VIA MEDICA

REVIEWS

Anaesthesiology Intensive Therapy
2015, vol. 47, no 5, 487–500
ISSN 0209–1712
10.5603/AIT.a2015.0073
www.ait.viamedica.pl

Hemodynamic monitoring: To calibrate or not to calibrate? Part 1 – Calibrated techniques

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Abstract

Over recent decades, hemodynamic monitoring has evolved from basic cardiac output monitoring techniques to a broad variety of sophisticated monitoring devices with extra parameters. In order to reduce morbidity and mortality and optimize therapeutic strategies, different monitoring techniques can be used to guide fluid resuscitation and other medical management. Generally, they can be divided in calibrated and non-calibrated techniques. In the first part of this review, the available calibrated techniques, ranging from invasive to non-invasive, will be discussed. We performed a review of the literature in order to give an overview of the current hemodynamic monitoring devices. For each monitoring system, a short overview of the physical principles, the advantages and disadvantages and the available literature with regard to validation is given. Currently, many promising hemodynamic monitoring devices are readily available in order to optimize therapeutic management in both perioperative and ICU settings. Although several of these calibrated techniques have been validated in the literature, not all techniques have been shown to reduce morbidity and mortality. Many new techniques, especially some non-calibrated devices, lack good validation data in different clinical settings (sepsis, trauma, burns, etc.). The cardiac output values obtained with these techniques need therefore to be interpreted with caution as will be discussed in the second part of this concise review. Transthoracic echocardiography forms a good initial choice to assess hemodynamics in critically ill patients after initial stabilisation. However in complex situations or in patients not responding to fluid resuscitation alone, advanced hemodynamic monitoring is recommended with the use of calibrated techniques like transpulmonary thermodilution. Calibrated techniques are preferred in patients with severe shock and changing conditions of preload, afterload and contractility. The use of the pulmonary artery catheter should be reserved for patients with right ventricular failure in order to assess the effect of medical treatment.

Key words: hemodynamic monitoring, calibrated, invasive, less invasive, non-invasive, thermodilution

Anaesthesiology Intensive Therapy 2015, vol. 47, no 5, 487–500

During the nineteen-seventies, cardiac output (CO) measurement and advanced hemodynamic monitoring was ignited by the widespread use of pulmonary artery catheters (PAC). As critical care medicine evolved, so did hemodynamic monitoring. At present, a multitude of monitoring devices, ranging from invasive over less invasive to non-invasive, are commercially available [1, 2]. Among this broad variety, a differentiation is made between calibrated and non-calibrated techniques.

A calibrated technique is a monitoring technique in which a calibration is performed in order to eliminate or reduce bias in the continuous measurements [3]. The calibration refers to the act of evaluating and adjusting the precision and accuracy of the measurement equipment. The precision of a technique is the degree to which repeated measurements (at the same time) show the same results while its accuracy is the degree of closeness of measurements of to its actual true value (obtained with the gold standard). A non-calibrated technique tries to reduce this bias by implementing correction factors that are pre-programmed in the monitoring device. For example a nomogram-scaling factor based on the patients' demographics (age, gender, height, weight) or an equation correction factor based on certain measurement characteristics.

Table 1. Types of hemodynamic monitoring with some form of calibration

1. Gold standard Fick principle
2. Invasive techniques: Pulmonary thermodilution
a. Pulmonary artery catheter (PAC)
3. Less invasive techniques: Transpulmonary thermodilution
a. PICCO
b. EV 1000
c. LiDCO
d. Transonic: ultrasound flow dilution CO
4. Minimal invasive techniques
a. Transesophageal echocardiography
b. Disposable TEE
c. Esophageal Doppler
5. Non-invasive techniques
a. Transthoracic echocardiography

CO — cardiac output; TEE —transesophageal echocardiography

Both calibrated and non-calibrated monitoring systems try to reduce bias in the instruments' readings; however, complete elimination of this bias is impossible compared to a gold standard technique. Moreover, in situations where substantial changes in preload, afterload or contractility occur, aortic compliance is not constant and recalibration should be performed (at least 3 to 4 times per day). The only known gold standard technique in CO measurement is based on the Fick principle. Because of the invasive, expensive and time-consuming aspect of this technique, it is not and cannot be used in current clinical practice at the bedside. Instead, the PAC with thermodilution is considered as the gold standard in the critical care literature.

In the first part of this review on hemodynamic monitoring we discuss the calibrated techniques, ranging from invasive to non-invasive, as shown in table 1. The different advantages and disadvantages are listed in table 2.

STATISTICAL ANALYSIS

When comparing two monitoring techniques, the best statistical method to perform so seems to be the Bland and Altman analysis. In this analysis the difference between comparative measurements, also known as the bias, is plotted against the mean value of the measurements. By doing so, one can measure the upper and lower limit of agreement by taking the mean difference and adding or subtracting twice the standard deviation of the differences. If these limits of agreement are acceptable for the parameter measured, one can argue that the two measurement techniques can be used interchangeably [4]. The limits of agreement depend on the parameter studied and the reference method being used. When studying CO monitoring devices, the accepted limits of agreement need to be around 30% with a percentage of error of 25% [5].

With new devices being developed that are capable of continuous CO measurement, there is growing interest in the trending capabilities of the devices. This is the possibility of a device to detect changes in CO. There are several ways to analyze trending. One method being used today is a 4-quadrant scatter plot, first proposed by Perrino *et al.* where the ΔCO of two measuring techniques are plotted against each other [6]. Investigators then measure the percentage of concordance between the two methods used. A central portion of the plot is usually eliminated because the small changes in ΔCO are less predictive. This exclusion zone usually lies between 5–15%, but can be optimized using receiver operating characteristics (ROC)-curve analysis [7]. Acceptable concordance rates for trending capability in CO monitoring should be > 90%. One of the pitfalls in using 4-quadrant plots is that very large changes in CO are virtually always in agreement and so can falsely augment the concordance rate. Although these large changes should ideally be excluded, where to lay the exact cut-off point is hard to say. A recent publication by Critchley *et al.* suggests a new way to present trend data by using a polar plot where data points are converted to an angle indicating the degree of deviation from the ideal line of agreement [7]. When studying trending with thermodilution being the reference method a radial limit of an agreement of 5° is proposed [8].

GOLD STANDARD: FICK PRINCIPLE

Described by Adolf Fick in 1870, the Fick principle is the oldest known method of measuring CO [9]. It is based on a special case of mass balance, basically stating that in a given compartment (the heart), what goes out (arterial rate of indicator) equals what went in (venous rate of indicator) plus the rate of indicator added. This can be represented by

$$Flow \times conc(art) = Flow \times conc(ven) + conc(add)$$

Or, after rearrangement, and using oxygen extraction as indicator removed (negatively added)

$$Flow(CO) = \frac{VO_2}{CaO_2 - CvO_2}$$

Where CO is cardiac output, VO_2 is the oxygen extraction (consumption) rate while CaO_2 and CvO_2 represent arterial and mixed venous oxygen content, respectively. In its original form, the equation is described as the amount of oxygen picked up by the blood as it passes through the lungs, which is equal to the amount of oxygen taken up by the patient's lungs during breathing. The amount of oxygen uptake can be measured non-invasively at the mouth, and blood oxygen concentrations are measured form mixed venous and peripheral arterial blood samples. While never actually measured by Adolf Fick himself, this constitutes the

Table 2. Overview of advantages and disadvantages of calibrated cardiac output monitoring techniques

	Technique	Invasiveness	Validation	Advantages	Disadvantages
Fick principle	Gold standard	Invasive	NA	NA	Cumbersome technique
PAC	Pulmonary thermodilution, surrogate gold standard	Invasive	NA	Information on right heart function, CEDV, SvO_2	Expensive and difficult catheter, no beat-to-beat data, complications
PiCCO	TPTD, new surrogate gold standard	Less invasive	Well validated compared to PAC	Beat-to-beat data, additional parameters (GEDV, lung water), identification of R/L shunt (no loss of indicator), fluid responsiveness	Effect of valvulopathy on TPTD, need for recalibration
EV1000	TPTD, PiCCO clone	Less invasive	Not well validated	Same as PiCCO	Continuous CVP tracings needed for calculations, effect of valvulopathy on TPTD, need for recalibration
LiDCO	TP Lithium dilution	Less invasive	Less validated	Uses existing access	Expensive, lithium toxicity, no added parameters, cannot be used in children, need for recalibration
COstatus	TP US dilution	Less invasive	Not well validated in adults	Uses existing access, can be used in children	During calibration MAP not available for 8 minutes, need for recalibration
TEE	Doppler flowmetry and VTI at LVOT	Minimally invasive	Well validated	Provides additional anatomical and functional information	Learning curve, not really continuous, contra-indications
hTEE	Fractional area contraction	Minimally invasive	Not well validated	Direct cardiac visualisation	Expensive, only monoplane, not really continuous, no Doppler, no colour or TDI, contraindications (cfr TEE)
Eso-phageal Doppler	Doppler flowmetry and VTI at descending aorta	Minimally invasive	Reasonably validated	Real time CO and afterload data	Learning curve, not really continuous, contraindications (cfr TEE)
TTE	Doppler flowmetry and VTI at LVOT	Non-invasive	Well validated	Modern stethoscope for the intensivist, no contraindications	Learning curve, not really continuous,

CEDV — continuous end-diastolic volume; CO — cardiac output; CVP — central venous pressure; GEDV — global end-diastolic volume; LVOT — left ventricular outflow tract; MAP — mean arterial pressure; TDI — tissue Doppler imaging; TEE — transesophageal echocardiography; TP — transpulmonary; TPTD — transpulmonary thermodilution; TTE — transthoracic echocardiography; US — ultrasound; VTI — velocity time integral

direct Fick method and is considered the gold standard for CO measurements. Major disadvantages are that it is very invasive and expensive in terms of equipment and staff. It requires a cardiac catheter, a central venous and arterial line and stable metabolic conditions.

INVASIVE TECHNIQUE: SURROGATE GOLD STANDARD WITH PULMONARY THERMODILUTION

TECHNIQUE

The flow-directed pulmonary artery catheter (PAC) was first introduced in the 1970s by Swan, Ganz and Forrester [10]. Its use has revolutionized intensive care medicine and, almost 40 years later, the PAC remains the undisputed gold standard in the clinical setting [11–13]. While there is ongoing debate about the risk/benefit ratio of the procedure, it remains one of the most commonly used procedures performed in the critically ill worldwide [14–17]. However, the clinician using the technique is faced with multiple pitfalls that can be related to the inherent pressure — preload relation, to technical artifacts and to special disease states such as shunts and valvulopathy that invalidate the obtained readings [18–21]. The complexity of possible variations in obtained pressure tracings has led to a large inter-observer variability, together with reports of very common misinterpretation of tracings even by experienced clinicians [22–25].

The technique consists of injecting a bolus of indicator (usually iced fluid) into the right atrium. The resulting indicator dilution curve is recorded by a probe (a thermistor) in the pulmonary artery. The integral of the dilution curve over time is inversely proportional to CO, as described by the Stewart-Hamilton equation. Later, catheters were introduced with the ability to measure CO continuously.

The PAC in itself provides — apart from calculated variables such as systemic and pulmonary vascular resistance, left and right ventricular stroke work and oxygen extraction ratio – a measurement of CO, central venous pressure (CVP),

pulmonary artery pressure (PAP) and pulmonary artery occlusion pressure (PAOP).

Nevertheless, a clear survival benefit resulting from the use of PACs remains unproven despite the placement of over 2 million devices worldwide since its introduction. Most classic surgical studies have been invalidated by prospective trials [15]. Thus, the accepted indications for pulmonary artery catheterization have been generated largely on the basis of expert opinion [26].

Additionally, PACs can be used to obtain blood samples from the distal port (in the pulmonary artery position), which allow the measurement of mixed venous oxygen saturation (S_vO_2). To automate this process, PACs have been introduced that monitor S_vO_2 continuously using fiberoptic reflectometry. Continuous S_vO_2 monitoring allows for an insight into the trends and oxygen supply/demand ratio [27].

Several varieties of the PAC have been developed, some also with cardiac pacing capabilities. These can be used for temporary transvenous pacing using right ventricular, atrial, or A-V sequential pacing modes in case of sinus node dysfunction, brady dysrhythmias or atrioventricular heart block.

Further technological improvement of the PAC has allowed the measurement of "volumetric" parameters, such as the measurement of right ventricular ejection fraction (RVEF) and continuous assessment of right ventricular end-diastolic volume (CEDV). The RVEF provides information on right ventricular contractility, while the right ventricular preload is reflected by RVEDV.

These "volumetric" PACs have intracardiac electrodes to monitor the R-R interval and a rapid response thermistor (response between 50 and 70 ms). The RVEF can be determined through a beat-to-beat analysis of the thermodilution curve. The RVEDV can be calculated using the following equation [28]:

$$RVEDV = CO/(heart\ rate \times RVEF)$$

Theoretically, the continuous assessment of end-diastolic volume and ejection fraction could be used in order to better guide hemodynamic and fluid treatment in relation to a volumetric preload parameter. This ability, however, was not confirmed in studies (Reuse 1990, Wagner 1998) where RVEDV was not significantly elevated after fluid challenge, making it a poor predictor of fluid responsiveness [29, 30]. This has also been seen in patients undergoing cardiac surgery, where the correlation between RVEDV and preload dependency was absent [31]. It should be noted, when interpreting RVEDV, one should take RVEF in consideration as this is influenced by contractility and afterload [32]. Right ventricular failure could be an indication for the use of a "volumetric" PAC.

ADVANTAGES

The PAC is the most widely used and available catheter. With the modern continuous CO (CCO) methods, there is no added fluid and no need for manual calibration. The values are operator independent and continuous measurements of S_vO_2 and right ventricular end diastolic volumes are available.

DISADVANTAGES

Despite the fact that it is the most widely used tool to obtain CCO, it provides rather complex hemodynamic parameters which may be difficult to interpret, even for experienced clinicians. It is the most invasive and a very expensive option for CCO, and is not truly continuous since an average CO is provided over 5 to 10 minute periods (so it cannot be used to assess fluid responsiveness). It has a slow response time to changes in preload or afterload, and has a poor signal to noise ratio. Although it is often used as the gold or reference standard, the data it provides are not verifiable [9].

LESS INVASIVE TECHNIQUE: TRANSPULMONARY THERMODILUTION WITH THE PICCO SYSTEM

TECHNIQUE

The intermittent CO is measured using a transpulmonary thermodilution technique also based on the following Stewart Hamilton equation:

$$CO = (Tb - Ti) \times V_{inj} \times K \,/\, \int \Delta Tb \times dt$$

Where Tb is blood temperature, Ti is injectate temperature, V_{inj} is injectate volume, K is the correction constant and $\int \Delta$ Tb x dt (area under the thermodilution curve). By using an algorithm based on the analysis of the arterial pulse contour, it is possible to continuously monitor CO (PCCO, pulse contour continuous CO) since the contour of the arterial pressure curve is proportional to the SV [33]. This technique allows one to assess beat-to-beat variations of stroke volume (SV) and thus CO in response to changing preload conditions.

$$PCCO = cal\ x\ HR\ x \int \left(\frac{P(t)}{SVR}\right) + C(p) x \frac{dP}{dt}\ dt$$

With cal being a patient-specific calibration factor determined by intermittent transpulmonary thermodilution, HR the heart rate, $\left(\frac{P(t)}{SVR}\right)$ the area under the arterial pressure curve, C(p) the aortic compliance and $\left(\frac{dP}{dt}\right)$ the shape of the arterial pressure curve. The first commercially available device was the PiCCO system (Pulsion Medical Systems, Feldkierchen, Germany).

The PiCCO device allows the measurement of global end-diastolic volume (GEDV) and intrathoracic blood volume (ITBV), with ITBV = 1.25 × GEDV as surrogate preload markers together with extravascular lung water (EVLW) and the pulmonary vascular permeability index (PVPI) [2, 33, 34]. Determination of EVLW by single transpulmonary thermodilution depends on measurement of the intrathoracic thermal volume (ITTV), and the pulmonary thermal volume (PTV), which is the largest accessible volume transversed by the thermal indicator.

With the modern less invasive PiCCO system, the ITTV and PTV are calculated from the mean transit time (MTT) and the exponential downslope time (DST) of the thermodilution curve of the cold injectate:

$$ITTV = CO \times MTT$$
$$PTV = CO \times DST$$

The ITTV consists of the PTV and the sum of the end-diastolic volumes of all cardiac chambers. Accordingly, the global end-diastolic volume (GEDV) can be calculated as:

$$GEDV = ITTV - PTV$$

Based on the above-mentioned linear relation between GEDV and ITBV (ITBV = 1.25 × GEDV), the EVLW can be calculated as follows:

$$EVLWI = ITTV - ITBV$$

Pulmonary blood volume (PBV), PVPI, SV, global ejection fraction (GEF), cardiac function index (CFI) and systemic vascular resistance (SVR) are derived from these values. Absolute values for CO, GEDV, ITBV, SV and SVR are normalized as indexed by body surface area (CI, GEDVI, ITBVI, SVI and SVRI) and for EVLW by predicted body weight (EVLWI).

The SV variation (SVV), which is the percentage change between maximal and minimal SV divided by the average of the minimum and maximum over a floating period of 30 seconds, is continuously displayed by the PiCCO monitor. The pulse pressure variation (PPV) is calculated as the difference in maximal and minimal PP divided by the mean of the two values expressed as a percentage.

As described above, the SVV and PPV have been proposed as parameters to guide fluid loading in critical care settings [35]. Their use, however, is limited to completely sedated patients under controlled mechanical ventilation in the absence of arrhythmias.

Obtaining an idea of the EVLWI together with the PVPI will help in classifying patients with or without acute respiratory distress syndrome, or acute lung injury, and differentiating them from acute lung oedema, atelectasis, or pleural effusions [36].

Many studies performed in animals and different patient groups following cardiac surgery, heart or liver transplantation, septic or hypovolemic shock and burn patients found a good correlation between CO obtained with the PiCCO by transpulmonary thermodilution and the gold standard thermodilution CO with the PAC [33, 34, 37–49]. On overview of the published validation studies shows a mean number of study subjects of 27.9 ± 15, with a mean correlation coefficient of 0.95 ± 0.02. The mean CO was 5.7 ± 1.9 L min^{-1} (with a reasonable range), the bias ± precision was 0.2 ± 0.3 L min^{-1} and the limits of agreement (defined as bias ± 1.96 standard deviations according to the Bland and Altman analysis) ranged from –0.4 ± 0.5 for the lower LA and 1.0 ± 0.5 for the upper LA. The standard errors were also within an acceptable range from 15 to 23% with one outlier of 35% [1, 43].

A recent prospective study compared the PAC and PiCCO in postoperative cardiac surgery patients (50). The mean CO values for PAC and PiCCO and FloTrac were similar (5.6 ± 1.5 and 5.4 ± 1.5 L min^{-1} respectively). The mean CO bias was 0.24 (PAC-PiCCO), with limits of agreement (1.96 standard deviation, 95% confidence interval) of ± 2.22. The instantaneous directional changes between any paired CO measurements displayed 72% (PAC-PiCCO), but poor correlation (r^2 = 0.11). For mean CO < 5 L min^{-1}, the bias decreased slightly.

ADVANTAGES

PiCCO monitoring has several advantages. Firstly, it is less invasive; secondly, it provides a CO that it is less dependent on respiratory variations compared to the PAC [51]. It provides rapid available parameters that are directly clinical applicable. It is reproducible for less-experienced users and simple to operate and understand. It provides volume quantification that is independent of positive end-expiratory pressure (PEEP) or intra-abdominal pressure (IAP) and can be used in a large range of patients (from small children to adults) [52, 53]. There is no loss of indicator in cases of right-left shunt (as with ARDS, pulmonary hypertension) [54–58]. It gives real-time beat-to-beat cardiac output and real-time beat-to-beat fluid responsiveness and afterload [59]. It provides additional information (volumes) and functional hemodynamics (PPV, SVV). It is supported by literature data in humans (validation, clinical use etc. that show good correlation between intermittent and continuous transpulmonary thermodilution CO with the PAC as the gold standard. There is no need for an additional chest X-ray. As it is less invasive, the technique has evolved as the new gold standard against which newer less-invasive and uncalibrated CO monitoring techniques are validated.

DISADVANTAGES

Possible drawbacks of transpulmonary (TP) thermodilution are: the need for a specialized arterial catheter and (iced)

solution with extra fluid. The fact that central circulation and proximal arterial catheterization is necessary is of limited relevance since most sick ICU patients require or already have these vascular accesses. The PiCCO system is less useful in valvulopathies (severe tricuspid or mitral insufficiency or aortic stenosis), abdominal aortic aneurysm or enlarged atria, as this can alter the values of GEDV and EVLW. The volume measurement is not automated and not continuous. Finally, the Pulse Contour Calibration is performed at a given time point with a given aortic compliance at that time. The accuracy of pulse contour analysis is influenced by the location of the arterial line (being less accurate the more distal the arterial catheter). In a number of conditions, vasomotor tone changes and so will resistance; therefore there is a need for recalibration in patients on high doses of vasopressors since these can distort the arterial waveform [51]. In general, these problems can be prevented if the device is calibrated 3 to 4 times a day. The current pulse contour algorithm is also not applicable in arrhythmias or during intra-aortic balloon counterpulsation.

LESS INVASIVE TECHNIQUE: TRANSPULMONARY THERMODILUTION WITH THE VOLUMEVIEW/ EV1000 SYSTEM

TECHNIQUE

Recently, an alternative system for transpulmonary thermodilution has been developed by Edwards Lifesciences (Irvine, California, USA), consisting of the VolumeView thermistor-tipped arterial catheter and EV1000 monitoring platform/software. The concept is very similar to the TPTD technique employed by the PiCCO system as both use the Stewart-Hamilton-equation in order to calculate the thermodilution derived CO. However, in order to calculate GEDVI, the VolumeView/EV1000 system uses a formula implementing the maximum up- and downslope time of the thermodilution curve, whereas the PiCCO system employs time constants derived from the mean appearance, mean transit and down-slope of the thermodilution curve.

$$GEDV\ VolumeView = CO \times Mtt \times f\ (S1/S2)$$

Where Mtt is the mean transit time, S1 is the maximum up stroke and S2 is the maximum down-slope.

The EVLW is calculated using the same formula as the PiCCO [60]. An animal study found a good agreement between the new VolumeView system and the PiCCO system to assess GEDV and EVLW [61]. In 2012, in a mixed population of 72 ICU patients, the CO, GEDV and EVLW values assessed with the VolumeView/EV1000 system were interchangeable with the gold standard PiCCO method [60]. For CO, GEDV, and EVLW, both methods showed good correlation ($r^2 = 0.981$, 0.926 and 0.97 L, respectively), minimal bias (0.2 L min^{-1}, 29.4 mL and 36.8 mL), and a low percentage error (9.7%, 11.5% and 12.2%). Changes in CO, GEDV and EVLW were tracked with a high concordance rate between the two systems, with traditional concordance for CO, GEDV, and EVLW of 98.5%, 95.1%, and 97.7% and a polar plot concordance of 100%, 99.8% and 99.8% for CO, GEDV, and EVLW, respectively. Radial limits of agreement for CO, GEDV and EVLW were 0.31 mL min^{-1}, 81 mL and 40 mL, respectively. A presumed higher precision of GEDV measurements was seen when the VolumeView/EV1000 method was used. The precision of GEDV measurements was significantly better using the VolumeView algorithm compared to the PiCCO algorithm (0.033 (0.03) versus 0.040 (0.03; median (interquartile range), $P < 0.0001$) [60]. This might suggest the increased robustness of the VolumeView/EV1000 algorithm against thermal noise and recirculation. However, further research is needed for a trustworthy validation of the VolumeView/EV1000 system. Because of the similarity between the VolumeView/EV1000 and the PiCCO system, one can say the advantages and disadvantages are similar to those of the PiCCO system as discussed above. However, the fact that continuous CVP tracing is needed to identify the time of injection of the thermal bolus with the EV1000 makes the technique much more cumbersome. It should be considered as a "PiCCO clone" and as such the original has been much better validated in different patient populations.

LESS INVASIVE TECHNIQUE: TRANSPULMONARY DYE DILUTION WITH THE LIDCO SYSTEM

TECHNIQUE

Using the Stewart-Hamilton equation, CO can be calculated by the use of an intravascular indicator (lithium) which is injected in a central or peripheral vein and measured in a peripheral artery using a specialized sensor probe attached to the pressure line [62]. Correct application of this equation requires three conditions to be present: a constant blood flow, a homogenous mixing of blood and indicator, and absence of loss of indicator between injection and detection. Cardiac output is calculated as follows:

$$CO = \frac{LiCL \times 60}{area \times 1\ (1 - PCV)}$$

Where LiCl is the dose of lithium chloride in mmol, area the area under the dilution curve and PCV the packed cell volume (derived from hemoglobin concentration). Currently, only one commercially available lithium dilution system exists (LiDCO; LiDCO Ltd, London, UK). The CO obtained with lithium dilution can be used for calibration of a pulse contour analysis system, commercially available as an add-on for the LiDCO system (PulseCO).

Multiple studies have shown good to excellent correlation of the lithium dilution technique with pulmonary or

transpulmonary thermodilution, especially in surgical and paediatric settings. However, the company manufacturing the LiDCO systems lists body weight below 40 kgs as a contraindication to using the system (as well as treatment with lithium salts and during the first trimester of pregnancy).

While the lithium dilution method provides an indicator dilution curve similar to the thermal transpulmonary dilution, and could be used in analogy with the PiCCO system to calculate volumes of mixing chambers, no such algorithms currently exist. On their website, the LiDCO Company states that such algorithms are in active development. The only additional measured parameter compared to PAC monitoring is the variation of pulse pressure and stroke volume (PPV, SVV). As described above, the SVV and PPV have been proposed as parameters to guide fluid loading in critical care settings [35, 63, 64]. Their use however is limited to completely sedated patients under controlled mechanical ventilation who are in sinus rhythm.

In a recent prospective study, the mean CO values for PAC and LiDCO (5.6 ± 1.5 vs. 5.4 ± 1.6, respectively) were similar [50]. The mean CO bias was −0.18, with limits of agreement (1.96 standard deviation, 95% confidence interval) of ± 1.56. The instantaneous directional changes between any paired CO measurements displayed 74% concordance, but poor correlation ($r^2 = 0.36$). The mean CO bias of LiDCO and PiCCO compared was 0.06 with limits of agreement of ± 2.03 L min^{-1}. At this moment, no studies have shown a difference in outcome with LiDCO technology.

ADVANTAGES

The technique seems less invasive and the data are rapid available. It uses existing access, does not require central circulation catheterization and provides real time beat-to-beat variations in cardiac output together with functional hemodynamic parameters as the PiCCO (PPV, SVV). The algorithm for analyzing the arterial waveform is different from that of the PiCCO, site unspecific and morphology independent. There is no need for an additional chest X-ray.

DISADVANTAGES

Regarding the lithium dilution, in contrast to the PiCCO and EV1000, volume quantification is not provided and the technique cannot be used in small children or patients under muscle relaxants. Little is known about any possible toxic effects or accumulation with the long-term use of lithium, especially in ICU patients with organ failure (especially kidney and liver failure). Validation has been mainly performed in animals and human data is scarce. The ion selective electrode is delicate, expensive and needs to be replaced every 3 days (according to the CE mark). The disposables and the lithium needed for CO calibration are also expensive. Finally, it provides little or no additional information to the PAC, basically it offers the clinician no direct idea of preload and it is more expensive. Moreover, the 3 mL blood draw required for each calibration may contribute to anaemia and increased transfusion rates. Regarding the pulse contour analysis, the same remarks apply as for the PiCCO and EV1000 system.

LESS INVASIVE TECHNIQUE: ULTRASOUND FLOW DILUTION WITH THE COSTATUS SYSTEM

TECHNIQUE

The COstatus (Transonic, Ithaca, NY, USA) is a minimally invasive system, which calculates CO by using transpulmonary ultrasound dilution technology to measure changes in blood ultrasound velocity and blood flow following an injection of saline [65]. The COstatus requires a primed extra-corporeal arteriovenous tube set (AV loop) connected between the *in situ* standard arterial catheter and central venous catheter where two ultrasound flow-dilution sensors are placed on the arterial and venous ends. During the calibration, a small roller pump is used to circulate blood through the AV loop from the artery to the vein. The ultrasound sensors provide an ultrasound dilution curve through which CO can be calculated using a formula derived from the Stewart-Hamilton principle.

$$CO = (V_{inj}) / \int (Ca(t)dt$$

Where V_{inj} is volume of injected isotonic saline as measured by the venous sensor, and $\int Ca(t)\, dt$ is the area under the dilution curve of the saline concentration in arterial blood as measured by the arterial sensor (66). After calibration, a continuous CO can be calculated through the arterial waveform.

Besides these cardiac function parameters, such as Cardiac Output (CO), Cardiac Index (CI), volumetric indices such as Total End Diastolic Volume Index (TEDVI), Central Blood Volume Index (CBVI) and Active Circulation Volume Index (ACVI) can be obtained as well. The COstatus system can also detect intracardiac shunts (left-to-right as well as right-to-left shunts).

In 2009, a prospective study compared CO measurement by pulmonary artery thermodilution and ultrasound dilution in 29 adult patients undergoing surgery [67]. The correlation coefficient between the two techniques was r = 0.91 and Bland-Altman analysis did not produce any significant bias (bias = 0.02, standard deviation = 0.56). The COstatus system is also well validated in paediatric patients [68, 69]. Recalibration however is needed in unstable conditions [70].

ADVANTAGES

All measurements can be calculated using the existing central venous and arterial catheters, so no additional invasive procedures should be performed; furthermore,

no blood loss is involved which is especially possible in the paediatric population. Because the measurements are independent of the patient's size, this system can provide advanced hemodynamic monitoring in the paediatric population, a population where commercially available hemodynamic monitoring is very limited.

DISADVANTAGES

One of the limitations of the system is that during calibration, the arterial pressure line is not available for 5 to 8 minutes. The injection volume for calibration, about 1 mL kg^{-1}, can be disadvantageous, especially in young infants who are hypervolemic. Furthermore, the continuous CO measurement requires recalibration during vasoconstriction and vasodilation.

MINIMAL INVASIVE TECHNIQUES

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TECHNIQUE

Transesophageal echocardiography (TEE) still remains the most powerful cardiovascular diagnostic technique available in perioperative and intensive care medicine today. Thousands of published reports document its role in the monitoring of hemodynamics, the detection of myocardial ischemia and cardiovascular pathology, among others. Esophageal echocardiography was first introduced in 1976 by Dr. Leon Frazin *et al.* by publishing the results of studies using an esophageal M-mode transducer [71]. Since M-mode alone does not provide sufficient information for intra-operative monitoring, researchers started to expand on the idea. In the early 1980s Hanrath *et al.* mounted a 2 dimensional phased-array transducer on a flexible gastroscope and thus the concept and possibilities of intraoperative TEE were introduced [72]. However, wide adoption of TEE did not occur until the mid-1980s, when TEE transducer design was refined and the colour flow Doppler became commercially available. With these advances, TEE was able to provide high-resolution, real-time images of structure and blood flow that we use on a daily basis today. The original single-plane and subsequent biplane TEE probes limited the potential imaging planes. Multi-plane TEE using a rotatable 2D transducer within the probe tip resolved these limitations substantially and remains the current standard of practice [73].

To noninvasively visualize structures inside the body, ultrasound machines generate a vibration within the transducer that, when put next to tissue surfaces, vibrates the surrounding tissue. During this vibration, particles within the tissue compress (compression) and then spread apart (rarefaction). The sequence of compression and rarefaction is described by sinusoidal waves and is characterized in terms of wavelength, frequency, amplitude, and propagation velocity [74].

Wavelength is the distance (in millimetres) between two peaks of the sinusoidal wave. Frequency is the number of cycles that occur in 1 second. One cycle per second is defined as 1 hertz (abbreviated Hz). Ultrasound uses frequencies higher than the audible range for humans (greater than 20,000 cycles per second or 20 kHz). Frequencies typically used for ultrasound imaging are 2 to 10 mega hertz (MHz). Wavelength is inversely related to frequency. Amplitude is a measure of tissue compression and represents the loudness of an ultrasound wave and is described by decibels (dB). Decibels are a logarithmic transformation that allows large amplitudes to be presented next to small amplitudes (i.e., 1000 and 0.001) on the same display. Propagation velocity describes the speed of an ultrasound wave travelling through tissue. In blood, it is 1540 m sec^{-1}. The relationship between propagation velocity, frequency, and wavelength is described as follows:

$$\textit{Propagation velocity} = \textit{Frequency} \times \textit{Wavelength}$$

Assuming that propagation velocity is constant, the wavelength for any frequency can hence be calculated. To generate 2D images, ultrasound machines were configured to sequentially redirect the beam over an area (sector) of interest. Transducers contain a row of piezoelectric crystals (a linear array). By introducing a small delay in the firing of adjacent crystals in the array (a phased array), the ultrasound machine is able to guide the resultant ultrasound beam through a sector of interest (typically a 90-degree sector). Images are displayed in "real time" on a monitor screen and digitally recorded for later review and post-processing.

Since TEE is not without risk, its use is restricted to selected indications as much of the information gathered by TEE can also be obtained by the less invasive TTE. Guidelines published by the ACA reflect this in saying that TEE should be used for critical care patients with persistent hypotension or hypoxia when diagnostic information expected to alter management cannot be obtained by TTE or other modalities in a timely manner [74].

Following this statement, it becomes clear that while TEE will not replace the PAC or other non-invasive continuous CO monitoring devices in critically ill patients, both TEE and TTE can still be of enormous value in the diagnostic setting. They may help to define pathophysiological (anatomical) abnormalities in patients (wall motion abnormalities, pulmonary hypertension, valvulopathy) in conjunction with other invasive or less invasive monitoring techniques. In several studies, echocardiography was found to be more reliable than PAC in determining the cause of hypotension

[75–77]. Although the measurement of CO by TEE and Doppler using special views appears to be feasible, clinical use on a continuous basis is not yet available [78–80].

Since critically ill patients are often intubated and mechanically ventilated with positive pressure ventilation, adequate imaging by TTE proves to be difficult in nearly half of these patients. Factors that contribute to this problem are high PEEP, sustained chest injuries, improper positioning, post-operative dressings and chest tubes [81]. In these cases, TEE is often required to obtain valuable imaging and diagnosis.

Most of the studies in the critical care setting are retrospective while in most both TTE and TEE were used, which allows a comparison between the two. Patient selection covers both critically ill and post-operative patients. TEE produces an increased number of critical findings when standard 2D Doppler TTE supplies insufficient information. In these cases, TEE resulted in a change of treatment or surgery [75, 82–87]. A prospective but nonrandomized trial comparing the value of TTE and TEE for evaluating unexplained hypotension found that 64% of 45 TTE studies were inadequate, compared with 3% of 61 TEE studies [75]. Transesophageal studies contributed to new clinically significant diagnoses (not seen by TTE) in 17 patients (28%), leading to surgery in 12 (20%).

ADVANTAGES

TEE has great diagnostic value and causes fewer disturbances in critically ill patients. It is considered by some as the modern stethoscope for the intensivist. It provides additional anatomical information to the CO that can be obtained with hemodynamic monitoring. Knowing the presence of valvolopathy or heart chamber dilatation can help to interpret the data that can be obtained with transpulmonary thermodilution.

DISADVANTAGES

There is a significant learning curve (with the recommended number of performed TEEs by the ACA for basic use at 50 supervised TEEs). TEE is expensive and continuous monitoring is not an option. The use of TEE is contraindicated in esophageal pathologies and severe coagulation abnormalities.

DISPOSABLE TEE

TECHNIQUE

Imacor ImaCor (Garden City, NY, USA) has developed a highly differentiated product and Hemodynamic Management Program that seems cost effective in high risk critically ill patients. A growing population of older, more-ill patients with multiple comorbidities demands continuous hemodynamic management. Indeed, hTEE (hemodynamic transesophageal echo) is a technology in critical care that provides continuously available direct cardiac visualization. The product consists of the ClariTEE®, a purpose-built miniaturized disposable TEE probe, and a customized ultrasound system, known as the Zura EVO™

ImaCor's disposable probe has a piezoelectric design providing high quality imaging at 7 MHz with 15 cm penetration. Miniaturization, detachability and disposability enable real-time direct visualization of the heart for up to 72 hours. As direct cardiac visualization is available with hTEE in the ICU setting, clinicians are able to determine the causes of instability and optimize cardiac performance, with the possibility of preventing complications, reducing resource utilization and shortening length-of-stay.

In 41 patients (51.2% female, 73.2% after cardiac surgery), hemodynamic support probe insertion was accomplished without major complications (88). A total of 195 hTEE studies were performed, resulting in changes in treatment in 37 (90.2%) patients, leading to an improvement in hemodynamic parameters in 33 (80.5%). Right ventricular (RV) failure was diagnosed in 25 patients (67.6%) while hTEE had a direct therapeutic impact on management of RV failure in 17 patients (68 %). Other studies showed a significant correlation between the fractional area contraction (FAC) measured by ICU operators with hTEE and the reference ($r = 0.794$, $P < 0.0001$) (89).

ADVANTAGES

Same as above for TEE

DISADVANTAGES

The hTEE probe is expensive and is only for single use for up to 72 hours. The hTEE probe only allows monoplane images. Colour imaging and Doppler studies are not possible.

ESOPHAGEAL DOPPLER

TECHNIQUE

One of the most promising techniques for non-invasive assessment of cardiac output is esophageal Doppler (ED) monitoring. First described in 1971 and later refined by Singer in 1989, the basis of the technique is that flow in a cylinder can be calculated from flow velocity and cross-sectional area of the cylinder [90, 91]. The Doppler Effect describes an apparent change in the frequency of a wave noticed by an observer moving relative to the source of the wave. The frequency shift is directly proportional to the relative velocity between the emitter and the receiver [2]. With a continuous or pulsed-wave Doppler beam, blood flow velocity can be calculated from the frequency shift of the reflected ultrasound waves using the Doppler principle and the standard Doppler equation:

$$V = \frac{\Delta \int \times c}{2 \int T \times \cos \theta}$$

Where c is the velocity of the ultrasound waves and f_T the transmitted frequency. The cosine of the angle between the Doppler beam and blood flow serves as a correction factor to adjust for angle of insonation [92, 93].

By using the pulsatile nature of aortic flow, a velocity-time integral (VTI) can be constructed that is defined as the area under the flow curve from the onset (t1) to the end (t2) of flow (Fig. 1). This represents the stroke distance, or the distance travelled by the red blood cells down the aorta during the stroke cycle. Stroke volume (SV) determination then comes down to volume calculation of a cylinder (the aorta), with a base defined as the cross-sectional area where flow was measured and the height the stroke distance or VTI. CO can easily be calculated from SV as shown below:

$$Area = \pi \times r^2$$

$$Stroke\ distance = \int_{t1}^{t2} \frac{dV}{dT}$$

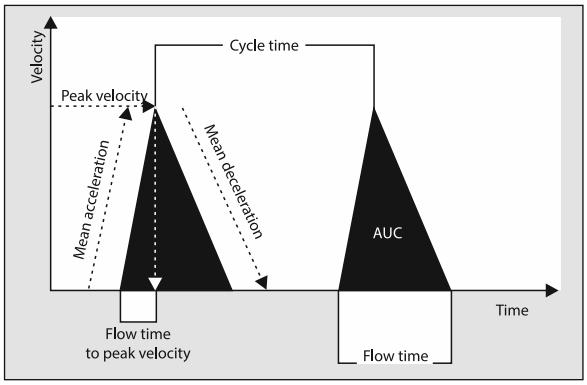

Figure 1. Velocity over time as assessed by Doppler

The systolic portion is triangular-shaped and its base represents the systolic ejection or flow time. The peak of the waveform depicts the peak velocity in the descending aorta. Flow acceleration and deceleration are derived from the upslope and downslope of the velocity curve. The area under the systolic portion of the curve (AUC), also called the velocity time integral, represents the stroke distance, corresponding to the distance that the blood column has moved forward in the aorta during systole or, thus, the stroke volume (SV). The SV multiplied by the heart rate gives the cardiac output.

Stroke distance is only proportional to stroke volume under the assumption that aortic diameter and distribution of blood flow between the supra-aortic vessels and the descending aorta remains constant. The exact mode of how stroke distance is translated to CO varies according to the manufacturer. As will be discussed further, the CardioQ uses a nomogram based on the patient's age, weight and height while the Hemosonic 100 uses its M-mode to more accurately measure the cross-sectional area of the aorta.

In contrast to the PAC, the ED probe can be inserted within minutes and after only very limited training. Literature suggests that training in not more than 12 patients is needed to achieve adequate probe positioning and reliable CO measurements [94]. The ED probe has been reported left *in situ* for over 2 weeks without complications [95].

From the above description, it is clear that a few prerequisite assumptions are required to be true for ED to give an accurate estimate of CO:

- The aorta descendens is assumed to be cylindrical, while in reality its shape can change depending on pulse pressure and aortic compliance.
- In some devices, aortic diameter is derived from a nomogram based on age and body weight
- The flow in the aorta is assumed to be laminar, while tachycardia, anemia and aortic valve disease can cause turbulent flow [96].
- Narrow alignment of the Doppler beam with the direction of aortic flow is required for accurate measurement, as is apparent from the Doppler equation. Generally, an angle of less than 20° is recommended.
- For derivation of CO from aortic flow, the fraction of blood going to the brachiocephalic and coronary arteries (30%) is assumed to be constant. However, this is variable among patients and disease states [97]. One must also take in account that epidural anesthesia alters the proportionality of blood flow in upper and lower body.
- Diastolic flow in the descending aorta is assumed to be negligible

As a result, studies comparing ED to some reference techniques have reported a wide range in reliability. Although CO is probably the most valuable parameter obtained by ED, assessment of left ventricular contractility and preload with ED has been reported using flow waveform analysis [98]. Parameters of interest are the flow time, index of preload, defined as the time required from start of waveform upstroke to return to baseline, peak flow velocity and index of contractility [91, 99]. Since flow time is heart rate dependent, it is usually corrected by dividing flow time by the square root of the cycle length (FTc).

Many studies have shown that FTc and PPV are better than CVP and LVEDAI in predicting fluid responsiveness. For instance, Singer and Bennett manipulated ventricular filling in ICU patients by IV loading or IV nitrates and observed a relationship between PCWP, CO and FTc that seemed to indicate a use for FTc as an optimal filling marker [100]. Madan *et al.* observed a better correlation between FTc and CO (r = 0.52) than with PCWP and CO (r = 0.2) [101]. How-

ever, more recent studies seem to contradict these findings and even warn about the risk associated with FTc when it is used inadequately to guide fluid therapy (102). Singer himself published a consequent study in 2006 claiming FTc alone is not an accurate measure for left ventricular preload [103]. These findings can be explained by understanding the specific characteristics of FTc. It is affected not only by preload but also other factors and it is inversely proportional to afterload [100]. Furthermore, there are many pathological conditions in which patients with low FTc may not respond to fluid challenge when adequate filling of the left ventricle is impeded e.g. pericardial tamponade, pulmonary embolism or severe mitral valve stenosis [104]. Consequently, low FTc does not always correspond to low ventricular preload, as low FTc can even represent a volume overload state [100].

In a prospective, randomized controlled trial, Sinclair demonstrated a significant shorter hospital stay for patients whose volume status during proximal femur fracture repair had been optimized using ED (goal FTc > 350 msec and optimized stroke volume vs. usual care) [105]. Mythen showed a decrease in major complications, a lower incidence of gut hypoperfusion (measured by intramucosal gastric pH) and a shorter length of hospital stay in an unblinded cardiac surgery trial where stroke volume was optimized perioperatively [106].

McKendry used a nurse-delivered protocol to optimise the circulatory status of patients early after cardiac surgery, esophageal Doppler flowmetry and targeted at improving stroke volume, reduced the length of hospital stay. This protocol was also associated with a trend towards fewer complications and reduced stay in intensive care [107].

In 2011, NICE guidelines recommend use of CardioQ esophageal Doppler intraoperatively in patients undergoing major or high-risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring, They also claim there is a reduction in post-operative complications, use of central venous catheters and in-hospital stay (with no increase in the rate of re-admission or repeat surgery) compared with conventional clinical assessment with or without invasive cardiovascular monitoring [108].

TYPES OF AVAILABLE ED MONITORING

CARDIOQ

Manufactured by Deltex. Continuous waved Doppler with a frequency of 4 MHz. Angle of insonation is 45°. No M-mode available. The probe diameters are 14–17 French and are single use. The translation of flow measurement into cardiac output is based on a nomogram using patient's age, weight and height.

HEMOSONIC

Manufactured by Arrow International (Teleflex Medical Europe, Athlone, Co Westmeath, Ireland), this is a pulsed wave Doppler with a frequency of 5 MHz. Angle of insonation is 60°. M mode is available and also used for determination of aortic diameter through aortography. It utilizes a 20 French reusable probe.

WAKI

Manufactured by Atys Medical (Soucieu-en-Jarrest, France), it is a 4 MHz Doppler with a reusable probe. Translation into cardiac output is achieved through nomogram, despite having M-mode available. Although very little info is readily available it seems M-mode is only marketed to help positioning of the probe and is not used for aortography.

ADVANTAGES

ED provides rapidly and real-time CO as well as afterload data interpretation. It is less invasive than, for instance, the PiCCO or LiDCO. The data interpretation is fully automated and presented via a user-friendly interface. It provides many additional parameters, as well as an estimate for preload via the corrected flow time. Although it is associated with reduced hospital stay and better perioperative volume optimalisation, no study yet has proven better overall outcome of changes in mortality.

DISADVANTAGES

As with any technique there is a learning curve. It is not a really continuous CO device since it is dependent on patient movement (the probe tends to move in the esophagus) and requires specialized training. Readjustment of the probe is often necessary during even short-term use. The measurement is approximate (especially if there is no M-mode available to correctly measure aortic diameter) and does not measure total CO but only descending aortic blood flow. During surgery, there is high interference with cauterization while in ICU settings, frequent control of positioning is necessary. There are also a number of contra-indications for use of this device: local esophageal pathology, esophageal varices, recent surgery, severe bleeding disorders, long-term corticosteroid treatment etc. In some conditions, the readings may be inaccurate: aortic coarctation, severe aortic stenosis or insufficiency and intra-aortic balloon counterpulsation etc.

NON-INVASIVE TECHNIQUE

TRANSTHORACIC ECHOCARDIOGRAPHY

Cardiac output can also be measured with TTE, by convention, in the left ventricular outflow tract (LVOT) using pulsed wave Doppler velocity. The first description of CO measurement with ultrasound at the LVOT was described in the 1990s. Although CO can also be measured at other locations, such as the mitral valve annulus, the ascending aorta (as discussed above regarding the ED techniques), the right ventricular outflow tract and pulmonary artery,

these have been less validated. The literature also contains differences which have been observed with regard to CO measurements with TTE versus TEE related to differences in LVOT (TTE tends to underestimate the LVOT by 0.1 cm). However, the discussion of the other different parameters that can be obtained with TTE do not fall within the scope of this paper

CONCLUSION

Over recent decades, many new less invasive techniques to monitor cardiac output have evolved. Transthoracic echocardiography forms a good first choice to assess hemodynamics in critically ill patients after initial stabilisation. However, in complex situations or in patients not responding to fluid resuscitation alone, advanced hemodynamic monitoring is recommended with the use of transpulmonary thermodilution techniques offering not only cardiac output assessment, but also information regarding organ function, perfusion and lung water. Calibrated techniques are preferred in patients with severe shock and changing conditions of preload, afterload and contractility. The use of the pulmonary artery catheter should be reserved for patients with right ventricular failure to assess the effect of medical treatment with phosphodiesterase inhibitors or nitric oxide inhalation on pulmonary artery pressures.

ACKNOWLEDGEMENTS

1. The authors do not have any financial disclosures to make with regard to the writing of this review paper.
2. Manu L.N.G. Malbrain is founding president and current Treasurer of the World Society of Abdominal Compartment Syndrome (WSACS, www.wsacs.org) and member of the medical advisory board of Pulsion Medical Systems (Maquet Getinge group). The other authors declare no potential conflict of interest with regard to the content of this paper.

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Received: 26.08.2015
Accepted: 13.11.2015