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Cardiac output measurement : evaluation of methods in ICU patients

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Chapter 4

Review of the PiCCO device; our experience in the ICU

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Introduction

Many intensivists consider it very useful to know the cardiac output of hemodynamically unstable patients. For more than 30 years the pulmonary artery catheter (PAC) has been delivering this information. Modern PACs also permit continuous monitoring of right atrial pressure (RAP), right ventricular pressure (RV), pulmonary artery pressure, pulmonary artery wedge pressure, continuous cardiac output (CCO), mixed venous oxygen saturation,
RV ventricular ejection fraction and RV end diastolic volume. These parameters allow diagnosis of right ventricular failure (low mean arterial pressure, low CCO, and low mixed venous oxygen saturation, combined with a high RAP) as well as pulmonary hypertension. Besides the pulmonary artery catheter, echocardiography is the most commonly-used technique to diagnose right heart failure and pulmonary hypertension.
Nowadays, some authors consider the pulmonary artery catheter to be out of date, [1]. However, we should realize that the long history of monitoring with the PAC has resulted in a great deal of experience with its technology and its clinical implications and inadequacies, whereas the new techniques are still standing on the threshold of being tested in clinical practice and their shortcomings are still to be discovered. Besides giving information on cardiac output, these modern devices provide specific information about intra-vascular volume status. In mechanically ventilated subjects, physiological experiments on heart lung interaction showed that stroke volume decreases during inspiration and recovers during expiration. In the early nineteen-eighties, a strong relationship between the magnitude of these tidal changes in stroke volume variations and hemodynamic filling status was shown in animals [2]. Several modern cardiac output devices are using this physiological principle to offer information about fluid responsiveness, i.e. they provide information to answer the question: Will fluid administration increase cardiac output in this patient? This clinical application has generated many papers and reviews over the past few years [3-7].

In this review we focus on the PiCCO device (Pulsion Medical Systems, Munich, Germany), the first widely available commercial system for measuring and monitoring of cardiac output by arterial pulse contour analysis. We will describe the basic principle of the device and the monitoring approach. Furthermore, we will review the main parameters and we will discuss the use as well as the limitations of this device in the light of our own experience.

The PiCCO system

This system combines a transpulmonary thermodilution technique and an arterial pulse contour method into one instrument (Fig. 4a.1).

PiCCO's pulse contour method

The estimation of cardiac output via pulse contour analysis is an indirect method, computed from arterial pressure pulsation based on a model of the circulation. The original concept of the pulse contour method for estimation of beat-to-beat stroke volume was first described by Otto Frank in 1899 as the classic Windkessel model. Most pulse contour methods used today are derived from this model.

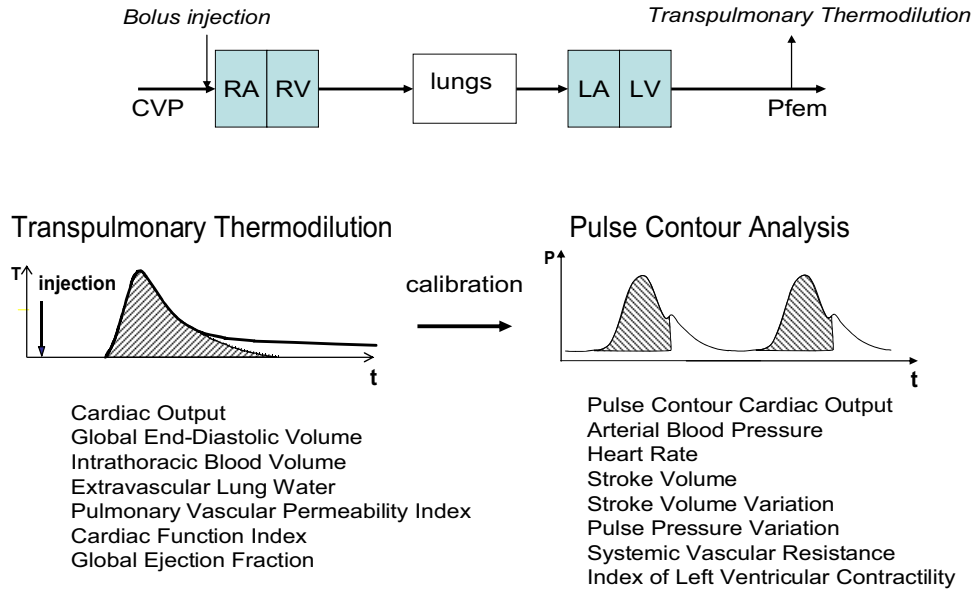

Figure 4a.1 The PiCCO system with the transpulmonary thermodilution technique and the pulse contour technique. In the upper panel a schematic diagram of the transpulmonary thermodilution method, with injection of cold fluid central venously and detection of the dilution curve in the femoral artery. CVP, central venous pressure; RA, right atria; RV, right ventricle; LA, left atria pressure; LV, left ventricular; Pfem, femoral artery pressure. In the lower panels the parameters derived from these two techniques are given.

The PiCCO - system utilizes pulse contour analysis according to a modified version of Wesseling's cZ algorithm [8, 9]. This pulsecontour algorithm analyzes the actual shape of the pressure waveform in addition to the area under the systolic portion of the pressure wave (Fig. 4a.2).

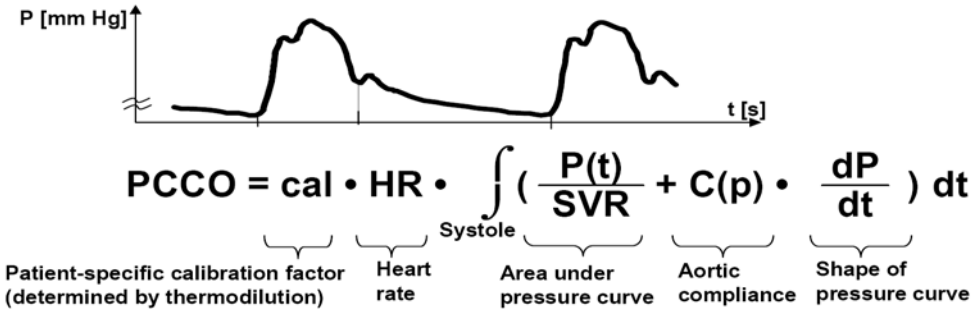

Figure 4a.2 The pulse contour algorithm. After calibration by the transpulmonary thermodilution technique the system is able to follow cardiac output beat by beat. For further explanation see text.

The software takes into account the individual aortic compliance and systemic vascular resistance based on the following considerations. During systole, more blood

is ejected from the left ventricle into the aorta than blood that actually leaves the aorta. During the subsequent diastole, the volume stored in the aorta flows into the arterial network at a rate determined by the aortic compliance (C), systemic vascular resistance (R), and the blood pressure (Windkessel effect). The shape of the arterial pressure curve (exponential decay time = R x C) after the dicrotic notch is representative for this passive emptying of the aorta. The systemic vascular resistance, R, is determined by the quotient of mean arterial pressure (MAP) and cardiac output measured by the reference method (R=MAP/CO). As the decay time and R are known, compliance, C, can be computed. The PiCCO algorithm is summarized in the equation in figure 4a.2.

$$PCCO = cal \times HR \times \int (P(t)/SVR + C_{(P)} \times dP/dt)dt$$

Where: PCCO, cardiac output; cal, calibration factor; HR, heart rate; P, arterial blood pressure; $\int P(t)dt$, area under the systolic part of the pressure curve; SVR, systemic vascular resistance; $C_{(P)}$, pressure dependent arterial compliance; dP/dt, describes the shape of the pressure wave. This version of the PiCCO device was published by Godje et al. [10] in 2002.

Input pressure for pulse contour analysis

In clinical practice, aortic pressure cannot be measured and the radial artery or femoral artery pressure are used instead. Although radial and femoral pressure waves are distorted by reflections, pulse contour methods should accept these pressures. As was shown by Wesseling KH et al. [9], cardiac output derived from aortic pressure is not different from that derived from radial artery pressure. Recently, we [11] showed the interchangeability of femoral and radial pressure signals as input for the PiCCO device. These findings are in agreement with the results reported by Mignini et al. [12] who demonstrated that mean arterial blood pressure from radial or femoral arteries are clinically interchangeable. In addition, Soderstrom et al. [13] showed that left ventricular afterload can be derived from the radial artery pressure, after backward filtering to the aortic pressure. It is not clear which type of backward filtering has been integrated into the PiCCO device.

PiCCO's transpulmonary thermodilution method

To derive the calibration factor "cal" and the individual compliance function C(p) a reference cardiac output is needed. PiCCO utilizes a transpulmonary thermodilution technique, where cardiac output is determined after central venous injection of a volume (Vi) of at least 10mL indicator with a temperature (Ti) of at least 10 °C below blood temperature (Tb). After passage through the right heart, lungs and left heart (Fig. 4a.1), the resulting temperature change (ΔTb) is measured with a thermistor tipped catheter, usually sited in the femoral artery. Cardiac output is calculated by the classical Steward - Hamilton equation: $COao=k*(Tb-Ti)*Vi/(\int \Delta Tb.dt)$, where: $\int \Delta Tb.dt$ is the area under the thermodilution dilution curve (Fig.4a.1), k is a computation constant depending on type of injection catheter and on specific heat and specific mass of blood and injection fluid respectively.

To measure the transpulmonary thermodilution curve, L'E Orme et al. [14] tested an alternative site. They compared the results obtained with a standard femoral artery catheter with a thermistor tipped, 50cm long, radial artery catheter. With a bias, for the difference between the two approaches, of 0.38 (SD 0.77), they concluded that

both approaches are interchangeable. Many authors compared conventional pulmonary thermodilution (COpa) with transpulmonary thermodilution (COao) and found an acceptable agreement between the two methods, see [15] for references. However, in most papers a small overestimation of COao compared to COpa was found, explained by incomplete recovery of cold indicator after its passage through the pulmonary circulation.

Validation studies on accuracy and precision

Several comparisons have been made between PiCCO's new pulse contour cardiac output and conventional bolus thermodilution cardiac output (COpa) [10, 16-20] (Table 4a.1). An individual example of such a comparison is shown in figure 4a.3.

Table 4a.1 Comparison between conventional thermodilution cardiac output and PiCCO's pulse contour cardiac output.

Authors and references		Number of Patients / Measurements	Bias ±SD L/min	Limits of agreement L/min
Gödje O et al.	[10]	24 / 517	-0.2 ± 1.15	-2.32 to 2.28
Felbinger et al.*	[16]	20 / 360	-0.28 ± 0.66	-1.46 to 1.18
Della Rocca et al.	[17]	62 / 186	-0.02 ± 0.74	-1.50 to 1.46
Dell Rocca et al.	[18]	58 / 318	-0.04 ± 0.85	-1.65 to 1.73
Mielck et al.	[19]	22 / 96	-0.40 ± 1.3	-3.00 to 2.20
De Wilde et al.**	[20]	27 / 199	0.14 ± 0.87	-1.60 to 1.88

Cardiac output estimated from cardiac index, ** radial artery pressure used instead of femoral artery pressure.

Although these evaluations of the PiCCO pulse contour device reveal acceptable results with respect to the bias (range from -0.40 to 0.31 L/min), the limits of agreement show considerable differences between studies. Possible explanations of these phenomena are probably related to alterations in vascular compliance and to peripheral vascular resistance during the studies. Therefore, in our opinion, due to re-warming during the first few hours on the ICU, a regular recalibration of cardiac output at 4-6 hr intervals seems necessary in postoperative cardiac surgical patients. During our studies [11, 15, 20] two more problems came to light, namely the phenomenon of misclassification of a heartbeat, and false detection of the dicrotic notch in the pressure recording. Under these circumstances we found false high cardiac output values in combination with a false high value of stroke volume variation. In using the radial artery pulse wave with the PiCCO [11], we incidentally also encountered temporarily false low cardiac output values, due to damping of the arterial waveform by clotting and due to local vasospasm after flushing the arterial line.

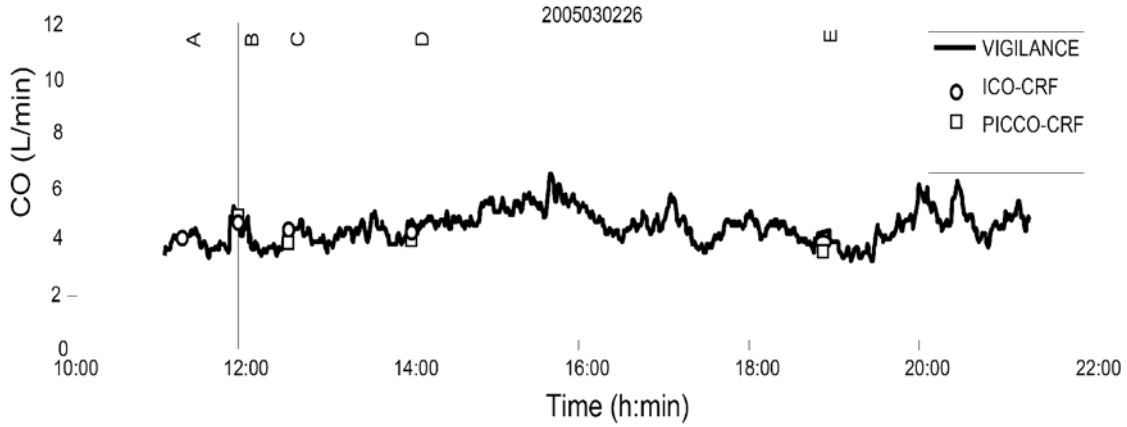

Figure 4a.3 Trend recording of an individual patient. Observation moments are indicated by A to E. Solid line cardiac output (CO) by the continuous thermodilution method (CCO). At point A PiCCO's pulse contour method is calibrated. At the observation moments, the bolus thermodilution CO is indicated by symbol ○ and PiCCO's pulse contour CO is indicated by symbol □.

Why not comparing PCCO with COao?

In a recent study, Della Rocca et al. [17] compared the results of cardiac output of two intermittent methods; -pulmonary thermodilution (COpa) and transpulmonary thermodilution (COao) - with the results of two continuous cardiac output methods - PCCO (PiCCO) and CCO (Edwards)- (Table 4a.1). Measurement of COpa by the PiCCO device results in an automatic calibration of PiCCO's pulse contour cardiac output, PCCO. Therefore, during each comparison of COao and PCCO the system automatically recalibrates PCCO. Tzenkov and Perez Peña [21] questioned, correctly, the method of automatic recalibration of the PiCCO system as used by Della Rocca and colleagues [17] as well as of other authors. Because of this automatic recalibration of the PiCCO system, the value of PCCO after recalibration is in principle equal to thermodilution COao. This automatic recalibration was considered to be misleading [21], figure 4a.4.

When performing a comparative study it is normal that the necessary practical operations are first carried out before recording the results of COao and PCCO. But, with the PiCCO it is necessary to record PCCO results first and then perform three or more thermodilution measurements and to make a note of the average results of these three measurements afterwards. In their answer to Tzenkov and Perez Peña, Della Rocca and colleagues stated: "As previously reported by Rödig et al. [22], Gödje et al. [23, 24] and Bottiger et al. [25]: we measured PCCO immediately before and after the series of intermittent COao measurements, and the averages of these data pairs were recorded". If we understand this statement correctly, the difference found between PCCO and COao must be multiplied by two, because PCCO after performing the measurement of COao (recalibration) is equal to COao. *Difference= COao-(PCCObefore+PCCOafter)/2, as PCCOafter=COao it follows that the computed Difference=(COao-CCObefore)/2.* To prevent such uncertainty about the presented data, authors should explicitly mention the way in which they performed their study. In addition, the manufacturer should adapt the software in such a way that the user gets the simultaneously collected values of PCCO and COao as well as the choice of deciding whether to calibrate or not.

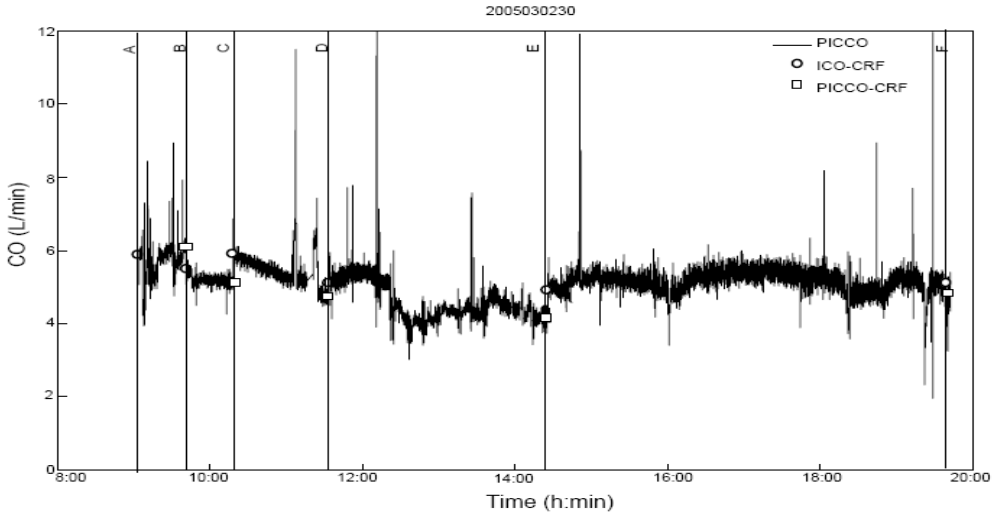

Figure 4a.4 Trend recording of an individual patient. Observation moments are indicated by A to F. Solid line PiCCO's pulse contour cardiac output. At the observation moments, bolus thermodilution CO is indicated by symbol ○ and PiCCO's pulse contour CO is indicated by symbol □. Observe the recalibration after performing a bolus thermodilution measurement at all moments A to F.

A remarkable difference in study setup compared to Della Rocca et al has become apparent from the study of Rödig et al. [22]. Rödig et al. as well as Rauch et al. [26] explicitly mentioned that they used the transpulmonary thermodilution technique (COao) only to calibrate PCCO at two or three points (at the start and after transfer to the ICU). Further comparisons were made with the conventional thermodilution (COpa) instead of the COao method to prevent a sequential automatic recalibration of PCCO.

Comparison with other pulse contour methods

In a recent publication [20] we compared the bias precision and the tracking ability of five pulse contour methods. The bias between the methods was low; however the limits of agreement differed between the methods for the PiCCO pulse contour; these values were 0.14 and -1.60 to 1.89 L/min. For the LiDCO-PulseCO device (LiDCO, Cambridge, UK) they were -0.17 and -1.55 to 1.20 L/min. The Modelflow method (BMEYE, Academic Medical Center, Amsterdam, the Netherlands) and the Hemac program (author JRC Jansen) performed the best with 0.00 and -0.74 to 0.74 L/min. and 0.06 and -0.81 to 0.93 L/min. respectively. Also tracking changes in cardiac output were performed significantly better by the Modelflow and Hemac methods.

SVV and PPV as spin-offs of pulse contour analysis

Measurement of left ventricular stroke volume variation due to mechanical ventilation has become clinically available since the introduction of pulse contour analysis. Stroke volume variation (SVV) is the difference between maximal and minimal stroke volume during a mechanical breath divided by the average of the two values, figure 4a.5. SVV has been shown to be a functional indicator to predict the effects of volume loading on cardiac output [3].

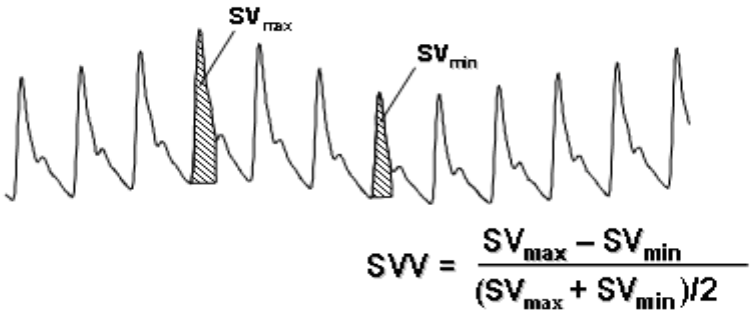

Figure 4a.5 Stroke Volume Variation (SVV) over the ventilatory cycle. SVV is measured over last 30s time window.

In general, a patient with a SVV larger than 9.5 to 15% will respond with a positive increase in CO after volume loading with 500 mL [27]. A similar approach has been introduced for pulse pressure variation (PPV). Here, a PPV value larger than 13% predicts an increase in CO larger than 15% after volume loading of the patient with 500 mL fluid [3]. These precise percentage value of SVV and PPV were postulated despite Reuter et al. [28] having shown SVV and PPV to be dependent on tidal volume. De Backer et al. [29] recommended tidal volumes larger than 8 mL/kg body weight. However, the use of larger tidal volumes is in contradiction with the recommendations in the literature which advises that patients be ventilated with low tidal volumes and PEEP to prevent barotrauma [30, 31]. Nevertheless, because of their high sensitivity and specificity, SVV and PPV are the most popular hemodynamic monitoring parameters in recent literature [32-36].
Quality control of conditions The use of SVV and PPV as predictors of fluid responsiveness is only possible in fully ventilator dependent patients with a regular heart rate. However, in many postoperative cardiac surgical patients weaning from a ventilator has already started on arrival in the ICU, or is started shortly after. Furthermore, irregular heart rates are quite common in cardiac surgical patients. The software in the PiCCO device does not perform a quality check for these conditions which impels the physician to do so, especially in the event of a high SVV or PPV value. In our opinion, this all makes the use of SVV or PPV as predictors for volume loading on cardiac output of limited value in daily clinical use.

GEDV and ITBV as spin-off of transpulmonary thermodilution
Transpulmonary thermodilution-derived global end-diastolic volume index (GEDVI) and intrathoracic blood volume index (ITBVI) may reflect left ventricular end-diastolic volume and are supposed to reflect preload and predict fluid responses after cardiac surgery much better than cardiac filling pressures [37-42]. The superior value of these volume indices over pressures is questionable, since fluid loading guided by CVP changes has been shown to increase volumes and cardiac output in patients after cardiac surgery for instance [43]. In addition, the predictive value may be confounded by mathematical rather than physiological coupling, as in the PiCCO system both cardiac output and volumes are derived from the same transpulmonary thermodilution curve. The coupling may contribute to falsely high correlations between volumes and cardiac output (changes) as a consequence of shared measurement error [44].

Mundigler et al. [45] demonstrated the insensitivity of GEDV or ITBV in monitoring the effects of volume loading in patients with reduced left ventricular function. They concluded that cardiac filling pressures rather than intra-thoracic volumes should be used to monitor fluid loading. Remark: consider a patient with a normal heart having an end diastolic volume of 100 mL, the same volume in a patient with a large heart due to cardiomyopathy will not generate an end diastolic wall tension at all! Furthermore, based on theory and observation, we have the impression that the precision of these variables is dependent on SVV.
In a recent prospective multicentre study, Uchino et al. [46] compared hemodynamic monitoring by PAC with that by PiCCO derived variables. The major outcome of this study was that on direct comparison, the use of the PiCCO was associated with a greater positive fluid balance and fewer ventilator-free days. After adjustments for confounding variables, the choice of monitoring technique was shown not to predict outcome, but a large positive fluid balance was a significant predictor of greater mortality. As many of our patients have congestive heart failure we found GEDV and ITBV of limited use, despite the publications that demonstrate the superiority of these parameters [37-42].

Limitations and remarks based on own experience
Quality control of the arterial pressure waveform Radial artery pressure is usually measured with fluid-filled catheter-transducer systems. The catheter lines are routinely kept open with continuous flush devices. Malfunction of flush devices or catheter-related problems are of direct influence on the measured pulse contour cardiac output and derived variables. Therefore, frequent visual control of the pressure wave form is advisable, or better still, a detection of damped waveforms is greatly needed and should be built into pulse contour systems.
Patient related concerns The performance of all pulse contour methods is compromised in those patients who have aortic valve regurgitation, an aortic aneurysm or an intra-aortic balloon pump, as well as during cardiopulmonary bypass and aortic clamping. Also, the physiological properties of the aorta may change with the patient's position. No data is available on changes when going from supine to upright - nor on changes from supine to prone position. In two adult patients, we [15] showed clinical significant differences in PiCCO cardiac output values for PCCO and COao compared with the continuous thermodilution cardiac output from the pulmonary artery catheter (Vigilance, Edwards). These differences appeared to be dependent upon the site of measurement and the underlying pathology. In one patient with a severe haemorrhage the difference in CO was related to excessive loss of cold indicator during the passage through the pulmonary circulation. In the other patient, the difference could be explained by the presence of a partial anomalous pulmonary vein entering the right atrial cavity. From these observations we learned that improved analysis of the transpulmonary dilution curve may help to alert the operator in the event of intrathoracic abnormalities. Detection of the false high cardiac output by the PiCCO system in the patient with severe haemorrhage and the real difference between the output of the right and left heart in the patient with intrathoracic abnormalities was possible because these patients were participating in a study protocol. Ong et al. [47] reported a third patient with induced hypothermia for anoxic brain injury, in which the PiCCO system failed to calibrate, even after several attempts with increased injection volumes of cold injectate (temperature lower than 8^{o}C) and exchange of the PiCCO device and of the femoral arterial line.

Summary and conclusions

From the literature and our own comparative studies using different pulse contour cardiac output systems, we concluded that the accuracy (bias), precision (SD) as well as the tracking of changes in cardiac output by the PiCCO system is inferior to most of its competitors. During our use of the PiCCO system, several technical and patient related limitations were uncovered by coincidence. The technical limitations were related to i) incorrect detection of heart beats, ii) incorrect detection of ejection phase, iii) no detection of damped arterial pressure tracings, all leading to incorrect computations of cardiac output. Patient-related problems were found during severe episodes of bleeding and cardio-pulmonary anatomical abnormalities. In most cardiothoracic patients, SVV or PPV to monitor preload dependency was only useful for a short time as most patients were weaned from the ventilator shortly after arrival in the ICU. In patients who are candidates for a heart assist device (intra-aortic balloon pump) a femoral arterial puncture for application of the PiCCO device is contra-indicated. We experienced, consistent with the literature, that measurement of GEDVI and ITBVI in cardiomyoplasty patients is irrelevant.

Furthermore we have, based on theory and observation, the impression that the precision of these variables is dependent on SVV. From the foregoing we consider that the PiCCO system is of limited value in monitoring cardiothoracic patients.

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Letter to the Editor

The PiCCO device in cardiothoracic patients – more useful than suggested

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To the editors:
With interest we read the review of de Wilde and colleagues about the use of the PiCCO device in cardiothoracic patients in relation to their own extensive experience [1]. We are pleased they took effort to explain how this interesting technique works and what the possible advantages and disadvantages are. However, we do not agree with the authors that the PiCCO system is of limited value in monitoring cardiothoracic patients. We feel that the authors have omitted several potentially beneficial possibilities of the PiCCO device that might be of interest to the readers of the Netherlands Journal of Critical Care.

Determination of cardiac output
As de Wilde et al. correctly mention, despite a small overestimation, the transpulmonary thermodilution technology (TPTD) is a reliable method to measure cardiac output (CO) but also tracks changes in CO over time. We, like many others, have proven this in an animal model [2]. It is therefore even considered the gold standard for measuring cardiac output in critically ill pediatric patients [3].
Using the TPTD technique the PiCCO device calibrates it's arterial pressure driven pulse contour cardiac output method and subsequently provides the clinician with a fast beat-to-beat CO measurement. Although some types of pulmonary artery catheters automatically measure CO, these measurements are not continuous and do not provide insight when fast changes in CO (might) occur.
The accuracy and precision of the pulse contour method are not as good as the TPTD method, therefore frequent recalibration is needed. However the accuracy of the pulse contour method of the PiCCO device is comparable to the only other commercially available calibrated pulse contour method (LiDCO system, Cambridge, UK). The uncalibrated techniques mentioned by the authors namely Modelflow (BMEYE, Amsterdam) and Hemac (from one of the authors) may perform better but do not have the essential ability to be calibrated against an established and incorporated method. Besides that, they are not commercially available for use in the critical care environment.
The conclusion that accuracy, precision and ability to track changes in CO of the PiCCO device are inferior to its competitors is therefore not substantiated by the authors.

Determination of fluid responsiveness

The authors correctly mention the ability of the PiCCO device to record stroke volume variation (SVV) and pulse pressure variation (PPV), which are potentially useful predictors of fluid responsiveness. The authors state that these measurements are of limited use because “irregular heart rates are quit common in cardiac surgery patients”. We think this has little clinical consequences since the use of preload parameters is most important on the first or second postoperative day while most rhythm disturbances (e.g. atrial fibrillation) occur after this time period. In a recent series from our own hospital (CORRAD database registration, UMC St Radboud) an episode of atrial fibrillation developed in only 7.7% of postoperative cardiac surgery patients during their ICU treatment.

We do not agree with the authors that SVV and PV are of limited value in spontaneously breathing patients. SVV and PPV appear to have a high specificity in patients breathing spontaneously without mechanical supportand only the sensitivity appears to be low. In that case the possibility of a passive leg raising test should be considered. As the PiCCO device provides a fast beat-to-beat CO measurement it enables the determination of fluid responsiveness using the passive leg raising (PLR) test [4].

Although we agree with the authors that measurement of global end diastolic volume (GEDV) is of limited value in predicting fluid responsiveness in patients with reduced myocardial function, we believe this measurement can be of value for many other patients. The opinion that SVV influences the precision of the GEDV measurement is interesting but has never been substantiated. We have never observed this phenomenon; neither can we explain this on basis of theory. Since stroke volume variation occurs almost beat to beat while the TPTD measurement technique measures GEDV during a time interval of at least 10 seconds, and comprises many heartbeats, we find this difficult to accept. We certainly encourage the authors to publish this observation because it can be of importance to clinicians using this device.

Determination of extra vascular lung volume

Using the PiCCO device extra vascular lung water (EVLW) can reliably be measured by means of the TPTD technique. It offers the clinician the opportunity to quantify the amount of pulmonary edema [5]. A therapeutic strategy aimed at reducing EVLW has been shown to decrease ventilator- and ICU days [6]. Measurement of EVLW in adults can therefore be regarded as a relevant parameter for the management of critically ill patients [7].

Unfortunately the authors have left the capability of the PiCCO device to measure EVLW completely unmentioned. We are aware of at least one other ongoing trial comparing a strategy of increasing cardiac output versus a strategy limiting extravascular lung water.

Conclusion

We consider the PiCCO device as reliable as the PAC in measuring CO using the transpulmonary thermodilution technique. Furthermore using pulse contour analysis this technology enables the determination of fluid responsiveness using either arterial pressure variations or the passive leg raising test. Also it offers the possibility to measure extra vascular lung water en thereby quantify the amount of pulmonary edema. Potentially the PiCCO system could thus be superior to other devices and

useful to all ICU patients, including children. However like the pulmonary artery catheter, it's clinical value still needs to be quantified.
As with every other medical device it is not the technology that cures ICU patients, but the doctors and nurses who must interpret the obtained data and translate them into appropriate therapeutic protocols.

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Review of the PiCCO device; our experience in the ICU

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Reply

The authors, Lemson and van der Hoeven (L&H), do not agree with us that the PiCCO system is of limited value in monitoring cardiothoracic patients. They feel that we omitted several potentially beneficial possibilities of the PiCCO device that might be of interest to the readers of the Netherlands Journal of Critical Care.
Before responding in this discussion about the limitations of the PiCCO system, we need to draw attention for the main assumptions made in the calculation of (transpulmonary) thermodilution cardiac output. Furthermore, definitions about accuracy and precision of cardiac output methods and about interpretation of differences between methods must be made.

Introduction

In the analysis of accuracy (also called bias) and precision (standard deviation of measurements), the thermodilution method is generally considered accurate but not precise whereas pulse contour methods are considered precise but inaccurate, figure 4b.1. However, after calibration by thermodilution pulse contour methods are supposed to be accurate and precise.

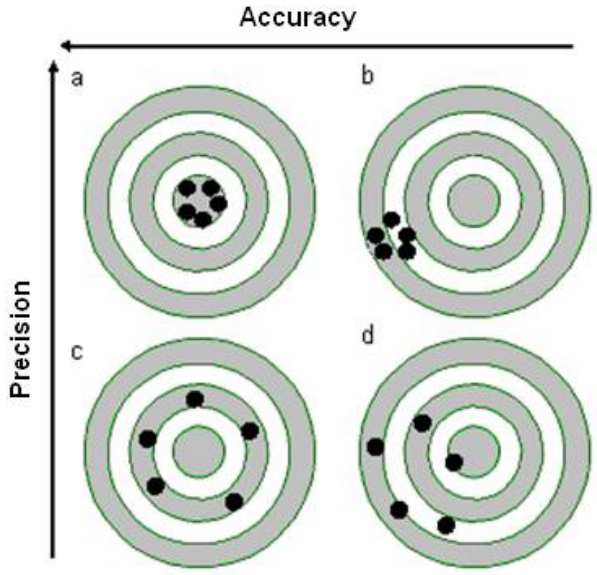


Figure 4b.1 Schematic representation of accuracy and precision.

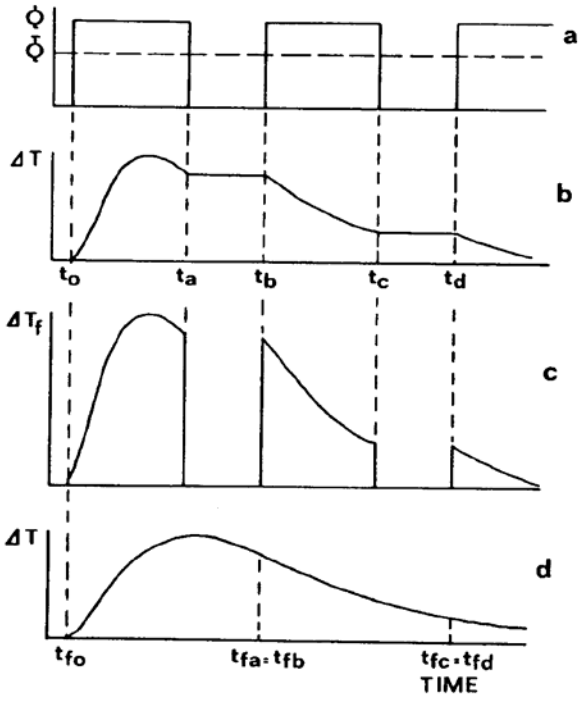
What makes the thermodilution methods less precise? Or what causes sequential measurements to differ so much?
The thermodilution method is based on the law of conservation of thermal energy. If and only if *blood flow is constant*, if *no loss of indicator* between injection site and detection site occurs, if mixing of blood and indicator is complete and if a bolus injection of a limited amount of cold indicator is applied then the classical Stewart Hamilton equation can be used. Neglecting these assumptions may lead to considerable spread in cardiac output (CO) values as has been reported by several authors. So, the results of many CO measurements must be averaged to acquire one accurate estimate of mean cardiac output. More then 25 years ago we [1] showed this spread in CO estimates was mainly caused by violation of the assumption of constant blood flow. As known from physiology, during mechanical ventilation, blood flow decreases during inspiration and recovers during expiration. This violation of the assumption of constant blood flow resulted into a cyclic pattern of thermodilution cardiac values related to ventilation. The amplitude of this cyclic modulation appeared to be larger during hypovolemia and smaller during hypervolemia. As a practical solution we proposed to estimate mean cardiac output by taking the mean value of three or four measurements performed equally spread over the ventilatory cycle [2]. In patients, this approach has shown to improve the precision from 10-15% to 3-5% [2]. These findings were confirmed in many of our studies as well as of others, among them Groeneveld et al. [3]. We still support our conclusion that in the ICU and OR the estimation of cardiac output by thermodilution can be accurate and precise if the limitations of the method are taken into account.

More then 25 years ago we developed an equation that did not require the assumption of constant blood flow [patent NL 189547, Patent USA 4595015, 4]. However, for this solution a relative measure of blood flow is needed. For this purpose we used pulse contour analysis. A simplified schematic graphical representation of the underlying mathematics is shown in figure 4b.2.
In this figure we illustrate the effects of non constant blood flow, panel a, on the thermodilution curve, panel b. During periods of no flow the temperature change measured with a thermistor is constant, panel b. In panel c, the temperature change after weighing with a measure of relative flow is given (ΔTf). It is obvious that there is no transport of cold indicator during periods of no flow and the area under the temperature curve is zero during these periods as it should be. In panel d, a normal dilution curve is found after transformation of the time axis according to our invention. This is the curve that might be found in case of a measurement with a constant flow and averaged value as indicated by the dashed line in panel a.
In animal experiments [4] as well as in patients [5] we showed that during mechanical ventilation cardiac output can be estimated with high accuracy and precision by single measurements (precision improved from 20 to 5%).

By changing ventilatory frequency and tidal volume we found the spread of CO estimates to increase with tidal volume and to decrease with ventilatory rate. Furthermore, we showed that model fits of the dilution curves with a mixing chamber model (model used in the PiCCO system) improved significantly after application of our patented equation.
The PiCCO device with its incorporated transpulmonary thermodilution technique calculates CO with use of the Steward-Hamilton equation based on the assumption of constant blood flow. However, the same device may show, by pulse contour analysis,

that stroke volume is varying with the phase of mechanical ventilation (SVV), implying a violation of the Steward-Hamilton equation. This limits the application of the PiCCO device.

What is the meaning of the conclusion of several authors that a clinical acceptable agreement between transpulmonary thermodilution and pulmonary thermodilution exists? Comparing the results of two methods that have a large spread (low precision) (Fig. 4b.1, c and d) may easily lead to the invalid conclusion that no significant difference between methods exists. So that one method can replace the other. Whereas, comparing two methods with high precision (Fig. 4b.1, a and b) would show a significant difference. Therefore, it is highly relevant to improve the precision of the methods. This is especially of importance for the reference method or gold standard.



$$\Delta T_f = T_b(t) \cdot \frac{\dot{Q}(t)}{\bar{\dot{Q}}}$$

$$t_f = t_{n-1} + \frac{\dot{Q}(t)}{\bar{\dot{Q}}} \cdot (t_n - t_{n-1})$$

Fig. 4b.2 Schematic diagram of flow averaging of concentration and of time. In panel a, $\dot{Q}$ actual blood flow and mean blood $\bar{\dot{Q}}$ mean flow (dashed line). In panel b, ΔT temperature change of the blood after injection of a bolus cold fluid. In panel c, ΔTf the temperature change after flow averaging. In panel d, blood temperature as a function of transformed time t_f.

Determination of cardiac output

Based on the forgoing one may conclude that we should consider a precision of 10 to 15% for the thermodilution unacceptable. We therefore consider it premature to accept the transpulmonary thermodilution as gold standard in critically ill pediatric patients.

The remark of L&H that the continuous pulmonary thermodilution technique is not continuous is wrong, it is most certainly a continuous measurement but its value will not necessarily change in synchrony with fast changes in cardiac output.

According to the definition given for accuracy and precision, the accuracy (not the precision) of PiCCO's pulse contour method is less than the thermodilution method and, indeed, frequent recalibration may be needed. However, this frequent need for recalibration turns the method from continuous to intermittent. The uncertainty to measure cardiac output correctly, shortly after a recalibration, limits the applicability of the method. It is our experience that during the first hour after admission of a patient to the ICU a regularly a recalibration is needed. After this first hour intervals of 8 hours between calibrations will normally be sufficient under standard clinical conditions.

L&H miss the ball by stating that the Modelflow and Hemac methods do not have the essential ability to be calibrated against an established method. We have extensively given attention to this item in several publications [6-9].

In several comparative studies [10-13] the PiCCO device was ranked low with respect to accuracy and precision. Therefore, we have arguments to repeat our conclusion that the PiCCO device has been outperformed by its competitors. With this conclusion, we intent to push forward the development of pulse contour methods with a better performance, so that changes in cardiac output during passive leg raising or during small amounts of fluid loading can be used to predict fluid responsiveness of a patient reliably and safely.

Determination of fluid response

One of our statements mentioned by L&H is that because of commonly observed irregular heart rates in the ICU the use of SVV and PPV to predict fluid responsiveness is limited. In their letter L&H mentioned that in a recent series from their own hospital (CORRAD database registration, UMC St Radboud, the Netherlands) an episode of atrial fibrillation developed in only 7.7% of postoperative cardiac surgery patients during their ICU treatment. Their results differ from ours and from results given in literature [14, 15]. According to Parrikka et al [15] postoperative arrhythmias in the first two to three days after cardiothoracic surgery appear to happen in up to 43% of the patients. We are very interested in explanations of this difference and look forward to a publication on this subject. Based on the relatively high incidence of arrhythmias, we still come to the conclusion that the PiCCO device is limited in its use.

Of course the use of SVV and PPV is of no value in patients with spontaneously breathing activity. This is indeed illustrated, for instance, by the fact that even in patients with a regular breathing pattern (constant tidal volume and rate of ventilation) the sensitivity to predict fluid responsiveness is low.

L&H state that the opinion that SVV influences the precision of the GEDV measurement has never been substantiated. From the introduction given in the current reply it must be clear that this is not an opinion but a conclusion based on scientific work performed more then 25 years ago [4, 5]. Indeed, neglecting the modulation on

stroke volume by mechanical ventilation (duration approximately 5 sec) may clearly influence the determination of the down slope time of the transpulmonary dilution curve. We encourage the readers of the Netherlands Journal of Critical Care to discuss this item with the developers of the PiCCO system in order to gain more accurate and precise apparatus (with fewer limitations) in the near future.

Conclusion

The letter of L&H did not change our opinion about the use of the PiCCO device. This letter illustrates that definitions about accuracy and precision are needed. Furthermore, that a comparison between methods is only valid when the reference method is precise and accurate. Thermodilution methods as reference methods with a precision of 10-15% are unacceptable. To archive unambiguous results knowledge of basic physiology and physics is imperatively needed. Only then, with data that can be relied on, the development of an appropriate scientifically based protocol is possible which can help the doctors and nurses to cure the patient.

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