, and it is thus important that anaesthesia should be expeditious, and essential monitoring that could detect any deterioration, particularly of cerebral perfusion status, is rapidly instituted. During surgery there are several crucial timepoints where *de novo* malperfusion may occur and rapid detection is needed to alter surgical strategy and prevent fatality.

*4.2. Malperfusion at Institution of Cardiopulmonary Bypass.* Arterial cannulation at any peripheral sites for example, femoral artery or axillary artery, can, on institution of cardiopulmonary bypass (CPB), precipitate or worsen malperfusion. The retrograde arterial flow towards the heart, even when the cannula lies within the vessel's true lumen, may lead to differential false luminal dominance via a primary or secondary tear, false luminal pressurization, and cerebral, cardiac, or other organ malperfusion. Cerebral malperfusion, at normothermia and during cooling, if sustained will lead to neurological injury. Thus, an otherwise flawless operative strategy with an adequately performed distal anastomosis performed under conditions of hypothermic circulatory arrest (HCA) with or without perfusion adjuncts will have an unsatisfactory outcome unless the phenomenon is detected and corrected. Historically, the femoral artery has often been used for arterial cannulation due to ease of access, size, and ability to achieve adequate flow rates [18, 19]. However, retrograde femoral perfusion carries the risk of pressurisation of the dissection false lumen, leading to compromise of true luminal flow and malperfusion [20–22]. Increasingly the right axillary or subclavian artery has been used for arterial cannulation with well-documented results [23]. Commonly, an 8 mm graft is anastomosed to the artery in an end-to-side fashion which then allows antegrade blood flow during CPB without further aortic manipulation. It may also reduce emboli from an atheromatous aorta or retrograde femoral arterial flow. Such cannulation may have a lower propensity to induce cerebral malperfusion at this stage of the procedure [24] but even this perceived lower risk of malperfusion and retrograde embolism may result in further dissection propagation and malperfusion [25, 26]. Direct aortic cannulation, carotid artery cannulation, and transapical left ventricular-aortic cannulation have all been utilised to try and ensure true luminal flow [27–32]. No method is exempt from generating malperfusion at commencement of CPB. Thus, the institution of CPB is a timepoint for extravigilant monitoring. Detection of malperfusion at this point should prompt the surgeon to change the arterial cannulation site immediately to ensure true luminal flow.

*4.3. Malperfusion Occurring after Aortic Cross-Clamping.* Many surgeons clamp the ascending aorta after the institution of CPB in order to proceed with the proximal aortic repair. Others prefer not to clamp and to undertake a distal anastomosis first without instrumenting the aorta [34]. Clamping may be undertaken even when there is an intention to proceed to hypothermic circulatory arrest (HCA) to undertake an open distal anastomosis. Although comparative studies have shown little difference in patient outcome, placement of an ascending aortic cross-clamp may obstruct communication between true and false lumina leading to false luminal pressurisation and as a consequence, cerebral malperfusion or even aortic rupture. Thus, if clamp placement during cooling is the preferred surgical technique, vigilant monitoring at this time is essential and the proximal aorta should not be opened until surgeon and anaesthetist are satisfied that brain perfusion at least is not compromised.

*4.4. Malperfusion Postdistal Aortic Anastomotic Construction.* A further hazardous timepoint occurs at reinstitution of CPB flow following construction of the distal aortic anastomosis. When the distal anastomosis is constructed, the surgeon attempts to reapproximate the dissected aortic wall and close entry to the false lumen. If peripheral arterial cannulation has been used, there is again the potential for perfusion of the false lumen now closed at the site of the anastomosis. Thus depending upon the position of the anastomosis, false luminal pressurisation and vessel compromise may occur. For this reason, it is recommended that orthograde distal reperfusion is instituted either directly via the prosthetic graft or via a graft side-arm.

For these reasons it is important to have several intraoperative monitoring techniques in order to continuously and rigorously evaluate cerebral perfusion and allow changes to operative decision making should a problem occur.

## 5. The Impact of Cerebral Malperfusion

The incidence of neurological compromise evidenced by cerebral ischaemia and malperfusion at presentation is

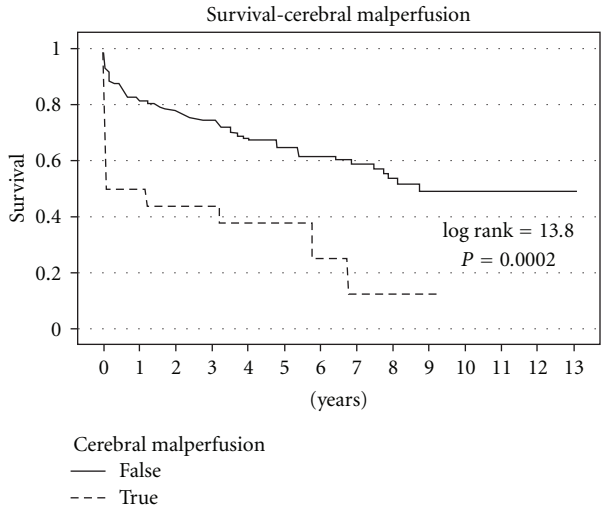


Figure 3: Kaplan Meier survival curves of actuarial survival of patients with cerebral malperfusion syndrome undergoing acute type A aortic dissection repair. Reproduced with permission from Geirsson et al. [36].

quoted to be between 5–14% [9, 35–37] and is associated with poor early and midterm outcomes (Figure 3) [35, 36, 38]. Neurological injury may be secondary to hypotension, malperfusion, or thromboembolic phenomenon. In approximately half of patients with neurological deficits, these are temporary, and in a third of patients the presenting symptom may not be associated with chest pain, which further complicates the diagnosis [39]. Not only are patients with ATAAD subject to neurological compromise at presentation, but surgery itself for treatment of ATAAD is associated with permanent neurological injury rates of as high as 26% depending on the age of the patient with temporary deficit rates of up to 32% [40–42]. A shorter time between symptom onset and surgical reperfusion is associated with improved outcomes particularly if presentation is less than five hours and has a reasonable prospect of limiting stroke progression [43, 44]. A precise cutoff time above which recovery is unlikely is as yet undefined. A ten-hour threshold, below which neurological conservation and recovery may be higher than has been suggested [37, 45] but reperfusion is no guarantee that stroke will be prevented or that full independent rehabilitation will occur [35, 37, 46]. Conscious patients who have either a temporary or permanent neurological deficit have similar outcomes and long-term survival to patients presenting without a neurological deficit and in more than half, the deficit can be expected to improve [36, 37]. However, for patients who are either moribund or comatose due to the consequences of established cerebral malperfusion, operative mortality may be excessively high and nonoperative intervention in such cases may be justifiable.

## 6. Cerebral Protection

The generally accepted repair of ATAAD involves proximal aortic replacement with either aortic valve resuspension or replacement and an open distal anastomosis employing HCA as the mainstay of cerebral protection. The main premise of HCA is that by using profound hypothermia (20°C or below) it is possible to reduce cerebral metabolic requirements enough to allow a period of circulatory arrest during which it is technically feasible to construct the distal anastomoses [47]. HCA enables visualisation of the aortic arch to inspect for intimal tears. However, HCA only allows for limited periods of repair as the rate of adverse cerebral outcomes is closely related to time and the temperature at which arrest occurs [48–51] (Table 2). Adjunctive cerebral protective techniques have been developed in an attempt to reduce the risks associated with HCA and to prolong the potential "safe" duration of arrest. The first adjunctive technique to be used widely was retrograde cerebral perfusion (RCP) which entails retrograde perfusion via the superior vena cava (SVC) during the HCA period [52, 53]. The potential benefits of RCP are of brain cooling, cerebral perfusion, and elimination of embolic debris and metabolites. One of the complications, however, was a potential increase in the incidence of cerebral oedema. Thus it is important to monitor the pressure delivered via the SVC usually measured via the central venous line with a target of 25 mm Hg [54]. In many centres, RCP has been abandoned due to lack of evidence of benefit [25, 55]; however, some centres have documented improved outcomes versus HCA alone [56–58], and it remains a centre-specific adjunct used in an attempt to extend the safe duration of cerebral circulatory arrest.

The more common adjunctive technique now used when surgery is performed on the aortic arch is selective antegrade cerebral perfusion (SACP), which entails selective cannulation of the head and neck vessels, providing either unilateral cerebral perfusion or bilateral perfusion if both innominate and left common carotid are cannulated, either with or without snaring of the left subclavian artery. SACP is intuitively more physiological than RCP, and may provide both cooling and perfusion to the brain, although there were initial concerns over a potential for increase in embolic phenomena. The head and neck arteries are then able to be perfused for the majority of the corporeal arrest period apart from the time taken to insert and remove the cannulae and place the final few sutures. SACP has been demonstrated to reduce the cerebral metabolic deficit accrued following a period of HCA [59] and is widely associated with improving clinical outcomes [60–63]. As yet optimal SACP perfusate characteristics such as temperature, pressure, and flow rates remain undetermined and under investigation [64]. There is significant debate regarding the use of unilateral or bilateral SACP. Unilateral cannulation of either the innominate or the left common carotid only is technically simpler and involves less time and cumbersome equipment in the operative field. It has been demonstrated to produce satisfactory results [65] but has mainly been reported in the context of short arrest durations. Also, it relies upon a complex pre- and perioperative neurological monitoring strategy in order to detect and manage malperfusion, the scope of which is beyond most centres dealing with emergency ATAAD. Unilateral SACP has the potential to result in malperfusion if the patient has an anatomical variation of the Circle

of Willis. In cadaveric studies, between 40 and 50% of the population have anatomical variations, which may be clinically significant in 14 to 40% of cases [66]. There have been no randomised studies between unilateral and bilateral cerebral perfusion, though most authors would agree that for emergency procedures and those with an expected long duration of HCA and SACP, bilateral perfusion is probably a safer option [67].

Over the past decade although an increasing number of cerebral protective techniques have become available, each with the potential to reduce the risk of neurological injury [41]. As yet there have been no universally accepted standards of both haemodynamic and neurological monitoring for repair of ATAAD. The aim of this review is to summarise the available evidence with regard to currently utilised monitoring techniques in ATAAD and to discuss potential novel techniques.

## 7. Aims of Monitoring in ATAAD

Aside from providing vital information with regard to haemodynamic status and conduct of the operation, one of the primary reasons for continuous and detailed monitoring in patients undergoing surgery for ATAAD is to alert anaesthetic, surgical, and perfusion staff to ongoing events and potential catastrophes that may occur during surgery. This enables the teams involved to be aware of potential complications, formulate plans for their management, and be alerted once the patient leaves the operating theatre to problems that may be encountered on the intensive care unit.

There are a number of monitoring techniques employed during the operative management of ATAAD. Due to the emergency nature of this condition, there is very little randomised data providing evidence for such monitoring therefore the following review combines both published available evidence along with our experience-based recommendations in developing practicable monitoring techniques for this condition. From our experience we believe some are essential and others desirable; these are listed in Table 1.

All patients requiring emergent surgery for ATAAD repair should have a minimum standard of monitoring including electrocardiography, arterial oxygen saturations, capnography, arterial blood pressure, urine volumes, central venous pressure, as well as peripheral and core temperatures.

Table 1: Essential and desirable monitoring techniques for use in repair of acute type A aortic dissection.

| *Essential monitoring* |
|---|
| Electrocardiogram |
| Arterial oxygen saturations |
| Peripheral and core temperatures |
| Central venous pressure |
| Pre- and postarch arterial lines |
| Transoesophageal echocardiogram |
| *Desirable monitoring* |
| Pulmonary artery flotation catheter |
| Continuous intra-arterial blood gas monitor |
| Near infrared spectroscopy (cerebral and peripheral) |
| Jugular venous oxygen saturations |
| Transcranial Doppler |
| Electroencephalography |

Table 2: Calculations of the safe duration of hypothermic circulatory arrest (HCA) based on 100% metabolic activity at 37°C and a safe HCA period of five minutes. Reproduced with permission from McCullough et al. [33].

| Temperature (°C) | Cerebral metabolic activity (percentage of baseline) | Estimated safe duration of HCA (minutes (95% CI)) |
|---|---|---|
| 37 | 100 | 5 |
| 30 | 56 (52–60) | 9 (8–10) |
| 25 | 37 (33–42) | 14 (12–15) |
| 20 | 24 (21–29) | 21 (17–24) |
| 15 | 16 (13–20) | 31 (25–38) |
| 10 | 11 (8–14) | 45 (36–62) |

## 8. Essential Monitoring

*8.1. Electrocardiography.* Monitoring of the electrocardiogram (ECG) gives pertinent information to the teams involved in care of the patient with ATAAD. As well as giving basic information on heart rate and rhythm, ECG monitoring with ST segment analysis may allow for diagnosis of coronary malperfusion in the perioperative phase and after the operation is completed give important information with regard to the adequacy of coronary perfusion if root replacement with coronary reimplantation is required.

*8.2. Temperature Monitoring.* Temperature regulation with profound cooling is an essential component of surgery for ATAAD with open distal anastomoses being performed under hypothermic circulatory arrest (HCA). There are a number of temperature sites that can be measured as surrogates of brain temperature. If inadequate brain cooling is performed then the "safe" duration of HCA may not be as long as perceived. There are a number of potential sites at which temperatures may be obtained during cardiac surgery. These include arterial inflow, nasopharyngeal, oesophageal, bladder, skin, rectum, and tympanic membrane. Whilst surrogates of brain temperature, some of these sites may not accurately reflect true brain temperature. Perhaps the best surrogate of brain temperature (and the most invasive) is jugular bulb temperature [68]. In a study by Kaukuntla et al., nasopharyngeal temperature lagged behind arterial inflow and jugular bulb temperature during cooling for HCA with these temperatures all equilibrating at 15°C. During the rewarming phase both arterial inflow and nasopharyngeal temperature lagged behind jugular bulb temperature and the authors concluded that nasopharyngeal temperature is able to act as a safe surrogate for brain temperature although peripheral temperature measurements underestimate brain

temperature and care is therefore required to avoid hyperthermic arterial inflow [69]. Partial rewarming utilising prolonged hypothermia has been demonstrated experimentally to have a better outcome when compared to normothermia [70] and animal studies after HCA have confirmed a worse neurological outcome when rewarmed to 40°C compared to 34°C. Most authors recommend the discontinuation of rewarming at a temperature of 36 to 37°C [71, 72]. We would recommend rewarming to an NP temperature of 36°C with a maximum arterial inflow of 37°C.

*8.3. Choice of Arterial Line.* Due to the potential for malperfusion at varying sites in the aorta, it is important to monitor pressure at more than one site. The brain is the organ most sensitive to malperfusion and therefore detection of this is crucial. Innominate artery blood flow is essential for cerebral perfusion and a simple indicator of this is right radial artery pressure. Depending on the position of the intimal tear, malperfusion of the innominate artery will result in a reduction in right radial pressure which should be closely monitored to detect any potential changes in cerebral perfusion. Malperfusion of the left subclavian artery will result in reduced left radial pressure.

Therefore, the use of bilateral arterial line monitoring one placed proximal and the other distal to the aortic arch is strongly recommended. Changes in the arterial pressures monitored may alert the operating team to malperfusion phenomenon occurring across the aortic arch. These may be a combination of bilateral radial, or right radial and femoral lines. There is some debate whether the arterial monitoring site distal to the arch should be left radial or a femoral artery but there is no data to say which is preferable. Left arm monitoring in the presence of preoperative left subclavian malperfusion will not provide reliable pressure monitoring. Conversely, a distal femoral line may frustrate cannulation site selection, and if iliac malperfusion is present may give false readings of intra-arterial pressure. For this reason our own practice is to use 3-site monitoring when possible; right radial, left radial, and left femoral. This is partly dictated by the surgical choice of arterial cannulation; in our practice the most common scenario is of right axillary or right femoral artery cannulation for arterial inflow to establish cardiopulmonary bypass with bilateral radial arterial lines for monitoring. Where femoral cannulation is used, if pressurisation of the false lumen occurs resulting in cerebral malperfusion, a reduction in right radial pressure may be observed and expeditious alternative arterial cannulation needs to be performed, the most common scenario here is to rapidly transect the ascending aorta, remove the femoral arterial cannula, and place it into the true lumen of the open ascending aorta. An alternative strategy is to use a transapical approach via the left ventricle [73, 74]. Right axillary artery cannulation may carry a theoretically lower incidence of malperfusion but may still propagate the dissection. When the right axillary artery is cannulated directly, right radial artery monitoring no longer provides an index of innominate artery and thus right carotid pressure. When cannulated via an end-to-side graft, radial artery pressures may be increased spuriously and intraoperative pressure monitoring then becomes dependent upon monitoring at other sites, that is, left radial or femoral pressure. For this reason, pressure monitoring alone, when right axillary cannulation is used, is insufficient to monitor for evidence of malperfusion. It is important to heed and interpret any arterial line which reveals a low pressure and seek a cause.

*8.4. Transoesophageal Echocardiography.* The use of transoesophageal echocardiography (TOE) has become commonplace in cardiac surgery, and many would regard it as an essential monitoring technique during surgery for ATAAD as well as being able to guide diagnosis [75–77]. Caution should be exercised on passage of the TOE probe as there is potential for acute haemodynamic compromise on insertion. In the face of haemodynamic instability, insertion of the TOE probe should be deferred until the patient is haemodynamically stable. In the preoperative phase, TOE [73, 78] can be used to assess the presence of pericardial fluid, aortic valvular competence, and regional wall abnormalities resulting from coronary ischaemia [79, 80] as well as also being a diagnostic tool in detecting the aortic dissection flap. It can also be used to assess the presence of atheroma in the descending aorta which is important if femoral arterial cannulation is planned and the IRAD group has demonstrated that TOE is able to add prognostic information above that gained from clinical risk factors at diagnosis [81]. In addition, TOE has been used to monitor cerebral and visceral malperfusion by direct visualisation of arch and visceral vessels to alert surgeon and anaesthetist to the development of malperfusion phenomena [82, 83]. Furthermore, Voci et al. have reported a technique of albumin microbubble injection via a side-port in the bypass circuit to aid in detection of true/false lumen detection at the time of institution of retrograde femoral perfusion. Detection of isolated false lumen perfusion utilising TOE can facilitate alternative cannulation strategies to minimise potential complications [84]. In the perioperative phase it may be used to position a femoral venous drainage cannula. after repair and separation from CPB, it is used to assess the competence of aortic valve resuspension, assess cardiac function, regional wall motion abnormality, and filling status.

## 9. Intraoperative Blood Gas and Lactate Measurement

All patients undergoing surgery for ATAAD will undergo routine sampling of arterial blood gases via the in-dwelling arterial line. Information available from this includes ventilatory status, haemoglobin, and haematocrit estimation as well as acid-base status. Mixed venous oxygen saturation sampled from the cardiopulmonary bypass circuit gives an indication of global organ perfusion. Evidence of ongoing profound lactic acidosis may alert the team to the possibility of malperfusion phenomenon either related to limb or visceral ischaemia [85]. Examination of the peripheral circulation may demonstrate peripheral ischaemia, potentially secondary to femoral artery cannulation. In extreme circumstances, extension of the median sternotomy via laparotomy may be required to assess and address visceral ischaemia.

## 10. Desirable Monitoring

*10.1. Pulmonary Artery Catheter.* Pulmonary artery catheterisation for thermodilution cardiac output and mixed venous oxygen saturation monitoring is highly desirable, but the timing of catheter flotation is discretional and should not delay surgery in a haemodynamically compromised patient. However, during line placement, expeditious insertion of an additional sheath for later pulmonary artery catheterisation is our preferred technique. Recent evidence from a meta-analysis in patients undergoing intermediate and high risk surgery [86] shows that preemptive haemodynamic optimization with a PAC may reduce mortality in some high-risk settings, but we would stress that preoperative optimization with a PAC is not always appropriate in the case of acute type A aortic dissection, where the priority is emergency surgery which should not be delayed. Flotation of a PAC is, however, desirable after separation from cardiopulmonary bypass when it can be used to best direct volume replacement and inotrope/vasoconstrictor requirements. Time spent undertaking preemptive haemodynamic optimisation is inappropriate if the cause of instability is tamponade or coronary malperfusion. In those situations we believe that rapid surgical relief of tamponade and coronary reperfusion are most likely to achieve better patient outcomes.

*10.2. Continuous Intra-Arterial Blood Gas Analysis.* Technology is available for continuous intra-arterial blood gas analysis [87]. During cardiac and aortic surgery this technology has been demonstrated to be accurate and allow for early detection of changes in acid-base status [88, 89]. Although these technologies are not commonplace, they may allow for more detailed monitoring and recognition of malperfusion in patients undergoing surgery for ATAAD.

The vast majority of desirable monitoring techniques fall under the category of neurological monitoring. These techniques are mainly utilised and unlikely to be found outside large specialised aortic centres with an interest in neurological protection during aortic surgery.

In order to optimise cerebral protection during surgery for repair of ATAAD, whether or not standard HCA or adjunctive SACP are being used, it is important to monitor surrogates of cerebral blood flow and metabolism. There are now a number of techniques available for such purposes. These techniques require varying degrees of expertise.

## 11. Surrogate Measures of Cerebral Flow and Metabolism

*11.1. Transcranial Doppler.* Transcranial doppler (TCD) is used to measure middle cerebral artery velocity (MCAV) via an acoustic window in the temporal bone. MCAV is used as a surrogate for cerebral blood flow and may be useful in arch surgery using RCP or SACP to monitor changes in blood flow. Changes in TCD velocity mirror changes in CBF but do not provide a direct measurement of CBF [90]. It is a noninvasive technique, using Doppler ultrasound, with the ability to obtain reasonable signals in 95% of individuals. It does require a limited amount of training, however, and for this reason its use is largely limited to research studies [59, 91]. On occasion, reversal of MCAV signalling may be detected in RCP [92] and in this circumstance has been used as an index of RCP adequacy. In a nonrandomised study, TCD utilised as an adjunct in patients undergoing ATAAD repair altered operative cannulation strategy and RCP perfusion in 28.5% and 78.6% of cases, respectively. Patients managed with TCD were also noted to have a reduced incidence of temporary neurological deficit [91]. TCD is not routinely used in ATAAD surgery for several reasons: (i) it requires a level of expertise and experience for correct signal acquisition, (ii) placement may be time consuming and inappropriate in ATAAD, (iii) loss of signal may occur due to minor displacement of probes and intraoperative correction once on bypass is difficult, and (iii) during periods of low flow, signals may be relatively poor and it may be difficult to differentiate between cerebral hypoperfusion and technical issues. However, as technology improves it can be expected that cerebral perfusion monitoring will play an increasing role.

*11.2. Orbital Ultrasound Monitoring.* Doppler imaging allows for visualisation of orbital vessels [93]. It is noninvasive, inexpensive, and able to provide realtime information. Reductions in central retinal artery flow have been demonstrated to be associated with carotid artery stenosis [94], and maximal velocity within the CRA is correlated to perfusion pressure [93]. The absence of flow within the CRA and retrobulbar vessels has been demonstrated to be related to both transient and permanent neurological deficit. Absence of CRA flow for more than 100 minutes is associated with temporary neurological deficit and in a parallel with the data associated with neurological injury following 40 minutes of HCA, permanent neurological deficit has been observed in patients with an absence of retrobulbar flow for similar time periods [95]. Orbital ultrasound monitoring may have a role in monitoring during periods of selective cerebral perfusion with recommendations that perfusion pressures should be maintained to allow for detectable orbital Doppler flow. However, currently, this technique is not in widespread use.

*11.3. Electroencephalography.* The electroencephalogram (EEG) represents electrical activity within the cerebral cortex. In noncardiac surgery it has been demonstrated to be both a sensitive and specific means of detecting cerebral hypoperfusion and ischaemia [96–98]. It is used in some aortic centres in order to monitor cerebral metabolic activity during aortic surgery [78, 99, 100], but may not be in common use during the emergent situation of ATAAD. During cooling, EEG activity is seen to decrease until electrocerebral silence occurs usually around temperatures of 15–18°C, or after 45–50 minutes of cooling. Alterations to EEG activity prior to this may indicate interruption to cerebral blood flow due to malperfusion allowing for early detection of malperfusion but once electrocerebral suppression has been achieved by cooling and anaesthesia, EEG monitoring cannot provide further guidance on the possibility of ongoing ischaemia; an important technical limitation. Technically, however, use of EEG monitoring is largely limited by its availability and

logistical issues and is not always suitable for emergency cases. It is also affected by interference from diathermy and other electrical equipment. However, if routinely and expeditiously available, it should be used.

*11.4. Near-Infrared Spectroscopy.* Near-infrared spectroscopy (NIRS) provides continuous monitoring of regional cerebral tissue oxygen saturation ($rCSO_2$), it is noninvasive and a simple means of monitoring trends in $rCSO_2$. In combination with multisite pressure monitoring it is our preferred technique for cerebrospecific monitoring in ATAAD. It involves placement of two single use adhesive patches on the forehead, avoiding the sinuses and temporal muscles. Near-infrared light is largely absorbed in tissues by oxygenated and deoxygenated haemoglobin. Absorption is proportional to the concentration of the haemoglobin and thus tissue saturation can be derived. The majority of the blood in the region of the cortex monitored is venous blood. Therefore, changes in $rCSO_2$ reflect imbalances in either oxygen supply or consumption. Mean tissue oxygen saturation are estimated to be approximately 60–70%. It has demonstrated good reproducibility, and is being used more widely. In coronary artery bypass surgery use of monitoring of $rCSO_2$ avoids cerebral desaturation and is associated with a reduction of major organ dysfunction. In this trial by Murkin et al., the control group of patients had $rCSO_2$ monitoring but without intervention. In the intervention group most commonly fall in $rCSO_2$ was corrected by increased pump flow, increased mean arterial pressure, or normalization of $CO_2$ changes in levels of $CO_2$ may be pertinent in NIRS as the cerebral vasculature is sensitive to changes in levels of $CO_2$ and changing concentrations can lead to alterations in cerebral blood flow which may be detected by NIRS. A significantly greater number of patients in the control group experienced a composite endpoint of major organ morbidity or mortality. Control patients also had longer periods of cerebral desaturation and longer intensive care unit stay as well as a trend towards increased overall increase in length of hospitalization. Patients with major organ morbidity or mortality had lower baseline and mean $rCSO_2$ more episodes of cerebral desaturation, and longer intensive care and hospital stay [101]. Realtime monitoring with NIRS has also been utilised as a tool to detect cerebral malperfusion and change intraoperative strategies during aortic surgery [102]. However, data obtained in the form of $rCSO_2$ needs to be interpreted with caution. Depth of penetration is limited to about 2 cm with only around a 60% contribution from the capillary bed, thus it only monitors anterior cerebral blood flow and is therefore limited in detecting embolic events and hypoperfusion in the basilar region of the brain [103, 104]. Its main use is therefore in detecting global and differential hemispheric changes. The data available from NIRS is subject to a number of intrinsic and extrinsic factors. Variables which are known to effect $rCSO_2$ include haemoglobin concentration, arterial blood pressure, temperature, systemic oxygen saturations, and $pCO_2$ [105] all of which may be altered in ATAAD surgery. Hypotension, anaemia, reduced oxygen saturation, and reduced $pCO_2$ as a result of hyperventilation may all result in reduced $rCSO_2$. These variables need to be corrected to accurately interpret the results obtained. Furthermore, there is a lack of predefined values for warning or intervention associated with changes in $rCSO_2$ obtained with NIRS. It has been reported that levels of $rCSO_2$ reductions of greater than 20% from baseline or $rCSO_2$ levels less than 40–50% are associated with hypoxic ischemic neuronal injury [106, 107]. Clinically, it may be more relevant to monitor trends in $rCSO_2$ rather than look at absolute values [105, 108]. In aortic arch surgery using SACP, $rCSO_2$ monitoring can facilitate decision making regarding the number of supra-aortic vessels requiring cannulation. In one report, the use of right axillary perfusion with innominate and left carotid clamping alone was associated with a prompt deterioration of left-sided $rCSO_2$ signal in the majority of patients. This was correctable by the insertion of an additional perfusion cannula within the left carotid, following which left $rCSO_2$signals normalized [109]. As interpretation of $rCSO_2$ signalling is usually based upon relative changes from a stable baseline, its main utility appears to be ensuring that an anticipated effect of perfusion and cooling is achieved without major hemispheric discrepancies. At present an absolute or relative value at which safe brain arrest can be commenced is not available. However, a unilateral progressive discrepancy in $rCSO_2$ signalling, during the conduct of an ATAAD should raise major concerns that malperfusion is occurring.

*11.5. Jugular Venous Oxygen Saturation.* Jugular bulb venous oxygen saturation ($JbSVO_2$) monitoring may be used as an index of cerebral metabolic suppression. The normal JbSVO2 of a fully anaesthetised patient approximates 55–65% [110]. Provided oxygen delivery is normal with arterial $SaO_2$ approximating 98–100%, the $JbSVO_2$ reflects transcranial oxygen extraction. A low level is indicative of increased extraction or low flow and is a warning signal of inadequate perfusion. Reduction in jugular venous saturations ($JbSjVO_2$) implies an imbalance between cerebral blood flow (CBF) and cerebral oxygen consumption ($CMRO_2$). To achieve $JbSjVO_2$ desaturation either CBF must be reduced or $CMRO_2$ increased. $JbSjVO_2$ does not correlate well with mixed venous oxygen saturations [111]. In aortic dissection, low initial $JbSVO_2$ may be an index of either low cardiac output due to tamponade and cardiac insufficiency or cerebral malperfusion and if uncorrected may be associated with worse outcome.

During ATAAD surgery, cooling on bypass is a usual part of the brain protection strategy; during cooling, the $JbSVO_2$ rises. This is for two reasons, first as a direct consequence of hypothermic metabolic suppression and second due to increased haemoglobin avidity for oxygen in hypothermic conditions shifting the oxygen-haemoglobin dissociation curve leftwards and thereby reducing the P50. During CPB cooling, the $JbSVO_2$ has a linear inverse relationship with the cerebral metabolic rate for oxygen ($CMRO_2$) relative to baseline [71]. Thus, as $CMRO_2$ decreases, $JbSVO_2$ rises. A $JbSVO_2 \geq 95\%$ correlates with a $CMRO_2$ of <20% of CMR at 37°C and once this level of $JbSVO_2$ is attained, the medical team can be assured that near-maximal clinically practicable metabolic suppression has been achieved and

that it is safe to commit to a period of hypothermic circulatory arrest (subject to the time-limitations of HCA noted above). If a jugular bulb line is in place, the 95% $JbSVO_2$ threshold as a trigger to permit onset of HCA is a practical use of cerebral monitoring if isolated HCA without perfusion adjuncts is to be used as the mainstay of brain protection. However, there is little data in the literature to guide $JbSVO_2$ monitoring targets if arrest is to be undertaken at a higher temperature with early institution of SACP. Interestingly, the precise relationship between $JbSVO_2$ and NIRS $rSCO_2$ has not been defined, although the two have been demonstrated to be closely linked in a physiological clinical study [112]. Cutoffs for commitment to HCA using $rCSO_2$ are not available. Importantly, unilateral placement of a jugular bulb line will provide no information of differential hemispheric perfusion. It cannot therefore be used as a detection monitor for contralateral malperfusion. Its main role is in circumstances when bilateral carotid perfusion is assured and here it provides evidence of global perfusion. We are not aware of any studies using bilateral clinical bulb line monitoring.

The placement of a jugular bulb line is a relatively facile technique. The line is a simple central venous catheter and is inserted retrogradely through the internal jugular vein and positioned in the jugular bulb. As the line is advanced, gentle suction is applied on a connected syringe and once the jugular bulb is reached, a loss of resistance is felt within the syringe mechanism with increased ease of aspiration at low suction pressure. Usually, the left internal jugular vein is used for jugular bulb line placement assuming the right internal jugular will be used for the CVP and pulmonary artery catheter. Measurements of $JbSVO_2$ can then be obtained either continuously or intermittently [113]. Although $JbSVO_2$ allows monitoring of global oxygenation it does not provide regional information and is unlikely to detect focal events. Consequently, it is also not used to assess adequacy of SACP. If $JbSVO_2$ and EEG are not available but HCA is the intended brain protection strategy, our protocol is to cool on $2.4\,L\cdot min^{-1}\,m^{-2}$ flow cardiopulmonary bypass, using a 7°C maximum temperature exchange difference for at least 50 minutes to a nasopharyngeal temperature of 15°C [79]. This duration and depth of cooling is known to be sufficient to achieve electrocerebral silence and attain $JbSVO_2 \geq 95\%$ in the vast majority of patients and represents a practical guide when additional monitoring is not available.

After HCA, jugular venous saturations initially fall considerably and proportionately with the oxygen debt generated by the period of HCA. After a period of 5–15 minutes of rewarming, $JbSVO_2$ levels then gradually rise as the cerebral metabolic debt is repaid until prebypass values are restored. Beyond this timepoint, $jbSVO_2$ levels may fluctuate with changes in oxygen delivery and cardiac instability, reflecting the vulnerability of the recovering postischaemic brain to additional ischaemic insults. Although $JbSjVO_2$ is a useful technique, setup time is significant and it may therefore not be a practical monitoring technique in the acute setting of ATAAD except in the most stable patients.

## 12. Measures of Microcirculation and Regional Blood Flow

The majority of clinical monitoring tools used in the operating theatre and intensive care unit for assessment of cardiovascular performance evaluate global haemodynamics but these may not reflect derangements in regional organ perfusion. Tissue metabolic stress is dependent on microcirculatory flow and there are now a number of methods for examining microcirculatory perfusion that have been evaluated in the intensive care setting; these include microdialysis, laser doppler flowmetry, and side-stream dark imaging of mucosal capillary flow [114–116].

In terms of cardiac surgery, the most investigated and potentially most useful tool in monitoring of visceral blood flow is gastric tissue oxygenation and tonometry. Hypothermic CPB with nonpulsatile flow leads to somewhat predictable decreases in visceral blood flow measured by laser Doppler flowmetry and mucosal pH tonometry that could be of utility in the assessment and monitoring of visceral malperfusion during ATAAD surgery [117–121]. However, the use of such devices has to date been on a research basis and whether clinical implementation will prove worthwhile is not clear.

There has been recent interest in the use of near infra-red spectroscopy as a noninvasive measure of distal limb perfusion. The NIRS signal has been validated as an accurate index of perfusion in clinical experiments of brachial artery occlusion and reperfusion and strain gauge plethysmography [122]. It has been used to detect lower limb arterial graft occlusion during vascular surgery [123] and during femoral artery cannulation for minimally invasive cardiac surgery, NIRS demonstrates reductions in tissue oxygen saturations on clamping which are normalised with distal leg perfusion and comparable to the noncannulated side [124]. The detection of acute lower limb ischaemia following femoral cannulation after aortic cross-clamping has also been reported utilising NIRS during aortic surgery [125], and this is a potential regional monitoring technique that could be of utility during ATAAD surgery.

A further technique known as visible light spectroscopy has been used to detect gut mucosal oxygen saturation via probes placed either in the oesophagus or colon [126, 127]. This could potentially be a means of detecting regional mesenteric ischaemia in aortic surgery, although its use appears to be limited to case reports at the present time.

## 13. Conclusion

The propensity for pre- and intraoperative malperfusion during ATAAD surgery necessitates a unique approach to cardiovascular anaesthetic monitoring. The organ at greatest risk is the brain, and monitoring strategies are designed to try and ensure that brain perfusion remains adequate at all times during surgery. However, at the present time, there is no monitoring device available that can measure brain perfusion in all regions intraoperatively and each part of the strategy has limitations.

Our recommendations are evidence based where possible and where not are based upon considerable clinical experience. Individual circumstances including local facilities and expertise will dictate the particular monitoring strategy in each case and in reality evidence of clinical malperfusion is best demonstrated by a combination of techniques.

Our current practice is to use bilateral radial arterial lines and on occasion an additional femoral line, intraoperative transoesophageal echocardiography and bilateral frontal lobe NIRS assessment of $rCSO_2$ as standard in the emergency patient. In more stable patients this may be supplemented by other surrogate measures of cerebral metabolism such as transcranial Doppler and jugular bulb venous oximetry which we use, mainly, as research adjuncts. In addition we monitor nasopharyngeal temperature as a validated surrogate of direct brain temperature during cooling and rewarming [69] and adopt specific management protocols during these phases of the procedure [79]. Finally, all patients are monitored using pulmonary artery flotation catheters once separation form cardiopulmonary bypass has been achieved, thus enabling cardiac output to be optimised. We believe that the strategy we adopt provides as much information as currently possible in the ATAAD setting to detect and correct intraoperative malperfusion by adjustment of cannulation, anaesthetic, and perfusion techniques in an attempt to achieve improved outcomes in this difficult area.

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*Review Article*

# Assessing the Left Ventricular Systolic Function at the Bedside: The Role of Transpulmonary Thermodilution-Derived Indices

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Evaluating the systolic function of the left ventricle (LV) is important in the hemodynamic management of the critically ill patients with circulatory failure. Echocardiography is considered the standard monitor for estimating the LV function at the bedside in the intensive care unit. However, it requires a trained operator and is not a real-time monitoring tool. For monitoring of the systolic function, the pulmonary artery catheter has been the gold standard for a long time. However, now there are alternatives to this device, with transpulmonary thermodilution being one of them. This paper provides an overview of the usefulness of the transpulmonary thermodilution-derived indices for assessing systolic function at the bedside.

## 1. Introduction

Cardiovascular monitoring is essential for diagnostic and therapeutic management of critically ill patients and assessing the systolic function of the left ventricle (LV) is a key component in this strategy.

Echocardiography has become the standard tool for measuring LV ejection fraction (LEVF) at the bedside in the intensive care unit (ICU). This type of monitoring gives the physician a rapid and accurate etiologic diagnosis of the cause of hemodynamic instability in the critically ill patient. Thus, a hemodynamically unstable patient is a good reason to perform a cardiac ultrasound [1]. However, the use of echocardiography requires an expensive device and a trained operator. Additionally, conventional echocardiography cannot be considered as continuous monitoring, and although there is a commercially available continuous model, it has not received widespread acceptance.

The pulmonary artery catheter (PAC) has been the gold standard for monitoring of systolic function for decades, but concerns have been raised about its safety and the clinical usefulness of the data it provides [2–4]; thus, alternative monitoring methods have been evaluated.

More recently, the transpulmonary thermodilution technique with single thermal indicator (incorporated into the PiCCO monitor, Pulsion Medical System, Munich, Germany) was proposed as a "less invasive" hemodynamic monitoring system for critically care patients. The system provides intermittent (transpulmonary thermodilution-derived) and continuous (pulse contour-derived) assessment of cardiac output and estimations of intrathoracic volumes (intrathoracic blood volume, global-end diastolic volume, and extravascular lung water). Accuracy of cardiac output calculation using the PiCCO system has been demonstrated in several clinical studies [5–9] and intrathoracic blood volume (blood volume contained in the heart and in the intrathoracic vessels) and global end-diastolic volume (the volume of blood contained in the four cardiac chambers at the end of the diastole) have been shown to provide reliable and more sensitive estimates of cardiac preload than cardiac filling pressures obtained with the central venous and pulmonary artery catheters [10–17]. On the other hand, the use of the transpulmonary thermodilution arterial catheters do not increase the risk of complications when compared with the commonly used short peripheral arterial catheters or pulmonary artery catheters [18].

The PiCCO system also provides two transpulmonary thermodilution-derived indices of cardiac systolic function: the cardiac function index (CFI) and the global ejection fraction (GEF) which are automatically calculated by the monitor.

*1.1. Calculation of CFI and GEF by Transpulmonary Thermodilution.* A thermistor placed into a femoral, brachial, or axillary arterial catheter measures the downstream temperature changes induced by the injection of a cold saline bolus into the superior vena cava. The monitor calculates cardiac output (CO) from the thermodilution curve, using the Stewart-Hamilton algorithm, and also the mean transit time (MTt) and the exponential down slope time (DSt). The result of the product of CO times MTt is the intrathoracic thermal volume (ITTV):

$$\text{ITTV} = \text{CO} \times \text{MTt}. \quad (1)$$

And the product of CO times DSt is the pulmonary thermal volume (PTV):

$$\text{PTV} = \text{CO} \times \text{DSt}. \quad (2)$$

The difference between ITTV and PTV is the global end-diastolic volume (GEDV) which represents the volume of blood contained in the four chambers:

$$\text{GEDV} = \text{ITTV} - \text{PTV} = \text{CO} \times (\text{MTt} - \text{DSt}) \quad (\text{mL}). \quad (3)$$

The CFI is defined as the ratio of cardiac output to the global end-diastolic volume:

$$\text{CFI} = \frac{\text{CO}}{\text{GEDV}} \quad \left(\text{min}^{-1}\right). \quad (4)$$

The GEF is defined as the ratio of the stroke volume (SV) to the quarter of the global end-diastolic volume:

$$\text{GEF} = \frac{\text{SV}}{(\text{GEDV}/4)} \quad (\%). \quad (5)$$

CFI and GEF are, therefore, global ejection phase indices since they are the ratio of CO or stroke volume to the global end-diastolic volume of the heart. Therefore the difference between the two indices is that GEF takes into account the heart rate and stoke volume, and the GEF only considers the stroke volume. These indices are obtained very easily by the physician at the bedside while only an experienced operator can get similar information using echocardiography [17].

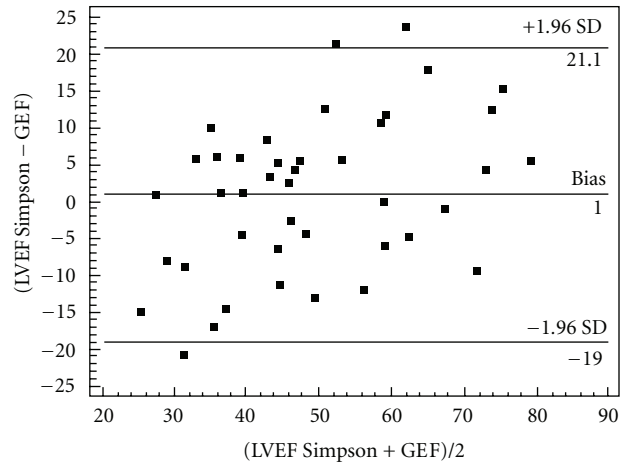
The purpose of this paper is to review the different studies that assess the accuracy of these transpulmonary thermodilution-derived indices for the estimation of left ventricular systolic function in the ICU patients at the bedside.

## 2. Evaluation of the Transpulmonary Thermodilution-Derived Indices with the Echocardiography

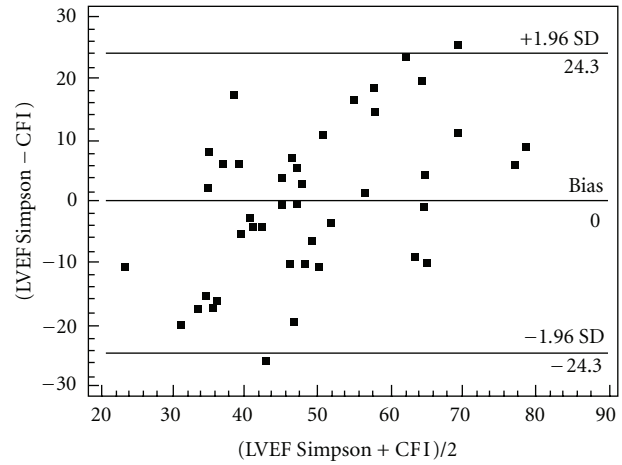
In 2004, Combes et al. used transesophageal echocardiography to compare these indices with left ventricular fractional area of change (LVFAC) [17]. They studied 33 adult ICU patients with no isolated right ventricular dysfunction in a prospective, open clinical study. During the measurements, echocardiography identified 3 patients with isolated right ventricular failure, in which transpulmonary thermodilution underestimated LVFAC. In the results, significant correlations were established between LVFAC and CFI ($r = 0.87$, $n = 30$, $P < 0.0001$) or GEF ($r = 0.82$, $n = 30$, $P < 0.0001$). The mean differences between LVFAC and LVFAC estimated with CFI or GEF were $0.8 \pm 8.5\%$ (range $-17$ to 14%) and $0.8 \pm 9.0\%$ (range $-21$ to 19%), respectively. Area under the receiver operating characteristics curves for the estimation of LVFAC $\geq 40\%$ using CFI or GEF was 0.92. Values of CFI $> 4$ and GEF $> 18\%$ estimated LVFAC $\geq 40\%$ with respective sensitivities of 86 and 88% and specificities of 88 and 79%. Additionally, significant correlations were found between changes of LVFAC and CFI and GEF over time. The authors concluded that in mechanically ventilated ICU patients, GEF and CFI provide reliable estimations of LV systolic function, but may underestimate it in cases of isolated right ventricular failure.

Five years later, Jabot et al. conducted a prospective study in 48 medical ICU patients with acute circulatory failure, to assess whether CFI could actually behave as an indicator of left ventricular systolic function [19]. For this purpose they tested if CFI fulfilled the following criteria: (1) it increased with inotropic stimulation (dobutamine infusion, $n = 24$); (2) it was not altered by fluid loading (500 mL of saline, $n = 24$); (3) it correlated with the echocardiographic left ventricular ejection fraction (LVEF). The authors simultaneously measured LVEF (monoplane or biplane Simpson method) and CFI at baseline, and after saline and dobutamine administration. Volume expansion altered neither LVEF ($47 \pm 11\%$ to $47 \pm 11\%$) nor CFI ($4.5 \pm 2.2$ to $4.5 \pm 2.1\ \text{min}^{-1}$), dobutamine infusion significantly increased LVEF (percentage of change: $32 \pm 28\%$) and CFI (percentage of change: $29 \pm 22\%$). Considering the effects of dobutamine, there was a significant correlation between the changes in CFI and the changes in LVEF ($r = 0.65$, $P = 0.0001$). Finally, a CFI $< 3.2\ \text{min}^{-1}$ predicted an LVEF of $\leq 35\%$ with a sensitivity of 81% and specificity of 88%. The authors concluded that CFI fulfilled the criteria required from a clinical indicator of left ventricular global systolic function and accurately tracked the effects of inotropic therapy.

Finally, our group conducted a prospective clinical study with 35 ICU patients, excluding those with severe changes in contractility and in nonsinus rhythm [20]. We compared these indices with the left ventricular ejection fraction obtained by transthoracic echocardiography. In the results we found significant correlations between the left ventricular ejection fraction and the GEF ($r = 0.79$, $P < 0.001$) and the CFI ($r = 0.66$, $P < 0.001$). The mean differences between LVEF and LVEF estimated with GEF or CFI (Figure 1) were $1.05 \pm 10.2\%$ (range $-19$ to 29.1%) and $0.001 \pm 12.4\%$ (range $-24.3$ to 24.3%), respectively. For predicting an LVEF of less than 40%, the area under the curve was 0.879 for the GEF and 0.805 for the CFI. Furthermore, a GEF of less than 13.5% and a CFI of less than $3.15\ \text{min}^{-1}$ predicted an LVEF of less than 40% with sensitivities of 97% and 96% and specificities of 85% and 77%, respectively. We concluded that in patients without marked changes in contractility, the GEF




(a)




(b)

Figure 1: Bland-Altman analyses of agreement between GEF (a) or CFI (b) and the LVEF measured by the Simpson method. The central line is the mean difference (bias) between the two methods whereas the outer lines represent the two SD limits of agreement. From Belda et al. [18] with permission.

and the CFI offer a reliable and simple way to assess the left ventricular ejection fraction.

## 3. Identifying Cardiac Dysfunction in Acute Heart Failure and Septic Patients

In 2009, Ritter et al. designed an observational study comparing the cardiac function of patients with acute heart failure (AHF) or sepsis using the pulmonary artery catheter and the PiCCO technology [21]. Twelve patients with AHF and nine patients with severe sepsis or septic shock had four simultaneous hemodynamic measurements by PAC or PiCCO during a 24-hour time period. In the results, compared to septic patients, AHF patients had significantly lower cardiac index (CI), CFI, GEF, mixed venous oxygen saturation ($SmvO_2$), and pulmonary vascular permeability index (PVPI), but higher pulmonary artery occlusion pressure (PAOP). The mean values in the groups for sepsis and AHF were, respectively: CI (PiCCO) 4.2 versus 2.9 $L \cdot min^{-1} \cdot m^{-2}$, CI (PAC) 4.3 versus 2.7 $L \cdot min^{-1} \cdot m^{-2}$, CFI 6.2 versus 2.7 $min^{-1}$, GEF 23 versus 13%, $SmvO_2$ 69 versus 54%, PVPI 2.8 versus 2.6 and PAOP 17 versus 20 mmHg. There were no significant differences between the two groups in the extra lung water index (ELWI, mean values): 16.7 versus 15.5 $mL \cdot kg^{-1}$. Additionally, PAOP did not correlate with ELWI and PVPI either in septic shock or in AHF patients.

All patients with a CFI less than 4.5 $min^{-1}$ had a $SmvO_2$ not greater than 70%. In both groups, the CFI show a weak but statistically significant correlation with the left ventricular stroke work index (sepsis: $r^2 = 0.30$, $P < 0.05$; AHF: $r^2 = 0.23$, $P < 0.05$) and the cardiac power (sepsis: $r^2 = 0.39$, $P < 0.05$; AHF: $r^2 = 0.45$, $P < 0.05$). The authors concluded that in critically ill medical patients, assessment of cardiac function using the transpulmonary thermodilution technique is an alternative to the PAC. Furthermore, a low CFI identifies cardiac dysfunction in both AHF and septic patients.

## 4. Conclusions

The transpulmonary thermodilution-derived indices, cardiac function index (CFI) and global ejection fraction (GEF), can be considered as useful indicators of left ventricular global systolic function. In fact, both could help the physician identify, easily and at the bedside, alterations in the left ventricular ejection fraction. On the other hand, normal values of these indices indicate a good systolic function and could avoid the need for immediate echocardiographic evaluation.

## Abbreviations

AHF: Acute heart failure
CFI: Cardiac function index
CI: Cardiac index
CO: Cardiac output
DSt: Downslope transit time
ELWI: Extra lung water index
GEDV: Global end-diastolic volume
GEF: Global ejection fraction
ICU: Intensive care unit
ITTV: Intrathoracic thermal volume
LV: Left ventricle
LVEF: Left ventricular ejection fraction
LVFAC: Left ventricular fractional area of change
MTt: Mean transit time
PAC: Pulmonary artery catheter
PAOP: Pulmonary artery occlusion pressure
PiCCO: Pulse-induced contour cardiac output
PTV: Pulmonary thermal volume
PVPI: Pulmonary vascular permeability index
SV: Stroke volume
$SmvO_2$: Mixed venous oxygen saturation.

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