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REVIEW ARTICLE

Minimally invasive or noninvasive cardiac output measurement: an update

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Abstract Although cardiac output (CO) by pulmonary artery catheterization (PAC) has been an important guideline in clinical management for more than four decades, some studies have questioned the clinical efficacy of CO in certain patient populations. Further, the use of CO by PAC has been linked to numerous complications including dysrhythmia, infection, rupture of pulmonary artery, injury to adjacent arteries, embolization, pulmonary infarction, cardiac valvular damage, pericardial effusion, and intracardiac catheter knotting. The use of PAC has been steadily declining over the past two decades. Minimally invasive and noninvasive CO monitoring have been studied in the past two decades with some evidence of efficacy. Several different devices based on pulse contour analysis are available currently, including the uncalibrated FloTrac/Vigileo system and the calibrated PiCCO and LiDCO systems. The pressure-recording analytical method (PRAM) system requires only an arterial line and is commercially available as the MostCare system. Transesophageal echocardiography (TEE) can measure CO by non-Doppler- or Doppler-based methods. The partial CO_2 rebreathing technique, another method to measure CO, is marketed by Novametrix Medical Systems as the NICO system. Thoracic electrical bioimpedance (TEB) and electric bioreactance (EB) are totally noninvasive CO monitoring. Nexfin HD and the newer ClearSight systems are examples of noninvasive CO monitoring devices currently being marketed by Edwards Lifesciences. The developing focus in CO monitoring devices appears to be shifting to tissue perfusion and microcirculatory flow and aimed more at markers that indicate the effectiveness of circulatory and microcirculatory resuscitations.

Keywords Minimally invasive cardiac output · Pulmonary artery catheter · Swan–Ganz catheter · Noninvasive cardiac output

Introduction

Cardiac output (CO) measurement has been considered one of the most important elements of perioperative hemodynamic monitoring in modern medicine ever since balloon-tip pulmonary artery catheterization (PAC) was introduced by Drs. Swan and Ganz in 1970 [1]. Perioperatively, PAC has been commonly used in major cardiothoracic surgery, in patients with significant coexisting cardiovascular diseases undergoing non-cardiovascular procedures, and other critically ill patients [2]. For the past four decades, PAC has been considered the "gold standard" in CO measurement. However, it has been controversial whether the utilization of PAC-derived parameters to guide the clinical management of critically ill patients improves clinical outcomes [3–7]. Clinicians worldwide have witnessed a gradual transition from the invasive PAC-thermodilution (TD) technique to less invasive techniques during the past decade [8]. This review is aimed at providing updates of the emerging and currently available minimally invasive and noninvasive techniques for the measurement of CO. The characteristics,

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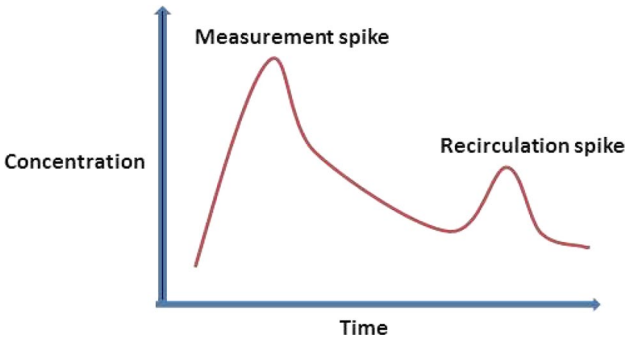

Fig. 1 Indicator-dilution curve. Cardiac output is inversely proportional to area under the curve (AUC). Second peak is an effect of recirculation

indications, contraindications, and typical limitations of these different devices are also discussed.

CO measurement and pulmonary artery catheter

In 1870, Dr. Adolf Fick discovered a method of computing an animal's CO based on the oxygen consumption and the difference in oxygen content between arterial and venous blood (Eq. 1) [9]:

$$\text{Fick's principle: } CO = (VO_2) / (CaO_2 - CvO_2), \quad (1)$$

where VO_2 = oxygen consumption per minute, CaO_2 = arterial oxygen content, and CvO_2 = mixed venous oxygen content.

In 1893, George Stewart developed an indicator-dilution technique, using hypertonic saline as an indicator, to determine CO [10]. Based on Stewart's work, William Hamilton used indocyanine green as the indicator, instead of saline, to measure the variation of concentrations over time in human circulation. CO is equal to the quantity of dye injected divided by the area under the time–concentration curve (Fig. 1; Eq. 2) [11].

$$\text{Stewart-Hamilton equation: Flow} = C_0 V_0 \Big/ \int C(t)\mathrm{d}t, \quad (2)$$

where C_0 = initial concentration of injector, V_0 = initial volume of injector, and the denominator = the integral of indicator concentration over time.

The application of Fick's principle for the measurement of CO was not possible in humans until Dr. Werner Forssman developed a technique to sample mixed venous blood from the pulmonary artery in 1929 [11]. However, widespread clinical use of CO measurement became practical only after the balloon-tipped PAC was introduced by Drs. Swan and Ganz in 1970 [1]. Obviously, PAC is invasive because it involves inserting a large-bore multi-lumen catheter from the internal jugular or subclavian vein to the pulmonary artery, going through two cardiac chambers and two cardiac valves. Its application has been associated with numerous complications (Table 1) [12, 13]. Beyond the complications associated with PAC placement, the efficacy and clinical benefit of PAC are questionable. Numerous studies indicated PAC lacks positive benefits in clinical outcomes [5, 7, 14, 15], and some studies even demonstrated an increase in hospital mortality [3, 4, 16]. However, these studies showed an improvement in mortality in surgical, critically ill, and septic patients [17, 18]. Thus, PAC may still have a role in some specific conditions such as right ventricular failure, pulmonary hypertension requiring vasodilator therapy, or septic patients [19]. For the aforementioned reasons, the clinical application of PAC has been noticed to experience a steady decline during the past decade. In the meantime, the race to develop alternative technology to replace PAC has been leaping forward [20]. Currently, there are some less invasive techniques already on the market. An ideal CO measurement should have the following features: advanced and comprehensive, minimally/

Table 1 Complications associated with pulmonary artery catheterization [12, 13, 120]

PAC complications	Reported incidence (%)
Central venous access	
Arterial puncture	0.1–13
Postoperative neuropathy	0.3–1.1
Pneumothorax	0.3–4.5
Air embolism	0.5
Catheterization	
Minor dysrhythmias	4.7–68.9
Severe dysrhythmias (ventricular tachycardia or fibrillation)	0.3–62.7
Minor increase in tricuspid regurgitation	17
Right bundle-branch block	0.1–4.3
Complete heart block (in patient with coexisting left bundle-branch block)	0–8.5
Catheter indwelling	
Pulmonary artery rupture	0.03–1.5
Positive catheter-tip cultures	1.4–34.8
Catheter-related sepsis	0.7–11.4
Thrombophlebitis	6.5
Venous thrombosis	0.5–66.7
Mural thrombus	28–61
Valvular/endocardial vegetations or endocarditis	2.2–100
Death (attributed to pulmonary artery catheter)	0.02–1.5
Catheter knotting intracardially	Several case reports

noninvasive, continuous, and reliable hemodynamic assessment, and be user friendly with minimal complication and ultimately improved outcome. Unfortunately, none of the current techniques yet meets all these criteria. In regard to acceptable precision of an alternative new development, Critchley and Critchley defined a cut-off value of 30 % agreement with current technology to be acceptable [21].

Minimally invasive CO monitoring

Arterial contour analysis

The idea that stroke volume (SV) can be derived from pulse pressure (PP) was observed by Erlanger and Hooker [22]. Currently, there are several different devices based on pulse contour analysis, including the uncalibrated FloTrac/Vigileo system (Edwards Lifesciences) [20] and the calibrated systems including PiCCO (PULSION Medical Systems) and LiDCO (London, UK) [22].

FloTrac/Vigileo: a noncalibrated arterial contour analysis technique

The technique and its mechanism The FloTrac/Vigileo system was first introduced by Edwards Lifesciences in 2005 [23]. It has a blood flow sensor (FloTrac) connecting to an arterial line and Vigileo monitor. The system provides a display of CO, SV, stroke volume variation (SVV), and systemic vascular resistance (SVR) without requiring external calibration [20]. The basic principle is based on the linear relationship between PP and SV (Eq. 3) [24]:

$$SV = SD_{AP} \times \chi. \quad (3)$$

where SD_{AP} = the standard deviation of the data points and reflects PP (Fig. 2a), and factor χ = the conversion factor that depends on arterial compliance (assessed by gender, age, height, weight), mean arterial pressure (MAP), and waveform characteristics. In the third-generation FloTrac/Vigileo, factor χ is calculated every minute [21], whereas in the fourth- generation device it is calculated every 20 s [20].

Advantages and limitations The FloTrac system is less invasive, provides continuous CO monitoring, and is relatively easy to use. However, its accuracy is limited in unstable patients, patients with severe arrhythmia, severe aortic valve regurgitation, and other factors disturbing the arterial waveform [25]. Because the FloTrac/Vigileo system does not require external calibration, the accuracy and precision may be slightly decreased when compared with the calibrated system in some conditions [22, 23, 26]. Hence, in patients with hemodynamic instability, the calibrated device may offer an advantage over the uncalibrated devices [24].

Validity studies The FloTrac system has released three different versions of software. The third-generation software is improved in accuracy as it relies on a much larger dataset, including larger proportions of hyperdynamic and vaso-

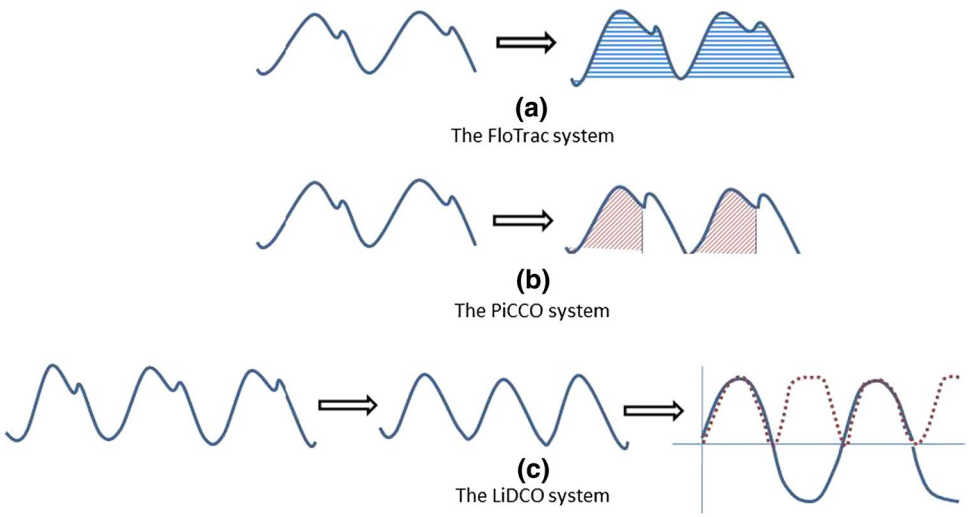

Fig. 2 Different methods of arterial waveform analysis. **a** The FloTrac system samples data points from the arterial waveform at a set frequency. Pulse pressure is assessed by calculating the standard deviation of the data point. **b** The PiCCO and PRAM system: the starting point is the area under the systolic portion of the arterial waveform. **c** The LiDCO system converts the arterial pressure waveform into a standardized volume waveform that is analyzed as sine wave [$F(X)$] using the root mean square (RMS) method, also known as pulse power analysis. (From [24], with permission)

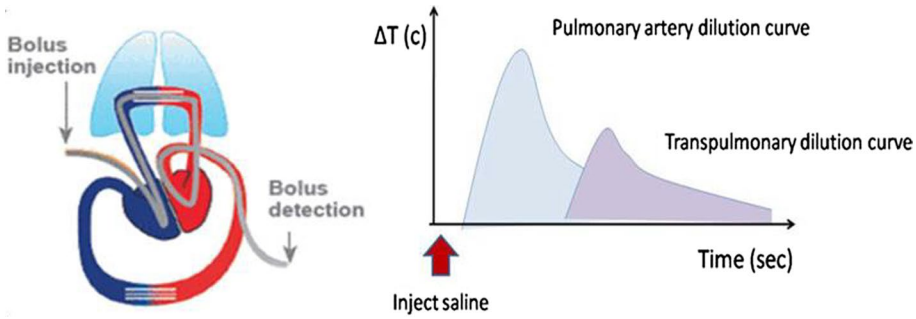

Fig. 3 Thermodilution curve after injection of cold saline (*red arrow*) via the superior vena cava. Peak temperature change arrives earlier when measured in the pulmonary artery (*first peak*) than if measured in the femoral artery (*second peak*). (Picture on *left* from Pulse Medical System, with permission)

plegic patients [27]. In septic patients and cardiac surgery patients, an acceptable agreement of the third-generation FloTrac system and PAC was established [27, 28], with a percentage error of 29 % and 20 %, respectively. In the perioperative period, the third-generation FloTrac system was able to track changes in CO induced by fluid preload [29]. A study by Slagt et al. found the ability to perform CO measurement in normodynamic or hypodynamic conditions but not in hyperdynamic CO status [30]. One meta-analysis study supported the use of the FloTrac system if used with consideration of its limitations [25]. However, the use of third-generation software was inaccurate in patients with low SVR [31–33], those using high doses of vasopressor therapy [34, 35], during liver transplantation surgery [33], and during cardiac surgery [36]. Therefore, some studies suggested even the third-generation software may still not be the replacement of PAC [37]. To overcome the limitations, Edward Lifesciences improved the software and released the FloTrac system 4.0 in May 2014 [20]. A study compared CO measurement by FloTrac and transesophageal echocardiography (TEE) during abdominal aortic aneurysm surgery. The FloTrac system was found not clinically acceptable for use in abdominal aortic aneurysm surgery [38]. In the study by Mutoh et al., CO measured by the third-generation FloTrac system was lower when compared to the PiCCO system during hyperdynamic therapy with dobutamine for reversing delayed cerebral ischemia [39].

PiCCO monitor (Pulse Medical System, Munich, Germany)

The technique and its mechanism The PiCCO system was approved for clinical use in 2000. PiCCO applies a special algorithm that combines real-time continuous monitoring through pulse contour analysis with intermittent transpulmonary thermodilution (TPTD) measurement (Fig. 3). PiCCO provides almost all the same hemodynamic parameters as other techniques [40]. The PiCCO system calculates CO by Eq. 4 [41].

$$\mathrm{CO} = \mathrm{cal} \times \mathrm{HR} \times \int_{\mathrm{systole}} \left(P(t)/\mathrm{SV} + C(p) \times \mathrm{d}P/\mathrm{d}t\right)\mathrm{d}t, \tag{4}$$

where cal = calibration factor derived from TPTD, HR = heart rate, $\int_{\mathrm{systole}}$ = systolic portion of curve (Fig. 2b), $P(t)$ = pressure change over time, SVR = systemic vascular resistance, $P(t)$/SVR = the area under the arterial pressure curve in systole where SVR is derived from mean arterial pressure/CO, $C(p)$ = aortic compliance, and $\mathrm{d}P/\mathrm{d}t$ = shape of the arterial waveform [41].

PiCCO arterial contour analysis uses the TPTD technique as an external calibration. The calibration interval is recommended to be every 8 h or whenever there is a clinically significant change in SVR. The central line catheterization should be placed in the central cardiopulmonary circulation; a common site is the internal jugular or subclavian vein. Placement in the femoral vein proved to be an alternative choice [42]. An arterial line is typically inserted at the femoral artery, although axillary, brachial, and radial arteries are acceptable alternative choices. In patients under high doses of catecholamine, pressure measurement in the femoral artery would be more advantageous than in the radial artery [43, 44].

Advantages and limitations The advantages for PiCCO are that it is less invasive and is useful in the pediatric population when a PAC is too large to be inserted [45–47]. Moreover, the TPTD method is independent of ventilator and respiratory cycles. Therefore, PiCCO gives consistent and reproducible results. The TPTD method has the unique ability to measure global end-diastolic volume (GEDV) and intrathoracic blood volume (ITBV), which can estimate the cardiac preload [48, 49].

Complications related to PiCCO were few, as reported by Belda et al. The incidence of site inflammation and catheter-related infection were 2 % and 0.78 %, respectively. Other complications were rare [50].

Contraindications to the use of PiCCO can be divided into two categories: contraindications to vascular device insertion (e.g., arterial grafting) and anatomical or physiological derangements that result in inaccurate measurement (e.g., regurgitant valve, intracardiac shunt, extracorporeal circulation).

Validity studies The PiCCO system was compared to PAC in septic patients and cardiac and lung transplant surgery

patients. The results showed satisfactory correlations [51, 52]. In conditions of insignificant changes of SVR, PiCCO was claimed to have 20 % percentage error with a bias of 0.23 l/min [53]. PiCCO was also compared to LiDCO and FloTrac as cross comparison against PAC; the results showed PiCCO and LiDCO measurements were comparable in a clinically acceptable range [54]. PiCCO was compared to Doppler ultrasound in critically ill patients, and good agreement was found with these two techniques [55]. Broch et al. measured CO by PiCCO and ccNexfin during cardiac surgery; a good correlation between them was also found [56]. Moreover, CO monitoring and using ITBV as guidance by the PiCCO system could reduce duration of mechanical ventilation and improve patient outcomes in septic patients [57]. However, some studies revealed large discrepancies between PiCCO and PAC in off-pump coronary artery bypass (OPCAB) surgery; the percentage error range can be as great as 32 % to 50 %, depending on the stage of operation [58].

LiDCOplus system (LiDCO, Cambridge, UK)

The technique and its mechanism The LiDCO system uses lithium as an indicator to determine CO, first described by Linton et al. [59]. This method is based on Stewart–Hamilton principles (Eq. 2). The LiDCOplus system is based on running two proprietary algorithms: an indicator dilution CO monitoring (LiDCO system) and a continuous arterial waveform analysis (PulseCO system). To increase its accuracy, the LiDCO system is used to calibrate the PulseCO system. The LiDCO system consists of a lithium sensor attached to the arterial line. Once lithium is injected into the venous circulation, blood samples from the arterial line are drawn, and a lithium concentration time curve is plotted. The area under the curve will determine CO. The lithium indicator can be injected via either central or peripheral venous access [60]. Thus, LiDCO system requires only an arterial line and a peripheral IV line.

The PulseCO system offers continuous CO monitoring. SV is calculated from the arterial pressure waveform using an autocorrelation algorithm. The volume of the arterial tree in arbitrary units is determined by the root mean square (RMS) method, which is independent of waveform morphology (Fig. 2c). The score value after the RMS method is called nominal SV, which is recalibrated with patient-specific factors to scale an "actual SV." These factors include the lithium indicator dilution and arterial compliance variations [24]. Therefore, the PulseCO system is recommended to be recalibrated every 8 h or with each major hemodynamic change [24, 61]. The LiDCOplus system provides various parameters including CO, intrathoracic blood volume (ITBV), MAP, SVR, SV, SVV, and pulse pressure variation (PPV) [61]. Recently, LiDCO Company has released "LiDCORapid," a new monitor that derives SV from the patient's arterial waveform using the PulseCO algorithm. The LiDCORapid helps optimally guide goal-directed therapy via PPV and SVV analysis.

Advantages and limitations The advantage of the LiDCOplus system is that it is less invasive than PAC and PiCCO because it needs only an arterial and a peripheral venous access [22, 40]. In addition, the LiDCOplus system can provide special parameters such as SVV or PPV. However, the accuracy of the LiDCOplus system may be compromised under circumstances such as patients with aortic regurgitation, severe arrhythmia, and severe peripheral vasoconstriction, and patients who receive lithium therapy [22, 40].

Contraindications of the LiDCOplus system include the following: (a) conditions related to a patient's extra lithium intake because this will lead to an overestimate of CO [40]; (b) patients who receive nondepolarizing muscle relaxant, which will interfere with the lithium sensor [62]; (c) other conditions including body weight <40 kg and first trimester of pregnancy [63]; and conditions related to anatomic cardiac abnormalities that lead to compromise in the accuracy of the PulseCO [61], such as patients with aortic valve regurgitation, intraaortic balloon pump (IABP), and poor quality of arterial signal.

Validity studies Linton et al. compared the CO measurements obtained by LiDCO and PAC thermodilution technique in immediate post-CABG patients. The results showed a good correlation of the two techniques [59]. LiDCO was also compared to PAC in post-liver transplant patients [64], post-cardiac surgery patients [65], and the postpartum period of patients with severe preeclampsia [66]. The results showed a satisfactory correlation between the two techniques. A randomized prospective controlled clinical trial conducted by Pearse et al. also demonstrated a significant reduction in complications and median hospital stay in high-risk surgical patients treated with LiDCOplus-based goal-directed therapy [63]. However, Yamashita et al. showed a poor correlation and large bias of PulseCO during off-pump CABG when compared to the PAC thermodilution technique. They concluded that PulseCO might be unsuitable for off-pump cardiac surgery patients [67]. Cross comparisons of LiDCO, PiCCO, FloTrac, and PAC were also performed. The results indicated LiDCO was the least erroneous compared to other less invasive devices [54]. In OPCAB surgery patients, when hemodynamic parameters as assessed by PAC thermodilution, LiDCOplus, and TEE were compared after fluid challenging, LiDCOplus showed a high sensitivity for assessing intravascular volume [68].

PRAM (pressure-recording analytical method)

The technique and its mechanism The pressure-recording analytical method (PRAM) is a technique designed for arterial pressure-derived continuous CO measurement with no need for any starting calibration or central venous catheterization. Therefore, PRAM needs only an arterial line as with FloTrac/Vigileo. PRAM technology is based on the principle that, in any given vessel, volume changes occur mainly because of radial expansion in response to pressure variations; simply put, the alterations of the systolic portion of the area under the curve reflect changes in SV [69]. This technique calculates CO using a number of physical parameters, including the force of left ventricular ejection, arterial impedance counteracting the pulsatile blood inflow, arterial compliance, and peripheral small vessel resistance [70]. What differentiates PRAM from other pulse contour analysis technology is that (1) PRAM calculates the area under curve by taking into account both pulsatile and continuous contribution of the physical forces underlying the relationship between pressure curve morphology and blood flow; and (2) the frequency sampling of PRAM is 1000 Hz whereas the other pulse contour methods use 100 Hz [71]. A higher frequency sampling allows a higher degree of precision. PRAM also provides various hemodynamic parameters including CO, SVV, PPV, and SVR.

Advantages and limitations PRAM is a less invasive technique that offers continuous monitoring of CO and other advanced hemodynamic parameters including SVV and PPV. PRAM can avoid the risk of CVP catheterization and is potentially more advantageous clinically. Although controversial, PRAM could be used for unstable patients with high doses of inotropic drugs and even for patients with IABP with sinus rhythm [72]. However, PRAM has some limitations: some are technically related (over-damping or under-damping of arterial waveforms) and some are patient related, such as inappropriate signal acquisition (e.g., aortic valve regurgitation) or abnormality of the peripheral arteries (e.g., aortic dissection, atherosclerotic plaque) [73, 74].

Validity studies The accuracy of PRAM has been studied over a wide range of conditions. Giomarelli et al. compared PRAM and PAC thermodilution technique in CABG patients, showing that PRAM is accurate for real-time monitoring of CO during surgery and the immediate postoperative period [75]. Similar results were also reported in unstable patients such as those with an intraaortic balloon pump (IABP) or patients with ongoing infusion of high doses of inotropic agents for low cardiac output syndrome [76]. A recent study in the post-cardiac surgery ICU also found a good agreement of cardiac index measurement between PRAM and PAC thermodilution technique in hemodynamically unstable patients, but not in those with atrial fibrillation [72].To further validate the use of PRAM, Donati et al. compared PRAM, PiCCO, and continuous PAC thermodilution in a mixed medical-surgical ICU. These results also showed a good concordance between PRAM, PAC, and PiCCO in hemodynamically stabilized patients, with percentage errors of 25 % and 28 %, respectively [77]. Romagnoli et al.investigated the utilization of PRAM, FloTrac/Vigileo, and transthoracic echocardiography in patients undergoing vascular surgery and showed PRAM had a good concordance with echocardiographic measurement [69]. However, some studies did show a lack of agreement between PRAM and PAC thermodilution technique in post-cardiac surgery patients [78] and in unstable patients with atrial fibrillation [79].

VolumeView (Edwards Lifesciences, Irvine, CA, USA)

VolumeView was introduced in 2010 by Edward Lifesciences. This system consists of a specific thermistor-tipped arterial catheter (the VolumeView catheter) and the EV1000 monitoring platform. It also has a special continuous central venous oxygen saturation ($ScvO_2$) monitoring via the PreSep oximetry catheter. The VolumeView system determines CO by continuous arterial pressure analysis on the femoral artery and external calibration using the TPTD technique. It provides various parameters, including EVLW, pulmonary vascular permeability index (PVPI), GEDV, ITBV, a new variable global ejection fraction (GEF), CO, SV, SVV, and SVR [80].The VolumeView was used in a surgical and interdisciplinary ICU and shown to be as reliable as the PiCCO system [81]. However, the technology is not yet fully validated in humans with larger sample size. Future studies would be required to evaluate the impact of the VolumeView system on morbidity and mortality.

Transpulmonary thermodilution (TPTD)

The transpulmonary thermodilution (TPTD) technique has been available for more than 20 years [82]. The PiCCO monitor and VolumeView are the only currently available devices applying the principle. TPTD is based on the Stewart–Hamilton principle and requires only central venous catheterization and arterial line [40]. After a bolus of cold saline (<8 °C) is injected via the central vein catheter, the cold saline is mixed with the blood in the circulation. The relative change in temperature reflects the CO flowing through the cardiovascular system (Fig. 3). A thermistor-tipped catheter is usually placed at a femoral artery or axillary or brachial artery [40, 41].

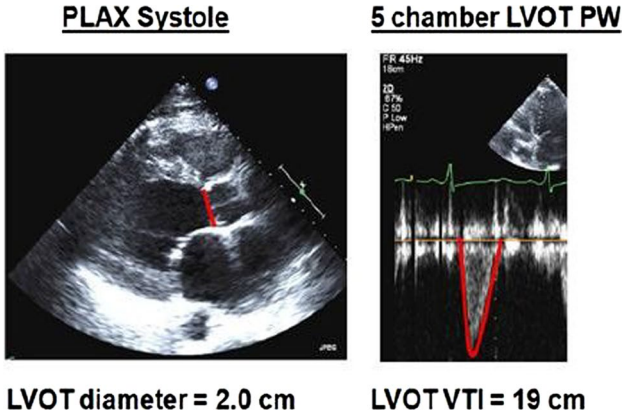

Fig. 4 Left ventricular outflow tract (LVOT) diameter measurement using LVOT long-axis view (*left*) and LVOT VTI measurement (*right*). (From [85], with permission)

Transesophageal echocardiography (TEE)

The technique and its mechanism

The first transesophageal echocardiography (TEE) was introduced in the early 1980s. Since then, TEE has evolved into an almost routinely used monitor and is an indispensable diagnostic tool in cardiovascular surgery [83]. Measurement of SV and CO with TEE can be accomplished by non-Doppler- or Doppler-based methods. However, the Doppler-based method is commonly used in clinical practice [23]. Blood flow is obtained by the Doppler frequency, which reflects the moving red blood cells (Eq. 5; Fig. 4) [23, 84, 85].

$$\mathrm{SV} = \mathrm{VTI} \times \mathrm{CSA}, \mathrm{CO} = \mathrm{SV} \times \mathrm{HR}, \quad (5)$$

where SV = stroke volume, VTI = Doppler velocity–time integral, and CSA = cross-sectional area.

CO measurement can be achieved by placing the TEE probe close to the left ventricular outflow tract (LVOT), which is essentially cylinder shaped, where diameter can easily be determined. So, the cross-sectional area (CSA) can be calculated by the formula πr^2. The "velocity time integral" (VTI) can be measured with continuous-wave Doppler at LVOT. With known CSA and VTI, SV can then be calculated (Fig. 4) [23]. TEE can provide not only hemodynamic assessment such as ventricular volume, SV, and CO, and estimation of ventricular systolic function (EF), but also anatomical information such as RV strain for suspected pulmonary embolism [85]. Furthermore, volume assessment can be obtained via TEE by measuring left ventricular end diastolic area (LVEDA). Therefore, TEE can be crucial in guiding proper treatment, such as cessation of inotropic treatment, or administration of volume or vasoconstrictors [82].

Advantages and limitations

TEE offers tremendous advantages, as it can detect anatomical abnormalities, volume status, myocardial contractility information, and other functional assessment as well as hemodynamic parameters. TEE provides relatively minimally invasive and real-time measurement of CO. However, TEE is usually limited to anesthetized patients. Moreover, it cannot be used in very small children because of the size of the probe. The accuracy is also highly dependent upon the quality of echocardiographic images and the operator's skill and experience [9, 22, 23]. Although overall it is very safe, TEE has its intrinsic risks. As the TEE probe is introduced blindly into the esophagus, it can potentially injure the hypopharynx or the esophagus [86]. The risk factors of the complications are often associated with preexisting esophageal pathologies. In a retrospective study of 7200 cardiac surgery patients, there was no TEE-associated mortality, and morbidity incidence was 0.2 %. The most common complication was severe odynophagia (0.1 %). Other complications could include dental injury (0.03 %), endotracheal tube malpositioning (0.03 %), upper gastrointestinal hemorrhage (0.03 %), and esophageal perforation (0.01 %) [83]. Therefore, TEE should not be used in patients with severe esophageal strictures and should be used cautiously in those with esophageal varices or recent esophageal surgery [87]. The general risk factors for TEE complications are gastroesophageal pathology, difficulty with TEE probe insertion, the elderly or children, history of thoracic radiation, cervical arthritis, and prolonged surgical duration/TEE probe insertion time [88].

Validity studies

The TEE and PAC thermodilution techniques were compared during cardiac surgery. The results indicated clinically acceptable agreement between the two techniques [89]. TEE was compared to PAC in mechanically ventilated patients. A significant correlation between the two techniques was identified. However, TEE had a wider range limits of concordance with PAC technique (−1.73 to 1.29 l/min) and higher percentage errors (38.6 %) [90]. Concha et al. compared TEE with FloTrac/Vigileo in laparoscopic colon surgery patients and found a clinically significant discrepancy in CO measurement by TEE and FloTrac/Vigileo (percentage error, 40 %) [91].

Partial CO_2 rebreathing technique: the NICO system

The technique and its mechanism

The partial CO_2 rebreathing technique was marketed by Novametrix Medical Systems as the NICO system in 1999

[22]. This method applies Fick's principle (Eq. 6) by using expired carbon dioxide (CO_2) concentration as an indicator. Venous CO_2 (VCO_2) can be calculated from the difference between inspired and expired gases. NICO system uses an extra loop of ventilatory circuit to create a transient partial CO_2 rebreathing system, thus increasing the end-tidal CO_2 ($EtCO_2$). The mixed venous CO_2 ($CvCO_2$) is estimated by this rebreathing process. The $CaCO_2$ can be approximated by the change in $EtCO_2$ and multiplied to the slope of the CO_2 dissociation curve (S). Because the intrapulmonary shunt can affect the estimation of CO, arterial blood gas is needed to evaluate for shunt estimation [22, 92].

$$\text{Modified Fick's equation: } CO = \Delta VCO_2 / S \times \Delta EtCO_2, \quad (6)$$

where VCO_2 = the difference between inspired and expired CO_2 content, $CvCO_2$ is estimated by using a partial rebreathing technique, and $CaCO_2$ is estimated from the $PaCO_2$ and the end-tidal CO_2.

The NICO system is limited to intubated, sedated, and mechanically ventilated patients. Moreover, NICO cannot be used in severe lung injury patients, as they often have increased shunt and this leads to potential errors in estimating CO [92]. Rocco et al. reported NICO worked very well when the pulmonary shunt level is low, but not when the pulmonary shunt was more than 35 % [93].

Advantages and limitations

The advantage of the NICO system is minimal invasiveness and capability of continuous monitoring of CO. However, NICO is restricted to intubated patients without severe gas-exchange abnormality and patients with $PaCO_2$ above 30 mmHg [22]. Moreover, it is contraindicated in patients who cannot tolerate a brief rebreathing period [23].

Validity studies

NICO was compared to the PAC technique in critically ill patients [94] and off-pump cardiac surgery patients [95]. The results showed a high degree of agreement of these two techniques. Some studies have demonstrated poor concordance between PAC and the NICO system in thoracic surgery and post-cardiac surgery [96]. Botero et al. reported a poor correlation between the PAC technique and the NICO system, as CO measured by NICO tends to be underestimated after separating from cardiopulmonary bypass (CPB). However, better correlation was seen before initiation of CPB [97]. Erroneous measurement of CO by the NICO system was observed in acute alterations of circulation [98], or in patients with decreased minute ventilation or increased intrapulmonary shunt

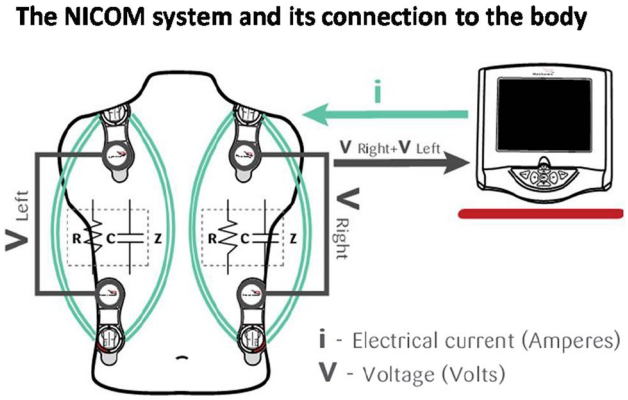

Fig. 5 The NICOM system. (Pictures from NICOM Cheetah Medical with permission)

[71, 99]. NICO was also compared to esophageal Doppler in major abdominal surgery and a poor concordance was observed between them [100]. Similarly, Mielck et al. found weak correlation between NICO and PiCCO systems [101]. Thus, the NICO system may serve as an alternative CO measurement to the PAC thermodilution technique in certain patient groups such as heart surgery patients [92].

Noninvasive CO measurement techniques

In the past decade, a number of truly noninvasive CO monitoring devices have been developed. However, most of them still have limitations and will need further refining for better accuracy and precision.

Thoracic electrical bioimpedance (TEB)

The technique and its mechanism

TEB involves delivery of a low-amplitude high-frequency electrical current across the thorax. The sensing electrodes measuring impedance are placed on the upper and lower thorax. Hemodynamic parameters are measured by TEB devices based on changes in the thoracic electrical conductivity to changes of thoracic aortic blood flow during the cardiac cycle. By measuring the impedance change generated by the pulsatile flow and the time intervals between the changes, SV can be calculated [22, 102].

Advantages and limitations

TEB is a completely noninvasive CO monitoring method. However, TEB is limited by arrhythmia, fluid in the thoracic component, and noise from mechanical ventilation or

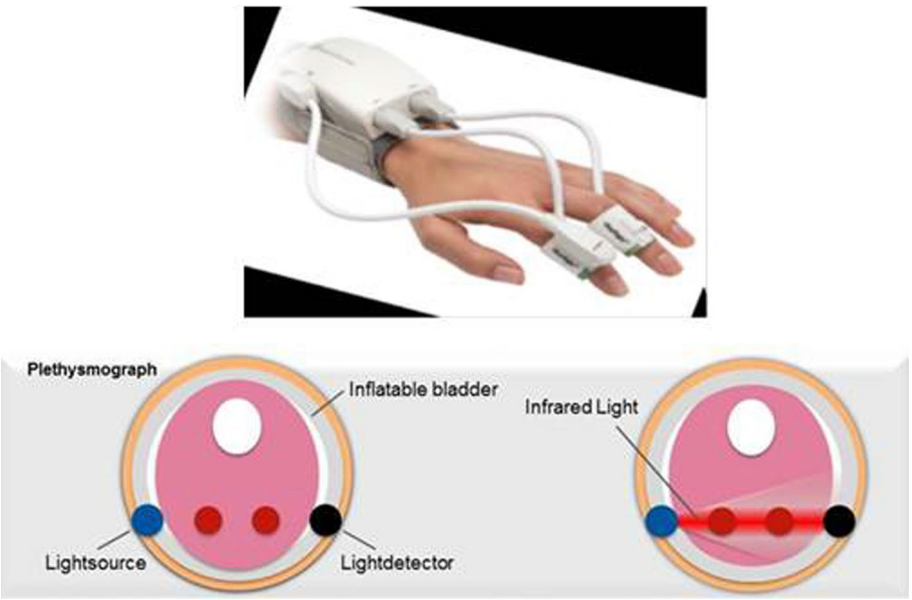

Fig. 6 Finger cuff and volume clamp method. (Pictures from Edwards Lifesciences website with permission)

surgical electrocautery. In addition, the patients need to be intubated, and signal stability often fades after 24 h of the application [22, 84]. Thus TEB is less likely to be used in routine CO monitoring alone. Subsequently, bioreactance was developed to overcome the limitations of TEB.

Validity studies

In post-cardiac surgery patients, CO measurement by the TEB and PAC techniques was compared. TEB had an acceptable accuracy but it might be more useful as a hemodynamic trending analysis, not as a diagnostic interpretation tool [103].

Electrical bioreactance cardiography

The technique and its mechanism

Electric bioreactance (EB) was developed to overcome the limitations of TEB. EB analysis is based on changes in frequency of electrical resistivity across the thorax. The EB signal is less susceptible to interference from chest wall movement, lung edema, and pleural effusion. EB technology is commercially available as the NICOM system in the U.S. [22, 102]. To evaluate CO, four dual electrodes are placed on the chest wall. Each sticker contains an electrode to inject an alternating current (i) with the frequency 75 kHz into the body, and the other electrode is the voltage input amplifier (v) to detect and summarize the return signal (Fig. 5). Then NICOM measures the time delay between these two signals (i and v), which is called a phase shift. In humans, the majority of phase shifts are pulsatile flow from the aorta [104]. The NICOM monitor has a highly sensitive "phase detector" that detects phase shifts and summarizes them into the NICOM signals [104]. The NICOM signals are mainly correlated with aortic blood volume. Flow is the change in volume over time; thus, NICOM flow signals (dNICOM) can be obtained by deriving the NICOM signals in time. The maximum flow (dX/dt_{max}) is measured by the maximum point of the dNICOM signals. The ventricular ejection time is measured from the first and second zero crossing. The SV is calculated based on Eq. 7:

$$\mathrm{SV} = dX/dt \times \mathrm{VET}, \mathrm{CO} = \mathrm{SV} \times \mathrm{HR}. \quad (7)$$

Stroke volume is calculated based on thoracic phase-shift signals.

Advantages and limitations

Bioreactance is a totally noninvasive, continuous monitoring with more variety in clinical applications (e.g., from small children to adults) and is very safe for clinical use. However, signal interference was reported by electrocautery, causing transiently impaired signals [105]. Moreover, during episodes of low flow, NICOM signals may lose their accuracy [106].

Validity studies

In post-cardiac surgery patients, NICOM was compared to PAC technique with good correlation observed [104, 106]. In a multicenter study of intensive care patients, the NICOM, PAC, Fick's principle, and bioreactance technique were simultaneously compared [107]. In the subset analysis, NICOM had a better correlation to PAC than did other techniques [107]. In major abdominal surgery patients and post-cardiac

Table 2 Specific characteristics of different cardiac output (CO) monitoring techniques

CO technique	Product system	Invasiveness	Intermittent or continuous	Advantage	Limitations	Additional information
Intermittent bolus PAC-TD	PAC	++++	Intermittent	Gold standard technique for CO	PAC-related complications such as arrhythmias, tricuspid regurgitation, infections, bleeding, vascular injury, and accuracy highly depends on indicator injection technique	PAP, PCWP, SvO_2
Continuous PAC-TD	Vigilance II CCO by Edwards	++++	Continuous	Correlates well with intermittent bolus PAC thermodilution technique	All PAC-related complications	PAP, PCWP, SvO_2
TPTD	PiCCO system	+++	Continuous	Useful in smaller children	Require A-line and CVP	EVLW, GEDV, ITBV, SVV, PVV, $ScvO_2$
				GEDV and EVLW	Inability to measure pulmonary artery pressure	
				Independent of ventilator and respiratory cycle	Unreliable in patients with arrhythmia, poor arterial signal quality, rapid changes in vascular motor tone, aortic valve pathology, and on mechanical circulatory assist devices	
				Measure and integrate a wide array of hemodynamic		
					Avoid in patient with severe peripheral vascular disease	
	LiDCOplus system	+++	Continuous	Need only arterial line and peripheral venous line	Arrhythmia	ITBV, SVV, PVV
					Require good quality of arterial waveform	
					Intracardiac and extracardiac shunts	
					Calibration affected by muscle relaxant and lithium therapy	
	VolumeView	+++	Continuous	Extra parameters: global ejection fraction (GEF)	Require A-line and CVP	EVLW, PVPI, GEDV, ITBV, GEF, SVV, PPV, $ScvO_2$
				Continuous $ScvO_2$ monitoring		
Arterial waveform contour derived	FloTrac/Vigileo	++	Continuous	No external calibration	Arterial signal quality	SVV, PPV, MAP
					Rapid changes in vascular motor tone	
					Not indicated for IABP	
					Inaccuracy in hemodynamic instability	

Table 2 continued

CO technique	Product system	Invasiveness	Intermittent or continuous	Advantage	Limitations	Additional information
	MostCare (PRAM)	++	Continuous	No external calibration	Arterial signal quality Rapid changes in vascular motor tone Inaccuracy in such an abnormal arteries (e.g., aortic dissection, atherosclerotic plaque)	SVV, PPV, MAP
	The ClearSight system	–	Continuous	Noninvasive Easy to set up	Measurement is restricted to 8 h Not suitable in patient whose presence of strong vasoconstriction, Raynaud disease or very edematous fingers Erroneous may occur in patient with aortic valve insufficiency or proximal aneurysm	MAP, SVV, PPV
	PiCCO, LiDCO, VolumeView, as illustrated above					
TEE	GE Vivid Philips IE33	+	Intermittent	Anatomic and functional cardiac assessment	Esophageal disorder Operator dependent Mainly suitable for perioperative field	EF, LVEDA, diameter of IVC/SVC
Partial CO_2 rebreathing	NICO	+	Continuous	Relative less invasive	Only intubated patients, needs A-line The accuracy limits in patient with abnormal *V*/*Q* mismatch Valid only with CO_2 >30 mmHg Limit in patient who cannot tolerate a brief rebreathing period	
Bioimpedance	BioMED	–	Continuous	Noninvasive	Movement artifacts, e.g., noise from mechanical ventilator, electrocautery Thoracic fluid overload Arrhythmia Need to be intubated Signal stability fails after 24 h	

Table 2 continued

CO technique	Product system	Invasiveness	Intermittent or continuous	Advantage	Limitations	Additional information
Bioreactance	NICOM	–	Continuous	Noninvasive	Limit in condition of low flow period Signal artifact, e.g., electrocautery Signal stability fails after 24 h	

PAP pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *SV* stroke volume, *SVV* stroke volume variation, *PPV* pulse pressure variation, *GEDV* global end diastolic volume, *EVLW* extravascular lung water, *PVPI* pulmonary vascular permeability index, *ITBV* intrathoracic blood volume, *GEF* global ejection fraction, *EF* ejection fraction, *LVEDA* left ventricular end diastolic area, SvO_2 mixed venous oxygen saturation, $ScvO_2$ central venous oxygen saturation

surgery patients, NICOM was compared to the FloTrac system, with good agreement between these two techniques observed [105, 108]. Squara et al. studied the performance of NICOM by using PiCCO device as the reference. NICOM was also showed a good agreement with the PiCCO system [109]. However, an inconsistent result was seen in critically ill patients, with a percentage error of 82 % [110].

The ccNexfin system

The technique and its mechanism

The ccNexfin system was first introduced in 2007 by Edwards Lifesciences. Recently, a newer version called the ClearSight system has been available. This system is a completely noninvasive continuous CO monitoring system. It measures CO by combining continuous blood pressure monitoring and a novel pulse contour method (Nexfin CO-Trek) [111]. The ccNexfin system includes the following components [112]:

1. Continuous finger BP measurement: the finger cuffs wrap around the middle phalanx of the fingers to measure BP. Each finger cuff includes a LED emitter-detector that measures the diameter of the finger arteries (Fig. 6); it inflates and deflates to keep the diameter of finger arteries constant throughout the cardiac cycle (volume clamp method). The latest version improves its accuracy by performing real-time finger pressure measurement 1000 times per second [113].
2. Brachial pressure reconstruction: the brachial pressure waveform is modified from the finger pressure waveform by a transfer function based on the vast clinical database and correcting for the brachial–finger pressure gradient waveform.
3. Pulse contour method: the pulse contour method is used to estimate CO, which is based on the interaction between the cardiac systole, arterial input impedance (Z_{in}), and the systolic and diastolic arterial pressures, as shown by this formula: $\Delta P/Q = Z_{in}$. Z_{in} is calculated from the characteristic impedance, the total arterial compliance, and the total peripheral resistance, whereas ΔP is calculated from the systolic pressure–time integral of the brachial arterial pressure waveform.

The ccNexfin system provides various hemodynamic parameters including continuous BP, SV, CO, SVV, and SVR.

Advantages and limitations

The ccNexfin system provides continuous, noninvasive CO monitoring, and it is very easy to use. It also provides SVV

Table 3 Accuracy and precision of different minimally and noninvasive CO monitoring techniques

Technology	References	Studied device	Patient population	Cases	Criterion standard	CO or CI	Bias or *r* value	Error (%)	Conclusion
FloTrac-Vigileo system	Vasdev [28]	Third-generation FloTrac-Vigileo	Cardiac surgery patients	40	PAC-TD	CO	0.21 (−0.86 to 1.00) l/min	19	The newer software correlates better to PAC derived CO in the post bypass period
	De Backer [27]	Third-generation FloTrac-Vigileo	Septic patients	58	PAC-TD	CO	−2.6 (−4.1 to −1.2) l/min	30	In patient with sepsis, the third generation is more accurate, as precise, and less influenced by SVR than the second-generation software
	Marqué [31]	Third-generation FloTrac-Vigileo	Septic shock patients	18	Continuous PAC-TD	CI	−0.1 (2.1) l/min/m^2	64	Third-generation FloTrac/Vigileo appears to be inaccurate for CI monitoring in septic shock
	Monnet [35]	Third-generation FloTrac-Vigileo	Circulatory failure patients	60	PAC-TD	CI	0.26 (0.94) l/min/m^2	54	Third-generation FloTrac/Vigileo device was moderately reliable for tracking changes in CI induced by volume expansion and poorly reliable for tracking changes in CI induced by norepinephrine
	Biancofiore [33]	Third-generation FloTrac-Vigileo	Liver transplant patient	21	PAC-TD	CI	0.4 (0.94) l/min/m^2	52	Third-generation FloTrac-Vigileo provided improvements over the previous version. Further algorithm refinements will increase reliability in the highly complex setting of cirrhotic patients undergoing liver transplantation

Table 3 continued

Technology	References	Studied device	Patient population	Cases	Criterion standard	CO or CI	Bias or *r* value	Error (%)	Conclusion
PiCCO monitor	Buhre [51]	PiCCO system	Minimally invasive cardiac surgery	36	PAC-TD	CO	0.003 (1.26) (0.94) l/min	–	PiCCO offers continuous CO in patients undergoing minimally invasive CABG
	Della Rocca	PiCCO system	Single lung transplantation	58	PAC-TD	CO	0.18 (1.59) l/min	–	PiCCO system gave continuous and intermittent values agreeing with PAC
LiDCOplus system	Sujatha [53]	PiCCO	Off-pump coronary bypass surgery	60	PAC-TD	CO	0.23 (0.5) l/min	20	Continuous CO by PiCCO and intermittent PAC TD technique were comparable during OPBAB surgery as long as no significant SVR changes
	Costa [64]	LiDCO system	Post-liver transplantation patients	23	PAC-TD	CO	0.1 (1.54) l/min	15.1 %	Patients with hyperdynamic circulation, intermittent and continuous CO values by LiDCO system showed good agreement with those by PAC TD
	McCoy [65]	LiDCO system	Postoperative cardiac surgery patients	8	PAC-TD	CI	−0.01 (1.3) l/min/m^2	–	LiDCO demonstrated low bias compared with continuous CI by PAC significant
	Dyer [66]	LiDCOplus system	Patients with postpartum complications of severe preeclampsia	18	PAC-TD	CO	−0.58 (−0.77 to −0.39) l/min	<30	LiDCOplus may have a valuable role in obstetric critical care
TEE	Parra [89]	Philips Sonos 5500	Cardiac surgery	50	PAC-TD	CO	0.015 (−1.21 to 1.22) l/min	29.1	CO by TEE and by PAC is acceptable and TEE is reliable to assess significant CO changes in selected patients
	Møller-Sorensen [90]	Philips X7-2t (Philips Healthcare)	Cardiac surgery	25	PAC-TD	CO	−0.22 (−0.54 to 0.1) l/min	38.6	CO by TEE and PAC TD had wide limits of agreement. TEE is not interchangeable with PAC TD for CO

Table 3 continued

Technology	References	Studied device	Patient population	Cases	Criterion standard	CO or CI	Bias or *r* value	Error (%)	Conclusion
Partial CO_2 rebreathing technique	Odenstedt [94]	NICO system	Undergoing major surgery or in ICU	15	PAC-TD	CO	−1.68 (1.76) l/min	–	NICO is a useful and accurate noninvasive estimate of CO. NICO cannot fully replace the PAC
	Gueret [95]	NICO system	During off-pump cardiac surgery	22	PAC-TD	CO	−3.1 (2.5) l/min	–	NICO reliably measured CO and more rapid than PAC. May be more useful to detect rapid hemodynamic changes
	Botero [97]	NICO system	Post-CABG surgery	68	PAC-TD	CO	0.18 (1.01) l/min	41.7	Before CPB, the accuracy of NICO, PAC TD, and transesophageal Doppler was similar. After CPB, NICO tends to underestimate CO
Electrical bioreactance cardiography	Squara [103]	NICOM system	Post-cardiac surgery	110	PAC-TD	CO	0.06 (0.71) l/min	–	CO measured by NICOM had acceptable accuracy, precision, and responsiveness in a wide range of circulatory situation
	Raval [107]	NICOM system	Intensive care unit	111	Continuous PAC-TD	CO	−0.09 (−2.5 to 2.3) l/min	–	NICOM has acceptable accuracy in challenging clinical environments
	Marqué [108]	NICOM system	Post-cardiac surgery	29	Continuous PAC-TD	CO	−0.01 (0.84) l/min	–	NICOM should be added to the array of CO monitoring tools in selected patients
ccNexfin	Ameloot [116]	Nexfin (Bmeye, Amsterdam)	Critically ill patients	45	PAC-TD	CO	0.4 (2.32) l/min	36	Nexfin has an acceptable concordance between TDCO and NexCO
	Stover [118]	Nexfin HD (Bmeye)	Critically ill patients	10	PAC-TD	CO	0.23 (2.1) l/min	29	Nexfin HD monitoring in the ICU cannot be recommended generally
	Sokolski [114]	Nexfin (Bmeye, Amsterdam)	Advanced heart failure patients	25	PAC-TD	CO	*r* values = 0.89	–	Nexfin reveal adequate concordance with the PAC TD

and PPV, which are used in goal-directed therapy. However, the volume clamp method requires the finger cuff to be inflated continuously. Therefore, the use of ccNexfin is restricted to a maximum of 8 h per finger. Also, the use of ccNexfin may not be suitable in patients with severe peripheral vasoconstriction, very edematous fingers, regurgitant aortic valve, and those with an aneurysm in the proximal aorta [112].

Validity studies

The ccNexfin system had a good concordance with the PAC technique in a small group of heart failure patients [114] and patients undergoing CABG [115]. Ameloot et al. compared ccNexfin with PiCCO system, with results showing moderate to good correlation [116]. Similar results were found when comparing the ccNexfin system with transthoracic echocardiography [117]. However, there are reports that in critically ill patients the ccNexfin system had a poor correlation with PAC technique, with a percentage error as high as 50 % [118]. Unfavorable results were also found when ccNexfin was compared to transesophageal Doppler [119]. Thus, the use of the ccNexfin system should take into consideration the clinical situations and its limitations.

Future trends in CO measurement and hemodynamic monitoring

The PAC thermodilution technique is invasive in nature and has well-documented complications [12, 13, 120]. The utilization of PAC has experienced a steady decline whereas less invasive and noninvasive CO measurement techniques have been increasingly used in clinical practice. The currently available minimally invasive and noninvasive techniques are summarized in Tables 2 and 3. Looking into the future, hemodynamic monitoring and CO measurement will have the following trends: the decline in use of PAC will likely continue; the current minimally invasive or noninvasive techniques will be improved in accuracy and precision, being more suitable for clinical use, thus their use will steadily increase; PAC and minimally/noninvasive techniques will be used in better defined and more-specific patient populations; and circulatory functional monitoring will very likely go beyond the assessment of global hemodynamic parameters and step into microcirculation monitoring [121]. The development focus in CO monitoring devices seems to be shifting gears to emphasize the alterations of microcirculatory flow, aiming more at the markers that indicate the effectiveness of circulatory and microcirculatory resuscitations (e.g., lactic acid, vascular endothelial growth factor) [122–124]. Better understanding of the physiology and pathophysiology of microcirculation, especially at the molecular level, needs to be emphasized to design monitors that will detect the alterations and reflect more genuinely the physiological changes in patients.

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