Review Article

Cardiac Output Assessed by Invasive and Minimally Invasive Techniques

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

1. Cardiac Output Assessed by Invasive and Minimally Invasive Techniques

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

2. History

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

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

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

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

$$Flow = \frac{C_0 V_0}{\int c(t)dt}, \quad (2)$$

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

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

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

3. Intermittent Bolus Pulmonary Artery Thermodilution

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

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

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

4. Reliability of Thermodilution

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

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

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

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

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

Spontaneous and mechanical ventilation both alter right ventricular output throughout the respiratory cycle more so than left ventricular outflow. Studies evaluating the effects of the mechanical ventilatory cycle on TD measurements reveal inspiratory decreases in right ventricular ejection fraction and subsequent increases in right ventricular end systolic volumes [16]. A fall in left-sided CO, however, is largely prevented by the increase in right ventricular end diastolic volume. These findings explain the greater ventilatory modulation of right ventricular volumes. In the past, measurements taken at the end of expiration were thought to produce the greatest reproducibility. On the contrary, it is argued that more reliable estimations of mean TD CO should be taken from three to four serial CO measurements at different phases of the cycle [6]. Some authors recommend at least eight measurements taken randomly at different times during the ventilatory cycle [16].
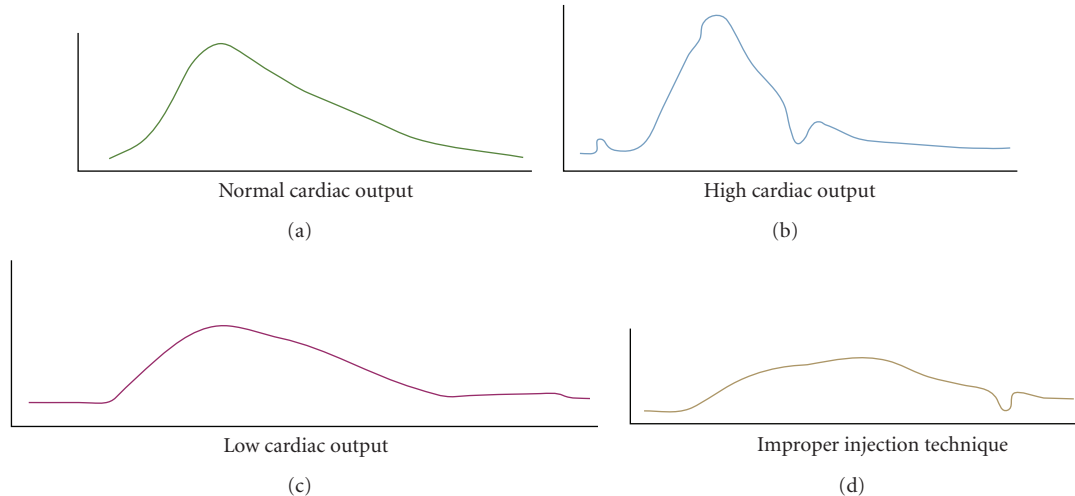
FIGURE 1: Thermodilution cardiac output curves. Used with permission from [8].

5. Continuous Pulmonary Artery Thermodilution

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

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

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

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

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

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

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

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

6. Minimally and Noninvasive Techniques

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

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

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

7. Pulse Power Analysis

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

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

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

(iii) Damping of the transducer system.

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

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

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

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

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

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

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

  (i) aortic valve regurgitation,

 (ii) post-aortic reconstruction,

 (iii) intra-aortic balloon pump,

(iv) highly damped peripheral arterial lines,

 (v) severe peripheral arterial vasoconstriction,

(vi) inaccurate sodium and hemoglobin measurements,

(vii) arrhythmias,

(viii) intra- or extracardiac shunts.

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

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

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

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

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

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

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

Yamashita et al. [46] compared bolus PATD with the PulseCO, calibrated with CO by the TD method in patients during cardiac-surgery. They found poor correlation ($r =$

0.49–0.55) and large bias (0.3–0.76), concluding that the methods were not interchangeable. In an observational study of 8 after-cardiac-surgery patients, McCoy et al. [45] compared continuous cardiac index monitoring (CCI) with LiDCO, using a peripheral iv line for indicator delivery. The investigators found minimal bias (-0.01) but wide 95% limits of agreement with respect to the mean, suggestive of clinically significant differences.

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

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

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

8. Pulse Contour Analysis

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

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

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

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

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

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

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

9. FloTrac/Vigileo

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

The FloTrac algorithm integrates multiple characteristics of the arterial pressure waveform with patient specific demographic data. Parameters include heart rate (HR), the sta-

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

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

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

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

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

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

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

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

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

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

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

$$CO = \frac{VCO_2}{Cv_{CO_2} - Ca_{CO_2}},\qquad(4)$$

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

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

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

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

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

$$\frac{Q_s}{Q_T} = \frac{CcO_2 - CaO_2}{Cc_{O_2} - CvO_2}\qquad(5)$$

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

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

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

11. Thoracic Bioimpedance

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

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

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

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

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

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

  (i) changes in tissue fluid volume,

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

  (iii) changes in electrode contact or position,

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

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

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

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

11.2. Validation Studies. Several investigators found that TEB compared favorably with PATD in varying settings including during cardiac catheterization, surgical patients, and emergency room patients [102, 104–108]. Van De Water et al. [109] found the TEB compared favorably with TD in post cardiac surgical patients. Kööbi et al. [110], using whole-body impedance cardiography in CABG patients, reported excellent repeatability which allowed for continuous monitoring. Spiess et al. [111] used BioZ (SonoSite Inc, Bothell, Wash,USA) intraoperatively for patients undergoing CABG and found that the technique initially compared well with TD, but, immediately postoperatively, the Bland-

Altman analysis was not as robust. Of note, good correlation was seen during opening of the chest. Spinale et al. [112] used TEB for post-CABG patients and found good correlation with TD but poor correlation in patients who developed severe tachycardia and frequent arrhythmias.

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

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

12. Thoracic Bioreactance

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

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

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

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

13. Endotracheal Cardiac Output Monitor

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

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

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

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

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

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

14. Ultrasound Dilution

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

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

14.1. Validation Studies. Relatively few studies investigating the technology have been undertaken thus far. Galstyan et al. [122] compared CO and blood volumes using UD and

PiCCO technology in adult ICU patients and concluded that the two were equivalent and interchangeable in that patient population. PiCCO blood volumes were significantly higher. The technology appears to be able to be used in different patient population groups. Krivitski et al. [123] performed in vitro studies to confirm the ability of UD technology to measure small flows and volumes in pediatric patients and neonates. Tsutsui et al. [124] found good correlation with TD in patients undergoing abdominal surgery.

15. Transesophageal Echocardiography

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

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

16. Esophageal Doppler

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

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

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

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

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

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

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

16.2. Validation Studies. Multiple studies have compared the validity of ED for measurement of CO against PATD under varying conditions [129, 137–139]. Dark and Singer [139] published a meta-analysis of eleven studies in critically ill patients, finding a pooled median bias of 0.19 L/min

(range: -0.69–2.0 L/min) for CO. Boulnois and Pechoux [140] reported the pooled limits of agreement for 3 studies including 90 patients under a range of flow states to be -2.21 to 2.33 L/min. Laupland and Bands [133], in a meta-analysis of 25 studies, concluded that ED was reliable, responsive to changes, was showed good agreement with low bias, however, the wide limits of agreement raised concerns about precision. The two techniques are therefore not thought to be interchangeable; however, ED may be used to track changes [137].

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

17. Conclusion

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

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

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