Minimally Invasive Cardiac Output Monitoring in the Perioperative Setting

Duane J. Funk, MD, FRCPC
Eugene W. Moretti, MD, MHsc
Tong J. Gan, MB, MHS, FRCA, FFARCS(I)

With advancing age and increased co-morbidities in patients, the need for monitoring devices during the perioperative period that allow clinicians to track physiologic variables, such as cardiac output (CO), fluid responsiveness and tissue perfusion, is increasing. Until recently, the only tool available to anesthesiologists to monitor CO was either a pulmonary artery catheter or transesophageal echocardiograph. These devices have their limitations and potential for morbidity. Several new devices (including esophageal Doppler monitors, pulse contour analysis, indicator dilution, thoracic bioimpedance and partial non-rebreathing systems) have recently been marketed which have the ability to monitor CO noninvasively and, in some cases, assess the patient’s ability to respond to fluid challenges. In this review, we will describe these new devices including the technology, studies on their efficacy and the limitations of their use.

A n integral role of the anesthesiologist in patient care is to monitor and interpret physiologic variables. Treatment strategies are guided by both clinical skills and information provided by monitoring tools. The value of patient monitors to real-time decision making during patient care is especially important when caring for critically ill patients. Routine monitoring of circulatory function includes heart rate (HR), arterial blood pressure, electrocardiography (ECG) and oxygenation. Clinical signs, such as jugular venous distension and urine output, are often used to judge intravascular volume status and adequacy of end organ blood flow but are not as reliable in critically ill patients. Anesthesiologists and intensivists have devoted most of their monitoring devices to the measurement of pressures. However, most organs are dependent on flow as well as pressure to achieve adequate function.

To this end, there have been several monitors developed that allow the clinician to monitor cardiac output (CO) and the response to fluid therapy. When these monitors are used in conjunction with the administration of fluids and vasopressors to specific therapeutic end points, patient care and outcome may be improved. These interventions, termed “goal-directed therapy” have been used widely both in the operating room (OR) and the intensive care unit (ICU).1,2

The most well-known monitor for measuring flow and pressure is the pulmonary artery catheter (PAC) described initially by Dexter,3 and later modified by Swan et al.,4 to measure CO and central filling pressures. Since that time, investigators have tried to develop the ideal monitor of CO measurement. Such a monitor would be totally noninvasive or minimally invasive as this would allow its use in a variety of clinical settings that may not be amenable to invasive hemodynamic monitoring, such as the labor suite, emergency room, during medical transport, ambulatory surgery suites or the recovery room. The ideal monitor would also need to be accurate and reproducible and have limits of agreement (as assessed by Bland–Altman5 analysis) that compared favorably with values derived from the PAC, often considered the “gold standard” when other devices are compared. Furthermore, such a monitor would also need to be reliable under many different physiologic conditions, such as different shock states or other conditions when dynamic changes in intravascular volume status and peripheral resistance are occurring. Finally, the ideal CO monitor would need to be continuous, and have the ability to assess the efficacy of therapeutic interventions (e.g., the hemodynamic response to administration of fluid challenges or vasoactive drugs). At present, no device meets all of these criteria. This article aims to discuss the minimally invasive technologies available to measure CO that require very little additional specialized training. The technologies that will be discussed include partial carbon dioxide rebreathing systems, pulse contour analysis, thoracic electrical bioimpedance (TEB), esophageal Doppler (ED) and indicator dilution methods, (e.g., lithium dilution).

The information presented is based upon a PubMed search for English language articles published up to
and including February 2008 using the following medical subject headings with the term CO: noninvasive, dye dilution, Fick principle, thermodilution, PAC, lithium dilution, pulse contour analysis, transpulmonary thermodilution, ED, Doppler echocardiography, carbon dioxide rebreathing, electrical velocimetry, bioimpedance and electrical impedance.

References were screened by title and by abstract before the full text was acquired. The bibliographies of original papers and review articles were also searched for any papers that may have been missed with the initial search criteria. When necessary, companies were contacted for further information. Representative articles from the search criteria were then used to create the review, including a description of the technology and representative studies.

When available, Bland–Altman analysis of bias, precision, and levels of agreement is reported. The Bland–Altman approach, which has become the preferred method of statistical analysis for assessing agreement between two methods of clinical measurement, is unfortunately not universally reported in studies investigating different methods of measuring CO, making comparison of different monitoring modalities difficult.

History of CO Measurements

Of the 27 million patients who undergo surgery in the United States each year, approximately 8 million have coronary artery disease or risk factors for cardiovascular disease. One million of these patients have perioperative cardiac ischemic events. Moreover, the prevalence of cardiovascular disease increases with age. The proportion of the United States population that is older than 65 years is predicted to increase from 25% to 35% within the next 30 years. This is also the patient group that has the largest number of surgical procedures performed. Thus, in an attempt to reduce cardiac morbidity, anesthesiologists have used the hemodynamic data obtained from the PAC to diagnose and treat these high-risk patients.

A major concern with the use of PACs is the risk associated with central venous catheterization. These risks include arrhythmias, pulmonary infarction, infection, pulmonary embolus, and rupture of the pulmonary artery to name just a few. Furthermore, PACs add significant cost to the care of the patient. These disadvantages of PAC use have motivated the search for a less invasive method to determine CO.

Minimally Invasive CO Monitors

Minimally invasive CO monitors include ED monitors, carbon dioxide rebreathing systems, indicator dilution methods, TEB and pulse contour analysis devices. We will discuss the theory behind the operation of these devices as well as studies addressing the use of these technologies for goal-directed therapy and, where available, the reliability of these devices when compared with gold standards, such as the PAC. Table 1 summarizes the advantages and disadvantages of the currently available CO monitors.

Esophageal Doppler Monitor

ED monitoring was first introduced in the 1970s as a noninvasive means to measure aortic blood flow. Suprasternal or transthoracic probes were used initially, but the difficulty of probe positioning and instability on the chest wall made their use for repeated measurements limited. This led to the development of the ED probe. It had several advantages, including the ability to remain in position for days to weeks and its proximity to the aorta. The ED probe is approximately the size of a nasogastric tube and can be positioned easily.

Since the Doppler methodology measures velocity not flow, certain assumptions are required to use this technology to estimate CO. The aorta is assumed to be a cylinder and the flow through it is calculated by multiplying the cross-sectional area (CSAa) by the velocity (Vf). Blood flow in the aorta is pulsatile and the velocity changes over time. Vf can thus be described as the area under a curve of a velocity-time graph. This area is computed mathematically as the integral of the derivative of velocity over time (dVf/dt) from T0 to T1 (where T0 is the start of aortic blood flow and T1 is the end of flow). This value is then multiplied by the CSAa (which is the area of a circle πr²) to give a value for stroke volume (SV). The radius of the descending aorta (which is used to calculate the area of the aorta) is derived from published nomograms based on age, sex, weight, and height (Deltex, West Sussex, England, www.deltexmedical.com) or through direct measurement (Arrow’s HemoSonic®, Reading, PA). CO is then calculated by multiplying SV by HR (CO = HR × SV).

Esophageal Doppler also has the ability to measure the corrected flow time (FTc) as a measure of cardiac preload. The FTc is the time from the beginning of the aortic pulse waveform upstroke to its return to baseline. The FTc is the systolic flow time corrected for HR of 60 bpm. Several studies have compared this measurement with other measures of cardiac preload (such as pulmonary artery occlusion pressure) and have found good agreement between the two (discussed below). One of the advantages of using the ED probe is that changes in SV after the administration of fluid challenges can be used to guide fluid administration. It thus functions as a monitor for titrating fluid to optimize preload.

There are several limitations to the use of ED. First, the ED only measures descending aortic blood flow, and excludes flow to the aortic arch vessels. CO is therefore calculated only from this descending aortic blood flow value. Aortic blood flow is approximately 70% of CO with 30% going to the cephalic blood vessels, and thus a correction, or K-factor of 30% must be introduced to account for blood flow to the arch
vessels. Although valid in young healthy patients, this ratio may not be constant due to changes in metabolic activity between different organs, or hemodynamic status.

Second, CSAa is not a constant, but rather dynamic due to changes in pulse pressure, vascular tone, aortic compliance, volume status or catecholamine use. The CSAa determination is crucial to CO calculation since any change in radius of the aorta is squared before use in the final equation. Thus, even small changes in aortic area can significantly affect CO determinations. This has led to the development of an ED probe that can directly measure CSAa (Arrow's HemoSonic®) rather than calculating it from a nomogram of typical aortic radii.12

Finally, probe position is critical to obtain accurate Vf. The Doppler beam must be within 20° of axial flow to obtain a good measure of aortic blood flow. This has led to the suggestion that ED monitoring is somewhat operator dependent,13–15 and that additional training is required to become proficient in its use.16 However, the learning curve is steep with some studies demonstrating a dramatic improvement in skill with only 10 to 12 insertions.14,16 Inter and intraobserver reliability of the technique is clinically acceptable, between 8% and 12%.17,18

There have been several studies that have compared ED measurements of CO with PAC-derived thermodilution CO (PAC_TDI). A meta-analysis of 11 ED studies demonstrated a pooled median bias of 0.19 L/min (range: –0.69–2.0 L/min) for CO.19 Based on three individual studies, the pooled limits of agreement were –2.21 to 2.33 L/min.20 These studies were conducted in hemodynamically stable patients or those who were undergoing coronary artery bypass grafting (CABG).

A completely noninvasive Doppler technology, the USCOM (Ultrasound CO monitor, USCOM, Sydney, Australia, www.uscom.com.au), is also available which uses Doppler technology to measure CO from a suprasternal Doppler probe. This nascent technology has been studied in a few patient population groups (mostly stable ICU patients) and has shown reasonable correlation with PAC_TDI.21,22 There is a concern that during the learning phase of the device, CO measurements may not be accurate.

Numerous clinical studies have demonstrated improvement in patient outcome with goal-directed fluid therapy using ED. Sinclair et al., conducted a randomized controlled trial of patients undergoing femur

Table 1. Advantages and Disadvantages of the Currently Available Minimally Invasive CO Monitors

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Esophageal Doppler</td>
<td>Simple to use; Does not require access to the circulation; Many clinical studies proving utility; Reliable; Can use as a monitor of volume responsiveness in goal directed therapy</td>
<td>Mathematical assumptions about aortic size might be erroneous; Only measures descending aortic blood flow; Occasional difficulty in obtaining optimal probe position; Learning curve.</td>
</tr>
<tr>
<td>Thoracic electrical bioimpedance</td>
<td>Completely noninvasive</td>
<td>Difficult to set up; Numerous mathematical assumptions; Not useful for patients with dysrhythmias; “Noise” from OR limits use; Requires hemodynamic stability; Have not been reported for use in goal directed therapy.</td>
</tr>
<tr>
<td>Partial non-rebreathing systems</td>
<td>Easy to set up; Does not require access to the circulation; Provides for continuous CO measurement</td>
<td>Have not been reported for use in goal directed therapy.</td>
</tr>
<tr>
<td>Arterial pulse contour</td>
<td>Simple to use; Only require arterial line; Can be used in goal directed therapy; Validated in clinical studies under many different conditions; Continuous CO measurements; Can be used to measure stroke volume and stroke volume variation</td>
<td>Requires access to the circulation; Requires high fidelity arterial tracing; Requirement for calibration (some systems). Need to re-calibrate during periods of hemodynamic instability (some systems).</td>
</tr>
<tr>
<td>Lithium dilution</td>
<td>Ease of set up; Only require arterial line; Continuous CO measurements; Can be used to measure stroke volume and stroke volume variation</td>
<td>Requires access to the circulation; Repetitive blood draws; Calibration interfered in the presence of neuromuscular blocking drugs.</td>
</tr>
<tr>
<td>Trans-pulmonary thermodilution techniques</td>
<td>Can use pre-existing arterial line or central line; Continuous CO measurements; Provides estimation of extravascular lung water; Can be used with goal directed therapy</td>
<td>Requires access to the central circulation; Radial artery not suitable; Not truly a noninvasive technology; Limited use in the OR.</td>
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CO = cardiac output; OR = operating room.
fracture repair.\textsuperscript{23} Patients were randomized to either routine care or ED-guided fluid loading. Study patients received significantly more fluid and had a statistically significant decrease in the primary outcome of median time to be declared fit for discharge (10 vs 15 days) and length of stay (12 vs 20 days) when compared with controls.\textsuperscript{23} A similar trial conducted by Venn et al., showed that, when compared to a control group of patients (central venous pressure monitoring), ED-monitored patients had less intraoperative hypotension and were considered medically fit for discharge sooner than the control group.\textsuperscript{24}

Gan et al., randomized elective noncardiac surgical patients to either routine care or goal-directed fluid therapy with an ED monitor. Patients in the intervention group received more colloid and had significantly shorter median length of stay (5 vs 7 days) and an earlier ability to tolerate solid food (3 vs 5 days, \( P < 0.05 \)).\textsuperscript{2} In another study, Mythen and Webb prospectively randomized elective cardiac surgery patients to usual care or extra boluses of a hydroxyethyl starch solution to maintain maximum SV based on ED monitoring. Patients in the intervention group had a statistically significant decrease in gut mucosal hypoperfusion, major complications, hospital and ICU stay.\textsuperscript{11} In a study by Wakeling et al., intraoperative ED-guided fluid management was associated with a 1.5-day median reduction in postoperative hospital stay. Patients recovered gut function significantly faster and suffered significantly less gastrointestinal and overall morbidity and had higher quality of recovery scores.\textsuperscript{25} A relevant finding of all these studies was a greater sensitivity of SV and CO when compared with arterial blood pressure and HR as measures of adequate intravascular volume status. It appeared that compensatory tachycardia tended to maintain CO in the face of moderate hypovolemia.\textsuperscript{26}

In a similar trial, Noblett et al., randomized patients undergoing elective colorectal surgery to either standard care with respect to fluid loading to those with an ED-titrated fluid regimen.\textsuperscript{27} They found that patients in the intervention group had higher COs and SVs. This translated into the clinically relevant findings that patients in the intervention group tolerated an oral diet earlier, had fewer postoperative complications, and had a shorter length of stay. Interestingly, patients in the intervention group also had lower levels of interleukin-6, which suggested an attenuated inflammatory response to surgery, perhaps due to the improved organ perfusion.

A study by Conway et al., (using the same algorithm as Sinclair et al.\textsuperscript{25}) in patients undergoing major bowel surgery compared ED-derived CO and goal-directed fluid therapy in a group of patients who underwent major bowel surgery.\textsuperscript{28} They demonstrated less use of critical care beds postoperatively in the intervention group. Furthermore, this trial of 57 patients also showed less congestive heart failure than the control group.

When comparing goal-directed studies of CO with ED, it is unclear as to whether the FTc or SV should be used to guide fluid therapy. It appears that the ability to respond to a fluid challenge is best determined by FTc. However, to use this value as a marker of fluid optimization may be potentially misleading. FTc is inversely proportional to systemic vascular resistance (SVR).\textsuperscript{29} In conditions in which SVR may be elevated, (heart failure, excessive vasopressor use or hypothermia) FTc is reduced and might lead clinicians to give more fluid without a clinical improvement in CO or organ flow. Furthermore, in pathological conditions such as pericardial tamponade, pulmonary embolus, or mitral stenosis, in which there is a pathological limitation of left ventricular filling, FTc will be reduced and not respond to a volume challenge and might lead the clinician to give fluid in a state where the patient might be on the optimal portion of their starling curve resulting in no improvement in CO with the risk of precipitating pulmonary edema.\textsuperscript{29}

For this reason, the SV might be a better variable to measure fluid optimization. In a study by Bundgaard-Nielsen et al., SV was compared with FTc to determine fluid optimization in radical prostatectomy patients.\textsuperscript{30} This study found that the change in FTc was inconsistent when used for fluid optimization and that SV was the preferable method in these patients.

ED monitoring has proven itself to be a reliable tool to monitor goal-directed therapy. It has the ability to measure CO, but its utility in situations with low CO is limited when compared with PAC\textsubscript{TTP}. Initial investigations also show its utility in reducing morbidity when coupled with a goal-directed fluid approach to surgical patients. Further clinical trials, however, are needed to determine its utility in different patient populations, specifically those who are hemodynamically unstable requiring vasopressor support and those with dynamic changes in SVR. Concerns about its precision in measurement need to be addressed and the optimal variable to measure for fluid optimization (either SV or FTc) in different patient populations needs to be clarified. Also, some have called into question the accuracy of this technology because of wide limits of agreement in some of the studies.\textsuperscript{31} ED may lead to fewer operative patients undergoing PAC placement in the future.

**THORACIC ELECTRICAL BIOIMPEDANCE**

TEB is the least invasive method of measuring CO. First proposed by Kubicek in 1966, TEB is based on the theory that the thorax is a cylinder that is perfused with a fluid (blood) of a specific resistivity. Thoracic bioimpedance is the electrical resistance to high frequency low amplitude current that is transmitted from electrodes placed on the upper and lower thorax. Six electrodes are placed on the patient, two on either side of the neck and four in the lower thorax. After injection of current by way of the outermost electrodes
on the body surface, the impedance of flow through the thorax is sensed by the innermost set of electrodes on the body surface. This value is indirectly proportional to the volume of thoracic fluids such that increasing fluid in the thorax results in less TEB. Therefore, the inverse of TEB, and thus changes in CO, are reflected as a change in total bioimpedance or fluid conductivity.

The measurement in changes in TEB to estimate SV is based on the equation:

\[ SV = p \left( \frac{L^2}{Z_\phi} \right) \cdot \left[ \frac{VET}{(dZ/dt)_{\text{max}}} \right] \]

where \( p \) is the resistivity of blood (ohm-cm), \( L \) is the distance between the electrodes (cm), \( Z_\phi \) is the mean thoracic impedance between electrodes (ohm), VET is the ventricular ejection time (sec) and \((dZ/dt)_{\text{max}}\) is the maximum negative slope of the bioimpedance signal (ohm/sec).32 SV is then derived based on several assumptions. First, the rate of change over time in TEB corresponds to aortic blood flow (and assumes that other factors that change impedance do not change). Second, \((dZ/dt)_{\text{max}}\) corresponds to peak aortic blood flow. Third, the ejection phase contractility index (EPCI) which is used in the calculation of SV is equal to EPCI = \((dZ/dt)_{\text{max}} \times \) total fluid conductivity. Fourth, VET can be measured from the distance between the QRS intervals of the surface ECG. Finally, the volume of electrically participating tissues (VEPT) is estimated from the patient’s height, weight, age, and sex.33,34 SV is thus estimated by the formula \( SV = (\text{VEPT/} VET) \cdot \text{EPCI}, \) and CO is determined by CO = SV \times HR. This equation has been modified by Bernstein to account for the non-cylindrical shape of the chest, which might result in an erroneous determination of the CO.35

It is readily apparent that an accurate determination of CO requires significant assumptions and hemodynamic stability. Thoracic bioimpedance is affected by tissue fluid volume and changes in the volume of pulmonary and venous blood induced by respiration. This “noise” must be filtered out from the desired changes in volumetric blood flow of the aorta. Any alteration in the position or contact of the electrodes will thus affect these measurements. Also, determining the VET by using the interval between QRS complexes precludes its use in patients with arrhythmias, since errors in CO determination will undoubtedly result. Any acute change in tissue water, such as the development of pulmonary edema or pleural effusions or chest wall edema, will alter bioimpedance readings and affect CO measurements.

The intraoperative environment is not conducive to TEB measurements of CO due to interference by noise from electrocautery, mechanical ventilation and surgical manipulation. In addition, alterations in myocardial contractility that are induced by anesthetics, loading conditions and ischemia can cause errors in TEB measurements of CO, further reducing its usefulness in patients with coronary artery disease and poor ventricular function (ironically, the patient population the clinician would be most interested in).36 Clinical trials of TEB have been shown to be reliable in young healthy volunteers, but in critically ill or surgical patients, the results have been inconsistent.36–38 A meta-analysis of TEB studies found an \( r^2 \) value of 0.53 when compared with a reference method which led the authors to conclude that the interpretation of CO values from TEB in cardiac patients should be undertaken with caution.39 Unfortunately, this meta-analysis did not use the Bland–Altman approach to analyze their data.

A new generation of TEB devices, including the BioZ (Cardiodynamics Intl., San Diego, CA, www.bioz.com) overcomes some of the initial limitations of the first generation TEB devices by having 1) faster signal processing, 2) better signal filtering, 3) improved ECG triggering, 4) improved arrhythmia detection, and 5) respiratory filtering.

In an intraoperative study of patients undergoing CABG surgery, the BioZ device did well initially in determining CO when compared with PAC_{TD}, however, during the immediate postoperative period, the correlation as measured by Bland–Altman analysis was not as robust.40 This could have been secondary to changes in the amount of fluid in the pleural spaces or changes in the intrinsic contractility of the heart or the use of steel wires to reapproximate the sternum. The lack of correlation at the end of surgery did not seem to be due to the effects of opening the chest as the correlation between PAC_{TD} and TEB remained good with the initial opening of the chest.

Further studies in postoperative CABG patients showed good bias and precision when compared with PAC_{TD}. These studies suggest that, while the new generation devices might be better than the first generation TEB machines, questions still remain about their ability to measure CO during dynamic conditions.

Without improvements in signal processing techniques, it is unlikely that TEB will become a standard monitor in the anesthesia or critical care setting.41 A newer monitor, the Aesculon (Osypka Medical, LA Jolla, CA) uses electrical velocimetry, which interprets the maximum rate of change of TEB to calculate CO. This monitor has shown some promise in postoperative cardiac surgical patients (both hemodynamically stable and unstable).42 Further studies are required to validate this technology. There have been no clinical studies demonstrating outcome benefits or studies discussing the use of TEB with goal-directed therapy.

**Methods Using the Fick Principle**

Use of the Fick method is another noninvasive way of determining CO. First proposed by Adolf Fick in 1870, it is based on the conservation of mass, such that the total uptake or release of a substance by an organ...
is the product of the blood flow to that organ multiplied by the arteriovenous concentration difference. Rearranging the original equation allows us to solve for CO

\[
\text{CO} = \frac{V_O^2}{c_aO_2 - c_vO_2}
\]

where \( V_O^2 \) is oxygen consumption, \( c_aO_2 \) is arterial oxygen content, and \( c_vO_2 \) is mixed venous oxygen content. This technique is commonly used in cardiac catheterization laboratories and is considered the gold standard for measuring CO. The procedure, however, is invasive and methodological error is common. It is not standard for measuring CO. The procedure, however, is catheterization laboratories and is considered the gold standard for measuring CO. The procedure, however, is invasive and methodological error is common. It is not used in the OR secondary to the difficulty in measuring oxygen uptake and the need for hemodynamic and respiratory stability to accurately measure CO.

The Fick principle can use many different indicators and, more recently, technologies have become available that have used CO2 as an indicator. The Fick equation can then be rewritten as

\[
\text{CO} = \frac{\dot{V}CO_2}{c_vCO_2 - c_aCO_2}
\]

where \( \dot{V}CO_2 \) is the CO2 elimination and \( c_vCO_2 \) and \( c_aCO_2 \) are the arterial and venous CO2 contents, respectively. It is possible to calculate \( c_aCO_2 \) from \( PaCO_2 \) or estimate it from the end tidal \( CO_2 \). This estimation only holds true in patients with no diffusion abnormalities. \( VCO_2 \) can be calculated from the difference between inspired and expired gas \( CO_2 \) content. Measuring \( c_vCO_2 \) is much more difficult.

Instead of using direct measurements of \( c_vCO_2 \), it can be estimated with the help of a partial rebreathing technique. This technique is called the differential CO2 Fick partial rebreathing method. To estimate \( c_vCO_2 \), 150 mls of dead-space are added to the ventilator circuit by opening a rebreathing valve and measurements of the change in CO2 elimination and end tidal CO2 are made first during a period of non-rebreathing and a subsequent rebreathing period. The Fick equation for the non-rebreathing (nonrebr) and the rebreathing (rebr) periods can then be combined

\[
\text{CO} = \frac{\dot{V}CO_{2\text{nonrebr}}}{c_vCO_{2\text{nonrebr}} - c_aCO_{2\text{nonrebr}}}
\]

(2)

\[
\text{CO} = \frac{\dot{V}CO_{2\text{rebr}}}{c_vCO_{2\text{rebr}} - c_aCO_{2\text{rebr}}}
\]

(3)

\[
\text{CO} = \frac{\dot{V}CO_{2\text{nonrebr}} - \dot{V}CO_{2\text{rebr}}}{(c_vCO_{2\text{nonrebr}} - c_aCO_{2\text{nonrebr}}) - (c_vCO_{2\text{rebr}} - c_aCO_{2\text{rebr}})}
\]

(4)

The body has large stores of CO2 and CO2 has a slow time constant for diffusion, therefore, it can be assumed that the mixed venous CO2 concentration will remain relatively constant throughout the breathing and non-rebreathing periods and as a result these terms cancel out. The equation then becomes

\[
\text{CO} = \frac{\dot{V}CO_{2\text{nonrebr}} - \dot{V}CO_{2\text{rebr}}}{c_aCO_{2\text{nonrebr}} - c_aCO_{2\text{rebr}}}
\]

(5)

Thus

\[
\text{CO} = \frac{\Delta VCO_2}{\Delta c_aCO_2}
\]

(6)

where \( \Delta VCO_2 \) is the change in CO2 elimination and \( \Delta c_aCO_2 \) is the change in alveolar blood CO2 content between the baseline and rebreathing periods. To calculate the alveolar CO2 content, the following equation is used

\[
c_aCO_2 = (6.957[Hgb] + 94.864) \times \log(1.0 + 0.1933 PaCO_2)
\]

(7)

where Hgb is hemoglobin concentration in g/L. The arterial CO2 content is estimated using the \( PaCO_2 \) and the CO2 dissociation curve.

This technique only measures non-shunted blood and, therefore, to get an accurate measure of CO, the shunt fraction must be estimated by using the shunt equation:

\[
\frac{Q_s}{Q_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}
\]

(8)

where \( C_cO_2 \), \( C_aO_2 \), and \( C_vO_2 \) are the end-capillary, venous and arterial oxygen contents. In order to measure these noninvasively, Nunn’s iso-shunt plots are used. These plots are a series of curves that describe the relationship between \( PaO_2 \) and \( FiO_2 \) for different levels of intrapulmonary shunt. Thus, shunt can be determined simply by using the \( PaO_2 \) and \( FiO_2 \).

Several technical problems are encountered with this method. The difference between mixed venous and arterial CO2 is usually only about 6 mm Hg. If this were to increase due to increases in dead-space, the calculated CO would change as well. The relationships between the \( PaCO_2 \) and \( PvCO_2 \) levels are only valid when the \( PaCO_2 \) is more than 30 mm Hg, and when the CO2-Hgb dissociation curve is linear. Thus, an increase in minute ventilation which reduces \( PaCO_2 \) to <30 mm Hg would render the CO inaccurate. There are very few intraoperative situations where the \( PaCO_2 \) would need to be decreased below this level (severe metabolic acidosis or decreases in intracranial elastance). Also, changes in mechanical ventilation that alter either the dead-space or ventilation perfusion matching may result in the calculated CO changing when, in fact, none has occurred. The only system currently on the market is the NICO® system (NICO® Sensor, Respironics, Wallingford, CT, www.nico.respironics.com).
Several studies have investigated the accuracy of the partial-rebreathing system for determining CO, mostly in patients undergoing cardiac surgery or in hemodynamically stable ICU patients with differing degrees of intrapulmonary shunt.41,45–53 Overall, this system seems to correlate well with traditional \( P_{AC,TT} \)-derived measurements of CO. The system seems to perform best at normal CO, but suffers lack of agreement when CO is high,46,49–50 during periods of increased intrapulmonary shunt,47 or during severe chest trauma.51 In the study by Rocco et al., bias was \(-2.3 \text{ L/min when } Q_s/Q_p \) exceeded 35%.47

Overall, the studies on the CO2 rebreathing system have shown significant bias (range: \(-0.58 \) to \(-1.73 \text{ L/min} \)) in several patient populations, e.g., intraoperative general or cardiac surgery, or stable postoperative patients. There have been no reports on the device when used in hemodynamically unstable patients.47–49,52,54

Another drawback to the partial-rebreathing technique is that it is only a measure of CO and has no method of monitoring intravascular volume status or fluid responsiveness. There have been no clinical studies demonstrating outcome benefits using the CO2 rebreathing device.

### Lithium Dilution Devices

Indicator dilution methods of measuring CO were initially described in 1932 by Hamilton.55 The initial indicator used was usually indocyanine green. The technique of using lithium dilution to measure CO was first described in 1993 by Linton et al.56 A bolus of lithium chloride is injected into either a peripheral or central vein, and the subsequent lithium concentration decay is measured with a lithium-sensitive electrode in a preexisting arterial line. This electrode uses the Nernst equation to relate the voltage change across the electrode with the lithium concentration while applying a correction factor for plasma sodium, as the electrode has a low sensitivity for distinguishing these two cations. This information is then used to calculate a concentration versus time graph and the CO is then calculated from integrating the area under the curve. This technique requires an approximately 3 mL blood sample to obtain the lithium concentration. One of the advantages of this technique is that lithium does not naturally occur in plasma, therefore, it has a high signal-to-noise ratio. This allows very small doses to be used, and therefore toxic levels are virtually impossible to achieve.57 Further, lithium is rapidly redistributed and has no first pass loss from the circulation.

Some of the concerns regarding the lithium dilution method are the need for the repetitive blood draws (and the concern of this precipitating blood transfusions) and the lack of ability to measure cardiac preload. Furthermore, the use of nondepolarizing neuromuscular antagonists has been shown to affect the lithium sensor. If this system is used intraoperatively, the recommendation is that the sensor be re-calibrated before injection of these drugs or after the peak concentration of the drug has had time to subside.58

Currently there is only one product on the market that uses a lithium dilution to measure CO (LiDCO®, LiDCO, London, UK, www.lidco-ir.co.uk). This device measures CO and then uses a pulse contour device to obtain subsequent continuous measurements of CO and assessment of preload.

### Pulse Contour Devices

The theory behind using the arterial pulse waveform to measure CO dates back to 1899 when Otto Frank described the circulation in terms of a Windkessel model. It was Frank’s goal to be able to calculate CO from arterial pulse pressure. Windkessel is the German word for an air chamber. This model described the loads faced by the heart when pumping against the pulmonary or systemic circulation and the relationship between the arterial blood pressure and flow in the systemic and pulmonary arteries.58 The model compares a hydraulic pump in a closed circuit that is comprised of a water pump connected to a chamber with a pocket of air in it to the heart and systemic arterial system. When water is pumped into the chamber, the pocket of air is compressed and water is pushed back out of the chamber into the pump. The compressibility of air in this chamber represents the elasticity and distensibility of the arterial system, commonly referred to as the arterial systems compliance. The resistance that is met by the water leaving the Windkessel and flowing back to the pump represents the SVR. This model is called a two element Windkessel model. Further refinements to this theory have led to the development of the three and four element Windkessel model.

In 1904, Erlanger and Hooker theorized that CO was proportional to arterial pulse pressure. Despite this early observation, it was only during the last several years that the technology to accurately measure CO with the arterial waveform has become available. It was soon discovered that, to accurately measure CO using the pulse waveform, some other method was needed to calibrate the system.

Further, the compliance of the arterial tree was a major impediment to the accurate measurement of CO. Simply stated, the compliance of the arterial tree is nonlinear. That is, when a volume of blood is introduced into the vasculature at higher pressures, the compliance decreases more rapidly than when the same volume of blood is introduced at a lower pressure. Such corrections for the nonlinearity of the system were not available until more information on the compliance of human aortas became known in 1948.59 This led to measuring the systolic area from a waveform. The waveform was then calibrated with...
another method for measuring CO, and then corrected for aortic compliance.

In 1983, Wesseling et al. developed an algorithm that can be used to define an area under the systemic arterial pulse waveform that establishes SV.60 By integrating the area under the pressure time curve from end systole to end diastole the SV can be calculated.

Changes in the systolic pressure between the inspiratory and expiratory phase during mechanical ventilation can be used to ascertain intravascular volume status.61,62 By calculating the systolic pressure variation and the SV variation (SVV) (derived from the continuous CO measurement), the pulse contour systems can also function as volume status monitors.

Since their inception, pulse contour devices have been extensively studied and validated with many studies showing a bias of 0.03 to 0.3 L/min.63–67 These studies were conducted in a variety of patient populations (postcardiac surgery, medical ICU patients) and bias and precision were clinically acceptable. The accuracy of CO measurement remained despite changes induced with esmolol in one study.64 However, in another study with cardiac surgical patients, the CO lost its correlation with PAC_TTD-derived CO when SVR was artificially increased with phenylephrine.68 The lack of correlation between pulse contour devices and PAC_TTD has also been demonstrated in conditions in which the arterial waveform is altered, such as aortic regurgitation and the use of an intraaortic balloon pump. Pulse contour devices are affected by extrinsic factors such as positive end-expiratory pressure and tidal volume. Several studies have shown that alterations in tidal volume or the level of positive end-expiratory pressure can alter the derived CO.32,69,70

Pulse contour devices have some advantages over other devices used to measure CO. They require little training, are simple to calibrate and provide an estimation of intravascular volume status. Their use in high-risk surgical patients in whom more invasive hemodynamic monitoring is desired will likely increase in the future.

A newer device to measure CO noninvasively is the FloTrac (FloTrac® Edwards LifeSciences LLP, Irvine CA, www.edwards.com/products/mininvasive). This device also uses the arterial pressure waveform to measure CO. The difference over other monitors (such as the LiDCCO®) is that it does not need to be calibrated with an indicator, such as lithium or with a transpulmonary-derived measure of CO. The essence of this technology is the application of advanced statistical principles to the arterial pressure tracing that result in the creation of a proprietary algorithm that recalibrates itself constantly. By measuring the arterial pressure over a 20 s period at 100 Hz, the system obtains 2000 data points for analysis. The standard deviation of these points is then compared with empirical data stored in the proprietary algorithm of the software correlating the standard deviation of the arterial pressure measurements with the appropriate SV. The FloTrac® is also able to account for changes in arterial compliance which allows for the device to remain accurate and reliable during periods when CO, vasomotor tone or both are changing.

A recent study in cardiac surgical patients comparing the FloTrac with PAC_TTD CO showed good correlation with the PAC with a bias of 0.55 L/min.71 The FloTrac also has the advantage of being able to determine SVV as a monitor of preload responsiveness. It is these features (the lack of need of a standard calibration and the ability to remain accurate in dynamic physiologic states) that could potentially make the FloTrac a useful addition to the group of noninvasive CO monitors. The disadvantages of the FloTrac and other pulse contour analysis systems (lack of correlation with PAC_TTD when the hemodynamics or arterial waveform are altered) are being rectified by the manufacturers. Newer generation pulse contour analysis monitors calculate the pulsatility of the arterial waveform more frequently, thus leading to better correlation with PAC_TTD when patients’ hemodynamics are changing.

The pulse contour devices are perhaps the most promising with regard to their ease of use, precision when compared with PAC_TTD ease of calibration, and their ability to measure intravascular volume responsiveness. However, more studies demonstrating clinical utility in different patient populations (such as those who are hemodynamically unstable) are needed.

**TRANSPULMONARY THERMODILUTION TECHNIQUES**

This technique uses a central venous catheter and an arterial line to intermittently measure the CO via transpulmonary thermodilution. The arterial catheter (that must be placed in a femoral, brachial or axillary artery) is then used as a pulse contour device to measure CO continuously. Radial artery catheterization is not sufficient, as the damped waveform that can occur with the use of vasopressors or changes in SVR has shown to invalidate the CO measurements. The PiCCO system (Pulsion Medical Systems, Munich, Germany, www.pulsion.com) uses this technology and provides the operator with several continuous variables to monitor patient’s hemodynamic status. SV and SVV are continuously measured, whereas variables, such as extravascular lung water are measured intermittently. Extravascular lung water is a potentially important measurement as it may be able to predict a patient’s risk of developing pulmonary edema with intravascular volume loading.

This technology is more widely used in Europe and has good agreement with other standard measures of CO. In patients undergoing liver transplant or CABG surgery bias ranged from 0.04 to 0.3 L/min.72–74 When trialed in patients with hemodynamic instability, the PiCCO system was not as accurate, with one study...
CONCLUSIONS

With the advancing age of the surgical population and the increasing prevalence of ischemic heart disease, the need for monitoring of organ flow is likely to increase. Because of the inherent limitations and complications of the use of a PAC, clinicians (both in the OR and the critical care setting) are looking more toward the use of minimally or noninvasive monitors of CO.

Of the available monitors, the ED and the arterial pulse contour devices seem to have the greatest potential at replacing the PAC for CO measurement. Some of the limitations of these devices, such as the inability to measure pressures in the central circulation (i.e., pulmonary artery occlusion pressure) will limit their use in patients in whom concern over the development of pulmonary edema is present. Furthermore, the inability of these devices to measure either central or true mixed venous oxygen saturation limits their use in the assessment of global tissue perfusion. However, some of the noninvasive CO monitors have the ability to predict fluid responsiveness. The ED and arterial pulse contour monitors have been shown (when combined with an intraoperative goal-directed fluid strategy) to reduce postoperative morbidity. A summary table of the studies that have demonstrated benefits of goal-directed therapy is shown in Table 2.

All of the currently available noninvasive monitors have advantages and limitations. With an increasing...
number of clinical studies being published on the applicability, suitability, and clinical utility of these monitors and more importantly demonstrating outcome differences, their use should continue to gain popularity.

REFERENCES
