

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Haemodynamic Monitoring in the Intensive Care Unit

---

Mainak Majumdar

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.68591>

---

## Abstract

Monitoring is a cognitive aid that allows clinicians to detect the nature and extent of pathology and helps assessment of response to therapy. The cardiovascular system is the most commonly monitored organ system in the critical care setting. It helps identify the presence and nature of shock and guides response to resuscitation by detection of cardiac rate and rhythm, evaluation of volume state, cardiac contractility and systemic vascular resistance. Newer technologies allow greater assessment of oxygen delivery to vulnerable tissues. We discuss the nature, history, modalities and interpretation of the most commonly available haemodynamic monitoring methods in clinical use currently.

**Keywords:** monitoring, arterial pressure, pressure transduction, oscillometry, plethysmography, volume state, central venous pressure, pulmonary artery occlusion pressure, stroke volume variation, cardiac output, pulmonary artery catheter, transpulmonary dilution, Fick principle, oesophageal Doppler, echocardiography, pulse contour analysis, tissue perfusion, lactate clearance, arteriovenous PCO<sub>2</sub> gradient, mixed venous saturation, central venous saturation, gastric tonometry

---

## 1. Introduction

The verb 'monitor' is derived from the Latin word *monere* - to warn. While there is little conclusive evidence that any one modality of monitoring changes patient outcomes significantly [1], all forms of critical care monitoring should be considered cognitive aids providing information beyond conventional physical examination. Synthesising this added information in the patient's individual context to improve clinical decision-making, thus enabling early aggressive manipulation of patient physiology is key to the management of critically unwell patients.

Monitoring is an integral part of critical care practice and is essential to the daily care of the critically ill patient. The goal of all resuscitation is prevention or treatment of organ dysfunction

and cellular injury by optimisation of tissue oxygen delivery according to the metabolic need. Manipulation of the macro-circulation to defend capillary autoregulation and micro-circulatory oxygen delivery relies heavily on the advanced haemodynamic monitoring to optimise volume state and cardiac function. Critical care monitoring and end points of resuscitation are now integrated into many resuscitation pathways and best practice guidelines [2, 3].

Invasive haemodynamic monitoring is now ubiquitous in critical care practice. Invasive monitoring assists both in the diagnosis and assessment of response to therapy in shock states and helps distinguish hypovolemic, cardiogenic, obstructive and distributive shock states.

It is incumbent on the critical care practitioner not only to be familiar with the commonly used modalities of haemodynamic monitoring but also to understand the physical principles underlying the monitoring equipment, allowing competent interpretation of haemodynamic data for use in clinical practice, identification of artefacts and effective troubleshooting of equipment.

## 2. Haemodynamic monitoring standards for critical care units

Patients admitted to critical care units in general show evidence of (single or multiple) organ failure or are at risk of such organ failure. Haemodynamic instability, leading to mismatch between tissue oxygen delivery and demand, is a major contributing factor for organ failure. All critically unwell patients should be monitored, but the degree of monitoring may vary depending on the severity of organ dysfunction [4].

The minimum standards of monitoring in a critical care environment are specified by the College of Intensive Care Medicine and they are as follows [5]:

- Continuous electrocardiography
- Non-invasive arterial pressure monitoring
- Pulse oximetry
- Central and cutaneous temperature monitoring
- End tidal capnography (to confirm tracheal placement of endotracheal or tracheostomy tubes and to monitor all patients receiving ventilatory support)
- Continuous monitoring of ventilation
- Endotracheal cuff monitoring
- Pressure monitoring—continuously and simultaneously display arterial, central venous and at least one other pressure
- Where indicated, monitoring and display of other physiologic variables such as cardiac output

Patients in or at high risk of respiratory or circulatory failure should have, at the very least, an arterial line for continuous invasive blood pressure monitoring and regular sampling of arterial blood gases and serum lactate.

Delivery of most pressors and inotropes necessitates central access. While the role of central venous pressures in estimating 'volume state' has been questioned repeatedly in literature, it does allow opportunity for central venous pressure monitoring.

Where indicated, further monitoring to monitor cardiac output, pulmonary artery pressures, volume state and tissue-oxygen extraction, may need to be instituted.

### 3. Physical principles of pressure transduction

Pressure transduction is in widespread use in the critical care environment, with pressure indices being measured for a variety of invasive haemodynamic variables such as arterial pressure, central venous pressure, pulmonary artery pressure and the like.

The basic transducer system is common to all means of invasive pressure monitoring. It consists of a fluid-coupled strain gauge system.

A cannula directly inserted into the lumen of the vessel whose pressure is being measured is connected through sterile plastic tubing containing fluid at high pressure to a strain gauge.

The strain gauge system itself, in modern clinical practice, is a semiconductor strain gauge integrated into a silicon diaphragm. The pressure wave transmitted through the fluid coupling system deforms the crystal lattice structure of the silicon, changing the resistance. Most modern transducers have four such piezoresistors within the diaphragm area (see **Figure 1**), with two being subject to tangential and two to radial stress [6].

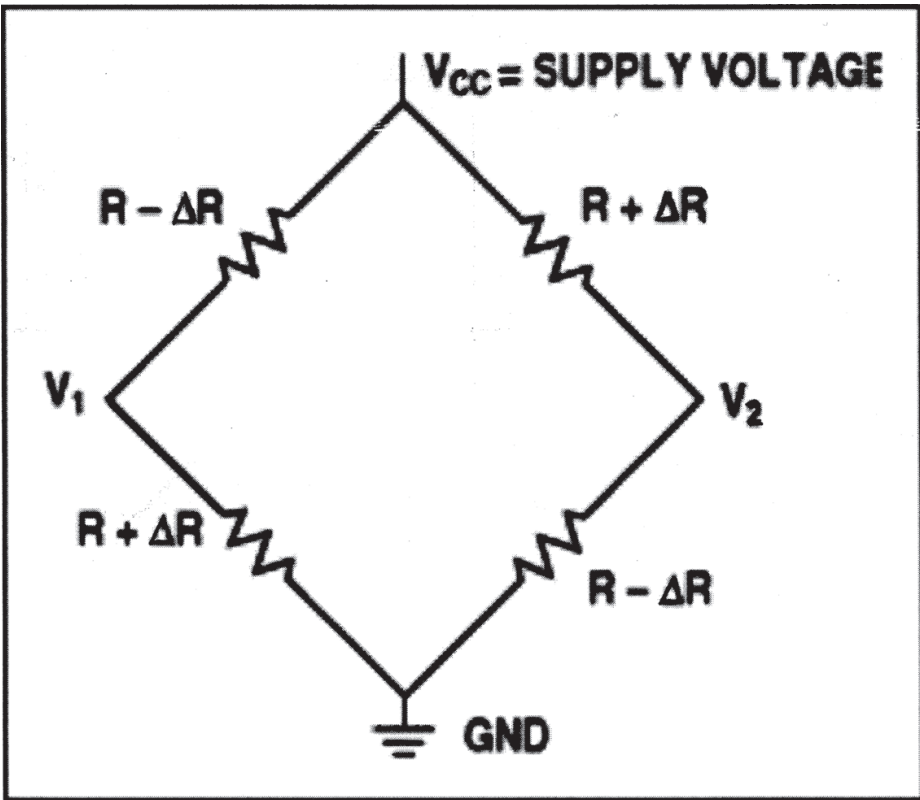
The resistors are connected in a four-arm configuration and provide an output such that

$$V_{\text{out}}/V_{\text{supplied}} = \Delta R/\Omega \quad (1)$$

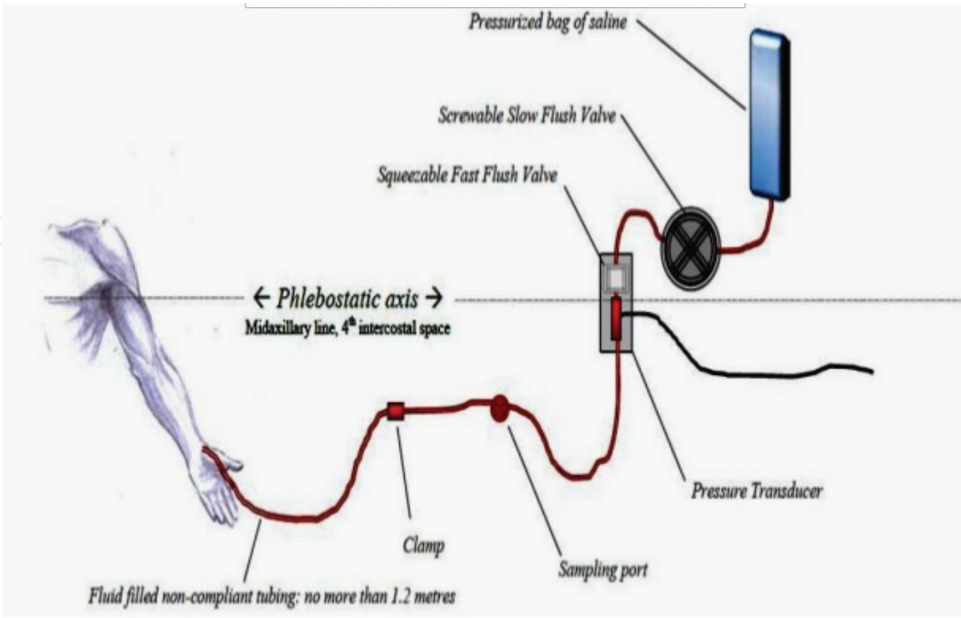
where  $V_{\text{out}}$  = measured output voltage;  $V_{\text{supplied}}$  = supply voltage (known);  $\Omega$  = base resistance of resistor (known) and  $\Delta R$  = change in resistance with applied pressure.

The output current is shielded from AC power supply pickup and displayed on the monitor. Commercially available transducers are individually calibrated and have a high level of accuracy.

The transducer is initially zeroed to ambient air pressure and then connected to the patient's circulation in a circuit as shown in **Figure 2**.



**Figure 1.** Piezoresistive integrated semiconductor pressure sensors incorporate four piezoresistors in the diaphragm. When the diaphragm is deflected, two resistors are subjected to tangential stress and two to radial stress. The four are connected to a four-element bridge.



**Figure 2.** Standard fluid-coupled transducer set up for pressure monitoring.

## 4. Continuous electrocardiography

Continuous electrocardiography is a common way of monitoring both cardiac rate and rhythm in critical care units and almost ubiquitously applied in regular critical care practice.

Adequate information can be gained from a three-lead single-channel display although it is often conventional to use a five-lead dual-channel display.

If there are specific concerns regarding evolving cardiac ischemia, most modern monitoring systems permit the use of conventional 12-lead continuous display. The need for on-going continuous 12-lead views is rarely necessary. As part of routine practice in most units, though, it is conventional to monitor 12-lead ECGs at least daily and serially where indicated (e.g. evolving myocardial ischaemia).

Critical care units involved with significant volumes of cardiothoracic surgical care and/or cardiology should use equipment that can accurately detect pacing activity and represent it on the continuous electrocardiography display.

## 5. Arterial pressure monitoring

Arterial blood pressure monitoring, whether by direct or indirect means, forms an essential part of any cardiovascular assessment and is one of the vital signs routinely assessed in every patient.

In 1733, Stephan Hales was the first to describe the measurement of 'the force of blood' in animal experiments using a water manometer in *Haema Statics*.

### 5.1. Non-invasive blood pressure monitoring

In 1896, Scipione Riva Rocci described the use of a pneumatic cuff using Vierordt and von Basch's adaptation of Poiseuille's mercury manometer. His technique, first published as '*Un nuovo sfigmomanometro*' in *Gazzetta Medical do Torino*, of inflating a rubber pneumatic cuff cased in a non-expansile material wrapped circumferentially round the arm to occlude the radial pulse, letting the air escape and measuring the pressure at which the pulse reappears (the systolic blood pressure), is still used in clinical practice worldwide.

In 1905, Nikolai Korotkoff described systolic and diastolic blood pressure measurement by auscultation. He combined Riva Rocci's cuff technique with a binaural stethoscope. Like Riva Rocci, he inflated the arm cuff till the pulse was occluded. He then auscultated the brachial artery, measuring both the pressure at which the brachial pulse became audible (systolic blood pressure) and then became inaudible again (diastolic blood pressure) as the cuff was slowly deflated [7].

Blood pressure measurement became widespread in clinical practice at the instigation of John Harvey Cushing. It is now standard of care to measure blood pressure in most healthcare settings and it is recognised as a vital sign.



Thus, simple non-invasive indirect arterial blood pressure management entered routine cardiovascular assessment as a measure additional to the classic palpation of rate, rhythm, volume and character of peripheral and central pulses described by Galen and Celsus—a practice dating back to ancient times and described in medical textbooks from India, China, Egypt and Greece.

All non-invasive measures of arterial pressure rely on the detection of blood flow. Over the latter half of the twentieth century, automated techniques of non-invasive blood pressure measurement were developed and refined. Oscillometry and finger plethysmography are currently the most commonly used techniques in Australasia.

Oscillometry is essentially an automated refinement of the Korotkoff technique. Oscillations at the cardiac frequency are high pass filtered out and plotted into an oscillometry envelope. Oscillations in the cuff pressure increase in amplitude as the cuff pressure falls between systolic and mean arterial pressures. The point of maximum oscillation amplitude corresponds closely with the mean arterial blood pressure. The amplitude of oscillations then falls between mean and diastolic blood pressure. The exact point on the oscillometry envelope used to determine systolic and diastolic blood pressure remains controversial and commercially available oscillometric systems use proprietary algorithms that are not available for public scrutiny. Overall, mean arterial pressures measured by oscillometry closely approximate invasive mean arterial pressures [8].

Since Jan Penaz first described the volume clamp technique of determining blood pressure using continuous finger plethysmography in the 1960s (based on the previous work of Karel Wesseling), various devices have been developed that provide arterial pressure tracings and continuous non-invasive measures of blood pressure using cuff-based finger plethysmography. Commercially available systems vary from the Finapres<sup>TM</sup> (Finapres Medical Systems BV, Netherlands) to the recently released ClearSight<sup>TM</sup> (Edwards Lifesciences, USA), which combines finger plethysmography with pulse contour analysis to estimate continuous cardiac output.

Ultrasound detection of arterial wall motion using devices like Puritan Bennett's Infrasonde<sup>TM</sup> [9] and photometric wave velocity measurement (pulse transit time bears an approximately inverse ratio to systolic blood pressure) has been described [10].

## 5.2. Invasive blood pressure monitoring

Invasive arterial pressure monitoring is standard of care in most modern critical care units. It consists of percutaneous insertion of a cannula into a peripheral artery identified either by palpation or under ultrasound guidance.

The common sites for arterial cannulation include radial, ulnar, brachial, axillary, femoral and dorsalis pedis arteries. Cannula sizes usually vary between 18 and 22 gauge.

The arterial cannula is attached to a fluid-coupled pressure transducer system as described above and provides accurate beat-by-beat measurement of arterial pressure besides providing a sampling port for arterial blood gases and blood tests.

There is little evidence that any one site is 'safer' than another for arterial cannulation. The shape, size or material of the catheter and the duration of insertion does not seem to influence the risk of complications. There is little evidence to support the utility of an Allen's test prior to radial artery cannulation [11]. The author prefers to avoid end arteries like the brachial.

Like all invasive procedures, arterial cannulation comes with potential risks including local haematoma formation, ischaemia of the distal limb, ischaemia of the overlying skin, retrograde embolisation, pseudo aneurysm, arteriovenous fistula formation and injury to surrounding structures. The sampling port remains an obvious source of infection, but, compared to central venous access devices, the risks of line-related sepsis are far lower from arterial catheters alone. Finally, it is good practice to clearly label the arterial line and its connections to minimise the risk of inadvertent retrograde injection.

In addition, technical factors associated with the fluid-coupled transduction system need to be taken into account. Specifically, it is important to verify that the transducer has been zeroed appropriately to ambient air pressure at the phlebostatic axis. It is vital to assess the pressure tracing itself to see if the dicrotic notch is visible and whether there is evidence of 'damping' (where there is an excess of compliance in the system, e.g. due to air in the fluid coupling, inadequately inflated pressure bag or excess length of transducer tubing) or 'ringing' (often noted as a spike or 'overshoot' of the systolic pressure trace caused by a poor compliant transduction system, and sometimes, due to resonance with reflected waves from the radial styloid process or similar anatomical structures).

### **5.3. Interpretation of arterial pressure monitoring data**

Over the years, blood pressure monitoring has been used as a surrogate measure of overall cardiovascular function, with an abnormal blood pressure being a significant marker of haemodynamic dysfunction.

In essence, blood pressure is directly proportional to both cardiac output and systemic vascular resistance.

Thus, arterial hypotension may indicate decreased stroke volume due to hypovolaemia and decreased systemic venous return, poor myocardial contractility or cardiac outflow obstruction due to pulmonary embolus or tamponade. Equally, it may be due to vasodilation due to sepsis or systemic inflammatory response. Often, it may be a combination of more than one factor. In short, hypotension is an excellent, if sometimes late marker of circulatory dysfunction and/or impairment of tissue perfusion. However, it is only one of the many parameters a clinician needs to assess the aetiology of circulatory dysfunction and distinguish between hypovolemic, distributive, cardiogenic and obstructive shock.

Significant persistent hypotension is often associated with evidence of end organ compromise due to failure of autoregulation of blood supply through the tissue capillary beds, evidenced by poor peripheral circulation (with decreased peripheral and central capillary refill), altered levels of consciousness, renal dysfunction with oligoanuria and abnormal renal function markers in the serum, hepatic dysfunction (commonly a transaminitis with aspartate transaminase rising higher than alanine transaminase) and evidence of increasing anaerobic metabolism



characterised by a rise in serum lactate. Similarly, resolution of these factors, together with return to baseline blood pressure or normotension, is a marker of successful resuscitation.

It is important to note that while the left ventricle generates pulsatile systemic blood flow, tissue capillary beds receive continuous blood flow at a constant pressure and most capillary beds are able to autoregulate the flow of blood within the organ at pressures between 55 and 110 mmHg. The aorta plays the vital role of converting pulsatile cardiac outflow into the steady blood flow perfusing the tissues. Thus, tissue perfusion relies on mean arterial pressure. The coronary circulation, on the other hand, relies on diastolic blood pressure for perfusion. Systolic blood pressure largely denotes the shear force of the pulsatile outflow on the elastic tissue of the aorta and the larger arteries. It is also important to remember that there are differences between pressures measured at different points in the arterial tree. The further out in the arterial tree the measurement is taken, the higher the measured systolic pressure and the lower the diastolic compared to pressures at the aortic root. The difference between systolic pressures measured in a proximal vessel (e.g. femoral artery) and a distal vessel (e.g. dorsalis pedis artery) is not clinically significant and the mean pressure, which determines tissue perfusion, is nearly identical regardless of the point of measurement.

With invasive measurement in an accurately zeroed and adequately damped transducer system, the measurement of systolic, diastolic and mean arterial pressure (defined as the area under the waveform-time curve divided by the time interval of the beat) is fairly accurate and reliable. The arterial waveform itself provides visual confirmation of the pulsatile blood flow in the vessel being transduced.

With non-invasive measures, the exact values of systolic and diastolic pressure vary depending on the technique and, to an extent, the operator. The mean arterial pressure may be approximated to diastolic pressure  $+1/3$  (difference between systolic and diastolic pressure). The Riva Rocci palpatory technique does not measure diastolic pressure and there may be significant inter-observer variability with both the palpatory and auscultatory (Korotkoff) methods of blood pressure determination, especially in haemodynamically unstable patients. Mean arterial pressures measured by oscillometry are usually accurate. However, the measurement of diastolic and systolic pressures is based on proprietary algorithms and the determination of diastolic pressure, especially, is problematic. Finger plethysmography and photoelectric methods using peripheral pulse transit time rely on adequate peripheral blood flow. They are difficult to acquire reliably in shocked, peripherally shut down patients—the subset whose management benefits most from regular arterial pressure monitoring.

## 6. Measurement of cardiac output

Cardiac output is the volume of blood pumped by the heart per unit time. It is the product of heart rate and stroke volume. It can be manipulated by alterations to heart rate and rhythm, preload, contractility and afterload.

Measurement and optimisation of cardiac output ultimately is the best way to guide and facilitate tissue perfusion and oxygenation.

There are different methods of measuring cardiac output based on the Fick principle, thermo dilution, pulse contour analysis, Doppler and bio-impedance. Each method comes with its own advantages and disadvantages. The ideal mode of monitoring would be minimally or non-invasive, cost effective, continuous, reproducible and reliable in a variety of physiologic states with a fast response time [12].

### 6.1. Fick principle

This is the gold standard for cardiac output measurement. The Fick principle is based on the fact that the total uptake (or release) of a substance by the peripheral tissues is equal to the product of the blood flow to the tissue and the arterial-venous concentration difference of the substance.

In practice, the simplest way to measure this is in terms of oxygen consumption, i.e. the difference between inspired and expired oxygen. The cardiac output is calculated thus

$$CO = VO_2 / (CaO_2 - CvO_2) \quad (2)$$

where CO = cardiac output;  $VO_2$  = oxygen consumption;  $CaO_2$  = arterial oxygen concentration;  $CvO_2$  = venous oxygen concentration.

Accurate measurement of  $VO_2$  outside of stringent physiology laboratory conditions is difficult and so this method is not commonly applied in clinical practice.

When used in clinical practice for ventilated patients, it is easier to estimate pulmonary capillary blood flow by measuring the volume of  $CO_2$  produced, the alveolar and mixed venous  $CO_2$  [13]. This is done by periodically introducing a dead space into the ventilator circuit and assuming pulmonary end capillary, arterial and end tidal  $CO_2$  rise instantly but mixed venous  $PCO_2$  does not. Cardiac output is estimated thus

$$CO = Q_{PCBF} = \Delta CO_2 / (C_V CO_2 - C_A CO_2) \quad (3)$$

where CO = cardiac output;  $Q_{PCBF}$  = pulmonary capillary blood flow;  $\Delta CO_2$  =  $CO_2$  excreted by lungs per minute = (expiratory flow)  $\times$  ( $CO_2$  fraction in expired air);  $C_V CO_2$  = mixed venous  $CO_2$ ;  $C_A CO_2$  = alveolar arteriolar  $CO_2$  = (end tidal  $CO_2$ )  $\times$  (slope of the  $CO_2$  dissociation curve).

The available systems are limited in that they are designed for use in patients who are intubated and ventilated. Concerns have previously been expressed about using rebreathed  $CO_2$  in the circuit, leading to raised  $E_T CO_2$  and tachycardia, leading to an artefactually elevated cardiac output measurement [14]. Moreover, measured expired  $PCO_2$  may not reflect change in pulmonary capillary and arterial  $PCO_2$  and  $CO_2$  may not have had a chance to reach a steady state within the limited sampling time. The actual slope of the  $CO_2$  dissociation curve also varies with both haemoglobin content and  $PCO_2$ . Errors in measurement may be introduced in patients with significant V/Q mismatch or intracardiac shunt (where pulmonary blood flow may not represent total cardiac output), severe chest trauma and high cardiac output states with low minute ventilation.

## 6.2. Pulmonary artery catheterisation

Pulmonary artery catheterisation [15] and thermo dilution to measure cardiac output has been the gold standard in clinical practice. In the end expiratory phase, a known volume of injectate (usually saline or dextrose at room temperature or cooler) is injected rapidly (in less than 4 s) to rapidly lower the temperature of the pulmonary artery and the change in blood temperature over time is monitored. In essence, the rate of blood flow is in inverse proportion to the change in temperature and mean change in temperature is therefore inversely proportional to the cardiac output. The Stewart Hamilton equation is then used to derive the output.

$$CO = [V(T_b - T_i)]K1[K2/T(b)t dt] \quad (4)$$

where CO = cardiac output; V = volume of injectate;  $T_b$  = temperature of blood;  $T_i$  = temperature of injectate; K1, K2 = correction constants for specific heat and density of injectate and for blood and dead space volume;  $T(b)t dt$  = change in blood temperature as a function of time.

Instead of thermo dilution, dye dilution has also been used to measure cardiac output with pulmonary artery catheters. If a dye like indocyanine green is injected into the pulmonary artery, the change in its concentration is related to the rate of blood flow and can be calculated from the Stewart Hamilton equation thus

$$CO = I \int Ci dt \quad (5)$$

where CO = cardiac output; I = amount of indicator (in moles);

$Ci dt$  = integral of indicator concentration over time.

There are commercially available cardiac output catheters capable of continuous cardiac output monitoring. These use intermittent heating of blood in the pulmonary artery through a heating filament integrated into the catheter and calculate the cardiac output by thermo dilution.

There is a significant margin of error of up to 15% in measurement of cardiac output by pulmonary artery catheter thermo dilution. There can be up to 10% variation in the measured output without significant change to the patient's clinical state.

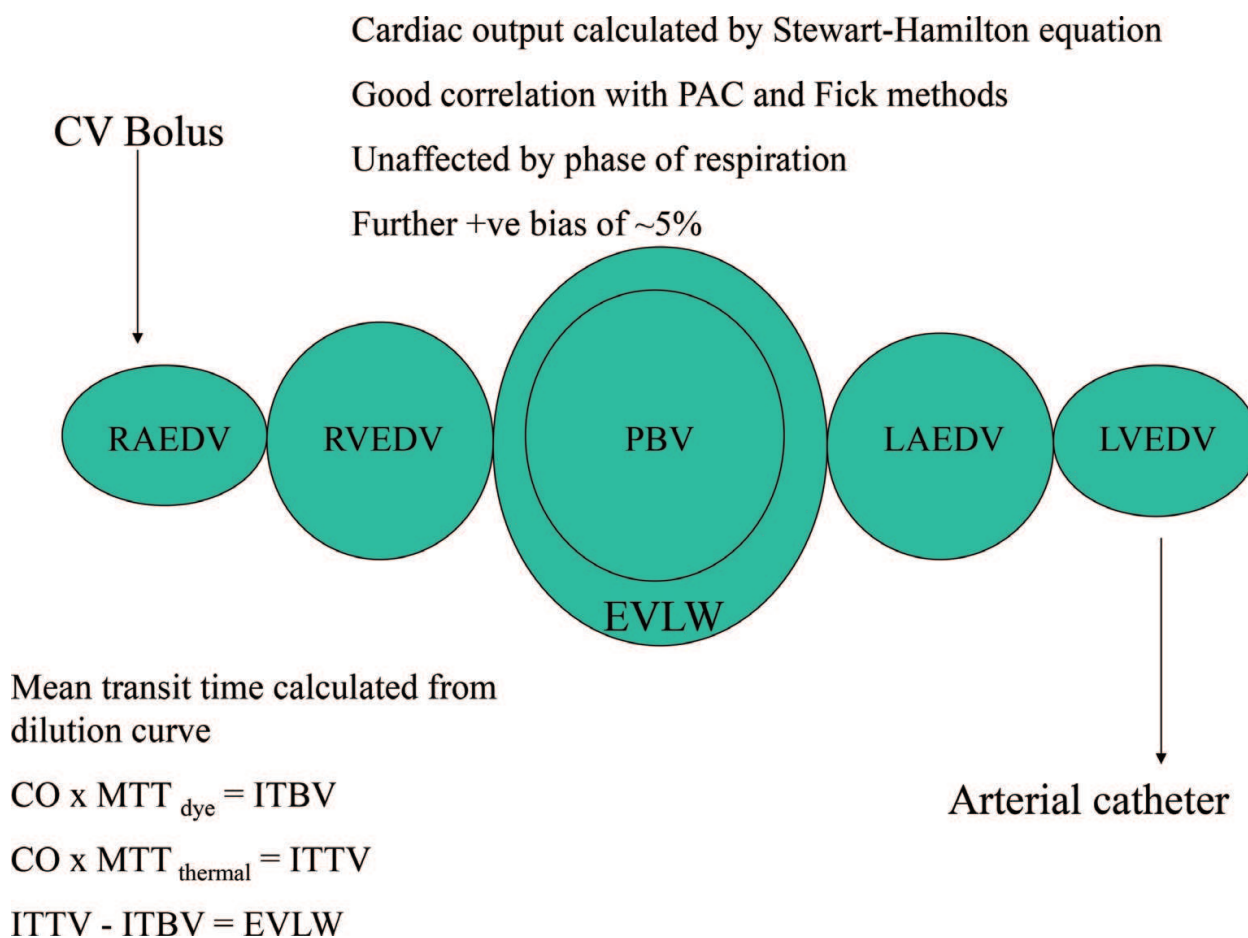
Pulmonary artery catheters carry a significant risk of complications including catheter malposition, catheter migration, catheter knotting, pulmonary artery rupture, valve injury, arrhythmia, thrombus on catheter leading to embolisation, air embolus from balloon rupture, infection and haematoma. Failure to inject at end expiration, injection time of greater than 4 s, temperature sensor touching the vessel wall, severe tricuspid regurgitation, profound hypothermia, intracardiac shunts and infusions running rapidly in other ports of the catheter may all lead to inaccuracies in the measured thermo dilution cardiac output. In a randomised control trial, risks of catheter-related complications rose significantly from 0.7% associated with central venous catheters to 1.5% associated with pulmonary artery catheters, though there was no significant increase in mortality or hospital length of stay [16]. Later, the PAC-Man trial was unable to demonstrate significant benefit or harm with the use of pulmonary artery catheters [17].

### 6.3. Transpulmonary dilution techniques

Over the last two decades, various techniques have been described and entered clinical practice, using thermo dilution or dye/indicator dilution techniques. These are all based around the injection of a bolus into the right atrium via a central venous catheter and the detection of temperature change or dye/indicator concentration at a proximal artery (femoral, axillary or brachial). Using the Stewart Hamilton equation as above, cardiac output can be calculated by any of these techniques.

In addition, it is possible to calculate the mean transit time of the injectate from the dilution curve. Multiplying the mean transit time with the cardiac output allows calculation of the total intrathoracic thermal (in thermo dilution), water (using lithium injectate) or blood (using indocyanine green) volumes with these devices. Subtracting intrathoracic blood volume (measured by indocyanine green dye dilution) from total intrathoracic fluid volume (measured using thermo dilution or lithium) allows assessment of extravascular lung water.

Measurements of cardiac output using transpulmonary dilution (see **Figure 3**) correlate well with measurements using pulmonary artery catheter or using the Fick principle, with an estimated added margin of error of around 5%.



**Figure 3.** Schematic diagram for transpulmonary dilution technique for measurement of cardiac output.

While the risks of inserting catheters for transpulmonary dilution are identical to the individual risks of inserting arterial and central venous catheters, it is important to recall that the central venous catheter tip must lie as close as practicable to the right atrium. Femoral central venous catheters are not appropriate—the volumes measured include the variable contents of an extremely compliant capacitance vessel—the inferior vena cava!

#### 6.4. Pulse contour analysis

Pulse contour analysis is predicated on the principle that the area under the systolic curve is proportional to the stroke volume. The arterial waveform ( $dP/dt$ ) is analysed, and after calibration for arterial compliance, systemic vascular resistance and patient-specific calibration factors, the stroke volume is calculated.

Various monitors such as the LiDCO Plus<sub>TM</sub> (Cambridge, UK) and the PiCCO<sub>TM</sub> (Pulsion Medical System, Germany) use transpulmonary dilution to calculate the cardiac output and correlate this to pulse contour analysis to provide continuous cardiac output monitoring. The continuous cardiac output is recalibrated every 4–8 hours (depending on the manufacturer's specifications) to cardiac output derived from transpulmonary dilution.

Devices like the FloTrac<sub>TM</sub>/EV1000<sub>TM</sub> system (Edwards Lifesciences, USA) allow pulse contour analysis of the arterial waveform acquired from any arterial catheter without the need to calibrate to other methods of cardiac output measurement. The EV1000<sub>TM</sub> monitor can also be combined with the ClearSight<sub>TM</sub> (Edwards Lifesciences, USA) probe, which uses a finger cuff-based volume clamp technique to acquire the arterial waveform.

#### 6.5. Oesophageal Doppler

Oesophageal Doppler uses a flexible probe with a transducer at the tip that can be inserted like an orogastric tube into the oesophagus to a distance of 30–40 cm from the teeth oriented parallel to the descending thoracic aorta. Blood flow velocity is determined from the shift in frequency of red blood cells. Velocity time integral (VTI) is calculated from the velocity time curve of the Doppler envelope. The diameter of the aorta is ideally determined by ultrasound. Assuming the descending thoracic aorta carries 70% of total cardiac output

$$CO = HR.CSA.VTI/0.7 \quad (6)$$

where CO = cardiac output; HR = heart rate; CSA = measured aortic cross-section area; VTI = velocity time integral of the Doppler curve.

It is contraindicated with intra-aortic balloon pumps, anatomical anomalies such as coarctation of aorta or extrinsic compression of the descending aorta. In children, there is significant variation in the cross-sectional diameter during each beat and CSA cannot be accurately measured. Finally, in shock states, it is hard to know if the assumption that 70% of cardiac output goes to the descending aorta is true or not. Nevertheless, it is a simple device to use, with few contraindications or significant risks and the cardiac output measured with this device correlates well with pulmonary arterial catheter measurements.



## 6.6. Echocardiography

Australasian critical care practice has enthusiastically embraced the use of echocardiography and most practitioners have reasonable familiarity with the technique [18].

Using a transthoracic or transoesophageal probe, valuable information is gained not just about the global contractile function and filling state of the patient but also regarding regional wall motion abnormalities, pericardial or proximal aortic pathology and valvular abnormalities. The greatest advantage in clinical practice is the direct view of left ventricular function and its ability to directly measure volumetric indices (e.g. left ventricular end diastolic volume, LVEDV) than surrogate pressure indices (e.g. pulmonary artery occlusion pressures) as markers of volume state.

Two-dimensional echocardiography provides valuable information on systolic function including fractional shortening or fractional area change, which can then be approximated to left ventricular ejection fraction. It also provides valuable information on the filling state (e.g. no specific training is needed to interpret the 'kissing' left ventricular walls in severe hypovolaemia or the dilated inferior vena cava with no diameter change during forced inspiration). In experienced hands, subtle abnormalities in relaxation patterns give excellent clues to diastolic ventricular function. Finally, Doppler interrogation allows estimation of the more 'traditional' pressure indices such as pulmonary artery pressures from the tricuspid regurgitation jet.

The Doppler envelope of the left ventricular outflow tract (LVOT) allows calculation of the velocity time integral (VTI). Given that the LVOT itself is a relatively constant dimension and its diameter is easy to measure, this is an easy way to measure cardiac output at the aortic root.

$$(\pi d^2 / 4) \cdot \text{HR} \cdot \text{LVOT VTI} \quad (7)$$

where d = LVOT diameter; HR = heart rate; LVOT VTI = velocity time integral of blood flow at the left ventricular outflow tract.

One of the great advantages of transthoracic echocardiographic haemodynamic assessments is the fact that it is non-invasive. A full left ventricular study is rarely necessary in acute situations where it is being used to guide resuscitation and adequate clinical information can still be gathered from limited views. This has to be balanced against the fact that echocardiography is more time consuming and requires the presence of both equipment and a skilled operator at all times to be of meaningful use in assessing response to therapy. There is also an element of interobserver variability depending on the level of skill of the operator. Transthoracic views are more difficult in the supine positive pressure ventilated critically ill patient, and patients with thoracic trauma, cardiac surgery and pneumothoraces are notoriously difficult to acquire windows on. The problem is easily bypassed by adding transoesophageal echocardiography to the skill mix. On the other hand, this not only requires an additional skill set but also necessitates insertion of a probe into the oesophagus with the attendant risks of oesophageal injury or rupture. Moreover, transoesophageal probes cannot be left for long periods of time in the patient.



Echocardiography offers an accurate non-invasive series of haemodynamic snapshot views in the hands of a skilled operator and probably represents, where available, the best modality of cardiac monitoring to assess circulatory failure and guide resuscitation.

### 6.7. Other techniques

Various other devices using a variety of techniques are available for clinical use. These include:

- Thoracic bioimpedance
- Thoracic bioreactance: NICOM monitor (Cheetah medical, USA)
- Impedance plethysmography: ECOM monitor (ECOM medical, USA)
- Suprasternal portable Doppler ultrasound probes: USCOM (Australia)

Though initial studies in many of these devices has looked promising, they are not in common use currently and often suffer the drawbacks of both clinical unfamiliarity and limited validation data in critically ill patients.

## 7. Assessment of volume state

Much has been written over the years about estimation of preload. By definition, it is the amount of stretch in the muscle fibre just prior to contraction and is related to the length of the individual sarcomere just prior to contraction. As sarcomere length increases, the force of muscle contraction increases. Once maximal sarcomere length is reached, there is no further increase in contraction strength. In a section of muscle tissue, as increasing numbers of sarcomeres are maximally stretched, the strength of contraction plateaus. This is represented by the Frank Starling curve in **Figure 4**.

The practical aspect of this means that contractility and stroke volume of the left ventricle increases up to a point as systemic venous return increases. Beyond that point, stroke volume does not increase and there is tissue and pulmonary oedema with right ventricular stretching and poor collapsibility of the vena cava.

Since sarcomere length cannot be measured in clinical situations, the closest approximation available is the left ventricular end diastolic volume, either measured directly using echocardiography or indirectly by measuring the left ventricular end diastolic pressure or its surrogate pressures—pulmonary capillary occlusion pressure, right atrial pressure or central venous pressure using appropriately placed catheters. Transpulmonary dilution techniques allow measurement of intrathoracic blood volume or global end diastolic volume. It is important to remember that these are static measures of preload (see **Figure 5**).

From the practical point of view, contemplation of preload is less relevant than answering the question—‘Is this patient fluid recruitable?’ Multiple studies have suggested that only 50% of haemodynamically unstable patients respond to fluid challenge [19, 20].

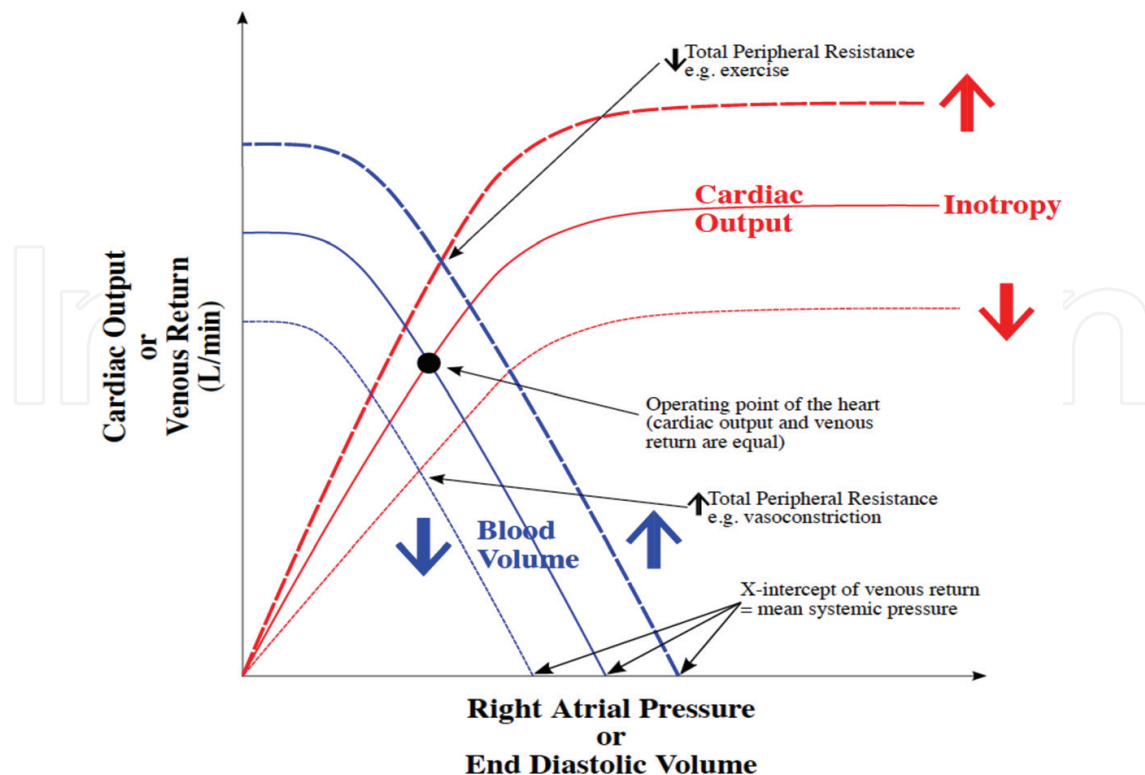


Figure 4. Frank Starling curve.

The most common static measure of preload used to answer this question is the central venous pressure. This correlates well with right atrial pressure and, in theory, is a reasonable pressure surrogate of right ventricular end diastolic volume. However, there is an extremely large body of literature demonstrating no correlation [21] between CVP and change in CVP and fluid responsiveness in a variety of clinical situations. Other measures of cardiac filling pressures like pulmonary artery occlusion pressure have also been shown to be poor predictors of volume responsiveness [22].

Increasingly, dynamic measures of preload estimation have been described and have entered clinical practice [19].

Passive leg raising to 45° in a supine patient provides the equivalent of a 500 mL fluid challenge in terms of increasing cardiac preload and the haemodynamic effects are detectable within minutes. Passive leg raise as a measure of volume responsiveness is well validated in critically unwell patients and may be considered a reversible autotransfusion.

Pulse pressure variation, derived from arterial waveform analysis, stroke volume variation (SVV) from pulse contour analysis and variation in the amplitude of the plethysmograph waveform in pulse oximetry have all been validated as measures of fluid responsiveness. Essentially, they reflect the changes to systemic venous return in hypovolemic patients as the intra-thoracic pressure changes during the respiratory cycle. SVV > 10% in positive pressure ventilated patients in sinus rhythm and a normally compliant chest wall is a sign of fluid recruitability.

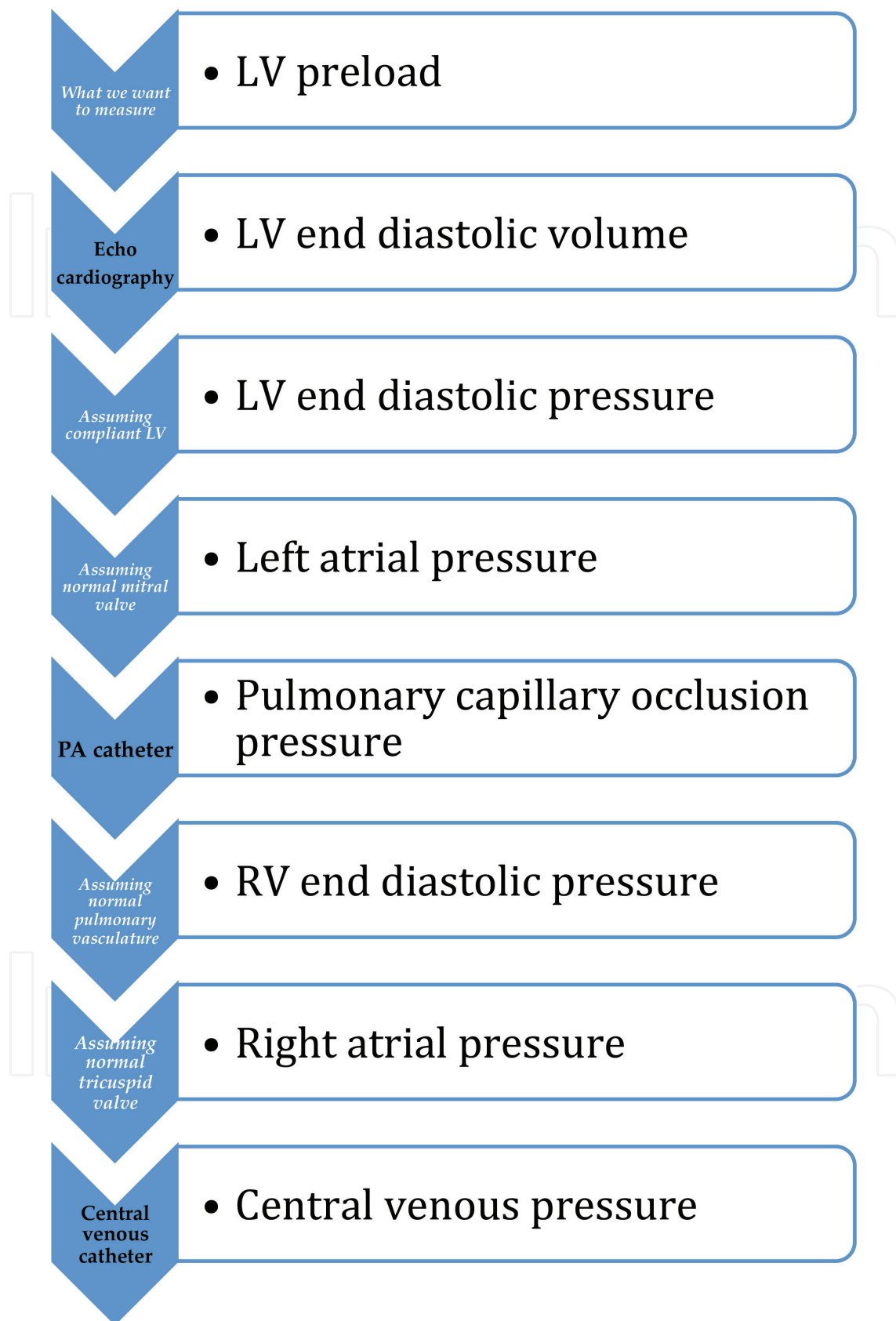


Figure 5. Static measures of LV preload.

Earlier work [23] using oesophageal tonometry suggests an increment of  $\geq 10\%$  in stroke volume after a volume challenge is a reasonable sign of fluid recruitability. In the end, the greatest measure of fluid responsiveness may be the administration of an empirical volume of fluid (the author prefers 250 mL aliquots) and monitoring haemodynamic changes resulting from the intervention.

## 8. Assessment of peripheral tissue perfusion

Shock is defined as 'inadequate tissue oxygen for aerobic cellular respiration'. Shock results from both macro-circulatory and micro-circulatory failure, leading to inadequate tissue perfusion. In addition, mitochondrial dysfunction may result in cellular oxygen misuse. Furthermore, stress and physiologic compensation can increase oxygen demand in situations of poor delivery. Thus, oxygen delivery and demand inadequacy can compound organ failure, resulting in death despite optimal management [24].

Shock resuscitation has been aimed at 'restoring' or 'maximising' oxygen delivery and tissue oxygenation. Kern and Shoemaker suggested that mortality decreased and oxygen delivery increased when management was guided by end points such as central venous pressure, mean arterial pressure, cardiac output, oxygen transport and mixed or central venous oxygen saturation [25]. Early goal-directed therapy advocated by Rivers and Nguyen [26] has found its echo in many resuscitation protocols, especially in the management of severe sepsis [3] and perioperative management of high-risk surgical patients. Ghaferi et al. described failure to identify and rescue patients with perioperative complications early as a potential reason for increased hospital mortality independent of case mix, patient characteristics and complication rates [27]. Combined with the global move towards rapid rescue and resuscitation teams for ward patients outside of critical care areas, this has moved goal-directed therapy outside of monitored critical care areas into the general ward population where invasive monitoring may not be safely accessible.

Yet, in situations like septic shock [28] and cardiac failure [29], despite optimisation of the macro-circulation with mean arterial pressure and cardiac output targets, micro-circulatory failure can result in persistent tissue failure [30]. Thus, it is important to monitor patients for evidence of micro-circulatory failure.

### 8.1. Lactate clearance

Glycolysis produces pyruvate, which either enters aerobic mitochondrial metabolism with a high ATP yield from the Krebs cycle or is processed anaerobically to lactate with a much lower ATP yield. Thus, in the absence of hypovolaemia and severe hepatic dysfunction, high circulating levels of lactate may represent high incidence of anaerobic metabolism due to lack of oxygen uptake, poor tissue perfusion or mitochondrial dysfunction. The Sepsis-3 guidelines acknowledge serum lactate  $>2$  mmol/L to be a marker of septic shock [31].

Persistent hyperlactatemia is considered to reflect occult hypoperfusion and has been associated with poor outcomes in trauma [32], cardiac arrest [33] and high-risk surgery [34].

Modern blood gas sampling machines, easily accessible to critical care teams, provide a rapid and convenient method of quantifying and serially monitoring serum lactate as a marker of successful resuscitation.

## 8.2. Venous-arterial CO<sub>2</sub> gradient

Carbon dioxide is a by-product of oxidative metabolism and tissue production of CO<sub>2</sub> is related to its oxygen uptake.

Thus,

$$VCO_2 = R.VO_2 \quad (8)$$

where  $VCO_2$  = tissue CO<sub>2</sub> production;  $VO_2$  = tissue O<sub>2</sub> uptake; R = respiratory quotient.

From the Fick principle (Eq. (2)), therefore

$$VCO_2 = CO(CaCO_2 - CvCO_2) \quad (9)$$

$$\text{i.e. } VCO_2 = CO.k.P(v - a)CO_2.$$

$$P(v - a)CO_2 = VCO_2/CO.k \quad (10)$$

where  $VCO_2$  = tissue CO<sub>2</sub> production; CO = cardiac output;  $P(v - a)CO_2$  = venous-arterial CO<sub>2</sub> gradient; K = coefficient of CO<sub>2</sub> concentration and partial pressure.

In other words, since k and R are constants,  $P(v - a)CO_2$  is directly proportional to tissue CO<sub>2</sub> clearance and inversely proportional to cardiac output. Given its diffusible nature, CO<sub>2</sub> washout depends on tissue oxygen uptake and cardiac output.

Thus,  $P(v - a)CO_2$  is dependent on cardiac output, tissue oxygen uptake and CO<sub>2</sub> washout. Thus,  $P(v - a)CO_2$  will increase in low cardiac output states.

CO<sub>2</sub> washout is extremely flow-dependent and any decrease in local or regional capillary hypoperfusion will increase tissue stagnation of PCO<sub>2</sub> and a rise in diffusion of CO<sub>2</sub> to venous capillary beds with residual circulation, increasing  $P(v - a)CO_2$ . Thus, in the presence of normal measured cardiac output, high  $P(v - a)CO_2$  may represent occult tissue hypoperfusion or impaired oxygen uptake.

In critically ill patients with normal cardiac index,  $P(v - a)CO_2 > 6$  mmHg seems to be a good discriminator of occult hypoperfusion identified by persistent hyperlactatemia [35]. This has since been corroborated in septic shock [36] and high-risk surgical patients [37, 38] resuscitated with early goal directed therapy.

Thus, after optimisation of cardiac output in patients with circulatory failure, it seems reasonable to target  $P(v - a)CO_2 < 6$  mmHg. How this is best achieved in clinical practice seems unclear.

### 8.3. Mixed venous saturation (SvO<sub>2</sub>) and central venous saturation (ScvO<sub>2</sub>): measures of global tissue oxygen extraction

Global tissue oxygen extraction is defined as the proportion of transported oxygen in the circulation taken up by the tissues. Thus,

$$ERO_2 = VO_2 / TO_2 \quad (11)$$

where  $ERO_2$  = extraction ratio of oxygen;  $VO_2$  = tissue oxygen uptake;  $TO_2$  = oxygen transported in the circulation = cardiac output  $\times$  O<sub>2</sub> content of arterial blood.

By the Fick principle (Eq. (2))

$$ERO_2 = CO(CaVO_2 - CvVO_2) / TO_2 \quad (12)$$

Since,

$$TO_2 = CO.CaVO_2 \quad (13)$$

$$ERO_2 = 1 - (CvVO_2 / CaVO_2) = 1 - SvO_2 / SaO_2 \quad (14)$$

where  $SaO_2$  = arterial O<sub>2</sub> saturation;  $SvO_2$  = mixed venous saturation.

When  $SaO_2$  is 100%,

$$ERO_2 = 1 - SvO_2 \quad (15)$$

Usual  $ERO_2$  is 25–30% and is a function of metabolic demand, activity and mitochondrial activity. With increasing tissue oxygen consumption due to exercise, stress or sepsis,  $ERO_2$  increases up to its maximum limit. Past  $ERO_{2max}$ , tissues are unable to take up further oxygen and anaerobic glycolysis resulting in lactate release occurs.

$ScvO_2$  is easier to sample and monitor through a central venous catheter than  $SvO_2$  which necessitates insertion of a pulmonary artery catheter.

It is worth noting that a falling  $SvO_2$  or  $ScvO_2$  should trigger optimisation of  $TO_2$  (increasing  $SaO_2$ , cardiac output, O<sub>2</sub> carrying capacity of blood, i.e. haemoglobin) before considering mitochondrial or tissue dysfunction. In essence, this forms the basis of goal directed therapy. While  $ScvO_2$  directed inotrope therapy has been described to reduce mortality from septic shock [26], it is important to understand that  $SvO_2$  and  $ScvO_2$  cannot discriminate between reasons for increased  $VO_2$  or decreased  $TO_2$ . A normal  $SvO_2$  does not imply adequacy of oxygen demand and supply. Finally, once  $TO_2$  has been optimised, it is unclear what therapies can be offered for mitochondrial dysfunction.

### 8.4. Gastric tonometry

Gastric tonometry has been described as a specific monitor for splanchnic perfusion, based on the phenomenon that early on in haemodynamic stress, there is diversion of blood flow away from splanchnic circulation.



Gastric luminal  $\text{PCO}_2$  is equilibrated to the medium contained in a balloon at the end of a nasogastric probe and gastric mucosal pH is calculated using the Henderson-Hasselbach equation. Arterial  $\text{HCO}_3^-$  is measured as a surrogate for mucosal  $\text{HCO}_3^-$ . Mucosal-arterial  $\text{PCO}_2$  gap  $>25$  mmHg or splanchnic pH  $< 7.3$  suggests poor splanchnic perfusion.

Unfortunately, in practice, it is limited by confounding factors such as enteral feeding and buffering of gastric acid by duodenal and oesophageal reflux.

### 8.5. Other techniques of micro-circulatory assessment

As discussed before, correction of macro-circulatory variables does not equate to successful oxygen supply at the tissue level.

Capillary blood flow can be visualised non-invasively at the bedside using sidestream dark field imaging in different capillary beds (e.g. sublingual, rectal, etc.) [39]. Currently, it is important to take multiple readings in several capillary beds for periods of 20 s or longer to eliminate measurement errors and inter-observer variability may exist. This technology shows promise and with refinement, may become a rapid, accurate and repeatable way of assessing capillary blood flow.

Tissue oxygenation in target tissue capillary beds ( $\text{StO}_2$ ) can be measured non-invasively using near-infrared spectroscopy (NIRS). Unfortunately, there is little evidence behind 'normal' or 'target' values specific to capillary beds in critically unwell patients and this modality of monitoring, though promising, is still not common in clinical practice.

Sublingual tonometry provides a simple, non-invasive and inexpensive measure of adequacy of tissue perfusion [37, 40]. Further studies with this promising technology are needed to establish its clinical utility in everyday clinical care.

## Acknowledgements

I like to acknowledge the input and encouragement of my critical care medical, nursing and technician colleagues. I thank my family for their patience and forbearance during the writing of this chapter. There are no conflicts of interest to declare in the writing of this chapter.

## Author details

Mainak Majumdar

Address all correspondence to: [mainak.majumdar@mh.org.au](mailto:mainak.majumdar@mh.org.au)

Intensive Care Unit, Royal Melbourne Hospital, Parkville, VIC, Australia

## References

- [1] Bellomo R, Uchino S. Cardiovascular monitoring tools: Use and misuse. *Current Opinion in Critical Care*. 2003;**9**(3):225–229
- [2] Brain Trauma Foundation September [Internet]. 2016. Guidelines available from: [https://braintrauma.org/uploads/03/12/Guidelines\\_for\\_Management\\_of\\_Severe\\_T-BI\\_4th\\_Edition.pdf](https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_T-BI_4th_Edition.pdf) [Accessed: 20 February 2017]
- [3] Dellinger RP, Levy MM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013;**41**(2):580–637. DOI: 10.1097/CCM.0b013e31827e83af
- [4] Huygh J, Peeters Y, Bernards J, Malbrain MLNG. Haemodynamic monitoring in the critically ill: An overview of current cardiac output monitoring methods. *F1000research*. 2016;**5**(F100 Faculty Rev):2855. DOI: 10.12688/f1000research.8991.1
- [5] Minimum Standards for Intensive Care Units (Professional Document IC-1), College of Intensive Care Medicine [Internet]. 2016. Available from: [http://cicm.org.au/CICM\\_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-1-Minimum-Standards-for-Intensive-Care-Units\\_1.pdf](http://cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-1-Minimum-Standards-for-Intensive-Care-Units_1.pdf) [Accessed: 20 February 2017]
- [6] Bicking RE. Fundamentals of Pressure Sensor Technology [Internet]. 1998. Available from: <http://www.sensorsmag.com/sensors/pressure/fundamentals-pressure-sensor-technology-846> [Accessed: 20 February 2017]
- [7] Booth J. A short history of blood pressure measurement. *Proceedings of the Royal Society of Medicine*. 1977;**70**(11):793–799
- [8] Babbs CF. Oscillometric measurement of systolic and diastolic blood pressures validated in a physiologic mathematical model. *Biomedical Engineering Online*. 2012;**11**:56. DOI: 10.1186/1475-925X-11-56
- [9] Zezulka AV, Sloan P, Davies P, Beevers DG. Oscillometric measurement of systolic and diastolic blood pressures validated in a physiologic mathematical model. *Postgraduate Medical Journal*. 1985;**61**:321–323
- [10] Chung E, Chen G, Alexander B, Canneson M. Non-invasive continuous blood pressure monitoring: A review of current applications. *Frontiers of Medicine*. 2013;**7**:91. DOI: 10.1007/s11684-013-0239-5
- [11] Slogoff S, Keats AS, Arlund C. On the safety of radial artery cannulation. *Anesthesiology*. 1983;**59**(1):42–47
- [12] Mehta Y, Arora D. Newer methods of cardiac output monitoring. *World Journal of Cardiology*. 2014;**6**(9):1022–1029. DOI: 10.4330/wjc.v6.i9.1022
- [13] Jaffe MB. Partial CO<sub>2</sub> rebreathing cardiac output- operating principles of the NICO system. *Journal of Clinical Monitoring and Computing*. 1999;**15**(6):387–401

- [14] Eger EI. Cardiovascular effects of carbon dioxide in man. *Anesthesiology*. 1974;**41**(4): 341–349
- [15] Swan HJ, Ganz W, Forrester J, Marcus H, Chonette D. Catheterisation of the heart in man with use of a flow directed balloon tipped catheter. *New England Journal of Medicine*. 1970;**283**:447–451
- [16] Sandham JD, Hull RD, Brant RF, Knox L, et al. A randomised controlled trial of the use of pulmonary artery catheters in high risk surgical patients. *New England Journal of Medicine*. 2003;**348**:5–14
- [17] Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-man): A randomised controlled trial. *Lancet*. 2005;**366**:472–477
- [18] Statement on the Role of Echocardiography in Intensive Care Medicine (Professional Document IC-24), College of Intensive Care Medicine [Internet]. 2016. Available from: [http://cicm.org.au/CICM\\_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-24-Statement-on-the-Role-of-Echocardiography-in-Intensive-Care-Medicine\\_1.pdf](http://cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-24-Statement-on-the-Role-of-Echocardiography-in-Intensive-Care-Medicine_1.pdf) [Accessed 20 February 2017]
- [19] Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Critical Care Medicine*. 2009;**37**:2642–2647
- [20] Boyd JH, Forbes J, Nakada T, Alley KR, Russell JA. Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure increase mortality. *Critical Care Medicine*. 2011;**39**(2):259–265
- [21] Marik PE, Baram M, Vahid B. Does the central venous pressure predict fluid responsiveness? A systematic review of the literature. *Chest*. 2008;**134**:172–178
- [22] Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Critical Care Medicine*. 2007;**35**(1):64–68
- [23] Kuper M, Gold SJ, et al. Intraoperative fluid management guided by esophageal Doppler monitoring. *British Medical Journal*. 2011;**342**:d3016. DOI: 10.1136/bmj.d3016
- [24] Kipnis E, Ramsingh D, Bhargava M, Dincer E, et al. Monitoring in the intensive care. *Critical Care Research and Practice*. 2012;**2012**:473507. DOI: 10.1155/2012/473507
- [25] Kern JW, Shoemaker WC. Meta analysis of haemodynamic optimisation in high risk patients. *Critical Care Medicine*. 2002;**30**(8):1686–1692
- [26] Rivers E, Nguyen B, Havstad S, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*. 2001;**345**(19):1368–1377
- [27] Ghaferi AA, Birkmeyer JD, et al. Variation in hospital mortality associated with inpatient surgery. *New England Journal of Medicine*. 2009;**361**:1368–1375

- [28] Sakr Y, Dubois MJ, De Backer B, Creteur J, Vincent JL. Persistent micro circulatory alterations are associated with organ failure and death in patients with septic shock. *Critical Care Medicine*. 2004;**32**(9):1825–1831
- [29] De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. *American Heart Journal*. 2004;**147**(1):91–99. DOI: 10.1016/j.ahj.2014.04.022
- [30] Siegenthaler N, Giraud R, Romand JA, Bendjelid K. Physiopathologic aspects of micro circulation in intensive care. *Revue Medicale Suisse*. 2008;**4**(183):2696–2701
- [31] Singer M, Deutschmann CS, Seymour CW, et al. The third international consensus definitions of sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association*. 2016;**315**(8):801–810. DOI: 10.1001/jama.2016.0287
- [32] Claridge JA, Crabtree TD, Pelletier SJ, et al. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *Journal of Trauma*. 2000;**48**(1):8–14
- [33] Kliegel A, Losert H, Sterz F, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine*. 2004;**83**(5):274–279
- [34] Meregalli A, Oliviera RP, Friedman G. Occult hypoperfusion is associated with increased mortality in haemodynamically stable high risk surgical patients. *Critical Care*. 2004;**8**(2): R60–R65
- [35] Mekontso-Dessap A, Castelain V, Anguel N, et al. Combination of venoarterial PCO<sub>2</sub> difference with arteriovenous O<sub>2</sub> content difference to detect anaerobic metabolism in patients. *Intensive Care Medicine*. 2002;**28**(3):272–277
- [36] Vallee F, Vallet B, Mathe O, et al. Central venous to arterial carbon dioxide difference: An additional target for goal directed therapy in septic shock? *Intensive Care Medicine*. 2008;**34**(12):2218–2225
- [37] Marik PE, Monnet X, Teboul JL. Haemodynamic parameters to guide fluid therapy. *Annals of Intensive Care*. 2011;**1**(1):1. DOI: 10.1186/2110-5820-1-1
- [38] Futier E, Robin E, Jabaudon M, et al. Central venous O<sub>2</sub> saturation and venous to arterial CO<sub>2</sub> difference as complementary tools for goal directed therapy during high risk surgery. *Critical Care*. 2010;**14**(5):R193
- [39] Boerma EC, Mathura KR, et al. Quantifying bedside derived imaging of microcirculatory abnormalities in septic patients: A prospective validation study. *Critical Care*. 2005;**9**(6): R601–R606
- [40] Marik PE. Regional carbon dioxide monitoring to assess the adequacy of tissue perfusion. *Current Opinion in Critical Care*. 2005;**11**(3):245–251

