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Cardiac output measurement : evaluation of methods in ICU patients

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Cardiac output measurement; evaluation of methods in ICU patients

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The research leading to this thesis is primarily conducted at the department of Intensive Care of Leiden University Medical Center in the Netherlands.

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Chapter 1

General introduction

General introduction

As for all mammals, we have to breathe for oxygen uptake and for the release of carbon dioxide. Most of the oxygen is consumed in the mitochondria. Thus, oxygen has to be transported from the lungs to the mitochondria and carbon dioxide has to be transported back to the lungs. It is the purpose of this thesis to evaluate methods that measure this transport function i.e. circulation or cardiac output. Furthermore we study factors that determine cardiac output. In a normal individual who is breathing spontaneously, blood pressure decreases on inspiration and recovers on expiration. However, the change in systolic pressure does not exceed 5 mmHg. This change in pressure as well as in blood flow with respiration is reversed and increased during applied intermittent positive pressure ventilation (IPPV) in mechanically ventilated patients, figure 1.1.

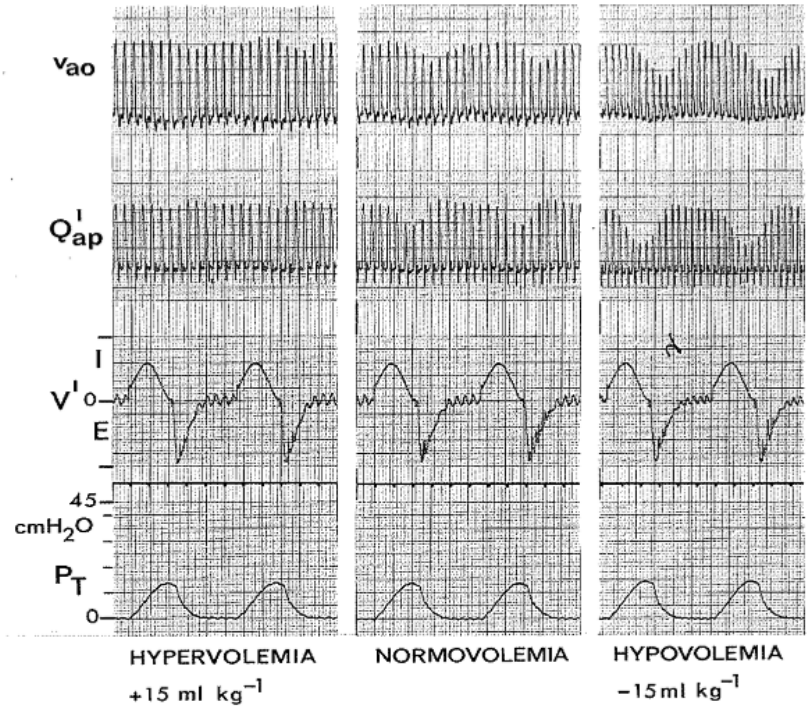

Figure 1.1 Fluctuations of blood flow dependent on blood volume. Recordings of flow velocity an the aorta (V_{ao}) and volume flow in the pulmonary artery (Q'_{ap}) during the ventilatory cycle (V' is air flow measured in tracheal cannula and P_T is airway pressure) at different blood volumes. From Versprille et al. 1982 [2].

For instance, Jansen [1] and Versprille [2] conducted in the early-1980s several studies describing the influence of mechanical ventilation on cardiac output (cardio-pulmonary interaction) in animals. From these results it became obvious that monitoring cardiac output and cardio-pulmonary interaction provides invaluable clinical information about an individual's hemodynamic status (such as amount of effective circulating blood, effects of volume loading on cardiac output and effects of different ventilator setting on cardiac output) and the abilities to transport oxygen.
Today, there are a number of companies that market devices for monitoring cardiac output and cardiac-pulmonary interaction. These devices all have a number of

characteristics that need to be understood before the devices can be used appropriately. Furthermore, these devices need to be extensively evaluated before they can be introduced safely and reliably in the Intensive Care Unit (ICU). The aim of the introduction is to give some historical, physiological and methodological background information.
This thesis aims to describe the evaluation of the cardiac output methods most often used in the ICU.

Historical and physiological aspects of cardiac output and respirator induced changes in blood flow and pressure
In early studies of continuous positive pressure ventilation (CPAP) and intermittent positive pressure ventilation (IPPV) in man and animals the measurement of blood flow was too time-consuming (Fick and indicator-dilution methods) for studying cyclic changes in blood flow. The presence of such fluctuations has been reported already in 1869 by Hering in a paper entitled: "Ūber den Einfluss der Athmung auf den Kreislauf" [3]. From the mid-1960s, after development of the electromagnetic flow meter, ventilator related changes in flow during IPPV and continuous positive airway pressure (CPAP) ventilation were published [2, 4-6]. Recordings made by Jansen [1] and Versprille [2], showed the characteristic phenomenon of flow modulation by IPPV, figure 1.1.

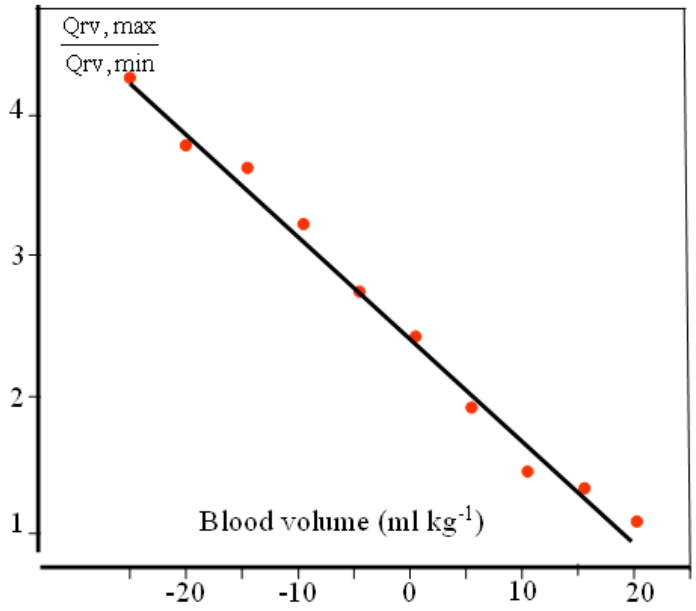

Figure 1.2 Fluctuation in right ventricular stroke volume dependent on blood volume. The ratio of maximum right ventricular stroke volume ($Q_{s,rv,max}$) and the minimum value ($Q_{s,rv,min}$) is plotted against changes of blood volume with respect to normovolemia, which is indicated on the abscissa. Note that at severe hypovolemia the ratio decreases; this is comparable to shock. A study in piglets. From Versprille et al. 1982 [2].

During inflation of the lungs, venous return is hindered by an increase in intra-thoracic pressure which results in a decrease in right ventricular output.

Right ventricular stroke volume is lowest at the end of lung inflation (and stays low during an end-inspiratory pause). When spontaneous expiration starts right ventricular output rapidly increases and stays at a constant level during the last part of expiration. Left ventricular output follows with a few heart beats behind right ventricular output due to the long (~ 2 seconds) transit time of blood through the pulmonary circulation. Left ventricular output is, however, slightly less modulated. In 1980 and 1982, Jansen [1] and Versprille [2] showed in their animal experiments that the amplitude of modulation was reversely related to mean blood flow and to the volemic status of the animals, figure 1.2. Here modulation of ventricular output is characterized by maximal blood flow divided by minimal blood flow (modulation =Q'max/Q'min).

According to the Frank-Starling mechanism [7] the decrease in transmural right ventricular pressure (Pra,tm) – i.e. the pressure difference over the wall of the right ventricle- with lung insufflation results in a decrease in right ventricular output [8, 9]. For a fixed change in transmural pressure the amount of decrease in ventricular output depends on the shape of and the work point on the Frank-Starling curve, figure 1.3.

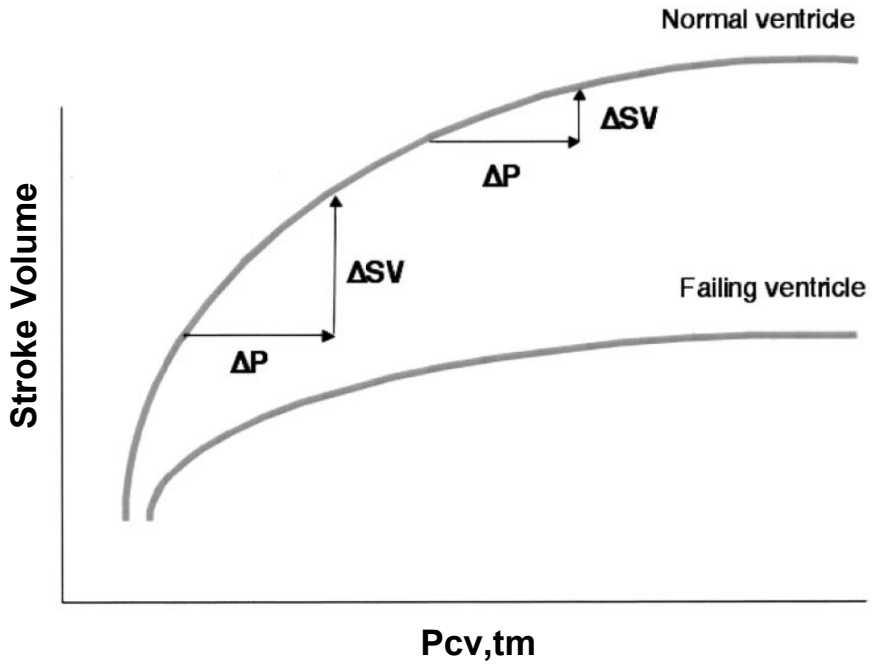

Figure 1.3 Schematic representation of the Frank-Starling relation between filling status and transmural pressure (X-axis) and stroke volume (Y-axis). During low filling status of the ventricle – with a low transmural pressure, the more likely the ventricle is operating on the steep portion of the curve and hence a given change in filling status (Δ Pcv,tm) will induce a significant change in stroke volume (ΔSV). From Michard 2005 [29].

During a low filling status of the ventricle -with a low transmural pressure- stroke volume diminishes markedly during insufflation whereas it diminishes less strikingly during a high filling status –with a high transmural pressure. Therefore, variation in

stroke volume during mechanical ventilation with a fixed tidal volume and respirator frequency is low in hypervolemia and high in hypovolemic filling status of the heart.

Perel et al. [10] used systolic arterial pressure as a surrogate for ventricular stroke volume and defined systolic pressure variation (SPV) during mechanical ventilation as the sum of Δup and Δdown, figure 1.4. For this determination a single prolonged end expiratory pause is needed.

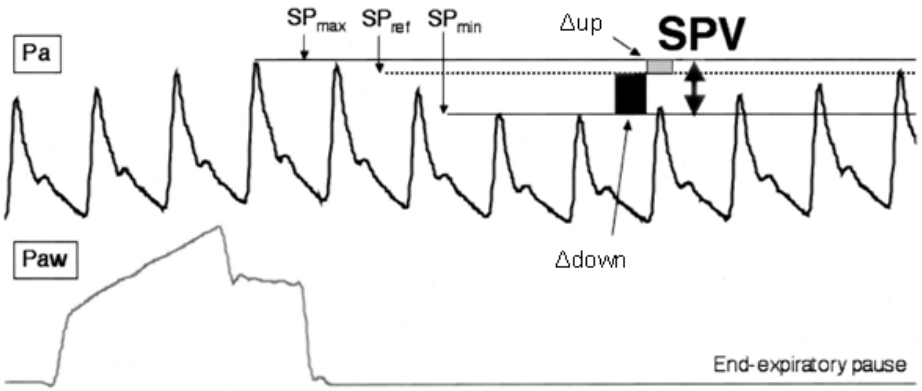

Figure 1.4 Description of respiratory changes in arterial pressure during mechanical ventilation. The systolic pressure variation (SPV) is the difference between SPmax and SPmin a few heart beats later, during expiration. Pa is arterial pressure; Paw is airway pressure. From Michard 2005 [29].

Michard et al. [11] proposed to quantify respirator induced variation in arterial pulse pressure (PP), as surrogate for stroke volume. Pulse pressure variation (PPV) is found by calculation the difference between maximum (PPmax) and minimum pulse pressure (PPmin) over a single mechanical breath divided by the mean of both values i.e. PPV(%) = 100*(PPmax-PPmin)/[(PPmax+PPmin)/2], figure 1.5.

Berkenstadt et al. [12] and Reuter et al. [13, 14] used a similar formula to determine pulse contour stroke volume variation. Stroke volume variation (SVV) is calculated as: SVV(%) = 100*(SVmax-SVmin)/[(SVmax+SVmin)/2]
Stroke volume variation (SVV) and pulse pressure variation (PPV) are an integral part of today's beat-to-beat pulse contour cardiac output monitoring systems (such as Pulsion's PiCCO system, LiDCO's PulseCO system and Edwards FloTrac-Vigileo system, which are evaluated in this thesis).

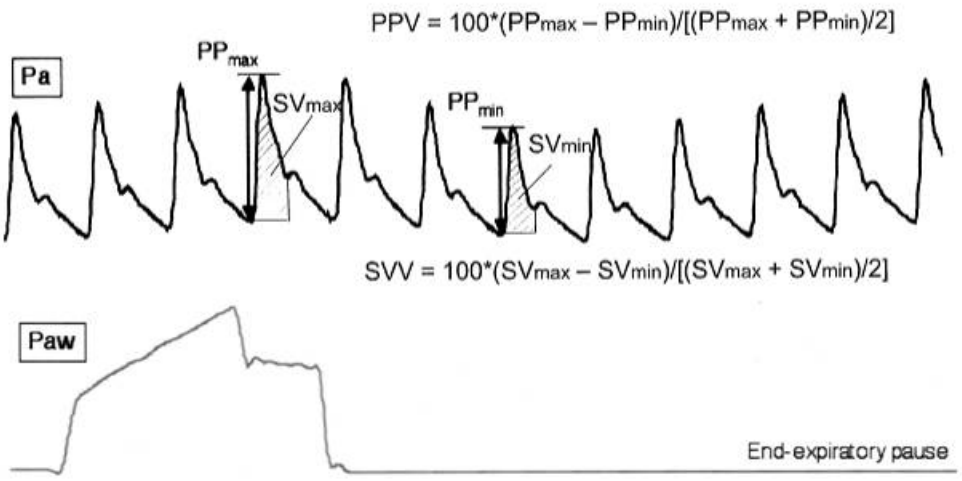

Figure 1.5 Description of resiratory changes in arterial pressure during mechanical ventilation. Pa is arterial pressure; Paw is airway pressure; PPV is pulse pressure variation; SVV is stroke volume variation. From Michard 2005 [29].

Also, Doppler recordings of aortic blood flow at the level of the aortic annulus or in the descending aorta have been used to quantify the respiratory variation in aortic peak velocity (APVV) or in aortic blood flow (ABFV) [15-17].

However, despite evidence generated in literature, the use of SPV, PPV or SVV (APVV and ABFV) for characterizing the volemic condition is limited to patients who are fully dependent on mechanical ventilation (with no spontaneous breathing activity), who are ventilated with tidal volumes larger than 8 mL/kg and who have a regular heart rate. These conditions are often not fulfilled in ICU patients.

Thermodilution as reference method for cardiac output

"In assessing any method of measurement it is clearly necessary to know the probable error of the standard against which it is compared" [18]. In this thesis pulmonary thermodilution is used as reference method for all methods evaluated. However, for a reliable application several conditions have to be fulfilled. First, complete mixing of cold injectate with blood; Second, no loss or gain of cold between the site of injection (entrance right atria) and site detection (pulmonary artery); Third, constant blood flow. The condition of constant blood flow is, as explained in the above paragraph, violated during mechanical ventilation. As shown in theoretical and physical models as well as in animal and patient studies [19-23], the errors in the estimation of mean flow –cardiac output- by the bolus injection technique may be very large, especially if the frequency content of the dilution curve is similar to that of the flow modulation as occurs during mechanical ventilation.

Among different solutions for this problem Jansen et al. [23] demonstrated a very practical one. By averaging the results of 4 estimates initiated at moments equally distributed over the ventilatory cycle highly reproducible results were found in animals and humans [23, 24] figure 1.6.

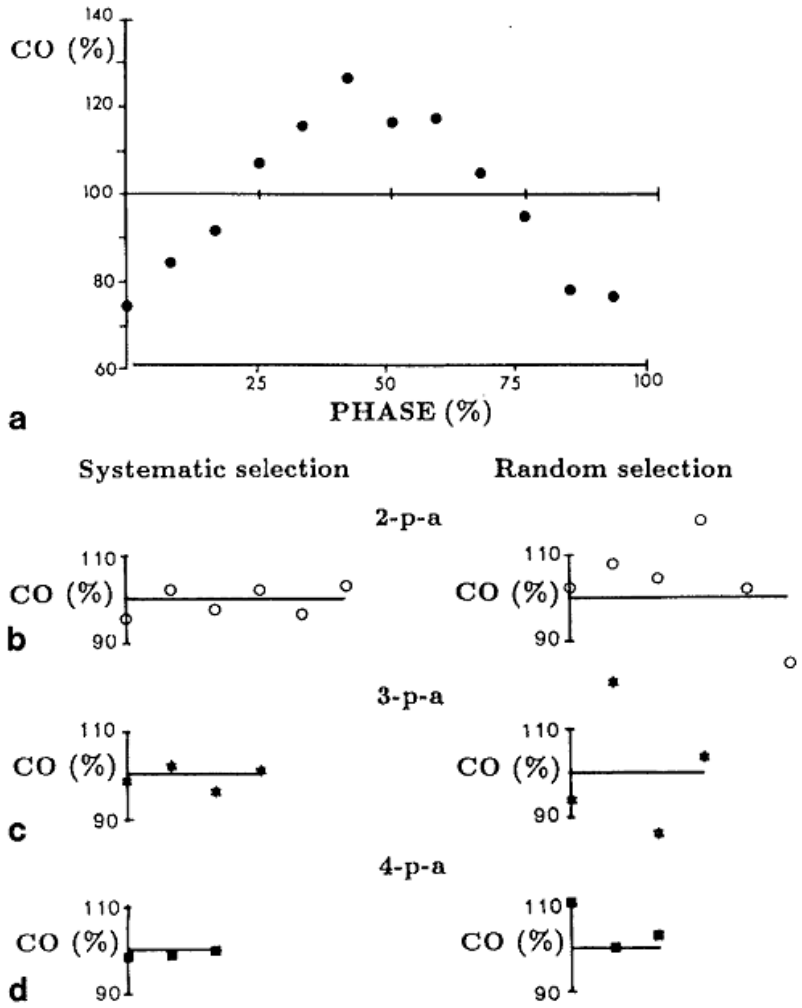

Figure 1.6 Calculation of cardiac output average based on a systematic selection and random selection of sinle estimates. Values are given in % of the mean of a series of all 12 estimates. a; 12 single estimates of a patient plotted against the moment of injection in the ventilatory cycle. Phase 100% is the same as 0% coincide with the start of insufflation. b; 6 two point averaged (2-p-a) values consecutively plotted on the horizontal axis, c; 4 three point averaged (3-p-a) values , and d a 3 four point averaged (4-p-a) value. From Jansen 1995 [25].

In a patient study [25], the standard deviation decreased from 13.0% for single thermodilution estimates to 3.2 % if the averaged value of 3 measurements equally distributed over the ventilatory cycle (for instance the first at 0% the second at 33% and the third at 66% of ventilatory cycle) was taken. This standard deviation was still 7.2% for the averaged value of three randomly applied measurements. In this thesis the averaged value of three measurements equally spread over the ventilatory cycle was taken, unless it was explicitly stated differently.

Analysis of agreement between methods of measurement
A correct evaluation of cardiac output devices from literature is often hampered by 1) incomplete description of the methods, patient characteristics and measurement conditions, 2) incomplete description of results, or 3) use of a non validated reference method or acceptance of an imprecise method. In this thesis different less invasive methods of cardiac output measurement and monitoring are evaluated against a well studied reference method with high precision, i.e. the bolus thermodilution method.

The evaluation of new methods to measure physiological variables is facilitated by standardization of reporting results. It has been proposed that assessing repeatability should be followed by assessing agreement with an established technique. Bland and Altman [26] advocated the use of a graphical method by plotting for each subject the difference between the method under study and the reference method against their mean and argued that if the new method agrees sufficiently with the old, the old may be replaced. Here the idea of agreement plays a crucial role. Limits of agreement are calculated as mean difference (bias) ± 1.96 * standard deviation (SD). SD is also called precision [26, 27]. Strict rules when a new method may replace an older reference method are given by Critchley and Critchley [28] and not by Bland-Altman. These rules as well as Bland-Altman plots are analysed throughout the thesis.

Outline of the thesis

In this thesis, different recently developed methods to monitor cardiac output and ventilator induced stroke volume and pulse pressure variation are evaluated in ICU patients. The thesis contains the following items:

- In the second chapter the interchange-ability of femoral artery pressure and radial artery pressure as input for the PiCCO pulse contour system is tested.
- In chapter 3 the quality and tracking ability of five different pulse contour methods are evaluated by simultaneous comparison of cardiac output values with that of the conventional thermodilution technique (COtd). The five different pulse contour methods enclosed in this study were: Wesseling's cZ method; the modified Modelflow method; the LiDCO system; the PiCCO system and a recently developed Hemac method.
- In chapter 4 a review of the PiCCO pulse contour cardiac output monitoring system is given addressing our clinical experiences with this device.
- In chapter 5 the FloTrac-Vigileo pulse contour cardiac output system is evaluated. Its results are compared with that of other pulse contour methods.
- In chapter 6 the tracking abilities of cardiac output changes by three less invasive cardiac output methods requiring no calibration were evaluated. The following methods were studied: 1. FloTrac-Vigileo, 2. uncalibrated modified Modelflow and 3. HemoSonic100 trans-esophageal ultrasound. In this study cardiac output changes were achieved by changing ventilator settings and by passive leg raising.
- In chapter 7 an alternative method for calibration of the modified Modelflow is tested. For this purpose aortic diameter is measured by the HemoSonic 100 transesophageal ultrasound system.

- In chapter 8 data of stroke volume variation (SVV) obtained with two different pulse contour systems were compared in different clinical conditions.
- The last chapter of this thesis the main results of previous chapters will be summarized in English and Dutch.

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Chapter 2

Monitoring cardiac output using the femoral and radial arterial pressure waveform

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Summary
This study was performed to determine the interchangeability of femoral artery pressure and radial artery pressure as input of the PiCCO system (Pulsion Medical Systems, Munich, Germany). We studied 15 intensive care patients after cardiac surgery. Five second averages of the cardiac output derive from the femoral artery pressure (COfem) were compared to 5 second averages derived from the radial artery pressure (COrad). The equality of the two PiCCO devices used in this study was confirmed.
One patient was excluded from our study because of problems in the pattern recognition of the arterial pressure signal. In the remaining fourteen patients, 14734 comparative cardiac output values were analysed. The mean sample time was 88 min, range [30-119 min]. Mean (SD) COfem was 6.24 (1.1) $l.min^{-1}$ and mean COrad was 6.23 (1.1) $l.min^{-1}$. The Bland-Altman analysis showed an excellent agreement with a bias of -0.01 $l.min^{-1}$, and limits of agreement from 0.60 to -0.62 $l.min^{-1}$. If changes in CO were larger than 0.5 $l.min^{-1}$, in 97% the direction of changes in COfem and COrad were equal. We conclude that femoral artery pressure and radial artery pressure are interchangeable as input of the PiCCO device allowing to change to the radial artery pressure line if the preferred femoral artery pressure line is no longer available for use.

Introduction
During cardiac surgery as well as during the first hours of ICU care, fluctuations in mean arterial pressure and cardiac index are the primary indicators for intervention [1]. When patients are hemodynamic unstable a continuous measurement of cardiac output is highly desirable. For this reason, different methods to monitor cardiac output continuously have found there way to the operating room (OR) and intensive care unit (ICU) [2-8]. Among the available pulse contour methods, the PiCCO system, with femoral artery pressure as input and calibrated by transpulmonary thermodilution, appears to have a clinical acceptable accuracy and tracking capability [9]. However, the femoral artery catheterization might become restrained in certain patients. In these patients, in whom the femoral arterial catheter is no longer available, the standard radial artery catheter seems a logical alternative, but this approach has not been validated yet.
Therefore the goal of the present study is to evaluate the interchangeability of femoral artery pressure and radial artery pressure as input of the pulse contour method of the PiCCO system in patients after cardiac surgery.

Patients and methods
Patients The study was approved by the hospital ethics committee and was conducted according to the principles stated in the Helsinki convention. Written informed consent was obtained the day before surgery. Fifteen patients (11 men and 4 women, mean age 73 years) scheduled to undergo elective cardiac surgery on cardiopulmonary bypass (11 patients with CAGB and 4 patients with mitral valve annuloplasty) were included in the study. Patients with significant valvular regurgitation and/or atrial fibrillation, aneurismal deformities to the aorta or symptomatic peripheral vascular disease were excluded. Patients were pre-medicated with sublingual lorazepam (0.05mg/kg). Radial arterial blood pressure was monitored via a 20 Gauge, 3.8 cm long radial catheter inserted by Seldinger technique and connected to a pressure

transducer (PX600F, Edwards Lifesciences). Central venous pressure was measured with a MultiCath 3 venous catheter (Vigon GmbH & Co, Aachen, Germany), connected to a pressure transducer (PX600F, Edwards Lifesciences). Anaesthesia during surgery was performed according to institutional standards.
After transfer of the patients to the ICU, a second arterial pressure line was inserted with a Seldinger technique into the right femoral artery (4F, 16cm long thermistor-tipped arterial catheter PV2014L16; Pulsion Medical Systems, Munich, Germany) and connected to a cardiac output monitor (PiCCO, Pulsion). Pulse contour cardiac output was calibrated with 3 transpulmonary thermodilution measurements. For each thermodilution measurement, 20ml cold (3-8^{o}C) saline was injected, via the central venous catheter. The results and calculated average of the 3 cardiac output measurements were documented.
All patients were mechanically ventilated with an oxygen level of 40%, a respiratory frequency of 12-14 min^{-1}, and positive end expiratory pressure of 5 cmH_2O. Tidal volume (6-8 $ml.kg^{-1}$) was adapted to maintain the arterial PCO_2 between 40 and 45 mmHg. A hemodynamic stable status was achieved using fluids and catecholamines. The observation period started after introduction of the femoral artery catheter and stopped at the onset of weaning. During the observation period, up to 6 hours, the radial artery pressure, femoral artery pressure and central venous pressure were continuously stored on computer disk. The sample frequency was 100Hz and the resolution 0.2 mmHg. It should be noted that during this recording sessions great care was taken to flush, check, and if necessary, re-zero the pressure transducers when necessary. Every patient experienced full recovery from anaesthesia within 8 hours and was discharged from ICU the next, first post-operative day.

Data analysis
Applying the same femoral blood pressure to both devices for 103 minutes, the equality of the two PiCCO monitoring devices was tested. The two devices were calibrated using the same calibration factor. The pulse contour output data of the PiCCO devices was collected with a computer program (PiCCOWin, Pulsion, Munich, Germany), with 5-second averages to allow statistical analysis.
Next, from each patient, the radial and femoral arterial pressure was played back from the computer disk (for at least a 1-hour period) to the two PiCCO monitoring devices. PiCCO1 was used for cardiac output from the femoral pressure (COfem) and PiCCO2 was used for cardiac output calculations of the simultaneously played back radial arterial pressure (COrad). At start the cardiac output values were set equal to the mean of the three values documented at the bedside. For both COfem and COrad the same calibration factor was used. The pulse contour output data of the PiCCO devices were collected with a computer program (PiCCOWin), and the averaged data were stored on a computer disk every five seconds.

Statistics
The mean statistical tool is the Bland-Altman analysis with differences in data pairs plotted against their mean [10]. The agreement between COfem and COrad was computed as bias [mean (SD)], with limits of agreement computers as bias ± 2SD. Of each patient, changes in COfem and changes in COrad were calculated by subtracting the measured cardiac output value from the mean cardiac output value of the patient. The agreement of changes in cardiac output were computed using a cross tabulation. Data are given as mean (SD). Statistical significance was considered present for $p < 0.05$.

Results

The equality of the two devices was tested with the same femoral artery pressure as input for both devices. We obtained two sets of 1243 data points, each data point being 5-second average of the pulse contour cardiac output. These two sets were marked with PiCCO1 and PiCCO2. Using these sets, no difference was found between the two monitoring devices (bias 0.03 l.min^{-1}, 95% CI -0.0015 to 0.0067, p = 0.215). The upper and lower limits of agreement were 0.151 and -0.145 l.min^{-1}, confirming an excellent agreement between both cardiac output devices.

In fifteen patients, radial and femoral artery blood pressure was recorded. An illustration of an individual patient is presented in figure 2a.1.

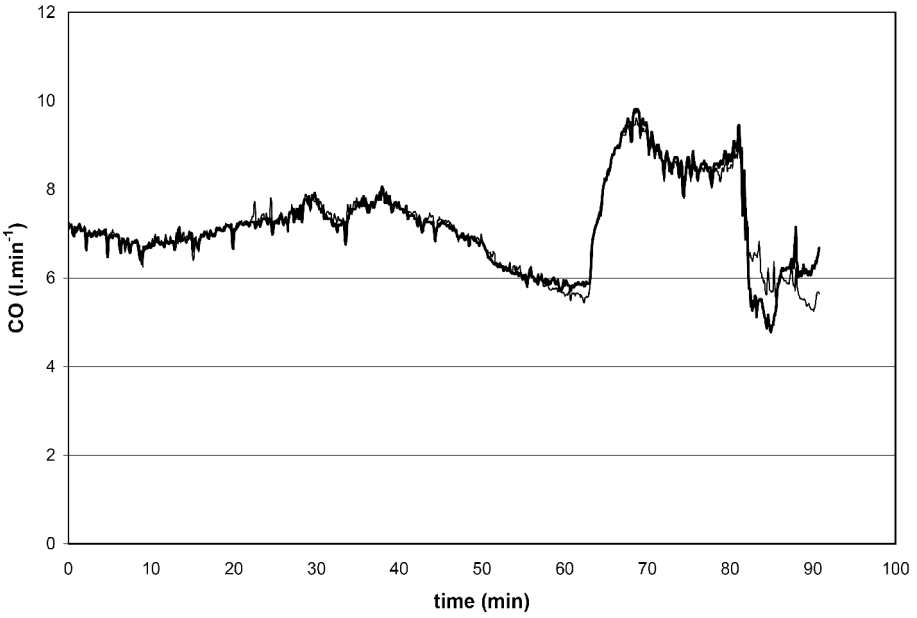

Figure 2a.1 Data of an individual patient. Thin line pulse contour cardiac output (CO) from the femoral artery pressure and solid line CO from the radial artery pressure.

One patient was excluded because of problems with the pattern recognition of the pressure signal, visualized on the screen of the PiCCO devices. From the remaining fourteen patients we analyzed a total of 1053 recording minutes (per patient mean 88 min, range [30-119 min]) resulting in 14734-paired values of COrad and COfem. The mean cardiac output measured with the femoral blood pressure was 6.24, SD (1.1) l.min^{-1} and with the radial arterial pressure 6.23, SD (1.1) l.min^{-1}. This irrelevant small difference was, however, statistically different from zero (p = 0.05).

The Bland-Altman analysis (Fig. 2a.2) showed in excellent agreement between COfem and COrad. The irrelevant small bias of -0.007 l.min^{-1} was significant different from zero (95% CI = -0.012 to -0.002, p = 0.05) with upper and lower limits of agreement of 0.60 and -0.62 l.min^{-1}, respectively.

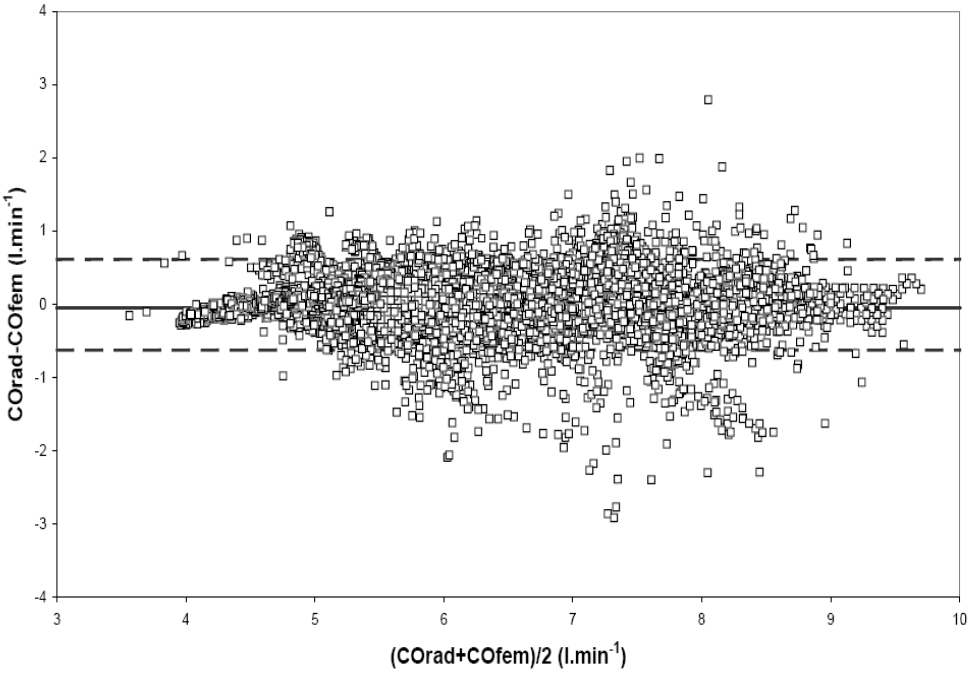

Figure 2a.2 Bland-Altman plot with pulse contour cardiac output from the femoral artery pressure (COfem) and from the radial artery pressure (COrad). The solid line represents the bias and the dashed lines the limits of agreement.

Trending capability of the methods is indicated by plotting the relationship of changes of COfem versus changes of COrad, figure 2a.3. It is noticeable that in this relationship ideally all data point should be placed in the upper-right and the lower-left quadrant. The agreement of positive and of negative changes of COfem and COrad was calculated by a cross tabulation. We found 84.8% of the changes in agreement with each other. When accepting a change in cardiac output smaller then ± 0.5 l.min^{-1}, as not clinically relevant, then 97.3 % of the changes are in agreement of each other.

Discussion

Our study demonstrated that the radial artery pressure is interchangeable with the femoral artery pressure as input of the PiCCO device. This result allows continuing cardiac output monitoring in case of a problem with the femoral artery pressure line by switching over to the more commonly used radial artery pressure line.

The accuracy of pulse contour cardiac output from the femoral artery pressure calibrated by the transpulmonary arterial thermodilution technique using the PiCCO system has been studied in a number of different patient populations with clinically accepted results [9]. However, in cardiac surgical patients, femoral artery catheterization is often avoided to keep unrestricted access to the groin for cardiopulmonary bypass cannulation or placement of an intra-aortic balloon pump when necessary [12]. Therefore, L'E Orme et al. [11] and Wouters et al. [12] investigated the feasibility of the brachial arterial approach to compute cardiac output.

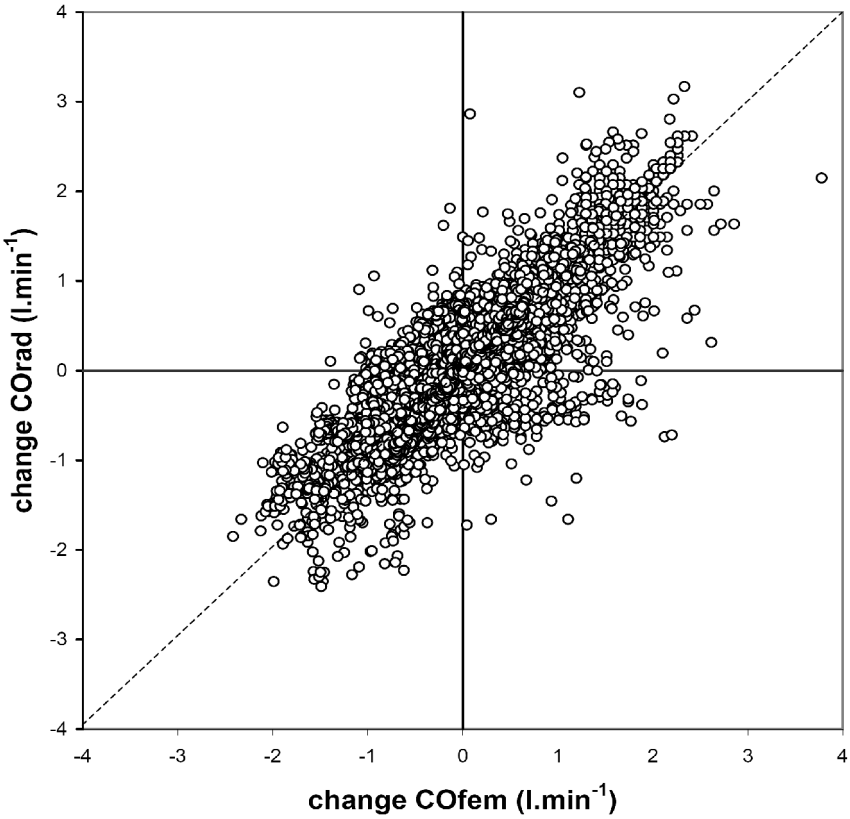

Figure 2a.3 Relationship between changes in femoral artery pulse contour cardiac output (change COfem) and changes in pulse contour radial artery cardiac output (change COrad). Ideally all data points should be in the upper right and in the lower left quadrant. The line of identical change is indicated, dashed line.

In both studies the transpulmonary thermodilution values found via the brachial artery agreed with the results obtained from the pulmonary artery catheter, bias 0.38, SD (0.77) l.min^{-1} and 0.91, SD (0.49) l.min^{-1}, respectively. Therefore, both authors concluded that transpulmonary thermodilution cardiac output measurement via the brachial artery catheter is interchangeable with the cardiac output derived from a pulmonary artery catheter. In addition, Wouters et al. [12] showed pulse contour analyses using a brachial arterial catheter to agree with pulmonary artery thermodilution, bias 1.08, SD (0.75) l.min^{-1}.

The main purpose of our study was to show the possibility to continue cardiac output monitoring, by pulse contour, in case of problems with the femoral arterial line and was not set up to prevent the placement of the femoral arterial line at start. To our opinion, the high agreement between COfem and COrad, bias -0.007, SD (0.31) l.min^{-1}, allows us to change from femoral to radial artery pressure line for continuation of the cardiac output monitoring. Furthermore, the high agreement between COfem and COrad indicate a sufficient pressure waveform quality of the radial artery pressure for pulse contour analysis. This although, different authors [13-15] reported that the systolic radial artery pressure is higher compared to systolic aortic pressure, diastolic and mean pressures were found to be equal between both sites.

The software in the PiCCO systems used is based on an extension of the original Wesseling algorithm [3]. In this algorithm stroke volume is related to the area under the systolic portion of the pressure wave with corrections made on basis of individual aortic compliance and systemic vascular resistance of the patient. As accounts for all pulse contour methods, ideally the aortic pressure waveform should be used as input of the pulse contour method. Certainly, the femoral artery pressure waveforms as well as the brachial artery waveform come closer to this aortic pressure waveform than the radial artery waveform. But, by integration the pressure over the whole systolic period, to obtain stroke volume, the pressure waveform purity becomes less relevant. Also, Wesseling et al. [3] observed no difference between pulse contour cardiac output derived from the aortic pressure and that from the radial artery pressure. Therefore, a dominant role of arterial pressure waveform on the computation of cardiac output by pulse contour seems not present. Our results confirmed this.

Conclusion

We conclude that the femoral artery pressure and radial artery pressure are interchangeable as input of the PiCCO device to compute cardiac output allowing to change to the radial artery pressure line if the preferred femoral artery pressure line is no longer available for use. Regular visual inspection of the pressure waveform on the monitor screen is strongly advised.

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Letter to the editor

Monitoring cardiac output from the radial artery pressure waveform

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We would like to raise a number of points concerning de Wilde and colleagues' paper [1] comparing the radial and femoral artery for measurement of cardiac output using the PiCCO system (Pulsion Medical Systems, Munich, Germany). Their study involved collecting radial and femoral artery pressures traces onto computer and then playing back the data through the PiCCO device. The radial artery pressure was recorded from a 3.5-cm catheter, whereas a 4 F 16cm PiCCO catheter was used for the femoral artery waveform. The calibration factor obtained from the femoral catheter by arterial thermodilution was then used to calculate cardiac output from the radial artery waveform. Bland-Altman analysis of radial vs femoral artery-derived cardiac output yielded acceptable bias and a precision of -0.01 $l.min^{-1}$ and 0.61 $l.min^{-1}$, respectively.

We believe that their conclusion that radial and femoral artery pressure waveforms are interchangeable for cardiac output determination using the PiCCO system fails to appreciate the fundamental issue of calibration. To determine cardiac output via pulse contour analysis, it is first measured by transpulmonary arterial thermodilution using a modified Stewart-Hamilton equation to obtain a value for aortic impedance. Previously, we have shown that to achieve successful calibration requires the thermistor-tipped arterial catheter to be sited centrally [2]. We compared thermodilution measurements of cardiac output from a 50 cm radial artery catheter using the PiCCO system with a pulmonary artery catheter. Although the catheter tip was likely to lie within either the distal subclavian or proximal brachial artery, we did not use the brachial route as stated by de Wilde and colleagues. In addition, we were unable to measure cardiac output and hence reliably calibrate the device for pulse contour analysis when the radial catheter was withdrawn by more than 5cm despite using iced injectate to improve the signal to noise ratio. Pulsion Medical Systems also recommend that the device is calibrated at least once every 24hrs to maintain acceptable accuracy.

We believe, therefore, that the authors' study has limited practical application as it is impossible accurately to measure cardiac output by pulse contour analysis using the PiCCO system via a short radial catheter without first inserting a centrally sited thermistor-tipped catheter. Only in the unlikely situation of the failure of the dedicated arterial catheter following successful calibration could a radial catheter be used; and then it could only be used for the short-term.

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A reply

We thank Drs Orme and Pigott for their comments. They questioned our conclusion that radial and femoral artery pressure waveforms are interchangeable because it fails to take into account the fundamental issue of calibration. This is only partially correct. Calibration by transpulmonary thermodilution with detection of the dilution curve in the radial artery leads to an overestimation of cardiac output [1]. This overestimation is not related to a poor signal-to noise ratio, which might otherwise be compensated for by using iced injectate.

It is related to loss of indicator during its transport from injection to detection site.

In their letter, Orme and Pigott conclude that after changing from the femoral to the radial pressure site, the pulse contour method could be used for a maximum of 24hrs because Pulsion Medical Systems recommend calibrating the PiCCO device at least once every 24hrs. In our opinion, they have concentrated too much on the use of monitoring absolute cardiac output over longer time periods and therefore the weakness in the pulse contour method. They have ignored the ability of this technique in monitoring changes in cardiac output due to interventions or treatments over short time periods (such as hours) as well as its ability to monitor changes in the patient's filling status by determining stroke volume variation or pulse pressure variation.

A further reason to undertake our study was our curiosity about whether the shape of the pressure wave form influences the results of pulse contour analyses. The pulse contour method used by Pulsion can be subdivided into two parts. The first part is related to the integration of the area under the systolic part of the pressure curve. This process filters out the shape of the curve. The second part is related to the shape of the pressure wave by multiplication of the arterial compliance with the first derivative of the arterial pressure. These two parts must be added to compute cardiac output. Although the shapes of the femoral and radial artery differ, the calculated cardiac output does not.

We showed that the more frequently available radial artery pressure is interchangeable with the femoral artery pressure. Both sites can be used to determine cardiac output estimates of equal quality. We hope this finding will result in more widespread use of this device and further work on its calibration by methods other than transpulmonary femoral thermodilution.

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Chapter 3

An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery

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Summary
The bias, precision and tracking ability of five different pulse contour methods were evaluated by simultaneous comparison of cardiac output values from the conventional thermodilution technique (COtd). The five different pulse contour methods included in this study were: Wesseling's method (cZ); the Modelflow method; the LiDCO system; the PiCCO system and a recently developed Hemac method. We studied 24 cardiac surgery patients undergoing uncomplicated coronary artery bypass grafting. In each patient, the first series of COtd was used to calibrate the five pulse contour methods. In all, 199 series of measurements were accepted by all methods and included in the study. COtd ranged from 2.14 to 7.55 $l.min^{-1}$, with a mean of 4.81 $l.min^{-1}$. Bland-Altman analysis showed the following bias and limits of agreement: Wesseling's cZ, 0.23 and -0.80 to 1.26 $l.min^{-1}$; Modelflow, 0.00 and -0.74 to 0.74 $l.min^{-1}$; LiDCO, -0.17 and -1.55 to 1.20 $l.min^{-1}$; PiCCO, 0.14 and -1.60 to 1.89 $l.min^{-1}$; and Hemac, 0.06 and -0.81 to 0.93 $l.min^{-1}$. Changes in cardiac output larger than 0.5 $l.min^{-1}$ (10%) were correctly followed by the Modelflow and the Hemac method in 96% of cases. In this group of subjects, without congestive heart failure, with normal heart rhythm and reasonable peripheral circulation, the best results in absolute values as well as in tracking changes in cardiac output were measured using the Modelflow and Hemac pulse contour methods, based on non-linear three-element Windkessel models.

Introduction
Monitoring of hemodynamic pressures and cardiac output are the keystones in general management of surgical and intensive care patients. A change in fluid management and use of catecholamines is often based on these findings. However, in recent years, the rationale behind and efficiency of hemodynamic monitoring to affect outcome has been questioned [1]. One of the reasons for the limited value of cardiac output monitoring is the non-continuous nature of most used methods, whereas in highly unstable patients continuous monitoring would be more appropriate. Among the methods to monitor cardiac output continuously an increasing amount of attention has been focused on pulse contour methods [2–19]. However, in a literature survey, we showed large differences between various pulse contour methods and the conventional bolus thermodilution method [20]. We evaluated the bias, precision and tracking ability of five different pulse contour techniques by simultaneous comparison of cardiac output values with that of the standard right heart bolus thermodilution technique (COtd). The five methods studied were Wesseling's cZ method (COcz); the Modelflow method (COmf); LiDCO's PulseCO method (COli); the PiCCO method (COpi); and a recently developed Hemac method integrated in a haemodynamic monitoring and blood pressure control unit (COhe).

Methods
Patients In a prospective study the bias, precision, limits of agreement and tracking ability of five different pulse contour cardiac output methods were compared with standard thermodilution cardiac output (COtd) under conditions of routine use during cardiac surgery. The study was conducted according to the principles of the Helsinki declaration. After approval from the local ethics committee, written informed consent for participation in the study was obtained from all patients. This consent was obtained the day before surgery. All patients had symptomatic coronary artery disease

without previous myocardial infarction. Patients with congestive heart failure (NYHA class IV), aortic aneurysm, extensive peripheral arterial occlusive disease, or concomitant heart valve disease, were not considered for this study. Patients with postoperative arrhythmia or the necessity for artificial pacing or heart assist devices were also not considered. No postoperative complications were monitored.
Following premedication with lorazepam 5 mg two hours before surgery, a peripheral venous cannula, a radial artery cannula (20G) and a 7F pulmonary artery catheter were sited. Anaesthesia was induced and maintained with continuous infusion of propofol and sufentanil. Muscle relaxation was maintained with pancuronium bromide. The lungs were ventilated with a PEEP of 2–5 cmH_2O, at a rate of 10–15 $breaths.min^{-1}$. Minute ventilation was adjusted to maintain arterial pCO_2 between 4.2 and 5.6 kPa. The patients were treated with vasodilators and/or inotropes according to local guidelines.

Study protocol
During the study we used the arterial pressure signal, a respiratory signal from a ventilator or a capnogram, a COM-2 thermodilution cardiac output computer (Edwards, Irvine, CA, USA), and a computer to control a proprietary electromechanical pump for bolus injection.

After specific identifiable changes in the patient's circulatory state a series of measurements was performed. We aimed to carry out a measurement series, at the following times; 3 min after the induction of anaesthesia, immediately after sternotomy, after opening of the pericardium, just before and just after cardio-pulmonary bypass, after sternal fixation, after the completion of surgery, and after changes in drug dose. Pulmonary artery thermodilution was carried out with a bolus injection of 10 ml iced dextrose 5% solution at 4–7 °C, as measured by the in-line injectate sensor. All thermodilution cardiac output measurements and pulse contour analyses were performed over the same time periods. The radial artery pressure was used as input for the five pulse contour methods. Figure 3.1 shows a schematic diagram of the connection of the five pulse contour methods to the radial artery pressure. As can be observed, one pressure line and one pressure transducer are used to create an electrical radial pressure signal that is used by all five methods. An electric signal input for the PiCCO device is created using a pressure transducer simulator (PC80200, Pulsion Medical Systems, Munich, Germany).

The PiCCO (Pulsion) device is calibrated by a thermodilution simulator that generates thermodilution curves from which cardiac output (COtd) is computed by the PiCCO device equal to the values found by the conventional pulmonary artery thermodilution method. Furthermore, we used the radial artery pressure instead of the preferred femoral artery pressure as input for the PiCCO device because a recent study [21] showed the interchangeability of both pressure sites.

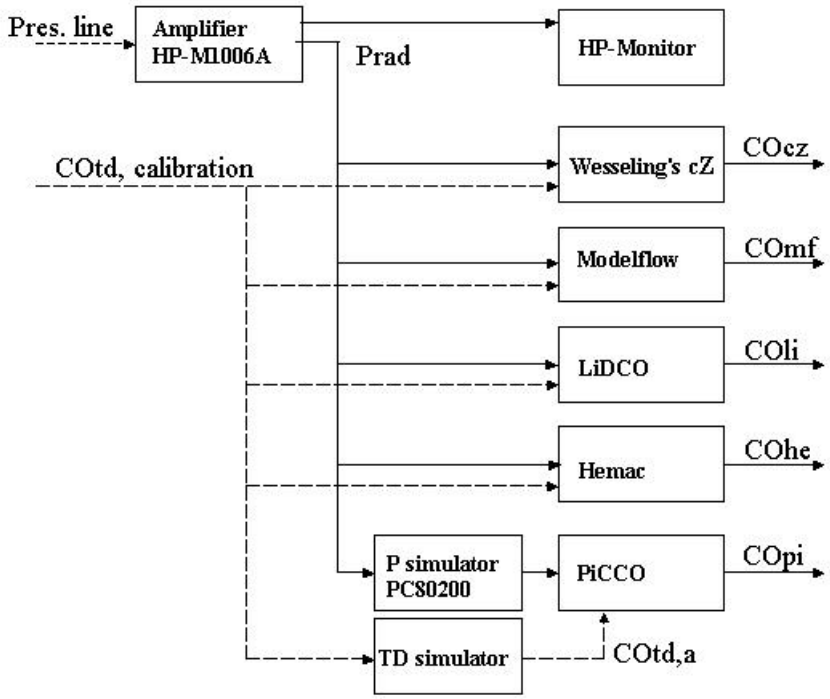

Figure 3.1 Schematic diagram of the setup in the five pulse contour methods with a single pressure transducer.

To compare the cardiac output found by each of the five different methods with thermodilution cardiac output, the beat-to beat values were first averaged over the beats recorded during a single thermodilution measurement. Next, the four averaged values of pulse contour cardiac output and four thermodilution cardiac output measurements were averaged to obtain one single pair of values for further analysis. All data were stored on computer disk for off-line analysis.

Arterial pulse contour techniques

The estimation of cardiac output via pulse contour analysis is an indirect method. Cardiac output is computed from a 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 [22]. Most pulse contour methods used today are derived from this model.

Wesseling's cZ method (BMEYE, Academic Medical Center, Amsterdam, the Netherlands) relates cardiac output to the area under the systolic portion of the arterial pressure wave (Asys). Dividing Asys by aortic impedance (Zao) provides a measure of stroke volume: Vz = Asys/Zao. In Wesseling's model the mean arterial pressure (Pmean) is used to correct the pressure dependent non-linear changes in cross

sectional area of the aorta. The heart rate (HR) is used to correct for pressure reflections from the periphery. The corrections for arterial pressure and heart rate are age (Age) dependent. A detailed description of this method can be found elsewhere [2, 6]. Briefly, the computation can be written as:

$$V_{CZ} = V_Z[0.66 + 0.005 \times HR - 0.01 \times Age \times (0.014 \times Pmean - 0.8)]$$

$$CO_{CZ} = cal \times HR \times V_{CZ}$$

where CO_{CZ} is Wesseling's pulse contour cardiac output. The calibration factor, cal = CO_{CZ}/CO_{ref}, is determined at least once for each patient by comparing pulse contour cardiac output with an absolute cardiac output estimate determined by thermodilution (CO_{ref}).

The *Modelflow* method (BMEYE) simulates the classical three-element Windkessel model to estimate cardiac output (COmf). The model includes three principal components of opposition: characteristic impedance, which represents the opposition of the aorta to pulsatile inflow; Windkessel compliance, which represents the resistance of the aorta to volume increases; and peripheral resistance, which represents the opposition of the vascular beds to the drainage of blood. Systemic peripheral resistance depends on many factors, including circulatory filling, metabolism, sympathetic tone and presence of vaso-active drugs. Aortic compliance decreases substantially when arterial pressure increases. This non-linear behaviour of the aorta would be a major source of error if not taken into account. These non-linear relationships were studied in vitro by Langewouters et al. [23] and described as mathematical functions whose properties regress closely dependent on patient age and gender, and slightly dependent on height and weight. A patient's aortic cross-sectional area is, however, not accurately known and true values in individual patients may deviate about 30% from Langewouters' study population average. Thus the uncertainty in computed cardiac output is also 30%. Therefore, to derive absolute cardiac output, calibration against thermodilution is performed once for each patient [6, 9].

The *Hemac* pulse contour method is part of a hemodynamic monitoring and automated blood pressure control program, recently developed by two of the authors. Its pulse contour method is based on a three-element Windkessel model, similar to the Modelflow method. However, instead of relying on in vitro, non-linear relations between cross-sectional area of the aorta and arterial pressure described by Langewouters [23] we used in vivo measurements of patients to correct the Langewouters relations. Via this new pressure/volume relationship we computed for each heartbeat the Windkessel compliance and aortic characteristic impedance, based on mean arterial pressure of the heartbeat. Total peripheral resistance was used from the previous heartbeat. Blood flow is found by solving the differential equation of the three-element Windkessel model. Stroke volume is given by integrated the flow over the ejection time of the heartbeat. Multiplying the stroke volume by the heart rate gives the cardiac output. Next, a new value of peripheral resistance is found by dividing the mean pressure by the computed cardiac output. Calibration with thermodilution improves the absolute accuracy of the method.

The *PulseCO* cardiac output method (LiDCO, London, UK) provides stroke volume from the arterial pressure waveform using an autocorrelation algorithm. The algorithm is not dependent on waveform morphology, but, it calculates nominal stroke volume after a pressure to volume transformation using a curvilinear pressure/volume relationship. The nominal stroke volume is converted to actual stroke volume by calibration of the algorithm. Usually, the calibration is performed by an independent indicator dilution measurement, e.g. lithium dilution cardiac output from the LiDCO system [10–12]. To allow comparisons with other measuring methods, in this study, a standard bolus thermodilution cardiac output method was used for calibration.

The *PiCCO* system (Pulsion Medical Systems, Munich, Germany) utilises pulse contour analysis according to a modified version of Wesseling's cZ algorithm [13, 16]. This pulse-contour algorithm analyses the actual shape of the pressure waveform in addition to the area under the systolic portion of the pressure wave. 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 actually leaves the aorta. During the subsequent diastole, the volume remaining 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 = $R \times C$) 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, the compliance, C, can be computed. The PiCCO algorithm is summarised in the following equation:

$$\mathrm{COpi} = \mathrm{K} \times \mathrm{HR} \times \int (\mathrm{P(t)/SVR} + \mathrm{C_{(P)}}) \times \mathrm{dP/dt})\mathrm{dt}$$

where COpi = cardiac output; K = 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; and dP/dt = describes the shape of the pressure wave.

The calibration and reference method

Thermodilution cardiac output measurements were performed with a computer controlled injectate syringe, an iced injectate container (CO-SET, Edwards, Irvine, CA, USA), a motor driven injectate syringe, a thermodilution pulmonary artery catheter, and a COM-2 cardiac output computer (Edwards). The start of a ventilatory cycle was derived from the ventilator. At precisely timed delays, four bolus injections (i.e. after 25% or 50% or 75% or 100% of respiratory cycle) were automatically started [24–26]. The averaged value of four measurements, equally spread over the ventilatory cycle, was assumed to represent the mean cardiac output [24].

Data analysis

We excluded the first series of cardiac output values in each patient from further analysis because it was used to calibrate the five pulse contour methods, and thus resulted in zero difference between the thermodilution measurements and the method to be evaluated.

To evaluate the tracking capability of the pulse contour methods for each patient, a trend score was computed. The trend score in an individual patient is found by subtracting the calibration (first cardiac output value) from consecutive cardiac output measurements. A positive trend is observed if the changes in cardiac output were in the same direction, whereas a negative trend was scored with changes in opposite direction. Ideally, only positive scores should be present. Separate scores were counted for changes when thermodilution cardiac output values differed by at least a clinically relevant 0.5 $l.min^{-1}$.
Hemodynamic stability was verified by analysis of mean arterial pressure and heart rate during a thermodilution series. Stability was considered absent if mean arterial pressure and heart rate averaged per injection period deviated more than 5% from their series average [9]. A condition of severe, persistent arrhythmias during thermodilution passage was additionally considered as absence of stability. If stability was not present, the series was excluded from further analysis.

Statistics
We used Bland-Altman analysis with the difference in cardiac output between COtd and each of the five pulse contour techniques plotted against their mean [27]. The agreement between pulse contour and thermodilution cardiac output is computed as the bias (mean (SD)), with limits of agreement computed as bias (2 SD) when differences followed normal distributions [27]. Normality was tested with the Kolmogorov-Smirnov one-sample test. The coefficient of variation was computed as CV = (SD/mean) × 100%. The agreement in changes was computed using cross tabulation. Data averages are given as mean (SD). A p-value < 0.05 was considered statistically significant.

Results
In five female and nineteen male patients, we performed 248 series of four cardiac output measurements. Twenty-four measurements were rejected due to heart rhythm irregularities or hemodynamic instability during measurements (defined as a deviation in mean arterial pressure of more than 5% within the series). Furthermore, 25 series were rejected because one or more of the pulse contour methods included in our study detected an abnormal/error condition. In four measurements an error caused dysfunction of all methods indicated by damped wave form detected by the Modelflow method, in 12 measurements the LiDCO device indicated unstable data, the dicrotic notch was not properly detected by the PiCCO and Hemac in twelve patients and in six patients by the cZ method. Some series were rejected by more than one device. Thus, 199 series of measurements fell within the pre-set criteria and were accepted by all five pulse contour methods, and these were analysed.

The range of thermodilution cardiac output values was 2.14 to 7.55 $l.min^{-1}$, mean value 4.81 $l.min^{-1}$. The values of the five different pulse contour methods and of thermodilution are presented in Table 3.1. Bland-Altman analysis (Fig. 3.2 and Table 3.2) showed the agreement between thermodilution cardiac output and each of the five different pulse contour methods.

Table 3.1 Cardiac output by thermodilution and each of the five pulse contour methods.

Method	Mean CO	Range of CO	
		min	max
	$l.min^{-1}$	$l.min^{-1}$	$l.min^{-1}$
COtd	4.81	2.14	7.55
cZ	4.57	2.22	7.21
MF	4.80	2.52	7.13
LiDCO	4.97	2.53	8.90
PiCCO	4.66	2.07	9.67
Hemac	4.74	2.38	7.99

Results of 199 observations. CO, cardiac output; mean, mean value of all series of CO measurements; max, min, maximal and minimal value of CO respectively; COtd, cardiac output by thermodilution.

No statistical difference could be detected between the normal distribution and the distributions of the differences of thermodilution and each of the five methods (the p value ranged from 0.08 to 0.86). The difference between thermodilution and Wesseling's cZ, the PiCCO and the LiDCO methods showed a small bias. The Bland-Altman plot (Fig. 3.2) shows that the spread of values is different among the methods. This is confirmed by ANOVA, which showed significant ($p < 0.001$) unequal homogeneity of the variances of the five methods.
The Modelflow and Hemac pulse contour methods have the smallest bias (0.00 and 0.06 $l.min^{-1}$) and the smallest range of the limits of agreement (-0.74 to 0.74, and -0.81 to 0.93 $l.min^{-1}$). Bias and limits of agreement for LiDCO were -0.17 and -1.55 to 1.20 $l.min^{-1}$, respectively, and for PiCCO, 0.14 and -1.60 to 1.89 $l.min^{-1}$, respectively.

Tracking cardiac output with serial measurements
The changes in cardiac output of each of the five pulse contour methods against changes in thermodilution cardiac output are shown in figure 3.3. The changes in cardiac output in all five pulse contour methods correlate significantly with the changes in cardiac output by thermodilution.
The agreement of positive and negative changes in COtd and CO in each of the five pulse contour methods are calculated using cross tabulation. We found the highest score for the Modelflow and Hemac methods, and a lower score for the LiDCO and PiCCO methods (Table 3.3). These scores improve if clinically irrelevant changes smaller than 0.5 $l.min^{-1}$ (i.e. < 10% change) are not counted. Of the changes 96% were in agreement with each other for the Modelflow and Hemac methods.

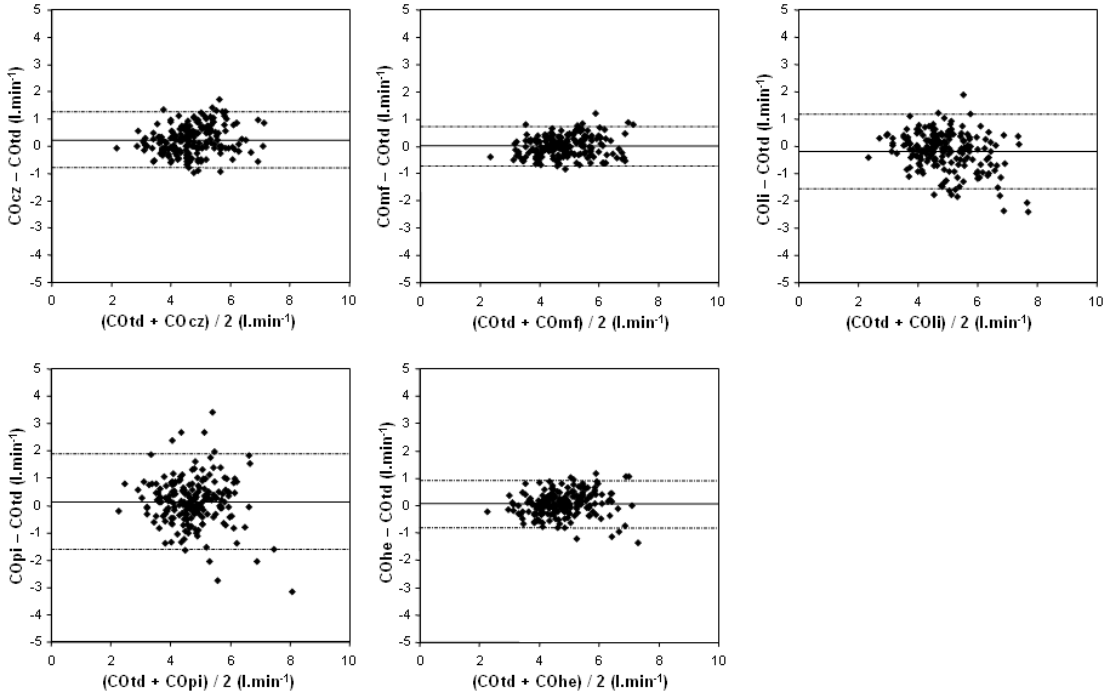

Figure 3.2 Bland-Altman plot with cardiac output values in five pulse contour methods and cardiac output values by conventional thermodilution method. CO, cardiac output; COtd, CO by thermodilution; COcz, CO by Wesselings cZ method; COmf, CO by Modelflow; COli, CO by the LiDCO system; COpi, CO by the PiCCO system; COhe, CO by the Hemac system. The solid line represents the bias and the dashed line the limits of agreement by 2 SD.

Table 3.2 Bland-Altman analysis of five pulse contour methods.

method	Npat	Nobs	Difference with COtd				Limits of agreement		Calculated precision with	
			Bias		Precision		lower	upper	COtd10%	COtd5%
			l.min^{-1}	%	l.min^{-1}	%	l.min^{-1}	l.min^{-1}	%	%
Current study										
cZ	27	199	0.23	4.81	0.52	10.74	-0.80	1.26	3.9	9.5
MF	27	199	0.00	0.03	0.37	7.70	-0.74	0.74	0.0	5.9
LiDCO	27	199	-0.17	-3.60	0.69	14.32	-1.55	1.20	10.2	13.4
PiCCO	27	199	0.14	3.00	0.87	18.17	-1.60	1.89	15.2	17.5
Hemac	27	199	0.06	1.21	0.44	9.05	-0.81	0.93	0.0	7.5
Literature survey										
cZ	193	675	0.07	1.33	0.64	11.57	-1.21	1.35	5.8	10.9
MF	103	796	-0.03	-0.48	0.56	9.89	-1.15	1.09	1.6	8.8
LiDCO	88	301	-0.02	-0.37	0.65	12.84	-1.32	1.28	6.2	10.7
PiCCO	144	1021	-0.07	-1.26	1.01	17.40	-2.09	1.95	15.4	17.7
Hemac	none									

Npat, number of patients; Nobs, number of observations; bias, mean difference between thermodilution cardiac output and each of the five pulse contour cardiac output; %, percentage of mean cardiac output; precision, is standard deviation (SD) of the bias; limits of agreement as bias ± 2SD; calculated precision assuming a precision of 5% or 10% of the thermodilution method.

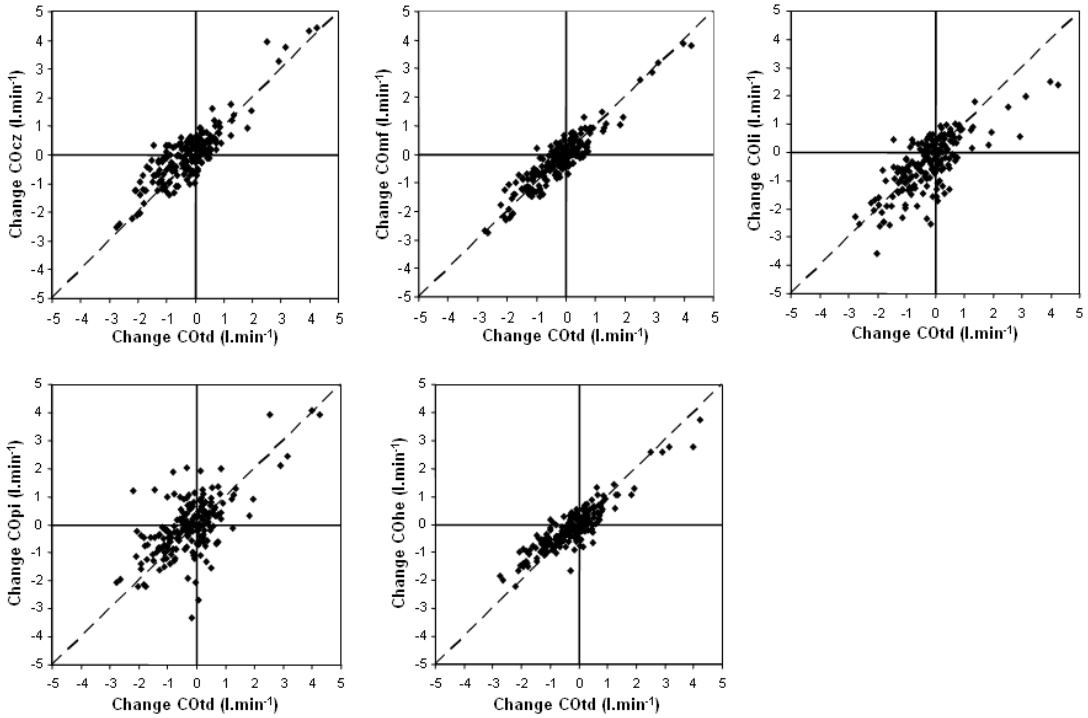

Figure 3.3 Relationship between changes in cardiac output values in five pulse contour plotted against changes and changes in cardiac output values by conventional thermodilution method. For abbreviations see figure 3.2. The line of identical change is indicated (dashed line).

Table 3.3 Trend score of changes in cardiac output by thermodilution and by five pulse contour methods.

Method	Agreement %	Disagreement %
All data n=199		
cZ	77	23
MF	81	19
LiDCO	72	28
PiCCO	70	30
Hemac	81	19
Data exclusion of changes COtd from -0.5 to +0.5 L/min n=99		
cZ	91	9
MF	96	4
LiDCO	88	12
PiCCO	84	16
Hemac	96	4

n, number of observations; agreement, sum of percentage of data points in the upper right quadrant and in the lower left quadrant of figure 3.3; disagreement, sum of percentage of data points in the upper left quadrant and in the lower right quadrant of figure 3.3.

Discussion

We evaluated the bias, precision and tracking ability of five different pulse contour techniques by simultaneous comparison of their cardiac output values with the cardiac output values measured by the conventional thermodilution technique. The mean difference in cardiac output between thermodilution and each of the five methods is low (range -0.17 to 0.33 $l.min^{-1}$). However, the limits of agreement differ considerably, with the best results being found for the Modelflow and Hemac methods. Besides this, the Modelflow and Hemac were the most reliable in tracking changes in cardiac output, compared with COtd.

Jansen and van den Berg recently published the results of a literature survey on continuous cardiac output monitoring [20], which reported the results of Wesseling's cZ, Modelflow, LiDCO and the PiCCO method. No published results are available yet for the Hemac pulse contour method.

We found in our study better precision and limits of agreement for each of the pulse contour methods than those published, except for the LiDCO (Table 3.2). This was true for the PiCCO method where we used the radial artery pressure instead of the femoral artery pressure.

The data used in this study were filtered out by preset exclusion criteria and needed to be accepted by all five pulse contour methods. We could include 199 measurement series of outspoken quality in our evaluation. Having data accepted by all five pulse contour methods is clinically impractical, but we consider this strategy as the fairest for the purpose of our study. As this study was set up to investigate the bias, precision and tracking changes in cardiac output, comparison of cardiac output should not be impaired by inadequate arterial pressure recordings or by a poor reference method.

We used the averaged result of four thermodilution measurements under stable hemodynamic and ventilatory conditions to calibrate each of the five pulse contour methods once per patient. Thereafter, we used the same technique as reference

method. The injections for thermodilution cardiac output measurement were synchronised with the mechanical ventilation, and spread over the ventilatory cycle. In this way much closer estimates of real mean cardiac output can be obtained [24–26] because ventilatory effects on circulation are taken into account. In a previous study we showed that our thermodilution errors are probably limited to no more than 5% SD, whereas in clinical practice an SD of 10–20% is accepted. Application of this precise calibration and reference method may have positively influenced our results.

Because aortic pressure is usually not available clinically, radial artery or femoral artery pressure is used instead. Although the radial and femoral pressure waves are distorted with respect to aortic pressure, the pulse contour methods should accept these pressures. Measurement of cardiac output using Wesseling's cZ and Modelflow methods is not affected by whether the arterial pressure is measured in the aorta or in the radial artery [6]. Our study shows that cardiac output estimates from radial pressure can be accurate. In a recently published study [21] we showed the interchangeability of femoral artery pressure and radial artery pressure measurements as the input for the PiCCO system (Bland-Altman analysis showed a bias of -0.01 $l.min^{-1}$, and limits of agreement from -0.62 to 0.60 $l.min^{-1}$). Therefore, it seemed justified to use the radial pressure as input for the PiCCO system as we did in our comparison.

Critchley and Critchley [28] stated that if a new method is to replace an older, established method, the new method should have errors not greater than the older method. Therefore, knowledge and a careful application of the older method as a reliable reference method are essential for a good evaluation of a new technique. Otherwise, the difference between the evaluated method and the reference method could be determined mainly by the reference method.

Clinically, the conventional thermodilution method has been accepted as the 'gold standard'. However, single estimates of cardiac output show substantial scatter (with a precision of 15%) [24, 26, 29, 30]. To improve the precision, the results of multiple measurements have to be averaged. A triplicate, randomly injected series of thermodilution measurements has an error of approximately 10% [24, 29, 30]. The averaged result of four thermodilution measurements at moments equally spread over the ventilatory cycle has an error of less than 5% [24].

The precision of the new method can be computed if the precision of the reference (ref) and the precision of the comparison (dif) are known using Pythagoras' law: $\text{new} = \sqrt{(\text{dif}^2 - \text{ref}^2)}$[28]. The averaged precision of each of the five pulse contour methods was calculated from the averaged differences between each of the five pulse contour methods and the conventional bolus thermodilution method, assuming two levels of precision for the thermodilution, i.e. 10% and 5% (Table 3.2).

None of the five pulse contour methods can replace the thermodilution technique with four measurements equally spread over the ventilatory cycle, even after calibration by a precise thermodilution technique. However, the Modelflow method (5% vs 6%) and the Hemac method (5% vs 7%) come close (Table 3.2). Most of the pulse contour methods can replace the thermodilution technique with three measurements randomly applied.

All pulse contour methods included in our study require calibration for each patient using a method such as thermodilution. After calibration, the purpose of the pulse contour methods is to track clinical changes in cardiac output accurately. To analyse the tracking capabilities of the five pulse contour method by Bland-Altman analysis seems insufficient. Therefore, we plotted the changes in cardiac output by the five methods against thermodilution cardiac output (Fig. 3.3). Furthermore, in an attempt

to quantify the tracking quality of the five methods, we compared the number of changes of the same direction in cardiac output found by thermodilution with those found by each of the five methods (Table 3.3). If we consider changes smaller than 10% (i.e. a change of 0.5 $l.min^{-1}$ on a mean CO of 5.0 $l.min^{-1}$) as clinical irrelevant, then 96% of the changes were correctly followed by the Modelflow and Hemac method. Therefore, these two methods are able to follow changes in cardiac output accurately.

Conclusion

All pulse contour techniques need a reliable invasive calibration. After calibration, most methods may replace the thermodilution method with a precision of 10% (i.e. the averaged result of three randomly performed measurements). The Modelflow and Hemac techniques could replace the thermodilution estimates based on the averaged result of four measurements done equally, spread over the ventilatory cycle. The slightly lower precision of the continuous pulse contour cardiac output techniques may, in clinical settings, be outweighed by the advantages of being automatic and continuous. Under research conditions the use of the conventional thermodilution method with four measurements equally spread over the ventilatory cycle remains the method of choice. Due to the character of the examined study population, it must be emphasised that the findings of this study are still restricted to patients without congestive heart failure, with normal heart rhythm and reasonable peripheral circulation.

Potential conflict of interest

None of the authors has any commercial interest either in the devices or in the manufacture of the devices named in this study.

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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.

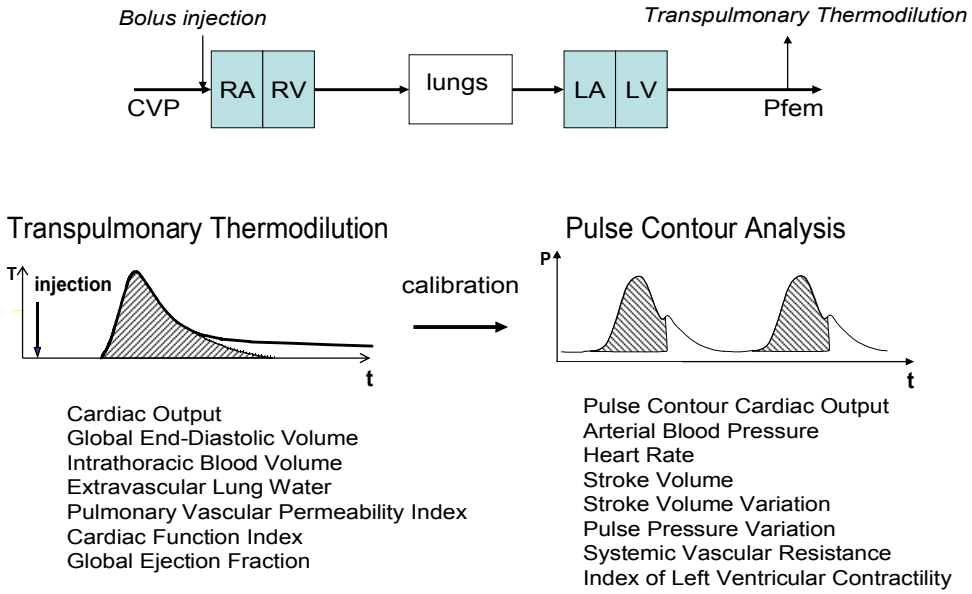

Figure 4a.1 The PiCCO system with the transpulmonary thermodilution technique and the pulse contour technique. In the upper panel a schematic diagram of the transpulmonary thermodilution method, with injection of cold fluid central venously and detection of the dilution curve in the femoral artery. CVP, 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).

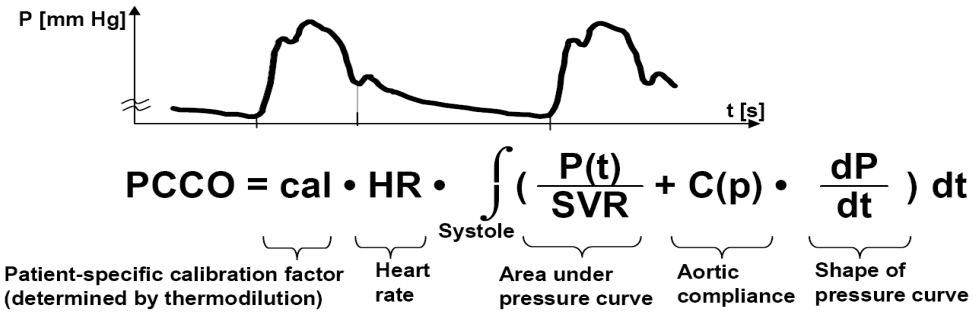

Figure 4a.2 The pulse contour algorithm. After calibration by the transpulmonary thermodilution technique the system is able to follow cardiac output beat by beat. For further explanation see text.

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.

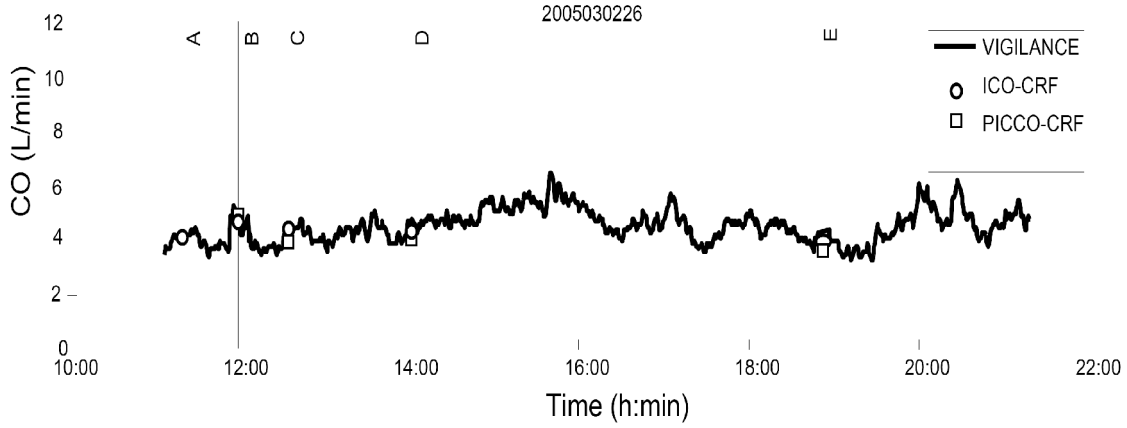

Figure 4a.3 Trend recording of an individual patient. Observation moments are indicated by A to E. Solid line cardiac output (CO) by the continuous thermodilution method (CCO). At point A PiCCO's pulse contour method is calibrated. At the observation moments, the bolus thermodilution CO is indicated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

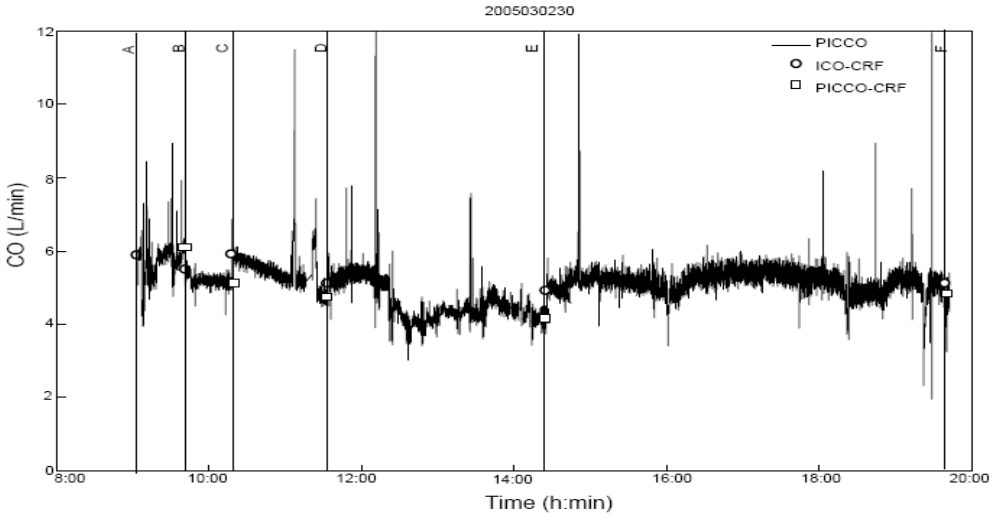

Figure 4a.4 Trend recording of an individual patient. Observation moments are indicated by A to F. Solid line PiCCO's pulse contour cardiac output. At the observation moments, bolus thermodilution CO is indicated by symbol ○ and PiCCO's pulse contour CO is indicated by symbol □. Observe the recalibration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

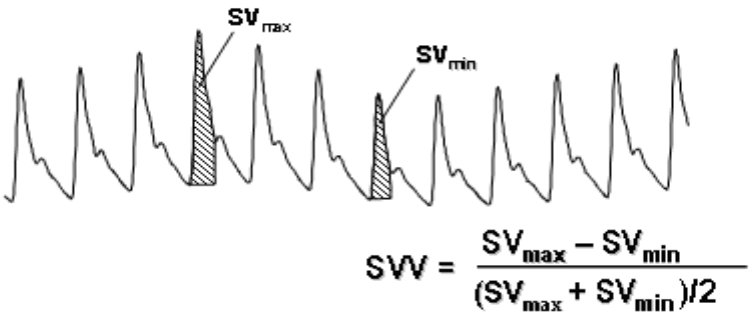

Figure 4a.5 Stroke Volume Variation (SVV) over the ventilatory cycle. SVV is measured over last 30s time window.

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.

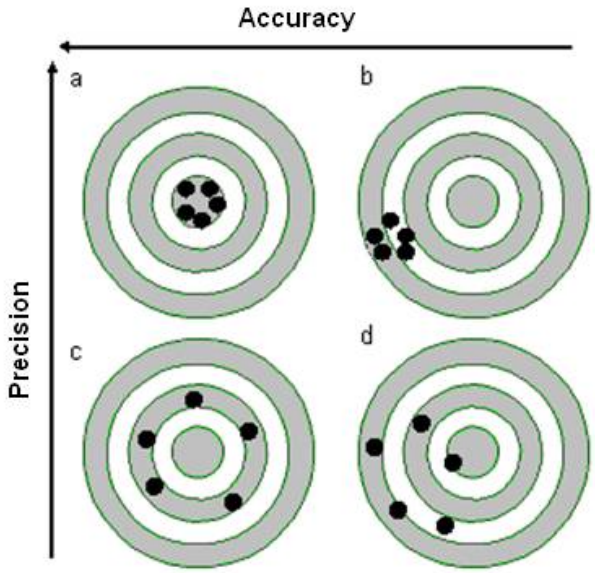


Figure 4b.1 Schematic representation of accuracy and precision.

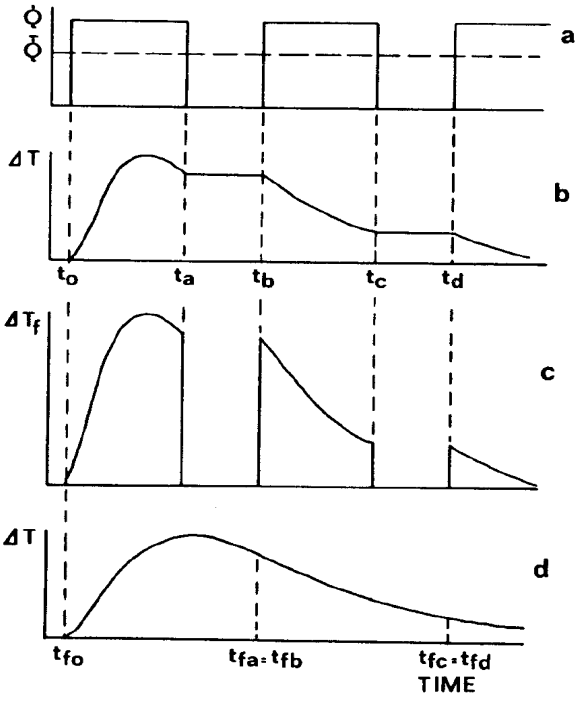
What makes the thermodilution methods less precise? Or what causes sequential measurements to differ so much?
The thermodilution method is based on the law of conservation of thermal energy. If and only if *blood flow is constant*, if *no loss of indicator* between injection site and detection site occurs, 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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Chapter 5

Performance of the FloTrac-Vigileo system in comparison to three other commercial available continuous cardiac output systems

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Summary
Background Evaluating the performance of the FloTrac-Vigileo system (FCO) in relation to simultaneously obtained cardiac output (CO) values with the PiCCOplus (PCO), PulseCO/LiDCOplus (LCO), Vigilance continuous pulmonary artery thermodilution (CCO) and intermittent bolus pulmonary artery thermodilution (ICO).
Methods Cardiac output data were collected during standard clinical care in 28 cardiac surgery patients, after ICU admission. The number observation periods per patient varied between 4 and 8. Data was analyzed with Bland Altman statistics, cross tables and linear regression.
Results We obtained 179 data sets. Mean CO's were 5.1 ± 1.0, 5.2 ± 1.3, 5.0 ± 1.4, 5.7 ±1.0, and 5.4 ± 1.1 litre·min^{-1} for ICO, LCO, PCO, FCO and CCO respectively. ICO ranged from 2.90 to 8.70 litre·min^{-1}. Ranking the results of Bland-Altman analysis in order from best to least yields precisions of: CCO (12%), FCO (18%), LCO (19%), and PCO (24%). When cardiac output changes of less than 10% were defined as clinically insignificant, directional changes with ICO were equally followed by LiDCO in 81%, by PiCCO in 82%, by FloTrac-Vigileo in 92%, and by CCO in 98% of the cases. FloTrac-Vigileo and PiCCO showed a slight but statistical significant, drift with time.
Conclusions The performance of pulse contour methods has significantly increased the last few years, which makes comparisons with older publications invalid. The auto-calibrated FloTrac-Vigileo system can replace the initially PAC-calibrated LiDCO and PiCCO system. The Vigilance continuous thermodilution method demonstrated the best agreement with bolus thermodilution and had the highest score in following slow changes in cardiac output.

Introduction
Cardiac output is considered as in important parameter to monitor adequate tissue perfusion. A pulmonary artery catheter (PAC) is frequently used in patients undergoing complex cardiac surgery. In other patient groups the use of the PAC to monitor cardiac output has been questioned frequently; and several, recently developed, less invasive methods have been proposed. The arterial waveform analysis performed by the PiCCO and LiDCO system are considered to be reliable alternatives.[1-3] However these devices require calibration to compensate for individual vascular compliance, either by transpulmonary thermodilution or lithium dilution. This vascular compliance may change soon after each calibration leading to uncertainties in cardiac output results.
The FloTrac-Vigileo system is the most recently introduced technology to determine cardiac output less invasively from arterial waveform analysis. The FloTrac-Vigileo system's continuous auto-calibration algorithm compensates for changes in vascular tone and thus does not require periodic external calibration. However, first studies ended with controversial conclusions ranging anywhere from in good agreement with intermittent pulmonary artery thermodilution to not recommended.[4]
The purpose of the current study is to evaluate the performance of the second generation FloTrac-Vigileo method in relation to other continuous cardiac output methods in a heterogeneous group of severely ill cardiac surgery patients. Hereto, simultaneously obtained cardiac output (CO) values with the PiCCOplus (PCO), LiDCOplus (LCO), FloTrac-Vigileo (FCO) and Vigilance continuous pulmonary artery thermodilution (CCO) were compared with CO values by intermittent bolus pulmonary artery thermodilution (ICO).

Methods

Patients In a prospective study the bias, precision, limits of agreement and tracking ability of three different pulse contour cardiac output devices and one continuous pulmonary artery thermodilution method were compared with standard thermodilution cardiac output under conditions of routine use in our ICU.

Twenty eight adult ICU patients scheduled for elective cardiac surgery were studied after IRB approval and written informed consent obtained one day prior to surgery. All patients with a pre-operative indication for placement of a pulmonary arterial catheter (PAC) were eligible candidates. Patients with severe peripheral vascular disease, aortic aneurysm, intra-cardiac shunts, as well as postoperative patients with arrhythmia, need for mechanical cardiac support or persistent valvular dysfunction were excluded. Before surgery, a peripheral venous cannula, a radial artery cannula (RA 04220, Arrow International, Reading, PA, USA) and a pulmonary artery catheter (139HF75P, Edwards Lifesciences, Irvine, CA, USA) were introduced. After surgery the patients were moved to the ICU where sedation was maintained with target infusion of propofol and sufentanil, the first 3 to 4 hours. Patient's lungs were ventilated with 40% oxygen in air, PEEP of 5 cmH_2O, and a respiratory frequency of 12-14 breaths min^{-1}. Minute ventilation was adjusted to maintain arterial pCO_2 between 4.2-5.6 kPa. When the clinical condition of the patients was considered hemodynamically stable, patients were weaned from the ventilator. Patients were treated with vasodilators, inotropes and/or fluids according to institutional guidelines.

Cardiac output methods

Cardiac output was measured with the use of three pulse contour devices and two thermodilution methods, i.e. FloTrac-Vigileo™ system with upgraded software version V1.07 (Edwards Lifesciences, Irvine, CA, USA), the PulseCO/LiDCOplus™ system (LiDCO Ltd, Cambridge, UK), PiCCO™ system (Pulsion Medical Systems, Munich, Germany), continuous (CCO) and intermittent bolus thermodilution cardiac output (ICO), with a Vigilance™ cardiac output monitor (Edwards Lifesciences, Irvine, CA, USA).

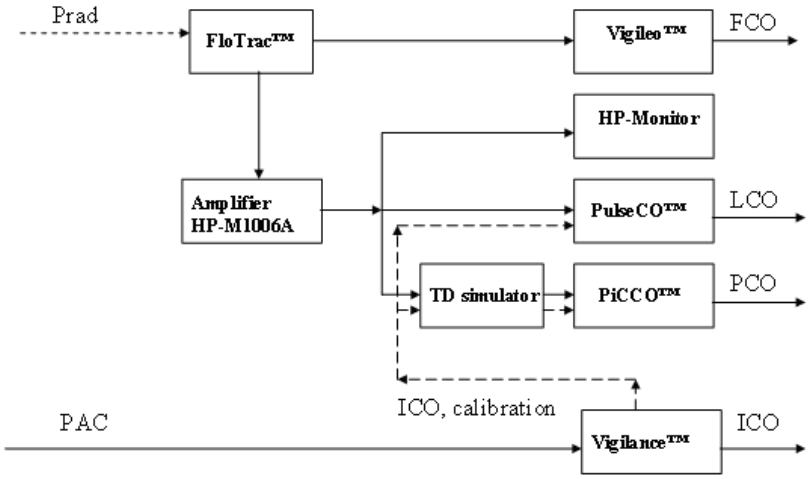

Figure 5.1 Schematic diagram of the setup of different pulse contour methods using a FloTrac pressure transducer. Prad, radial artery blood pressure; FCO, cardiac output (CO) by Vigileo system; LCO, CO by PulseCO/LiDCOplus system; PCO, CO by PiCCO system; ICO, CO by intermittent pulmonary thermodilution (TD); PAC, pulmonary artery catheter.

Intermittent pulmonary artery thermodilution (ICO) (reference method) was performed with a bolus injection of 10-ml iced-dextrose 5% at a temperature of 4-7 °Celsius, and calculated as an average of 3 randomly applied measurements. Pulse contour cardiac output values were averaged over 5 minutes at predefined time points. LCO and PCO were not calibrated per their manufacturer's recommended techniques due to the difficulty of performing these measurements concurrently. Instead the LCO and PCO systems were initially calibrated using the averaged value of ICO measured from the PAC. In clinical practice, the use of lithium dilution for LCO and transpulmonary thermodilution for PCO in lieu of PAC calibration will add additional error to the results measured in this study. All pulse contour devices used the same radial artery pressure signal derived from a FloTrac transducer, figure 5.1. The FloTrac transducer was referenced to the intersection of the anterior axillary line and the 5th intercostal space. The LiDCO system was calibrated by directly entering the PAC ICO measurement into the monitor. The PiCCO system is calibrated by a thermodilution simulator that generates thermal curves, which result in a CO computed by the the PiCCO system equal to the values measured by the conventional pulmonary artery thermodilution method.

Study protocol

Besides medical history and demographic information of the patients, we measured cardiac output values at predefined time points. These time points were at: arrival on the intensive care unit (*t0*, baseline); one hour (*t1*); two hours (*t2*); four hours (*t3*); eight hours (*t4*); twelve hours (*t5*); 24 hours (*t6*); 36 hours (*t7*), after baseline. In addition to cardiac output body core temperature, mean arterial blood pressure (MAP), central venous pressure (CVP), and heart rate (HR), fluid intake and concomitant medication were recorded. Data was stored on a computer disk for documentation and further analysis.

Data analysis

Paired data was analyzed using three different statistical methods. First method, the limits of agreement (LOA) method of Bland and Altman for assessment of agreement between methods was used.[5] The differences between ICO and LCO, PCO, FCO, and CCO were plotted against their average together with the LOA, given by bias ± 2SD. Second method, we investigated the ability of the different continuous cardiac output methods (LCO, PCO, FCO and CCO) to track changes in cardiac output. Percentage changes cardiac output (ΔCO%) within individual patients were calculated as: ΔCO% = 100**(CO(t)/COmean*). When simultaneously measured ICO and LCO, PCO, FCO or CCO both indicate a positive or negative trend, a positive score was counted. Changes in opposite direction resulted in a negative score. Ideally, only positive scores would be present. Similar scores were made when consecutive changes in cardiac output values differ by at least 10%, which is considered clinically relevant. Positive and negative counts are evaluated using cross tabulations and presented as percentages of identical changes in cardiac output. Third method, drift against time of each CO method was evaluated. To compute drift against time, at each time point, the ICO value was subtracted from the simultaneously obtained LCO, FCO, PCO and CCO value. Drift was quantified by the slope, with 95% confidence interval (CI95%), of the linear regression between time and the difference between ICO and method under study. This slope of the regression was tested against a horizontal line (reflecting no change over time). P values < 0.05 were considered as significant. Normality of distribution was tested with Kolmogorov–Smirnov analysis. All data are

presented as averages and SD. Statistical analysis was performed using SPSS for Windows Release 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics, surgical interventions and medication at admission to the ICU of 28 patents are presented in table 5.1. A large diversity in surgical interventions as well as use of cardiovascular drugs can be observed. In our study group no adverse events were experienced and all patients left the hospital alive.

Table 5.1 Patient characteristics (n=28).

Patient characteristics	Mean (SD)	Range
Age (year)	67 (9)	42 - 78
Weight (kg)	81.6 (14.5)	52 – 144
Height (cm)	175 (7)	162 - 188
BSA (m^2)	2.00 (0.20)	1.58 – 2.44
BMI (kg^{-1} m^{-2})	26.5 (3.9)	17.0 -32.3
Gender (male/female)	23/5	

Type of surgery	No of Patients
CABG	2
CABG & DOR	2
CABG & valve repair	7
Single valve repair	5
Two valve repair (in part with AF ablation)	7
DOR & LV-lead	2
DOR & MVP	1
DOR & AF ablation	1
CorCap & two valve repair & LV-lead	1

Vasoactive drugs *	No of Patients
Dobutamine	15
Enoximone	19
Norepinephrine	22
Nitroglycerin	1
* Single use 8, double use 8, and triple use 11	

BSA, body surface area; BMI, body mass index; CABG, coronary artery bypass grafting; DOR, endoventricular circular patch plasty; LV-lead, left ventricular pacemaker lead; MVP, mitral valve plastic; AF, atrial fibrillation.

We compared the results of four different continuous CO methods (LCO, PCO, FCO, and Vigilance-CCO) with CO by the standard pulmonary thermodilution method (ICO). The precision of ICO was 9.7% for single measurements and 5.7% for the averaged value of series of 3 measurements. A total of 183 series of measurements were collected at 8 time points. Four series with excessive measurement errors were deleted. Table 5.2 shows hemodynamic data at these time points. Due to calibration at baseline (*t0*), LCO and PCO are equal to reference ICO, whereas FCO and CCO differ from ICO. With time the number of patients enclosed in the study decline as patients were discharged from the ICU. Also the number of patients on the mechanical ventilator decreased with time. After 36 hours (*t7*) only 4 patients were

still treated in the ICU. All data showed normal distributions. Reference cardiac output (ICO) ranged from 2.90 to 8.70 litre·min^{-1}, with a mean value of 5.12 (SD=1.02) litre·min^{-1}. The distribution of CO values was not different for the different methods.

Agreement of methods with ICO

Bland-Altman error diagrams for the difference between ICO and the four continuous cardiac output methods are given in figure 5.2. For FCO and CCO 179 data points are available and for LCO and PCO 151 data points because the reference device (PAC ICO) was also used for calibration, thus the data points obtained during calibrations are invalid. Bland-Altman statistics for pooled data are in table 5.3. The difference between methods under study and the reference method showed an instrumental error as almost all data points fell within the limits of agreement if expressed in percentage (LOA%) , i.e. at low CO a small error and at high CO a higher error is observed. From figure 5.2 it is observable that the distribution of errors is different among the methods. This is confirmed by Levine's statistics, which showed significant (F-value = 20.5, $p < 0.001$) unequal homogeneity of the variances of the four methods. CCO has the smallest range of the limits of agreement -0.99 to 1.61.

The limits of agreement of FCO, LCO and PCO are larger, -1.37 to 2.54, -2.00 to 1.90 and -2.61 to 2.29 litre·min^{-1}, respectively.

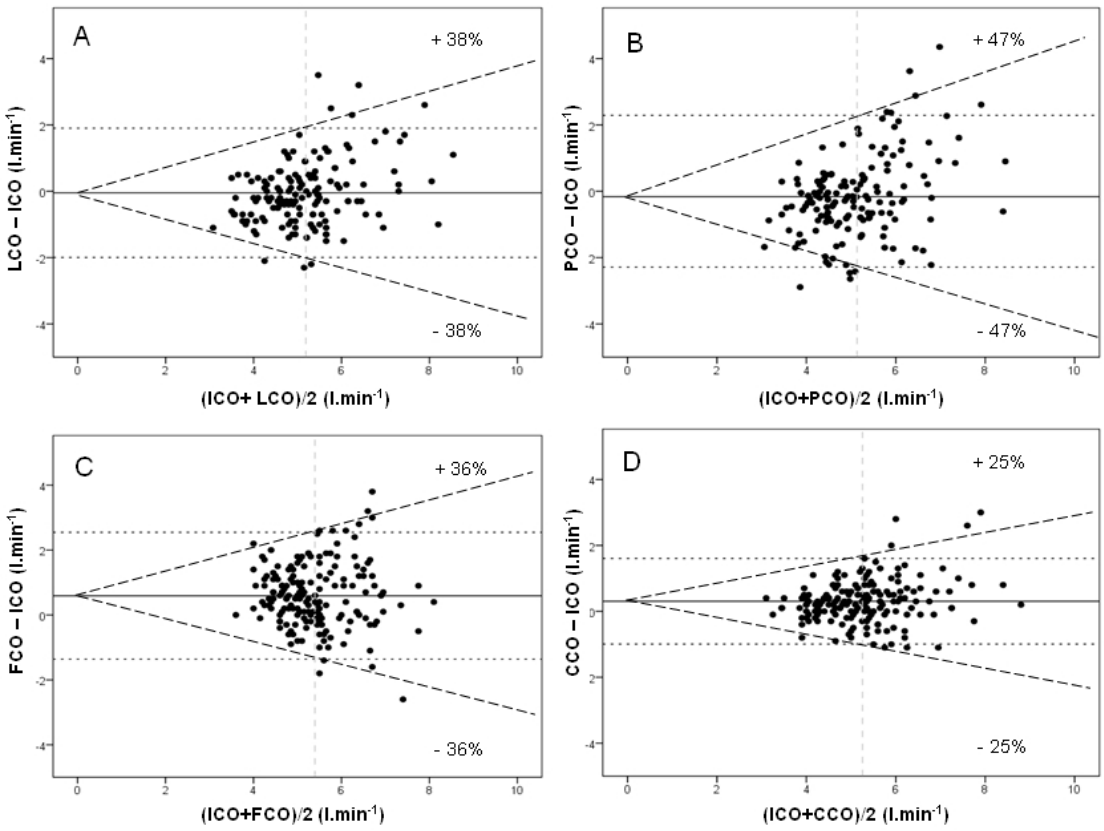

Figure 5.2 Graphical representation of Bland-Altman analysis. The bias for the difference is indicated by a solid line, limits of agreement by dotted lines and percentage limits of agreement (LOA%) by dashed lines. In panel A, the difference between intermitted thermodilution cardiac output (ICO) and cardiac output (CO) by the LiDCO system (LCO) against the mean value of ICO and LCO. In panel B, CO by the PiCCO system (PCO). In panel C, CO by the FloTrac-Vigileo system (FCO). In panel D, Vigilance continuous thermodilution cardiac output (CCO).

Table 5.2 Hemodynamic data obtained at each time point.

Time	*t0 Baseline*	*t1* (1hr)	*t2* (2hrs)	*t3* (4hrs)	*t4* (8hrs)	*t5* (12hrs)	*t6* (24hrs)	*t7* (36hrs)
Npatients	28	28	26	28	28	25	12	4
Nventilator	28	28	28	28	21	11	4	3
HR (beats·min^{-1})	82 (11)	82 (14)	85 (12)	83 (12)	83 (15)	84 (13)	83 (13)	83 (12)
MAP (mmHg)	76 (13)	79 (15)	75 (13)	74 (14)	76 (15)	83 (13)	73 (9)	75 (17)
PP (mmHg)	58 (11)	65 (13)	61 (12)	60 (12)	64 (19)	69 (16)	59 (11)	64 (15)
CVP (mmHg)	9 (4)	9 (3)	9 (4)	10 (4)	10 (3)	9 (3)	10 (3)	12 (4)
BCt (°C)	36.8 (0.7)	36.8 (0.7)	36.9 (0.8)	37.1 (0.8)	37.2 (0.6)	37.1 (0.6)	36.9 (0.4)	36.8 (0.7)
ICO (L·min^{-1})	4.60 (0.86)	4.98 (0.89)	5.10 (0.88)	5.19 (1.07)	5.40 (1.21)	5.40 (0.96)	5.12 (0.60)	5.73 (0.80)
LCO (L·min^{-1})		4.94 (0.96)	4.93 (0.99)	5.02 (1.31)	5.31 (1.33)	5.59 (0.92)	4.94 (0.83)	5.35 (1.10)
PCO (L·min^{-1})		4.56 (0.86)	4.71 (0.88)	4.76 (1.04)	4.94 (1.14)	5.05 (0.97)	4.56 (1.01)	4.83 (0.98)
FCO (L·min^{-1})	5.46 (0.62)	5.84 (0.94)	5.71 (0.82)	5.54 (0.90)	5.72 (1.18)	6.05 (1.16)	5.62 (1.11)	5.78 (0.97)
CCO (L·min^{-1})	4.70 (0.95)	5.28 (1.01)	5.32 (0.93)	5.85 (1.40)	5.67 (1.08)	5.79 (1.11)	5.29 (0.77)	5.80 (0.83)
dLCO (L·min^{-1})		-0.03 (0.61)	-0.17 (0.66)	-0.17 (0.72)	-0.09 (0.73)	0.18 (0.92)	-0.19 (0.89)	-0.38 (0.65)
dPCO (L·min^{-1})		-0.41 (0.87)	-0.39 (0.86)	-0.43 (0.78)	-0.46 (0.68)	-0.36 (0.96)	-0.57 (1.16)	-0.90 (1.13)
dFCO (L·min^{-1})	0.87 (0.73)	0.87 (0.94)	0.62 (0.87)	0.35 (0.98)	0.32 (1.16)	0.64 (1.13)	0.50 (0.94)	0.05 (0.79)
dCCO (L·min^{-1})	0.10 (0.41)	0.31 (0.44)	0.22 (0.43)	0.66 (0.91)	0.27 (0.63)	0.38 (0.81)	0.17 (0.68)	0.08 (0.29)

Npatients, number of patients; Nventilator number of patients on ventilator; HR, Heart rate; MAP, mean arterial; PP, pulse pressure; CVP, central venous pressure; ICO = intermittent thermodilution cardiac output (CO); PCO; LCO; FCO; CCO, cardiac output by, PiCCO, LiDCO, FloTrac and continuous thermodilution CO respectively; dLCO, dPCO, dFCO and dCCO, CO difference between the four methods and ICO; BCt, Body Core temperature.

Tracking cardiac output changes
Changes in cardiac output of each of the four continuous cardiac output methods versus change in thermodilution cardiac output are shown in figure 5.3. Changes in cardiac output in all four methods correlate significantly ($p<0.001$) with the changes in cardiac output by ICO (slope for CCO 0.87, CI95% 0.76 to 0.98; for FCO 0.43, CI95% 0.33 to 0.53; for LCO 0.75, CI95% 0.55 to 0.95; and for PCO 0.79, CI95% 0.51 to 1.07). The agreement of positive and negative changes of ICO and CO in each of the four methods was calculated using cross tabulation. The agreement in change was 76 (CI95% 70 to 83)% for CCO; 62 (CI95% 55 to 70)% for FCO; 68 (CI95% 61 to 75)% for LCO and 68 (CI95% 61 to 75)% for PCO. These scores improve if clinically irrelevant changes smaller then 0.5 litre·min^{-1} (i.e. < 10% change) are excluded from counting. Now, agreement is found in 98 (CI95% 93 to 100)%, 92 (CI95% 79 to 100)%, 81 (CI95% 68 to 94)%, and 82 (CI95% 70 to 94)% for changes in CO with CCO, FCO, LCO and PCO respectively**.**

Effects of time
In figure 5.4 we show changes in difference between the four continuous CO systems and ICO with time. We indicated a wanted stability range of ± 10% by dashed lines. As can be observed for the LCO system the data range indicated by the CI95% crosses the threshold value of 10% at 2, 12 and 24 hour, implying more than 2.5% of the data points are outside the chosen 10% limits at these time points. This occurs with PCO from 1 hour to 24 hour, with FCO at 4, 8, 12 and 24 hour, and with CCO at 4, 12 and 24 hour.
No change with time was found for the difference between CCO and ICO (slope 0.02 litre·min^{-1}·hr^{-1}, CI95% -0.12 to 0.17, p = 0.763) nor for the difference between LCO and ICO (slope = 0.011 litre·min^{-1}·hr^{-1}, CI95% -0.11 to 0.03, p = 0.322). However, a small but statistically significant drift with time was calculated for the difference between PCO and ICO (slope -0.017 litre·min^{-1}·hr^{-1}, CI95% -0.032 to -0.001, p = 0.036) as well as for FCO and ICO (slope 0.029 litre·min^{-1}·hr^{-1}, CI95% 0.003 to 0.055, p = 0.027).

Discussion
In ranking the methods, we found the results of the auto-calibrated FCO equivalent or better than those obtained by the initially PAC calibrated LCO and PCO methods. We anticipate that in clinical practice, when lithium and transpulmonary thermal dilution methods are used, the accuracy of these systems will be degraded by calibration errors. However, the best precision and limits of agreement were found for CCO. All continuous methods significantly followed changes in CO as measured by ICO. But, the tracking capabilities could be ranked from highest to lowest as CCO, FCO, LCO and PCO. The difference between ICO and PCO as well as ICO and FCO drifted slightly but statistically significantly with time. None of the continuous cardiac output methods can replace mean cardiac output obtained with three randomly applied intermittent bolus thermodilution measurements.

Acquiring precise data to allow a reliable comparison between methods requires several precautions. *Firstly*, in comparative studies, the quality of reference method is of utmost importance. Indeed, in evaluation of differences between the investigated method and a reference method the results are highly dependent on the precision of the reference method.

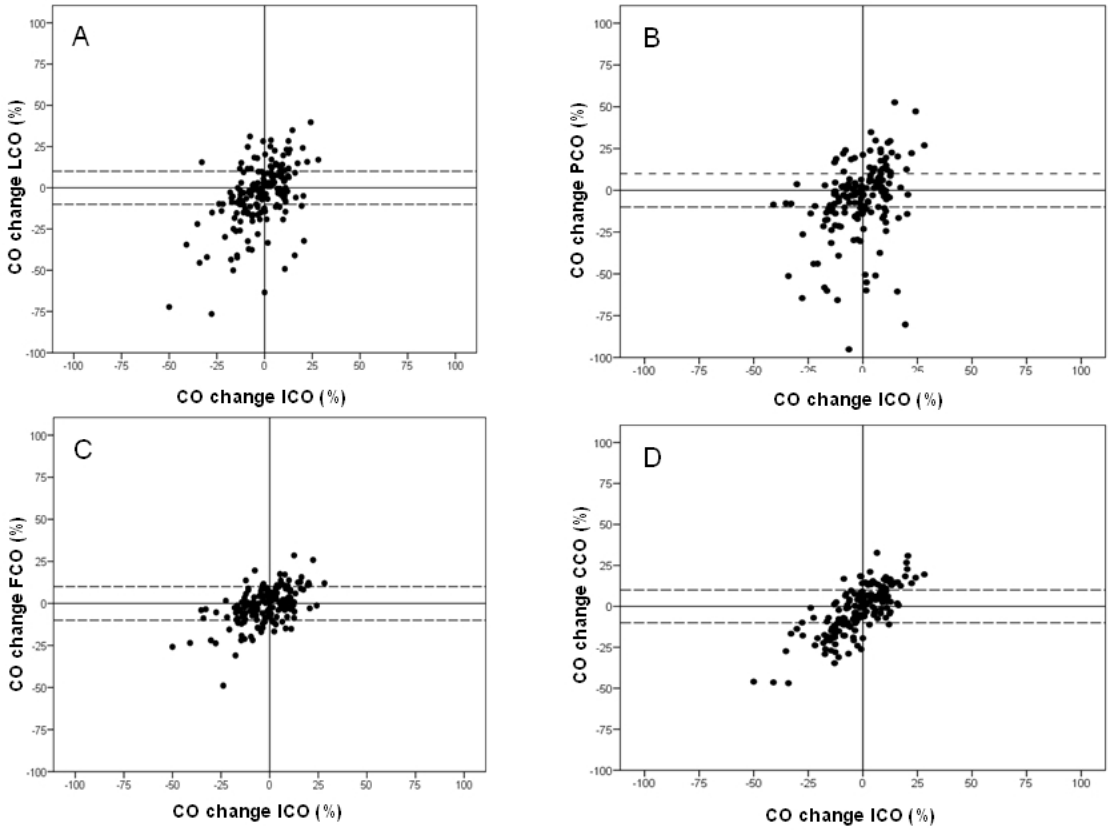

Figure 5.3 Changes in cardiac output by the four methods against changes in intermittent thermodilution cardiac output. The data in between the dotted lines indicated a clinical insignificant change of 10%. For abbreviations see figure 5.2.

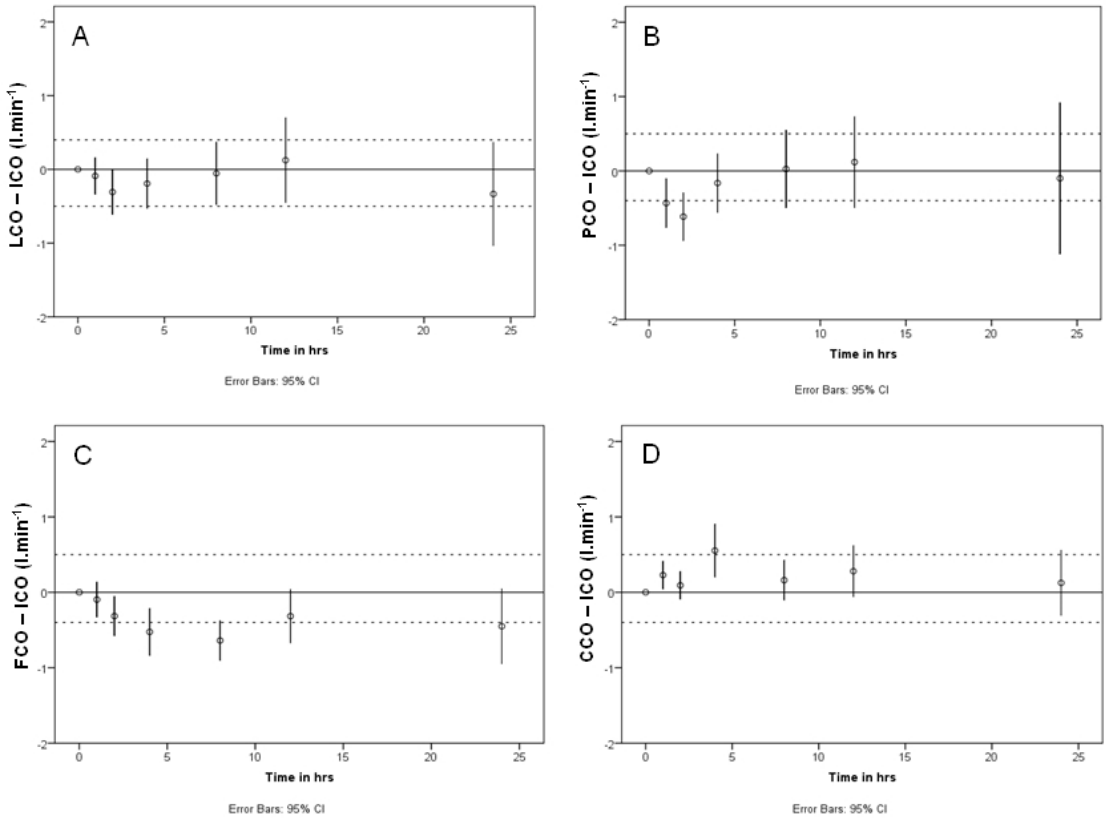

Figure 5.4 Effects of time on the difference between method under study and intermittent thermodilution cardiac output. To study time effects, FCO and CCO were calibrated at start (t0) against ICO. Dotted lines indicated values at start ± 10% of start value. For abbreviations see figure 5.2.

In our study individual thermodilution cardiac outputs differ by 10%. Averaging the results of three measurements randomly performed resulted in a precision of 6%. A better precision may be obtained by averaging the results of three measurements performed at equally spaced times over the ventilatory cycle.[6;7] In the present study, we accepted the clinically most used method of averaging three measurements randomly applied as precise enough. *Secondly, w*e selected sequentially all cardiac surgery patients that were equipped with a pulmonary artery catheter. The resulting patient selection was quite diverse in surgical intervention and use of vasoactive agents (Table 5.1).

However, none of the patients had aortic aneurism and none had, after cardiac surgery, signs of aortic regurgitation. An aortic aneurysm affects a patient's aortic compliance resulting in a mismatch between expected model and actual compliance. A patent aortic valve is needed because the three pulse contour methods compute forward blood flow into the aorta and in regurgitation ignores backward flow. We can not exclude the existence of small undetectable valve leakage. If so, this will increase the inaccuracy of our comparison with the ICO method. *Thirdly,* during each observation period, before performing measurements, the level of the arterial pressure

transducer was checked and, if needed corrected for. In addition a visual inspection of the arterial pressure waveform was done and the arterial pressure line was flushed in case of doubt on the quality of the pressure signal. *Fourthly,* during the observation period hemodynamic stability was promoted by constant (no changes in) management of the patients.

Agreement of methods with ICO

This is the first study which compared simultaneously, within the same patient population, intermittent pulmonary thermodilution cardiac output with four commercial available methods to monitor cardiac output continuously, with three of them based on arterial pulse contour (i.e. LCO, PCO, FCO) and one based on continuous thermodilution (i.e. CCO). Button et al.[8] compared FCO, PCO (with femoral artery catheter) and CCO with ICO and concluded that the three methods are comparable. The overall accuracy (bias) and precision calculated from their results agree with ours for FCO 0.21 and 1.13 vs. 0.59 and 0.98, PCO 0.29 and 1.30 vs. -0.16 and 1.22 (with radial artery catheter) and CCO 0.33 and 1.19 vs. 0.31 and 0.65 litre·min^{-1}. The simultaneous comparison of methods against the same reference method allows us to rank the performance of the methods. Ranking our results with respect to precision results in; first CCO, second LCO, third FCO and last PCO (Table 5.3). Button et al.[8] reported FCO as best, followed by CCO and PCO, where LCO was not evaluated. In the discussion focused on agreement between methods references based on animal studies are not included, because, especially, the LCO and FCO methods relies on the pressure dependent arterial compliance (pressure volume relationship) found in humans.[9]

Table 5.3 Comparison of four continuous cardiac output systems with cardiac output (CO) by intermittent thermodilution (ICO).

	Cardiac Output		difference			LOA	calculated precision	
	Mean	SD	Bias	precision		lower upper	ICO=6%	ICO=10%
	L·min^{-1}	L·min^{-1}	L·min^{-1}	L·min^{-1}	%	L·min^{-1}	%	%
Pooled data n=179 / 151(*)								
LCO*	5.15	1.26	-0.05	0.94	18.82	-2.00 to 1.90	17.84	15.95
PCO*	5.03	1.37	-0.16	1.22	23.93	-2.61 to 2.29	23.17	21.74
FCO	5.70	0.96	0.59	0.98	18.09	-1.37 to 2.54	17.07	15.07
CCO	5.41	1.11	0.31	0.65	12.37	-0.99 to 1.61	10.82	7.28

LOA, limits of agreement; LCO; PCO; FCO; CCO: cardiac output by, LiDCO, PiCCO, FloTrac and continuous thermodilution respectively.

FloTrac-Vigileo system Recent studies [4;8;10-20] investigating the FloTrac-Vigileo system showed inconsistent results, Table 5.4. Best accuracy and precision were found by Prasser et al.[15] Organizing the results with respect to software versions revealed that precision improved significantly (p = 0.004) after the introduction of software version 1.07. Furthermore, the transpulmonary thermodilution method compared to the pulmonary thermodilution method demonstrated a significant higher value for bias and precision (p = 0.015 and 0.045 respectively). Most comparisons were performed in the ICU with patients after cardiac surgery. With software version >1.07, less good or unacceptable results were found in studies with include septic

patients [16;19], or consisted solely out of patients with sepsis.[10] In our study good results for bias and precision were found for all observation periods (Table 5.2) as well as for the pooled data (Table 5.4), similar to the results presented by Breukers et al.[17] and Prasser et al.[15] This finding may be explained by the fact that we all used a software version >1.07, used the conventional pulmonary thermodilution method as reference method and studied patients in the ICU after cardiac surgery.

LiDCOplus system In recent patient evaluation studies with the LiDCO system[3;21;22] controversial conclusions were drawn. Pittman et al.[3] compared LCO with the lithium dilution method and considered a bias and precision of 0.01 and 0.82 litre·min^{-1} (14%) as accurate. Costa et al.[22] compared LCO with ICO and found an overall bias and precision of 0.29 and 1.09 litre·min^{-1} (13%) and concluded for a good agreement. Whereas Yamashita et al.[21] found bias and precision to be dependent of the level of prostaglandin E1, ranging from 0.02 and 0.14 litre·min^{-1} (4%) to -0.18 and 0.48 litre·min^{-1} (13%), overall results -0.15 and 0.36 litre·min^{-1} (10%), and concluded that the LCO system might be unsuitable in patients after cardiac surgery. Thus the study with the best results had a less positive conclusion than the two others. This illustrated the need for a more uniform judgment of the performance of monitoring systems. Our results for PAC calibrated LCO (Table 5.3) fit well with the cited studies.[3;21;22]
PiCCOplus system Our results of bias and precision (Table 5.3) are comparable to the results of recently published comparative studies with the PiCCO system (software version 6 and 7).[8;18;23] Bias and precision reported by Button et al.[8] with ICO as reference were 0.29 and 1.30 litre·min^{-1} (25%), by DeWaal et al.[18] with transpulmonary thermodilution as reference and repeated recalibrations were 0.02 and 0.93 litre·min^{-1} (17.5%) and from Hamzaoui et al.[23] with transpulmonary thermodilution as reference we recalculated 0.24 and 1.22 litre·min^{-1} (17.5%). They all concluded a clinical acceptable accuracy.

Concerns
Myles [24] criticized in a recent editorial the use of the original Bland-Altman technique, in repeated measurements. Indeed, the results of the studies summarized in table 5.4 as well as of our study in table 5.2 were obtained with multiple observations per patients, thus as repeated measures. However, to our opinion, performing multiple observations per patient does not automatically mean that we have to consider them as such. We realize that the measurements within a patient are not completely independent of each other. In our data the variation between patients is approximately equal to the variation within the patients. This is caused by the fact that the patient that enters the ICU (hemodynamically instable and highly in need of care) differs from the patient that leaves the ICU. Because of this we have chosen our time scale of performing observations with increasing time intervals (Table 5.2). Although based on the nature of our data the use of a random effects model [24] is most appropriate. Using this method we calculated the bias and precision for LCO 0.05 and 0.48; for PCO -0.04 and 0.54; for FCO 0.59 and 0.80 and for CCO 0.31 and 0.36 litre·min^{-1}. In this line of thought we have decided to use the data analyses as proposed in the original Bland-Altman analysis.[5] By doing so, we are able to compare our results with the results recently published, table 5.4. Furthermore, in this we have followed Bland-Altman's advice [25] that it is better not to run the risk of producing limits of agreement, which are too narrow. Incorrectly calculated limits would lead us to think that methods of measurement agreed more than they actually do, which could result in misleading conclusions.[25]

Table 5.4 Studies evaluating the FloTrac-Vigileo system. COtd cardiac output (CO) by thermodilution.

Publication	software version	Npat	Nobs	Site	CO mean $L \cdot min^{-1}$	difference bias $L \cdot min^{-1}$	difference precision $L \cdot min^{-1}$	%	Patients	
Comparison between CO FloTrac and pulmonary COtd										
Mayer et al.[13]	1.03	40	244	rad	5.6	0.92	2.30	41	CABG /Valve	OR, ICU
Lorsomradee et al.[20]	1.01	36	900	rad	5.1	0.12	1.69	33	CABG	OR
Sander et al.[14]	1.03	30	108	rad	5.3	-0.60	1.40	27	CABG	OR, ICU
Prasser et al.[15]	1.03	20	164	rad	5.9	-0.02	1.46	25	General / Neuro	ICU
Manecke et al.[4]	1.07	50	295	rad	NA	0.55	0.98	NA	CABG	ICU
Button et al. [8]	1.07	31	150	rad	5.2	0.25	1.14	22	CABG / Valve	OR, ICU
McGee et al.[16]	1.07	84	561	rad	5.9	0.20	1.28	22	General / Surg *	ICU
Breukers et al.[17]	1.07	20	56	rad	5.5	-0.14	1.00	18	Cardiac surgery	ICU
deWilde et al.	1.07	28	179	rad	5.7	0.59	0.98	17	Cardiac surgery	ICU
Mayer et al.[11]	1.10	40	282	rad	5.5	0.38	1.20	22	CABG / Valve	ICU
Prasser et al.[12]	1.10	20	158	rad	5.9	0.01	0.83	14	CABG	ICU
Comparison between CO FloTrac and transpulmonary COtd										
de Waal et al.[18]	1.07	22	189	fem	5.2	0.00	0.87	17	CABG	OR, ICU
Sakka et al.[10]	1.07	24	72	fem	6.2	-0.50	2.30	37	Sepsis	ICU
Compton et al.[19]	1.07	25	324	rad	6.5	-1.36	1.94	30	General	ICU
* Multi-center study										

Npat, number of patients; Nobs, number of observations; rad, radial artery signal; fem femoral artery signal; OR, operating room; ICU, intensive care unit; CABG, coronary artery bypass grafting; Valve, valve repair; Surg, surgery.

Interchangeability of methods

In answering the question which method can replace an older method we follow Critchley and Critchley [26] who stated "if a new method has to replace an older, established method, the new method itself should have errors not greater than the older method".

In our present study a single pulmonary thermodilution estimate of cardiac output, ICO, has a coefficient of variation, further called 'error', of 10%. The averaged result of a triplicate randomly injected pulmonary thermodilution has an error of 6%. Furthermore, we have found errors for the difference of 24, 19, 18 and 12% for PCO, LCO, FCO and CCO respectively, Table 5.3. By assuming the errors in ICO to be independent of the errors in PCO, LCO, FCO and CCO we can calculate their errors by applying Pythagoras law (Fig. 5.5). The results are given in the figure and table 5.3, column calculated precision, ICO 6%. So, if a triplicate random thermodilution determination is to be replaced by LCO, PCO, FCO or CCO, these methods should have an error < 6% too. Therefore, none of these methods (PCO 23%, LCO 18%, FCO 17%, CCO 11%) can replace this triplicate intermittent pulmonary thermodilution method. However single intermittent thermodilution measurements may be replace by the CCO method. Thanks to the simultaneous comparison of PCO, LCO and FCO against the same reference method we could raise the following questions. Can FCO replace the other methods? Yes, the FCO method may replace the LCO and PCO method. No, the FCO method cannot replace the CCO method.

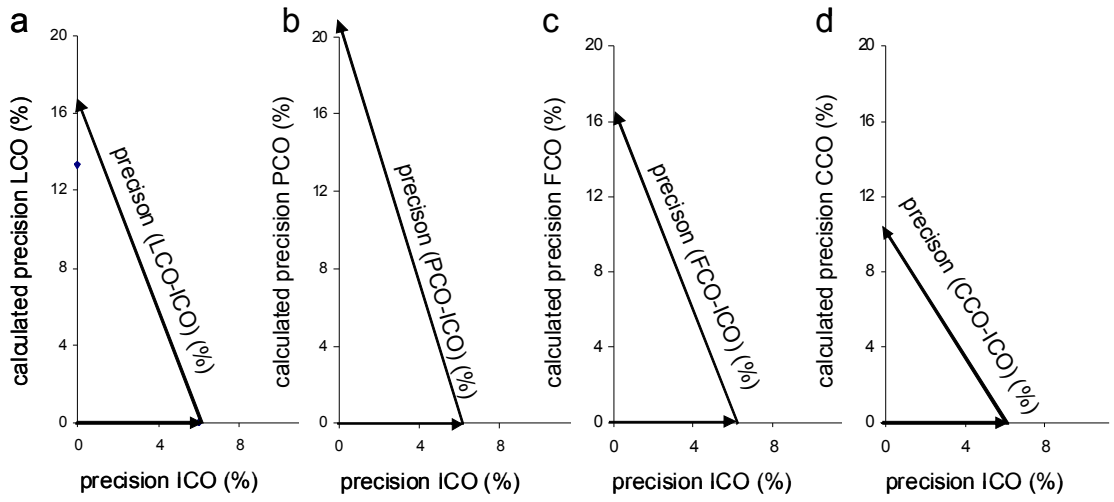

Figure 5.5 Graphical analysis of the precision of the four methods. Horizontally the precision of the reference method (ICO) is given. The hypotenuse is the precision of the difference between method under study and reference method. The precision of the method under study, on horizontal axis, is calculated with Pythagoras law. For abbreviations see figure 5.2.

A remark with respect to the PCO system must be made. We used the radial artery signal as input for the PiCCO system (Fig. 5.1) and disregarded the advice of the manufacture to use the femoral artery signal, because there was no clinical need for an additional arterial catheter. In addition, in previous studies [27;28] we showed the interchangeability of femoral and radial artery signal as input for the PiCCO system.

Furthermore, the PCO and LCO systems were calibrated using the reference device: intermittent thermodilution measurements from the pulmonary artery catheter, and not the transpulmonary dilution method provided by the manufacturer of each device. If the calibration methods provided by the manufacturers (transpulmonary thermal and lithium dilution respectively) had been used, the errors in calibration relative to the PAC-ICO reference would have increased the errors reported here as described by the law of Pythagoras. In our comparison the continuous thermodilution with a PAC, CCO, remained the superior performing system despite the much effort made to improve the pulse contour methods.

Tracking changes in cardiac output

Monitoring of changes in cardiac output in relation to changes in the clinical condition of a patient as well as the response to interventions is important for clinical decision making. We used a threshold for changes ≥ 10%. This threshold was chosen to evaluate the possibility of the four methods to detect fluid responsiveness of patients. Different authors [29-31] have demonstrated that stroke volume variations (SVV) larger than 10% are predictive for increase in cardiac output after fluid loading (i.e. responders). Also a fluid challenge of the circulation with 500 mL and observing an increase in cardiac output larger than 10% identifies a responder. In our study unidirectional changes (using a threshold of ± 10% CO change) were similar for LCO (81%), PCO (82%), FCO (92%) and CCO (98%), figure 5.3. It has to be emphasized that pulse contour methods follows changes in cardiac output on a beat-to-beat basis whereas CCO follows rapid changes with a considerable delay. [32] The good result for CCO may be explained by the presence of a hemodynamic stable circulation in our patients in the minutes before the observation periods and large time intervals between the observations (1 hour or longer), table 5.2. The pulse contour methods, with their beat-to-beat cardiac output, enables to monitor changes in CO during the ventilatory cycle or during a fluid loading and shortly thereafter (within 2 minutes), which is impossibility with the CCO method.

A special note must be made to the alarming results of Lorsomradee et al.[20] These authors showed an opposite change in cardiac output by the first generation FCO and CCO due to phenylephrine infusion. Phenylephrine is a rapid acting alpha antagonist that will increase vascular resistance and venous return. The earlier generation FCO showed a significant dynamic increase whereas the time averaged CCO showed a small decrease in cardiac output. This probably related to the fact that phenylephrine creates a complex and dynamic physiologic response which makes it difficult to compare measurements obtained over different time bases. The phenylephrine increased arterial pulse pressure by increasing systemic vascular resistance and venous return into the heart; and the earlier version of the FCO algorithm did not respond quickly to changes in vascular tone and likely overestimated the change in flow. The phenylephrine also increased pulmonary vascular resistance. Therefore, the slow averaged CCO was likely more reflective of the initial response of the right heart to the increased afterload and underestimated the real time change in flow. To what extent this accounts for PCO and LCO is still unclear**.**

Stability of calibration and drift

To our knowledge our study is the first that evaluate the FCO, LCO, PCO and CCO over time within the same study population. An uncertainty about the correctness of calibration during changing hemodynamic conditions has lead to a frequent recalibration for the PCO and LCO method.[18;23;33] However, a too frequent need for

recalibration turns the method from continuous to intermittent. Thus uncertainty to measure cardiac output correctly, shortly after a recalibration, limits the applicability of the PCO and LCO method. The auto-calibration of the FCO accounts for dynamic changes in vascular tone and is calculated from the pressure waveform and large vessel compliance obtained from arterial pressure, gender, age, weight and height according to Langewouters.[34] This auto-calibration is updated continuously based on a 60s average (software versions ≥ 1.07). The CCO method, by principle, is calibration free.

In our evaluation the difference between ICO and PCO or FCO showed a small but significant drift with time (Fig. 5.4). At first sight our results seems to differ from the results reported several authors [35-37] who reported an acceptable agreement between PCO and ICO over calibration-free periods ranging from 8 to 44 hrs, despite changes in SVR. However, the manufacturers of the PiCCO device advise their users to recalibrate on a regular basis every eight hours, or after changes in SVR of 20%.

Boyle et al.[33], however, demonstrated that the difference between PCO and reference method increased with time and conclude that a recalibration is needed after a 2-h calibration-free period. Also, Hamzaoui et al.[23] concluded, from the results in a recent retrospectively ICU study, that after 1-hr calibration-free period recalibration may be encouraged. In this way cumulative effects of drift can be eliminated, resulting in a better accuracy and precision for the difference between methods. Following this reasoning it seems prudent to confirm PCO values by measuring pulmonary or transpulmonary thermodilution cardiac output before considering changes in therapy even in patients who appear to be hemodynamically stable.[33]

Conclusions

The performance of pulse contour methods has significantly increased the last few years, which makes comparisons with older publications invalid. The auto-calibrated FlowTrac-Vigileo system can replace the initially PAC-calibrated LiDCO and PiCCO systems. The Vigilance continuous thermodilution method demonstrated the best agreement with bolus thermodilution and had the highest score in following slow changes in cardiac output. The auto calibrated FloTrac-Vigileo and the initially PAC-calibrated LiDCO system showed best performance in detecting beat-to-beat cardiac output changes.

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Chapter 6

Performance of three minimal invasive cardiac output monitoring systems

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In press

Summary
We evaluated cardiac output (CO) using three new methods - the auto-calibrated FloTrac-Vigileo (COed), the non-calibrated Modelflow (COmf) pulse contour method and the HemoSonic 100 ultra-sound system (COhs) - with bolus thermodilution (COtd) as the reference. In 13 postoperative cardiac surgical patients 104 paired CO values were assessed before, during and after four interventions: (a) an increase of tidal volume by 50%, (b) a 10 cmH_2O increase in positive end-expiratory pressure, (c) passive leg raising and (d) head up position. With the pooled data the difference between COed and COtd, COmf and COtd and COhs and COtd was 0.33 ± 0.90, 0.30 ± 0.69 and -0.41 ± 1.11 $l.min^{-1}$, respectively. Thus, Modelflow had the lowest mean squared error, suggesting that it had the best performance. COed significantly overestimates changes in cardiac output while COmf and COhs values are not significantly different from those of COtd. Directional changes in cardiac output by thermodilution were detected with a high score by all three methods.

Introduction
Ideally cardiac output monitoring is accurate, precise, operator independent, fast responding, non-invasive, continuous, easy of use, cost effectiveness and does not increase mortality and morbidity. Especially of interest are those methods that follow changes in cardiac output accurately. These methods may provide an early warning on changes in circulatory function and allow testing the circulation with applied interventions.
In the last three decades cardiac output was commonly monitored by using a thermodilution pulmonary artery catheter (PAC). The intermittent bolus thermodilution cardiac output (COtd), is still considered the best reference method. While continuous thermodilution cardiac output (CCO) may not be feasible to follow changes on interventions or applied challenges, due to time delay [1, 2]. Devices better equipped to monitor fast changes in cardiac output adequately are those based on beat-to-beat assessment of stroke volume. Two technologies currently available at bedside to monitor beat-to-beat changes in cardiac output reliably are based on arterial pulse contour and trans-esophageal ultrasound.
The recently introduced auto-calibrated FloTrac-Vigileo™ (Edwards Lifesciences, Irvine, CA, USA) is a pulse contour method for cardiac output monitoring that in contrast to devices, like the the PiCCO™ (Pulsion Medical Systems, Munich, Germany) and LiDCO™ (LiDCO Ltd., Cambridge, UK), does not require an independent calibration [3] and thus do not add invasiveness to the method. The system obtains like the Modelflow method the pressure signal from any standard peripheral arterial line and add by this no extra invasiveness to OR and ICU patients. The standard deviation of the pulse pressure is correlated to stroke volume based on patients age, gender, body height and weight) after an automatic adjustment to actual vascular compliance. Early validation showed conflicting results, however, after the introduction of software version 1.07, the results became more uniform [4-8].
The Modelflow method derives an aortic flow waveform from arterial pressure by using a three element input impedance model. Stroke volume is integrated from the flow waveform. The parameters of the model are based on aortic pressure, gender, age, height and weight of the patient under study. In different studies [9-12] the Modelflow (pulse contour) method have shown the ability to follow beat-to-beat cardiac output changes, both after calibration by thermodilution as well as non-calibrated [11, 12].

The HemoSonic™ 100 monitor system (Arrow International, Reading, PA, USA) comprises an ultrasound probe with both M-mode and pulsed Doppler transducers [13, 14]. The M-mode is used to measure (in real time) the diameter of the descending aorta and the Doppler transducer to measure the blood velocities across the aorta. From diameter and blood velocity aortic blood flow (ABF) is computed. Cardiac output is determined via a known relationship between ABF and cardiac output. Based on the continuous nature of the technique the system is used to measure ventilator induced changes in blood flow in patients as well as to quantify changes in ABF on passive leg raising in intensive care patients [15].
The aim of our study is to compare the accuracy, precision and monitoring ability of cardiac output measurements by FloTrac-Vigileo, Modelflow and HemoSonic with intermittent pulmonary artery thermodilution as reference method. To change cardiac output four types of interventions are applied to ICU patients after cardiac surgery.

Methods

Patients and anaesthesia

After approval of the study protocol by the University Medical Ethics committee**,** thirteen patients were studied after coronary arterial bypass grafting or mitral valve reconstruction. The study was conducted according to the principles of the Helsinki declaration and written informed consent was obtained from all patients prior to operation. All patients had symptomatic coronary artery disease without previous myocardial infarction. Patients with a history of abnormal ventricular function, aortic aneurysm, extensive peripheral arterial occlusive disease, aortic valve pathology, and pharyngeal or esophageal pathology were excluded. Patients with persistent postoperative arrhythmia or the necessity for artificial pacing or heart assist devices were also excluded. All patients were included in the study during their initial post-operative period in the Intensive Care Unit (ICU).
Anesthesia during surgery and stay in the ICU was with propofol, sufentanil and vasoactive medication according to institutional standards. The lungs were mechanically ventilated (Dräger EVITA 4, Dräger AG, Lübeck, Germany) in a volume-control mode with settings aimed to achieve normocapnia with a tidal volume of 8-12 $ml.kg^{-1}$ and a respiratory frequency of 12-14 $breaths.min^{-1}$. Fraction of inspired oxygen was 0.4 and PEEP 5 cmH_2O. During the observation period ventilator settings, sedation and vasoactive medication, when used, were unchanged.

Monitoring techniques

Prior to ICU admission, all patients were catheterized with a 20G radial artery catheter (RA 04220, Arrow Int., Reading, PA, USA) to monitor arterial pressure (Pa) and a pulmonary artery catheter (139HF75P, Edwards Lifesciences, Irvine, CA, USA) introduced into the right jugular vein to monitor central venous pressure (CVP), pulmonary artery pressure (PAP) and to estimate cardiac output (CO) by the intermittent thermodilution method (COtd).
COtd measurements were performed with an automated system under computer control. COtd was measured in triplicate (with 10 ml saline solution at room temperature) in two minutes, with the measurements equally spread over the ventilatory cycle. The three individual COtd measurements were averaged [16].Blood pressure transducers were referenced to the level of the tricuspid valve and zeroed to atmospheric pressure.

The radial artery pressure (Pa), derived via the radial artery catheter, was measured with a FloTrac™ pressure transducer (Edwards Lifesciences, Irvine, CA, USA)). Of the bifurcated cable, one limb was connected to the Vigileo system (Edwards Lifesciences) to measure pulse contour cardiac output (COed) and the other limb was connected to a bedside monitor pressure module (Hewlett Packard model M1006A, Hewlett Packard Company, Palo Alto, Ca, USA) which output was used as input signal to the modified Modelflow system (BMEYE, Academic Medical Center, Amsterdam, the Netherlands) to estimate pulse contour cardiac output (COmf). Detailed information about the FloTrac-Vigileo system [3] and Modelflow system [17, 18] can be found elsewhere.
The HemoSonic 100 ultra-sound probe (Arrow International, Reading, PA, USA) to monitor aortic blood flow (ABF) was inserted through the mouth and advanced in the esophagus to the level of the fourth intercostal space. Next, its position was adjusted to obtain the highest Doppler velocity signal along with simultaneous optimal visualization of aortic wall images [12, 14]. The final position of the probe was checked by chest X-ray, and readjusted after changes in position of the patient, if necessary. All measurements were made by the same clinician under supervision of team members experienced with HemoSonic100 cardiac output monitoring. Cardiac output (COhs) was calculated from ABF [14].
COtd, COed, COmf, COhs, Pa, PAP, CVP, blood temperature, heart rate (HR), were continuously recorded and stored on a personal computer for documentation and offline analysis.

Study protocol
Measurements were carried out within two hours after arrival in the ICU following Pa hemodynamical stabilization. Characteristics and treatment data of each patient were collected. During baseline 1 (Fig. 6.1) a series of measurements: HR, MAP, CVP, PAP, COtd, COed, COmf, and COhs were obtained. To change cardiac output four interventions were applied to the patients. Tidal volume of the ventilator was increased with 50% for five minutes, two 2 minutes after this change, the series of measurements were repeated (VT-series). Five minutes after return to baseline 2 series of measurements were performed. Next, positive airway pressure (PEEP) was increased with 10 cm H_2O for 5 minutes, and after 2 minutes the next series of measurements was started (PEEP-series). Five minutes after return from increased PEEP, baseline 3 series of measurements were carried out. Next, passive leg raising was performed from the supine position by lifting both legs at a 30° angle and holding them there for 5 minutes, 2 minutes after initial elevation of the legs with legs still elevated the series of measurements were repeated (PLR-series). Five minutes after return from passive leg raising, baseline 4 measurements were performed. Last, a head up tilting (HUT) procedure was done by rotating the bed to a 30^o head-up (anti-Trendelenburg) position, 2 minutes after rotation of the bed series of measurements were started (HUT-series). Five minutes after return from HUT, during baseline 5, the last series of measurements was performed.

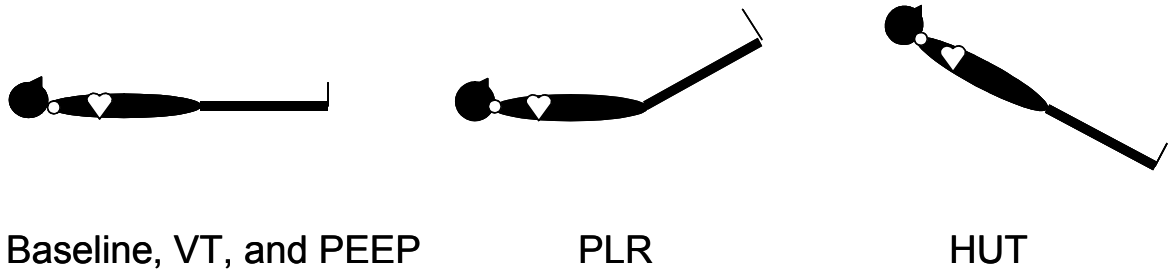

Figure 6.1 Different positions of the patient during the interventions. **A:** During supine position VT was increased with 50% and PEEP was increased with 10 cmH2O. **B:** PLR, Passive leg raising is performed by maintaining the patient in a supine position and raising the legs by repositioning of the bed. C: HUT, head up tilting. During all interventions except for HUT, the heart (symbol ♥) and baroreceptors (symbol ○) are in-level and blood pressure transducers do not have to be re-referenced. The Doppler probe may move during PLR and HUT and a repositioning of the probe is needed.

Calculations and Statistics

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, agreement between COed, COmf, COhs and COtd as well as agreement in changes in cardiac output was evaluated with Bland-Altman statistics. The agreement between COmf or COed or COhs and COtd was computed as the bias (i.e. accuracy) and standard deviation (SD) (i.e. precision), with the limits of agreement (LOA) computed as the bias ± 2 SD [19]. The coefficient of variation was computed as [CV=100*(SD/mean)]. Following Myles and Cui [20], we also used the random effects model to calculate precision and limits of agreement. When the mean of the repeated measurements is used, the variation of the differences of the original measurement between two methods will be underestimated because the measurement error has been removed. A random effects model was chosen to reflect the different intercept and slope for each individual on their repeated measurements. We included the effects of intervention (VT, PEEP, PLR and HUT) as a covariate in order to get a more precise estimate of the residual within-subject variation.

Differences in cardiac output were analysed further with factorial ANOVA, and there were three factors; monitoring method (fixed factor, four levels); intervention (fixed factor, eight levels, repeated) and subjects (random factor, 13 levels). If ANOVA indicated a statistically significant result in cardiac output between baseline and intervention, a post-hoc test (Tukey-HSD in multiple comparisons, LSD in pairwise comparison) was used to identify the significant effect.

Monitoring capability in cardiac output change (ΔCO) due to an intervention with VT, PEEP, PLR and HUT was calculated by subtraction the averaged cardiac output values (COavg) of the baseline values before and after the intervention from the cardiac output during the intervention (COi). Percentage change is calculated by expressing the change in percentage of averaged baseline value: ΔCO% = 100*(COi – COavg)/COavg. A positive trend is observed if the changes in cardiac output were in the same direction as those found for COtd, whereas, a negative trend was scored with changes in opposite direction. Ideally, only positive scores should be present. These scores were analysed using 2x2 tables and presented in percentages. Separate scores were counted for changes when thermodilution cardiac output values differed at least a clinically relevant 5 or 10%. A statistical test is considered to be significant if the associated *p*-value is less than 0.05.

Results

We included 13 cardiac surgical patients, 11 after coronary arterial bypass grafting and 2 after mitral valve reconstruction. A total of hunderd seventeen paired CO data sets with COtd, COed, COmf and COhs were obtained during 5 baselines periods and, VT, PEEP, PLR and HUT interventions. Averaging the baseline value before and the baseline value after the intervention resulted in 104 paired values for statistical evaluation. The data were normally distributed. Mean COtd was 5.28 l.min^{-1} (range 2.57 to 8.61 l.min^{-1}). The coefficient of variation for averages of three thermodilution measurements equally distributed over the ventilatory cycle was 5%.

Agreement of methods with intermittent thermodilution cardiac output

The error diagrams for the difference between COtd and COed, COmf or COhs are given in the three panels of basic Bland-Altman plots (Figure 6.2). For the three methods, i.e. COed, COmf and COhs 104 data points are available. Bland-Altman statistics for pooled data are indicated in the figure by bias and limits of agreement (LOA).

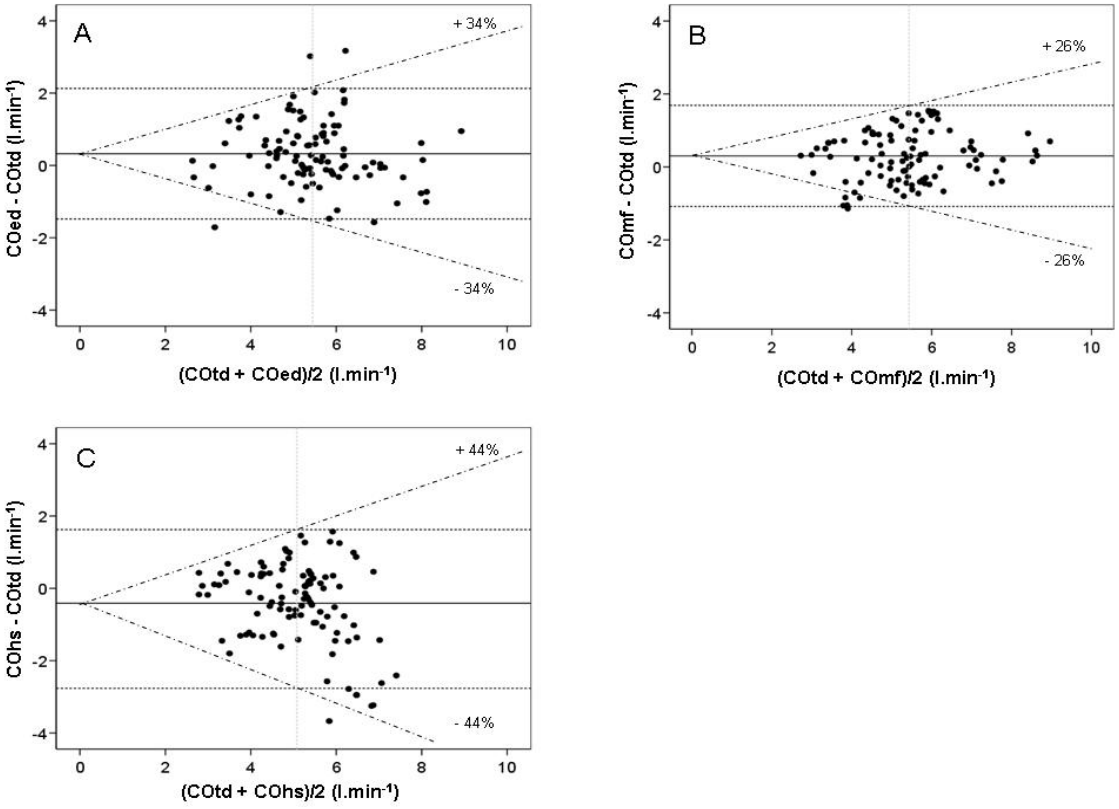

Figure 6.2 Bland-Altman plots of the difference of cardiac output (CO) values between conventional thermodilution (COtd) and three minimal invasive methods (n = 104). In panel A, COed, CO by auto-calibrated FloTrac-Vigileo system. In panel B, COmf, CO by non-calibrated Modelflow method. In panel C, COhs, CO by HemoSonic 100 ultrasound system. Solid line represents the bias, dotted lines absolute limits of agreement and dashed-dotted lines the limits of agreement in percentage.

Table 6.1 Comparison of bias and precision between the original and modified Bland-Altman methods.

Method	Bias $l.min^{-1}$	Precision $l.min^{-1}$	Error (%)
Classical Bland-Altman statistics			
COed – COtd	0.33	0.90	34
COmf – COtd	0.30	0.69	26
COhs – COtd	-0.41	1.11	44
Modified Bland-Altman statistics (Random effects model)			
COed – COtd	0.33	0.69	25
COmf – COtd	0.30	0.64	24
COhs – COtd	-0.41	1.07	42

COtd, intermitted thermodilution cardiac output (reference method); COed, CO measured with FloTrac-Vigileo; COmf, CO measured with non-calibrated Modelflow; COhs, CO measured with HemoSonic 100.

Bias between COtd and COed or COmf was 0.33 and 0.30 $l.min^{-1}$ respectively which was significantly different from the bias between COtd and COhs (-0.41 $l.min^{-1}$, for both $p < 0.001$). COmf has best precision (0.69 $l.min^{-1}$) and smallest range of the limits of agreement (-1.08 to 1.68 $l.min^{-1}$, 26%) whereas values of precision and limits of agreement for COed and COhs are larger (-1.47 to 2.13, 34% and -2.62 to 1.80 $l.min^{-1}$, 44%, respectively), table 6.1. Also, from figure 6.2 it is observable that the distribution of errors is different among the methods.

Based on the study design (in which multiple measurements per patient were obtained) we followed Myles and Cui [20] and used the random effects model (Table 6.1 and Figure 6.3).

The residual within-subject standard deviation was substantially smaller after adjusted for baseline. For example, the original within-subject standard deviation was 0.41 and 0.79 for COtd and COed, respectively. After adjusting for the relevant covariates, the within-subject standard deviation reduced to 0.21 and 0.20, respectively. This reduced the width of the 95% limits of agreements accordingly (Figs. 6.2 and 6.3). Bias and precision of both, the original and modified Bland-Altman methods are in table 6.1. Table 6.2 shows the pair wise comparison of mean CO in relation to measurement methods, post-hoc analysis. Except for COmf and COed pairs ($z = -0.023$, $p = 0.996$), the mean cardiac output between all other pairs are significantly different.

Effects of intervention on CO

The effects on cardiac output by the four applied interventions and four measurement techniques are in table 6.2. A 50% increase in tidal volume, did not resulted in a change in cardiac output according to all four cardiac output methods. Changes in CO were found for all three other interventions, during PEEP a decrease, during passive leg raising an increase and during head up tilt position a decrease. An increase of PEEP with 10 cm H_2O has the largest impact on cardiac output. With Factorial ANOVA the main effects on cardiac output values related to the measurement techniques was ($F = 23.73$, $p < 0.001$), and related to the interventions was ($F = 13.85$, $p < 0.001$). Differences between methods were consistent across all interventions ($F = 0.19$, $p = 1.000$).

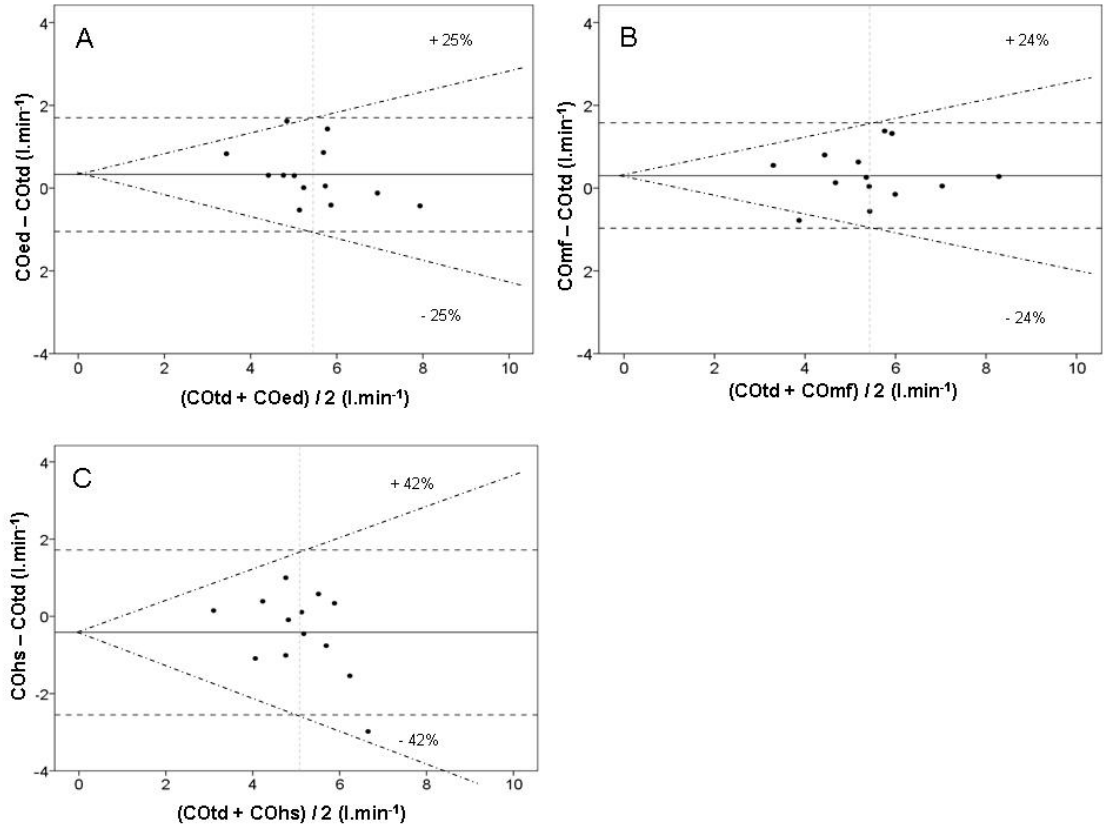

Figure 6.3 Modified Bland-Altman plots of the difference of cardiac output (CO) values between conventional thermodilution (COtd) and three minimal invasive methods, based on a random effects model (N =13). In panel A, COed, CO by auto-calibrated FloTrac-Vigileo system. In panel B, COmf, CO by non-calibrated Modelflow method. In panel C, COhs, CO by HemoSonic 100 ultrasound system. Solid line represents the bias, dotted lines absolute limits of agreement and dashed-dotted lines the limits of agreement in percentage

Monitoring cardiac output changes

Fifty-two data points are available to describe changes in cardiac output by COtd, COed, COmf or COhs due to interventions. Cardiac output changes by all three methods correlate significantly ($p \leq 0.001$) with cardiac output changes by COtd (COed v COtd, slope 1.46, CI95% 1.07 to 1.81; COmf v COtd, slope 0.82, CI95% 0.61 to 1.01; COhs v COtd, slope 0.88, CI95% 0.62 to 1.15). The change in COed is significantly overestimated compared to the change in COtd. The changes in COmf and COhs are not significantly different from identity. The agreement of positive and negative trend of COtd and CO in each of the three methods was calculated using cross tabulation. The score for agreement in change was 86% for COmf and 81% for COed and COhs. These scores improve if clinically irrelevant changes of <5% or <10% are excluded from counting. For a 5% threshold, agreement is found in 96%, 85% and 93% with COmf, COed and COhs respectively. For a 10% threshold, these values are 100%, 89% and 100% respectively.

The Bland-Altman plots for changes in cardiac output with LOA are shown in figure 6.4. Bias between change COtd and change COed, change COmf or change COhs is not significantly different (-3.03, -3.28, and -2.01 % respectively). COed (-29.59 to 23.52 %) has the largest range of the limits of agreement in contrast to COmf (-17.23 to 10.67 %) and COhs (-20.28 to 16.27%), respectively changes between COed and COtd clearly depends on the level of averaged change of COed and COtd (Fig. 6.4A).

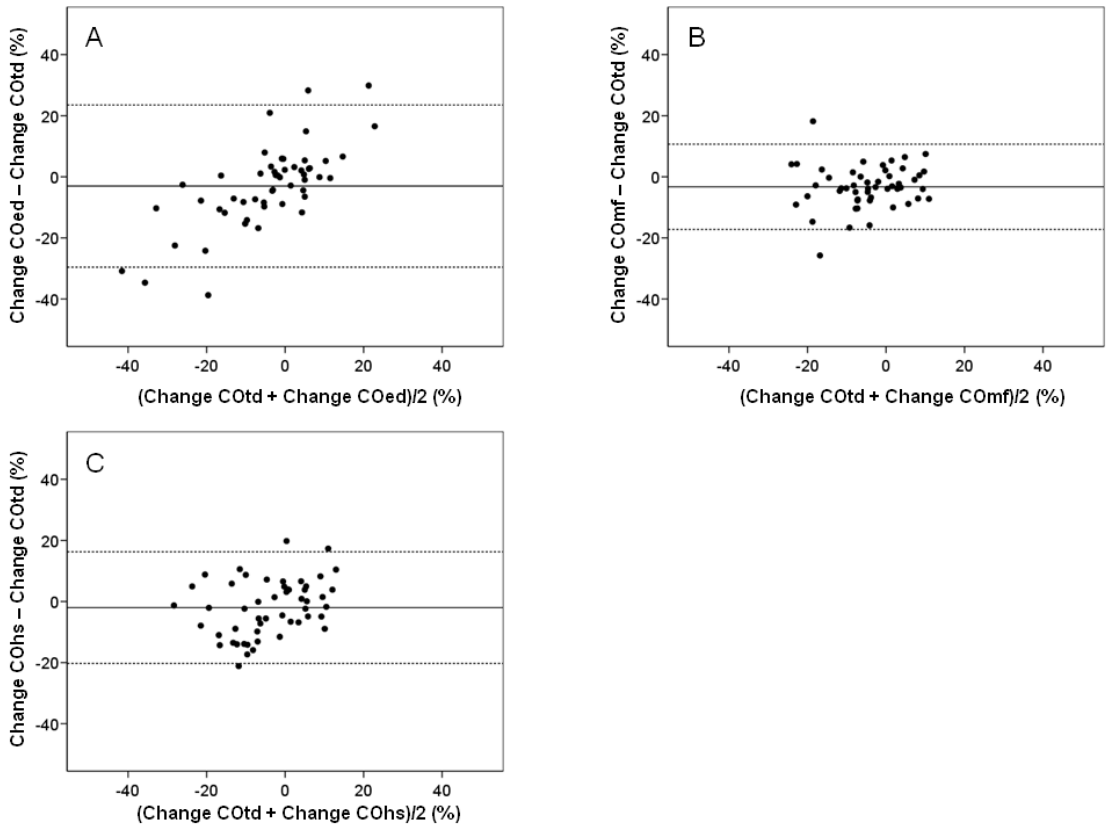

Figure 6.4 Bland-Altman plots with percentage changes in cardiac output by three minimal invasive methods and percentage changes by conventional thermodilution. For abbreviations see figure 6.2. Solid line presents bias and dotted lines limits of agreement.

Discussion

The present study was designed to evaluate the monitoring capabilities of minimal invasive cardiac output systems. The non-calibrated Modelflow method showed a good performance in estimation of cardiac output with bias 0.30 l.min^{-1}, precision 0.68 l.min^{-1} and limits of agreement of 26% in cardiac surgery patients. Only the % limits of agreement obtained with Modelflow (26%) are below the 30% criteria for limits of agreement for a theoretically acceptable alternative to thermodilution cardiac output [21]. Monitoring changes in cardiac output can be done accurately with non-calibrated Modelflow and HemoSonic, directional changes in cardiac output larger than 5% were correctly followed in 96% and 93% of the cases. For changes larger than 10% this was 100% for both methods. For the auto-calibrated FloTrac-Vigileo these percentages were calculated 85% and 89%.

Table 6.2 Changes in cardiac output (CO) related to increase of tidal volume, increase of PEEP, passive leg raising and head up tilt intervention.

	CO Baseline Mean (SD) $l.min^{-1}$	CO Intervention Mean (SD) l/min^{-1}	CO difference in %	p - value
Increased tidal volume				
COtd	5.28 (1.28)	5.28 (1.44)	0.0	0.954
COed	5.72 (0.88)	5.89 (1.47)	3.0	0.507
COmf	5.75 (1.38)	5.43 (1.48)	-5.6	0.052
COhs	4.83 (0.93)	4.75 (0.98)	-1.7	0.669
Increased PEEP				
COtd	5.37 (1.35)	4.66 (1.47)	-13.3	< 0.001
COed	5.99 (0.93)	4.61 (1.51)	-23.0	< 0.001
COmf	5.73 (1.45)	4.88 (1.47)	-14.8	< 0.001
COhs	4.86 (0.89)	4.17 (1.04)	-14.2	0.001
Passive leg raising				
COtd	5.39 (1.33)	5.79 (1.37)	7.4	< 0.001
COed	5.61 (0.93)	6.07 (0.97)	9.6	0.078
COmf	5.72 (1.44)	5.97 (1.46)	4.4	0.133
COhs	5.11 (0.74)	5.56 (0.76)	8.8	0.025
Head up tilt				
COtd	5.33 (1.20)	5.16 (1.21)	-3.8	0.089
COed	5.78 (1.06)	5.23 (1.35)	-9.5	0.041
COmf	5.81 (1.31)	5.38 (1.30)	-7.4	0.009
COhs	5.14 (1.13)	4.55 (1.01)	-11.5	0.004

COtd, intermitted thermodilution cardiac output; COed, CO measured with FloTrac-Vigileo; COmf, CO measured with non-calibrated Modelflow; COhs, CO measured with HemoSonic 100; CO difference is difference between CO intervention and CO baseline. Results of post-hoc analysis, pairwise comparison (LSD) of cardiac output differences related to interventions, factorial ANOVA ($F = 13.85$, $p < 0.001$).

Reference method of CO measurement
An important factor in our study was the availability of a reliable reference method. Indeed, the error in the reference method has a direct impact on the comparison between cardiac output by thermodilution and FloTrac-Vigileo, Modelflow or HemoSonic. Individual thermodilution cardiac output estimates show substantial scatter (10-15%) in their values even under stable hemodynamic and ventilatory conditions [22]. In such circumstances, in general, an average of at least three measurements, with randomly in time applied bolus injections, is advised to obtain cardiac output estimate with acceptable precision [11]. In ventilated patients, however, a better precision is obtained by doing these measurements equally spread over the ventilatory cycle. In this way ventilator effects on cardiac output are maximally averaged out [16]. However, this requires the injections to be performed by a motor driven syringe under computer control**.** In doing so, precision is enhanced further by limiting the deviation of injection time and of volume [23]. We used for thermodilution cardiac output measurement such a simple but not generally available system.

Agreement of cardiac output methods with literature
Auto-calibrated FloTrac-Vigileo In 5 recently published studies with software version 1.07 and 1.10 [4-8] averaged cardiac output ranged from 5.2 to 5.9 $l.min^{-1}$, bias from -0.14 to 0.58 $l.min^{-1}$ and precision from 0.83 to 1.28 $l.min^{-1}$. Thus, our present results characterized by a mean thermodilution cardiac output of 5.28 $l.min^{-1}$, a bias of 0.33 $l.min^{-1}$ and a precision of 0.90 $l.min^{-1}$ are consistent with those reported.

Non-calibrated Modelflow From Jansen's et al. [11] three centre study in 54 cardiac surgery patients, using the same methodology as in our present study, we deduced the following results for the non-calibrate Modelflow; compared to thermodilution (mean 4.9 $l.min^{-1}$) the bias was 0.32 $l.min^{-1}$ and the precision 0.90 $l.min^{-1}$ (LOA of -1.58 to 2.12 $l.min^{-1}$). From another study in ICU patients after complex cardiac surgery [12], again using the same methodology as in our present study, we recalculated for non-calibrated Modelflow method, after removing two out-layers, a bias of 0.34 $l.min^{-1}$, a precision of 1.16 $l.min^{-1}$ (LOA of -1.98 to 2.66 $l.min^{-1}$) and a mean thermodilution cardiac output of 5.45 $l.min^{-1}$. Thus, our present results for non-calibrated Modelflow (mean COtd 5.28 $l.min^{-1}$, bias 0.30 $l.min^{-1}$, precision 0.69 $l.min^{-1}$ and LOA -1.08 to 1.68 $l.min^{-1}$) are in range with these previous results.

HemoSonic 100 In 13 cardiac surgery patients Moxon et al. [24] compared 47 HemoSonic and thermodilution cardiac output pairs and found a bias of 0.23 $l.min^{-1}$ and a precision 1.06 $l.min^{-1}$ (LOA -1.89 to 2.35 $l.min^{-1}$). Su et al. [25] found in a similar setup a bias of 0.11 $l.min^{-1}$ and precision of 1.12 $l.min^{-1}$ (LOA -2.13 to 2.35 $l.min^{-1}$). Our results are in agreement with these two studies (bias = -0.41 $l.min^{-1}$, precision = 1.11 $l.min^{-1}$, LOA -2.62 to 1.80 $l.min^{-1}$).
In summary, the present study did not show conflicting results for cardiac output with respect to results of previous reports, obtained with either one of the three minimal invasive cardiac output methods.

Effects of interventions on cardiac output
During clinically stable conditions cardiac output was changed by increasing tidal volume of the ventilator, increasing PEEP, performing passive leg raising and positioning the patient in head up tilt position (Table 6.2). We found a decrease in

cardiac output due to PEEP with all four methods, as described in literature [26-29]. Passive legs raising recruits blood from the venous reservoirs in the legs (approximately 300ml) thereby converting unstressed volume to stressed volume resulting in an increase of cardiac output [15, 30]. This increase in cardiac output with passive leg raising is confirmed in our study by all four methods. Head up tilt mimics the cardiovascular response to haemorrhage in which the central blood volume is transmitted to the legs [31]. Thus head up tilt leads to a reduction of stressed volume resulting in a decrease in cardiac output. This is established by our results as well, where all four methods showed a decrease in cardiac output.

Monitoring changes in cardiac output

Reliability in monitoring changes of cardiac output on interventions or therapy is a cornerstone of medical practice. Therefore, we extensively evaluated the tracking ability of the three methods upon four interventions. Especially the passive legs raising intervention in combination with esophageal ultra-sound blood flow measurement has been used to separate those patients that respond to a fluid loading by an increase in cardiac output from those that do not benefit [32-34]. In a nice study Monnet at al. [33] investigated in 71 mechanically ventilated patients and 31 patients with spontaneous breathing activity and/or arrhythmias the feasibility of the HemoSonic device. They showed that based on an increase in aortic blood flow >10% by passive leg raising, responder, a volume expansion induced increase in cardiac output could be reliably predicted. Using the 10% threshold FloTrac-Vigileo scores cardiac output changes equally 89% whereas the non-calibrated Modelflow and HemoSonic scored 100%. Based on these results we may expect FloTrac-Vigileo and Modelflow to be valuable substitutes for the HemoSonic. With the advantage that these methods would provide the clinician with a simple, readily available robust measure of cardiac output change that is user independent.

Concerns

Myles and Cui [20] criticized in a recent editorial the use of standard Bland-Altman analysis to compare methodologies (such as ours in this study) where repeated measurements are used. We feel, however, that multiple observations in a patient really only apply when taken under the same experimental conditions. Where conditions are changing with time, it seems valid to take several observations and then assess response over time. Nonetheless, we took the precaution of applying both the 'classical' Bland-Altman statistics [19] and the random effects model proposed by Myles and Cui [20]. The differences in results of analysis are presented in the figures 6.2 and 6.3. For all three methods the limits of agreement of the classical Bland-Altman analysis are larger than with the random effects model. This can be explained by the removal of within patient variation in cardiac output. Especially the difference between COed and COtd (Fig. 6.2A) decreased considerably with the random effects model (Fig. 6.3A). This is account for the overestimation of changes in cardiac output by the FloTrac-Vigileo system (Fig. 6.4A).

In our study, patients remain in a supine position during the increased tidal volume, PEEP and passive leg raising intervention (Fig. 6.1). During passive leg raising only the legs are raised by repositioning of the bed. The heart and baroreceptors are in-level and blood pressure transducers do not have to be re-referenced. However, upon passive legs raising the esophageal probe can change position due to fixation of the probe to the bed and possible movement of the patient. We regular repositioned the probe to obtain an optimal signal again. Also during the head up tilt intervention the

position of the probe may be compromised and repositioning may be needed. During (re)positioning we focused on maximum for after wall distance, maximal acceleration of aortic blood flow and optimal aortic wall visualization [14]. In addition, the position of the pressure transducers needs to be corrected too, as we did. However, the position of baroreceptors in relation to the heart is changed which may influence arterial blood pressure by auto-regulation (Fig. 6.1). These differences may have influenced the results (Table 6.2) differently for the three methods of cardiac output measurement.

Conclusions

Non-calibrated Modelflow method showed best performance in estimation of cardiac output. Changes in cardiac output by thermodilution were tracked significantly by HemoSonic and non-calibrated Modelflow whereas auto-calibrated FloTrac-Vigileo overestimated the changes in cardiac output. Directional changes in cardiac output by thermodilution were detected with a high score by all three methods. Encouraged by the simplicity of setup procedure and advantage for the patient, we stress to further exploration of FloTrac-Vigileo and Modelflow system.

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Chapter 7

Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour

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Summary
Background Cardiac output by Modelflow pulse contour method can be monitored quantitatively and continuously only after an initial calibration, to adapt the model to an individual patient. The Modelflow method computes beat-to-beat cardiac output (COmf) from the radial artery pressure, by simulating a three-element model of aortic impedance with post-mortem data from human aortas.
Methods In our improved version of Modelflow (COmfc) we adapted this model to a real time measure of the aortic cross-sectional area (CSA) of the descending aorta just above the diaphragm, measured by a new transoesophageal echo device (HemoSonic 100). COmf and COmfc were compared with thermodilution cardiac output (COtd) in 24 patients in the intensive care unit. Each thermodilution value was the mean of four measurements equally spread over the ventilatory cycle.
Results Least squares regression of COtd *vs* COmf gave y = 1.09 x [95% confidence interval (CI) 0.96 to 1.22], R^2 = 0.15, and of COtd *vs* COmfc resulted in y = 1.02 x (95% CI 0.96 to 1.08), R^2 = 0.69. The limits of agreement of the un-calibrated COmf were -3.53 to 2.79, bias = 0.37 litre min^{-1} and of the diameter-calibrated method COmfc, -1.48 to 1.32, bias = -0.08 litre min^{-1}. The coefficient of variation for the difference between methods decreased from 28 (un-calibrated) to 12% after diameter-calibration.
Conclusions After diameter-calibration, the improved Modelflow pulse contour method reliably estimates cardiac output without the need of a calibration with thermodilution, leading to a less invasive cardiac output monitoring method.

Introduction

Different authors have shown in patients, by comparing the Modelflow estimates with thermodilution estimates, the ability of the Modelflow (pulse contour) method to replace the thermodilution method to follow cardiac output changes. [1-3] A patient calibration of the Modelflow method is, however, needed to obtain quantitative cardiac output with high accuracy. This calibration is usually carried out by thermodilution cardiac output.[1-3]
The parameters of Modelflow are based on aortic pressure, and post-mortem data of cross-sectional area (CSA) *vs* pressure of the aorta just above the diaphragm.[4] A recently developed M-mode ultrasound method, (HemoSonic 100, ARROW, Reading, PA, USA) has the ability to measure the diameter of the descending aortic just above the diaphragm. In addition, the system also measures aortic blood flow velocity.[5] The oesophageal ultrasound method is considered to be less invasive than thermodilution cardiac output measurement by a pulmonary artery catheter (PAC).
In this paper we would like to test the hypothesis that calibration of the Modelflow method by the measure of the aortic diameter results in an improvement of the accuracy of the method such that a calibration by thermodilution is no longer needed.

Methods

Patients and materials The study was approved by the hospital ethical committee and was conducted according to the principles stated in the Helsinki convention. Written informed consent from each patient was obtained the evening before surgery. The improved Modelflow method was evaluated in the intensive care unit (ICU) in 24 patients following coronary artery bypass graft and/or valve replacement. Exclusion

criteria were severe tricuspid heart valve insufficiency, aortic aneurysm, aortic valve pathologies, and known pharyngeal or oesophageal pathologies.
Anaesthesia during surgery was performed according to institutional standards, with invasive monitoring of arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and thermodilution cardiac output with a PAC (Edwards IntelliCath, Irvine, CA, USA).
After transfer of the patient to the ICU, the hemodynamic status was stabilized giving fluids and catecholamines as required. The lungs were ventilated with oxygen 40%, 12 bpm, and a positive airway pressure of 5 cm H_2O. Tidal volume was adapted to bring the arterial P_{CO_2} in the range of 40 – 45 mm Hg. The HemoSonic 100 probe was inserted into the oesophagus after hemodynamic and respiratory stability had been achieved. During this stage diameter-calibration of Modelflow was performed. To prevent instability during this period, nursing activities and treatment of the patients were minimized. Measurement series with changes in arterial pressure or heart rate larger than 5% were rejected and repeated.

Modelflow method Increase in aortic pressure as a result of left ventricular contraction causes inflow of blood into the arterial system. This inflow is, however, opposed and thus moderated by aortic and peripheral systemic properties such as arterial counter pressure and impedance.
The Modelflow method simulates this behaviour according to a three-element Windkessel model of arterial input impedance.[6] [7] The three-element model, representing the three major properties of the aorta and arterial system, has three principal components: aortic characteristic impedance, which represents the opposition of the aorta to pulsatile inflow; Windkessel compliance, which represents the ability of the aorta and arterial system to elastically store the cardiac stroke output of the left ventricle; and peripheral resistance, which represents the opposition of the vascular beds to the drainage of blood.
The impedance and compliance of the model depend on pressure itself,[4] and total systemic peripheral resistance depends on many factors including circulatory filling, metabolism, sympathetic tone, and vasoactive drugs.
The aortic Windkessel compliance decreases substantially when aortic pressure increases. This non-linear behaviour of the aortic wall would be a major source of error if not taken into account. The aortic characteristic impedance, in contrast to compliance, increases moderately when aortic pressure increases. These non-linear relationships were studied post-mortem by Langewouters and colleagues[4] and described as mathematical functions of the patient's age, gender, height, and weight. Individual inaccuracy in aortic diameter determination translate into an inaccuracy in the absolute level of cardiac output computed for an individual patient, but the ability to reliably track the changes in cardiac output remains intact.[3] To overcome the individual inaccuracy in aortic diameter determination, a real time measurement of aortic diameter was introduced using an ultrasound echo system (M-mode, HemoSonic 100). According to Langewouters and colleagues,[4] the thoracic aortic CSA can be predicted as a function of aortic pressure (*P*a) by the following formula:

$$\text{CSA } (P\text{a}) = \text{CSA max} \left[0.5 + \frac{1}{\pi} \arctan\left(\frac{Pa - Po}{P_1} \right) \right]$$

CSAmax is the maximal cross sectional area at a very high pressure; P_0 defines the position of the inflection point. P_1 defines the width between the point at one-half and

three-quarter amplitude. The measured CSA of the descending aorta is computed from the measured aortic diameter. The patient-dependent arctangent relation between pressure and CSA is next linearly scaled through the measured CSA (Fig. 7.1).

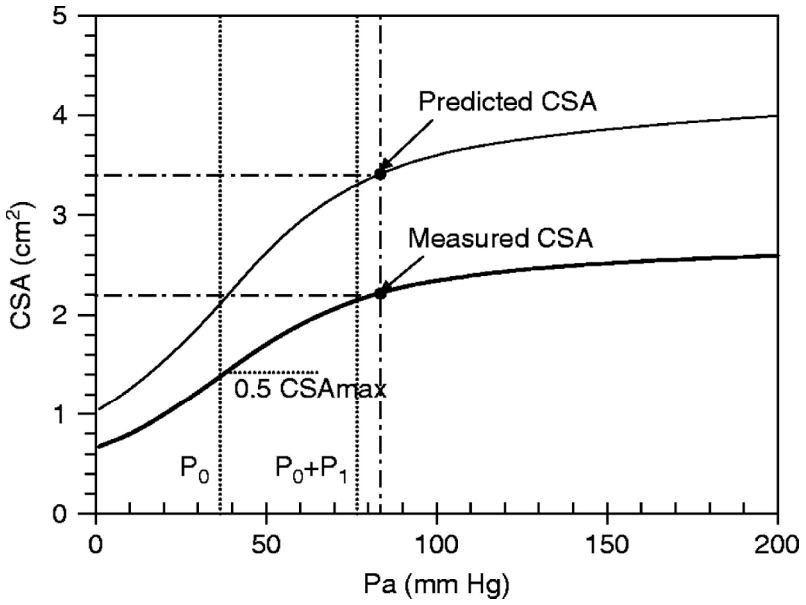

Figure 7.1 Pressure–area relationship. *P*a, arterial pressure; P_0, P_1, and CSAmax (for details see Methods). Thin line, predicted curve of a 59-yr-old female with a height of 160 cm and a weight of 48 kg. Solid line, corrected relation, scaled from the predicted diameter (20.7 mm) to the measured diameter (16.7 mm) at an arterial pressure of 82 mmHg.

Total systemic peripheral resistance is known only approximately from physiology. The uncertainty in this model parameter is removed as follows. For the first beat detected in the arterial pressure waveform a population average value for peripheral resistance is assumed in the model and mean arterial pressure and cardiac output is computed. The ratio of pressure to cardiac output for this first beat defines a new resistance value used in the model for the next beat, and so forth. Within 5 beats after start, usually, model resistance stabilizes to the systemic peripheral resistance value. The model follows changes in systemic peripheral resistance that further occurs. This self-adaptation scheme is possible because systemic peripheral resistance changes are slow, with time constant typically near 10 s.
Radial arterial pressure was taken from the monitor in use in the ICU, and HemoSonic 100 diameter was sampled by a computer system at 100 Hz and used as input to the model, to compute an aortic flow waveform. The flow waveform was integrated during arterial systole to deliver stroke volume. Cardiac output was computed for each beat as the product of stroke volume and heart rate. A detailed description of the computation can be found in previous papers.[1 3]

Measurement of aortic diameter Aortic diameter was obtained from the M-mode transducer of the oesophageal HemoSonic probe.[5] During probe positioning, first, best ultrasound signal quality was adjusted by rotation of the probe using the acoustic and visual Doppler signal. Secondly, the M-mode transducer was rotated giving the largest distance between anterior and posterior wall, is diameter, of the descending aorta.

After operator validation and adjustment of the edge detection of the anterior and posterior wall of the aorta, the measurement of the diameter is then automatically and continuously followed by the instrument, and displayed on the screen. A chest X-ray was taken to check the position of the probe.

Thermodilution method To improve the accuracy of the thermodilution method, measurements were performed with an automated system under computer control,[3 8-10] and included an injectate system (CO-SET, Edwards, Irvine, CA, USA), a proprietary, motor driven injectate syringe, a PAC (Edwards) and a cardiac output computer (COM2, Edwards).
Cardiac output was estimated four times, each measurement initiated in a different phase of the ventilatory cycle. Hence, each injection of 10 ml of glucose at room temperature was delayed from the start of the ventilatory period over either: 0, 25, 50, or 75% of the duration of the ventilatory cycle. The start of the ventilatory cycle and the cycle time were detected from the tracheal pressure waveform. The four cardiac output measurements were averaged to obtain one single value for averaged cardiac output. For this technique to work optimally, the hemodynamic and ventilatory frequency must be stable during the series.[11]

Data acquisition and analysis The best position of the ultrasound probe was checked shortly before the determination of mean cardiac output by performing one series of four thermodilution measurements. During this series of four measurements the position of the probe was not changed. As cardiac output in a patient can be quite variable it is important to acquire the data of each method simultaneously. Therefore, the data of arterial pressure, thermodilution cardiac output and aortic diameter was stored on computer disk, simultaneously. To obtain one single data pair per series, Modelflow cardiac output (COmf and COmfc) and thermodilution cardiac output (COtd) are averaged over the same period of time. Hemodynamic stability was verified by analysis of mean arterial pressure and heart rate (not cardiac output) during a series. Stability was considered absent if mean arterial pressure and heart rate averaged per injection deviate more than 5% from their overall average during a series.[3] Severe, persistent arrhythmias during passage of thermal indicator was additionally considered as absence of stability. If stability was not present, the series were repeated as one prerequisite for a precision comparison had not been fulfilled.

Statistical analyses The main statistical tool is the Bland–Altman analysis with differences in data pairs plotted against their average.[12] Agreement between Modelflow and thermodilution cardiac output was computed as the bias [mean (SD)], with limits of agreement computed as bias ± 2SD when the distribution of differences was normal as tested with the Kolmogorov - Smirnov test. The coefficient of variation was computed as [CV = (SD/mean) x 100%]. Data are given as mean (SD). Statistical significance was considered present if $P < 0.05$.

Results

Twenty-four paired sets of data were obtained in 24 patients. Individual thermodilution cardiac output measurements indicated a certain scatter within some series of four measurements, but no measurement was rejected. In all patients we were able to obtain a measure of the diameter of the aorta with the HemoSonic 100. In one

patient, with acromegaly, the measured diameter of 42.0 mm was used although it was not within the HemoSonic specified measurement range.
Table 7.1 summarizes the patient data and selected hemodynamic variables. These include thermodilution cardiac output and the differences between Modelflow and thermodilution cardiac output before and after diameter-calibration. The mean calibration factor of all patients was 0.99 and not significantly different from 1.00, $P > 0.05$.

Table 7.1 Patient characteristics and haemodynamic data.

Variable	Units	Mean	SD	Range
Age	Yr	61	12	35 - 79
Height	Cm	173	8	160 - 186
Weight	Kg	81	14	48 - 118
MAP	mmHg	91	16	70 -126
PAP	mmHg	22	5	15 - 30
CVP	mmHg	10	4	4 - 17
HR	min^{-1}	81	14	50 - 108
COtd	litre min^{-1}	5.43	1.23	3.11 to 8.82
COmf-COtd	litre mn^{-1}	-0.37	1.58	-4.45 to 4.48
COmfc-COtd	litre min^{-1}	-0.08	0.70	-1.41 to 1.08

MAP, mean arterial pressure; PAP, mean pulmonary artery pressure; CVP, central venous pressure; HR, heart rate; COtd, thermodilution cardiac output; COmf–COtd, difference between un-calibrated model and thermodilution cardiac output; COmfc–COtd, difference between calibrated model and thermodilution cardiac output.

The cardiac output bias of -0.37 litre min^{-1} before calibration decreased to -0.08, and are both not significantly different from 0.00, $P > 0.05$. The SD of the difference of 1.58 litre min^{-1} is halved after calibration to 0.70 litre min^{-1}.

Figure 7.2 shows un-calibrated and diameter-calibrated Modelflow *vs* thermodilution cardiac output. In the scatter diagram, upper panel, the line of identity is given. Least square regression of COtd *vs* COmf gave $y = 1.09$ x [95% confidence interval (CI) 0.96 to1.22], $R^2 = 0.15$ and of COtd *vs* COmfc gave $y = 1.02$ x (95% CI 0.96 to 1.08), $R^2 = 0.69$. The Bland–Altman analyses showed the limits of agreement of the un-calibrated COmf (-3.53 to 2.79, bias = 0.37 litre min^{-1}) and of the diameter-calibrated method (-1.48 to 1.32, bias = -0.08 litre min^{-1}). Two extreme values can be observed in Figure 7.2 (3.15 and -4.45 litre min^{-1}), one in the male patient with acromegaly and an aorta diameter of 42.0 mm and the other in a small lady with an aortic diameter of 16.7 mm. After calibration of Modelflow with the diameters measured by the HemoSonic system the differences became much smaller, 0.05 and -1.41 litre min^{-1}, respectively.

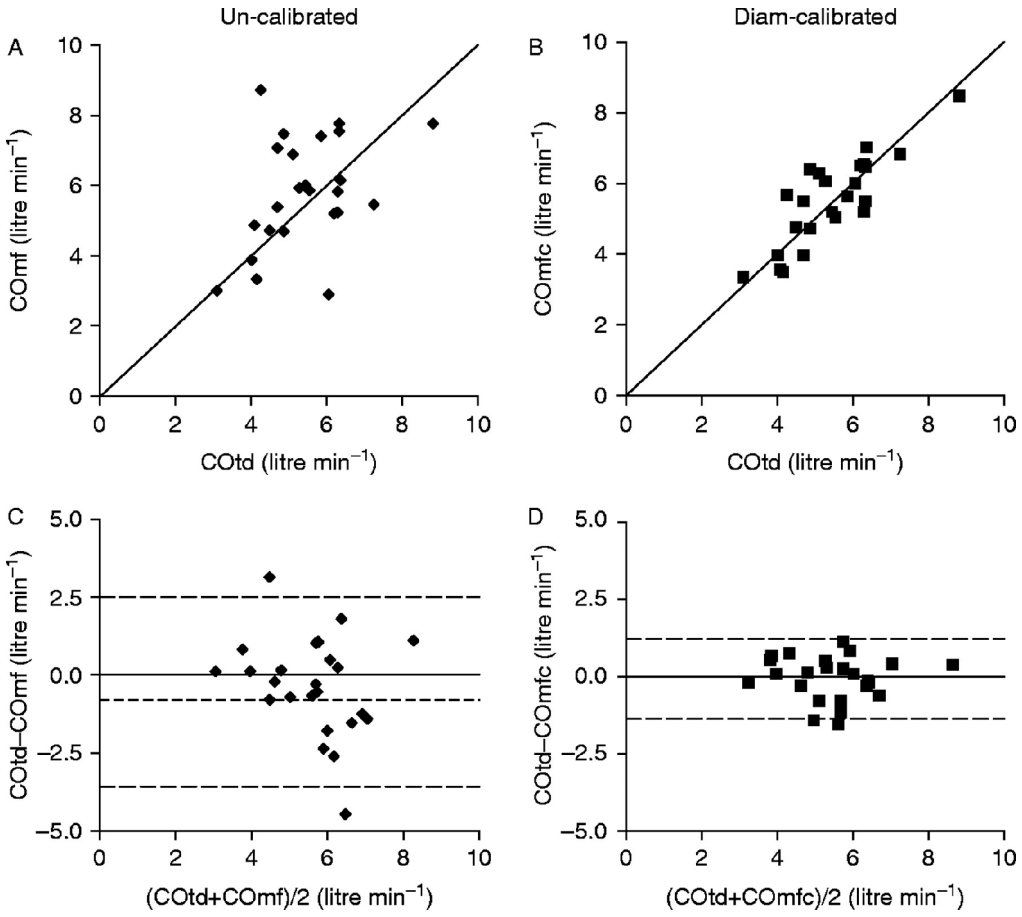

Figure 7.2 Diagrams showing the data pairs of all 24 patients before (left) and after (right) diameter (diam) calibration. In the scatter diagrams (A and B), the line of identity is given. The dashed lines in the Bland–Altman plots (C and D), indicate bias (–7 and 1%) and limits of agreement (–62 to +50% and –27 to 24%).

Discussion

In a previous study we found the Modelflow method can reliably track directional changes in thermodilution cardiac output larger than 0.5 litre·min^{-1}.[3] Cardiac output can be monitored quantitatively and continuously with little error by the Modelflow method only after an initial calibration to adapt the model to the individual patient. This study explored the feasibility to perform this initial calibration with a measurement of the aortic diameter in each patient. We found that the cardiac output values obtained with this adapted Modelflow method agreed with the mean of four bolus-thermodilution measurements equally spread over the ventilatory cycle.

HemoSonic A proper positioning of the M-mode echo probe is crucial. Therefore, to gain experience in using the HemoSonic 100, we underwent training, by the developers of this ultrasound device, followed by a learning population of six patients. Data of these patients were not included in this study. Despite such training, the aortic

walls could not always be automatically identified unambiguously by the edge detecting of the HemoSonic 100. To overcome the problem we regularly needed to change the edge detection window manually. This was especially so in patients with aortic valve replacement. In these patients, the anterior wall was often seen at a larger distance from the probe due to oedema between the oesophagus and the aorta. In addition, the acoustical energy absorbed by the oedema results in a less pronounced edge of the posterior wall.

Model calibration How the properties of the aorta depend on age, gender, pressure, and arteriosclerosis are well understood. We are, however, still left with the individual aortic diameter at maximal pressure, which may vary up to ± 30% from the population average.[4] Therefore, the absolute value of cardiac output cannot be computed with certainty. In contrast, changes in cardiac output can be detected with precision.[3] If we calibrate (scale) the parameter of the maximal CSA of the aorta with the quotient between predicted CSA and measured CSA at the mean arterial pressure during the comparison, the agreement between model calculated cardiac output and measured thermodilution cardiac output improved significantly. This was most explicitly demonstrated in the patient with acromegaly, where we found a model predicted diameter of 29.2 mm, and when measured with the echo probe, a diameter of 42.0 mm. After diameter-calibrating the Modelflow (calibrated = CSA-measured/CSA-predicted = 2.06), the computed cardiac output value increased from 2.90 to 6.01 litre min^{-1} and the difference between thermodilution and the model calculated cardiac output decreased from 3.15 to 0.05 litre min^{-1}. This patient-case illustrates the advantage of a direct measure of the aortic diameter with the HemoSonic 100, above a predicted diameter.

Error analysis Critchley and Critchley[13] stated that if a new method is to replace an older, established method, the new method should have not greater errors than the older method. Thermodilution is the reference cardiac output in almost all studies, as in the present one. A standard single thermodilution estimate of cardiac output has a coefficient of variation, further called error, of 15–20%.[11] A triplicate, randomly injected thermodilution has an error of 10% as the result of averaging.[11] The model mean error after diameter-calibration for the difference between methods is near zero (Table 7.1). Thus, only the scatter errors of thermodilution and Modelflow remain. They are statistically independent because the methods are based on different physical principles. The error that we found between the calibrated model and thermodilution is approximately 12% (Table 7.1). Our reference cardiac output only has a 5% error.[9] [10] Therefore, we may conclude that our calibrated model cardiac output has an error of $\sqrt{12^2 - 5^2} = 11\%$. This is not as good as a triplicate phase spread thermodilution (11 *vs* 5%),[11] but it is close to the most commonly performed mean of a triplicate random thermodilution method (10 *vs* 11%), and thus might replace it.[1]

Position of the model method In recent years, several studies based on different pulse contour models have attempted to provide reliable continuous cardiac output from the systemic arterial pressure. The method, proposed by Romano and Pistolesi,[14] based on real time extraction of the model parameters was tested in 22 patients. The error for the difference between cardiac output by their pulse contour method and thermodilution is approximately 13%. Linton and Linton[15] found an error of approximately 12% for the difference between their pulse contour method and thermodilution cardiac output, this after calibration with one series of thermodilution

cardiac output. Another pulse contour method based on the Windkessel model, however, with no dependency of model parameters on gender and age, has been build into the PiCCO device (Pulsion Medical Systems, Munich, Germany). Conflicting results were reported by various authors[16-18] using this simplified Windkessel model. Rauch and colleagues [17] demonstrated, after one initial calibration of the PiCCO system with a series of transpulmonary thermodilution measurements, that pulse contour cardiac output differs from thermodilution cardiac output by approximately 20% whereas others reported found values of 16 [18] and 10%.[16] In a former study [3] we used the averaged result of one series of four thermodilution measurements equally spread over the ventilatory cycle to calibrate Modelflow and found a probability error of 7% for Modelflow. Furthermore, it has been shown that one calibration of the Modelflow method was adequate for more than 48 hrs of monitoring in ICU patients.[2] In this study we calibrated Modelflow cardiac output by a measure of aortic diameter once per patient. Similar to calibration of Modelflow by thermodilution,[2] we expect that one calibration is adequate for more than 48 hrs of cardiac output monitoring. If we compare the results of our study to that of other pulse contour methods such as mentioned above, we found a similar error of comparison (12%). However, Modelflow calibrated by thermodilution measurements equally spread over the ventilatory cycle outperforms the other pulse contour methods. Therefore, if a patient is already equipped with a thermodilution catheter, we consider calibration by thermodilution preferable above diameter-calibration. In addition, diameter-calibration of Modelflow requires a trained operator to position the ultrasound probe whereas our thermodilution method runs under computer control and no extra training is needed.

Invasiveness The pressure that determines cardiac output is proximal aortic pressure, which is not routinely available. Although the model simulated blood flow shape from the radial artery pressure differs considerably from the one simulated from the pressure measured in the proximal aorta, the computed stroke volume was found to be not different.[1] In our ICU, almost all patients have a radial artery pressure monitoring system. Notwithstanding the calibration of our new method by measuring the aortic diameter with the transoesophageal M-mode ultrasound system, our new method can be considered as less invasive than other methods using indicator dilution methods to calibrate.

Conclusion

Previously, we showed the ability of Modelflow to continuously monitor changes in cardiac output.[3] After diameter-calibration, the improved Modelflow pulse contour method reliably estimates cardiac output without the need of a calibration with thermodilution, leading to a less invasive cardiac output monitoring method.

Declaration of interest ARROW International provided the equipment for this study. One of the authors (J.S.) is a consultant to this company.

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Chapter 8

A Comparison of Stroke Volume Variation measured by the LiDCO-plus and FloTrac-Vigileo system

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Summary
Background The aim of the study was to compare the accuracy of stroke volume variation (SVV) measured by the LiDCOplus system (SVVli) (LiDCO Ltd., Cambridge, UK) (SVVli) and by the FloTrac-Vigileo system (SVVed) (Edwards Lifesciences, Irvine, CA, USA).
Methods In fifteen postoperative cardiac surgical patients SVVli and SVVed was measured after; a 50% increase in tidal volume (VT), an increase of PEEP with 10 cm H_2O, passive legs raising (PLR), a head-up tilt procedure (HUT), and after fluid loading (FL). Between these applied study interventions baseline measurements were performed.
Results 136 data pairs were obtained. SVVli ranged from 1.4 to 26.8%, average 8.7 ± 4.6%, SVVed from 2.0 to 26.0%, average 10.2 ± 4.7%. The bias is significantly different from zero, 1.5 ± 2.5%, $p < 0.001$, (95% confidence interval 1.1 to 1.9). The upper and lower limits of agreement are 6.4 and -3.5%. The coefficient of variation for the differences between SVVli and SVVed is 26%. This result in a relative large range for the limits of agreement, expressed in percentages, is 52%. Analysis of repeated measurements shows a coefficient of variation of 21 and 22% for SVVli and SVVed, respectively.
Conclusion The LiDCOplus and FloTrac-Vigileo system are not interchangeable. Furthermore, the determination of SVVli and SVVed are too ambiguous, as can be concluded from the high values of the coefficient of variation for repeated measurements. These findings underlines Pinsky's warning to be careful in the clinical use of SVV by pulse contour techniques.

Introduction

With the introduction of continuous cardiac output measurement by arterial pulse contour analysis, real time measurement of stroke volume (SV) stroke volume variation (SVV) and pulse pressure variation (PPV) during mechanical ventilation was introduced in clinical practice. Most studies showed, SVV and PPV to be a good indicators of fluid responsiveness [1-3]. However, in two separate publications [4, 5] Pinsky advised caution in the clinical use of SVV based on the fact that beat-to-beat SV by the pulse contour technique has not been validated to monitor rapid changes in SV, as occur within a single breath. This is further complicated by the use of different algorithms to calculate SV and SVV by different monitoring systems. In this light, a clinical validation study on SVV seems important.
Aim of our study was to compare SVV estimates by the LiDCOplus system (SVVli) (LiDCO Ltd. Cambridge, UK) with SVV estimates by the FloTrac-Vigileo system (SVVed) (Edwards Lifesciences, Irvine, CA, USA) in post operative cardiac surgery patients. To induce changes in SVV we applied 6 different conditions to these study subjects; measurements in supine or baseline position, after an increase of tidal volume (VT), an increase in level of PEEP, after head up tilt procedure (HUT), during passive leg raising (PLR) and ater fluid loading (FL). Effects of these interventions on SVVli and SVVed, were compared with simultaneously measured PPV and bolus thermodilution cardiac output (COtd).

Methods

After approval of the study protocol by the University Medical Ethics committee**,** fifteen patients were studied after coronary arterial bypass grafting with or without

mitral valve repair. The study was conducted according to the principles of the Helsinki declaration and written informed consent was obtained from all patients the day before surgery. All patients had symptomatic coronary artery disease without previous myocardial infarction and were on β-adrenergic blocking medication. Patients with a history of abnormal ventricular function, aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiencies were not considered for this study. Patients with postoperative severe arrhythmia or the necessity for artificial pacing or heart assist devices were also excluded.
All patients were included in the study during their initial post-operative period in the ICU. Anesthesia during surgery and ICU-stay was maintained with propofol (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$), sufentanil (0.06-0.20 $mg \cdot kg^{-1} \cdot h^{-1}$) and vasoactive medication according to institutional standards. The lungs were mechanically ventilated (EVITA 4, Dräger AG, Lübeck, Germany) in a volume-control mode with settings aimed to achieve normocapnia with a tidal volume of 8-12 $ml \cdot kg^{-1}$ and a respiratory frequency of 12-14 $breaths \cdot min^{-1}$. Fraction of inspired oxygen was 0.4 and PEEP 5 cmH_2O. During the observation period sedation and vasoactive medication, when used, were unchanged.

Measurements
Measurements started in the postoperative period. Prior to ICU admission, all patients were catheterized with a 20G radial artery catheter (RA 04220, Arrow Int., Reading, PA, USA) to monitor arterial pressure (Pa) and a pulmonary artery catheter (139HF75P, Edwards Lifesciences, Irvine, CA, USA) introduced via the right jugular vein to monitor central venous pressure (CVP), pulmonary artery pressure (PAP) and to estimate cardiac output (CO) by the intermittent thermodilution method (COtd).
The radial artery pressure (Pa), derived via the radial artery catheter was measured with a FloTrac pressure transducer (Edwards Lifesciences). Of the bifurcated cable, one limb was connected to the Vigileo system (Edwards Lifesciences, software version v1.07) to measure pulse contour cardiac output and SVVed and the other limb was connected to a bedside monitor pressure module Hewlett Packard model M1006A, (Hewlett Packard Company, Palo Alto, CO, USA) of which the output signal was used as input signal for the LiDCOplus pulse contour system to deliver cardiac output, pulse pressure variation (PPVli) and SVVli. Detailed information about both pulse contour techniques can be found in recent literature [6-9]. Pa, PAP and CVP, were recorded online on computer disk for documentation and offline calculations. Pa, PAP and CVP transducers were referenced to the intersection of the anterior axillar line and 5^{th} intercostal space. After changes in position of the patient the transducers were re-referenced. Airway pressure (Paw) was measured at the proximal end of the endotracheal tube with an air-filled catheter connected to a pressure transducer. Paw was balanced at zero level against ambient air.
We calibrated the LiDCOplus system with 3 thermodilution cardiac output measurements at start of the observation period. The FloTrac-Vigileo system used its internal auto-calibration. From the beat-to-beat cardiac output values with the LiDCOplus and FloTrac-Vigileo system, stroke volume (SVli and SVed), stroke volume variation (SVVli and SVVed) and pulse pressure variation (PPVli) were determined. SVV and PPV were calculated over 20 second periods of Pa data.

Study protocol
To induce changes in CO, SVV and PPV, and evaluating clinical relevance, measurements were performed during baseline in supine position, after increased tidal volume (+50%) (VT), during increased PEEP (+10 cm H_2O), during passive leg

raising (PLR) of both legs with 30 degrees , during 30 degrees head up tilting (HUT) and in supine position after fluid loading (FL) with 500 ml Hydroxyethyl Starch (HES 130/0.4) in 15 minutes. Between study interventions, baseline conditions were re-established. Measurements of MAP, HR, COtd, SVVli, SVVed and PPV, from the Pa signal, were collected during each study period, 2 minutes after the change in study intervention, and between study interventions at baseline. The study protocol lasted about 90 minutes where after sedation was stopped and weaning procedures were started. During the protocol we encountered no adverse events. All patients were discharged from the intensive care unit on the first postoperative day.

Statistical analysis

After confirming a normal distribution of data with the Kolmogorov – Smirnov test, differences between SVVed and SVVli during study interventions and baseline were analyzed using a paired t-test. Values of SVV and changes in SVV based on interventions and devices are analysed with factorial ANOVA. Calculations of bias and precision and limits of agreement between SVVed and SVVli are performed using Bland-Altman analysis [10]. In which bias is the difference between SVVli and SVVed and precision the standard deviation (SD) of this difference. The upper and lower limits of agreement are calculated as the bias ± 2·SD. The coefficient of variation (CV) is calculated as 100%·SD/mean (SVVli and SVVed). The percentage limits of agreement are calculated as 2·CV. A p-value < 0.05 was considered statistically significant. Unless otherwise stated, data are presented as mean (SD).

Results

In fifteen post operative cardiac surgical patients, gender; male/female 12/3, mean age 66 (range 55 to 82) years, mean BSA 1.98 ± 0.20 m^2, were included. Only 8 patients received fluid loading. A total of 136 paired data sets were obtained. The data was normally distributed. COtd ranged from 2.6 to 7.7 with an average of 5.0 ± 1.1 $L.min^{-1}$. HR ranged from 54 to 92, average was 75 ± 8 min^{-1}. SVVli ranged from 1.4 and 26.8%, average 8.7 ± 4.6%, SVVed from 2.0 to 26.0%, average 10.2 ± 4.7% and PPVli from 1.9 to 25.3, average 8.8 ± 4.7%.

Agreement of SVVli and SVVed

Bland-Altman statistics are indicated in the figure by bias and limits of agreement (LOA). The bias is significantly different from zero, 1.5 ± 2.5%, p < 0.001, (95% confidence interval 1.1 to 1.9). The upper and lower limits of agreement are 6.4 and -3.5%.Coefficient of vanriance for the differences between SVVli and SVVed is 26%. This result in a large range for (error-percentage) limits of agreement of 52% (2·CV). The error diagram for difference between SVVli and SVVed is shown in figure 8.1.

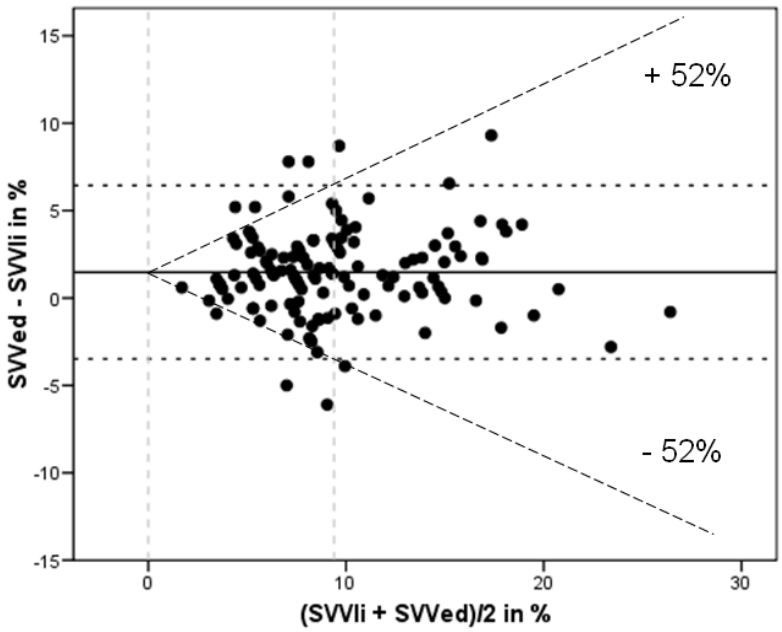

Figure 8.1 Bland-Altman plot (pooled data), representing agreement between stroke volume variation (SVV) by the LiDCO system (SVVli) and by Edwards FloTrac-Vigileo system (SVVed). The solid line represents the bias and the dotted lines the limits of agreement, dashed lines the limits of agreement in percentage.

Interventions

COtd, HR, PPVli, SVVli and SVVed as well as the differences between SVVli and SVVed for the different experimental conditions are presented in table 8.1. With Factorial ANOVA the main effects on SVV values related to the measurement techniques was ($F = 14.49$, $p = 0.02$), and related to the interventions was ($F = 8.29$, $p < 0.001$). Differences between SVV measurement methods were consistent across all interventions ($F = 1.54$, $p = 0.142$). One-way ANOVA statistics showed no significant difference between the five baseline measurements for COtd ($F = 0.203$, $p = 0.936$), HR ($F = 0.094$, $p = 0.984$), PPVli ($F = 0.184$, $p = 0.946$), SVVli ($F = 0.254$, $p = 0.906$) and SVVed ($F = 0.390$, $p = 0.815$) expressing that there were no significant effects over time. On average VT showed no change in COtd and an increase in PPVli, SVVli and SVVed; PEEP and HUT decreased COtd and increased PPVli, SVVli and SVVed whereas PLR and FL increase COtd and decreased PPVli, SVVli and SVVed. Heart rate did not change during study interventions. When analyzing our observations as repeated measures, analysis showed the following coefficient of variation, for PPVli = 23%, SVVli = 21% and SVVed = 22%.

Discussion

We found SVVli and SVVed to differ significantly. With percentage limits of agreement of 52% we conclude that the LiDCOplus and FloTrac-Vigileo devices are not interchangeable. Furthermore, the determination of SVVli and SVVed appeared to be ambiguously as can be concluded from the high value of coefficient of variation

(21 and 22%) for repeated measurements. These findings underlines Pinsky's warning to be careful in the clinical use of SVV by pulse contour techniques [5].

The significant mean difference between SVV measured by the LiDCO and FloTrac-Vigileo device is most probably not caused by the calculation of SVV because both systems use a similar computation i.e. SVV = 100·(SVmax – SVmin)/SVmean. Therefore, most likely, it must be explained by the difference in the calculation of SVmin, SV max and SVmean by the two systems. The main difference in computation of SV is based on the correction for individual arterial compliance. The LiDCO system uses a pressure dependent correction for compliance based on Remington's equations [11] whereas the FloTrac-Vigileo uses Langewouter's equations [12]. There is a large similarity between the computations of SV, figure 8.2. With both systems these equations lead to a diminished SV at higher pressure levels compared to lower pressure levels with the same arterial pressure curve. However, this correction for compliance may differ between the two systems. A difference in calibration between the two systems has no influence on SVV, indeed, assuming a calibration constant k leads to SVV = 100 (k·SVmax – k·SVmin)/ k·SVmean. With k in the nominator and denominator the calibration factor is ruled out in the determination of SVV.
In a recent paper Hofer et al. [13] compared the FloTrac-Vigileo and the PiCCOplus system for assessment of SVV to predict fluid responsiveness. The authors concluded for similar performance of the two systems. Although, the SVV threshold level of predicting fluid responsiveness, by the PiCCO system (12.1%) and FloTrac-Vigileo system (9.6%), differ.
Not confirmed by the small number of patients in our study, but based on similarity of their study with ours, and our results, we predict different threshold levels for the LiDCO and FloTrac-Vigileo system, as well.

Besides the difference in mean SVV we observed a wide range of the percentage limits of agreement (52%) between the two systems. This wide range for the percentage limits of agreement can be observed also in two recent papers [13, 14].

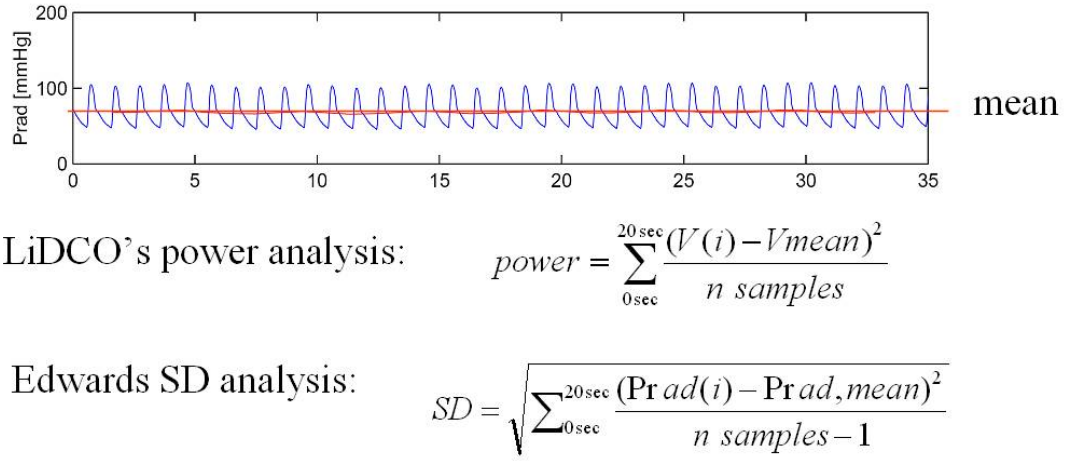

Figure 8.2 Similarity of calculation of cardiac output by the LiDCO system and by Edwards FloTrac-Vigileo system. Arterial volume (V) changes derived after transformation of the radial artery pressure (P_{rad}) with Remington's equations. Edward's corrects cardiac output after SD calculation with Langewouter's equation.

Table 8.1 Differences in cardiac output, heart rate (HR), pulse pressure variation (PPV) and stroke volume variation (SVV) at interventions.

Intervention	Cardiac Output	Heart rate	PPV	SVVli	SVVed	Difference SVVed-SVVli	Coefficient of variation	SVV difference
	$L.min^{-1}$	$Beats.min^{-1}$	(%)	(%)	(%)	(%)	(%)	*p*-value*
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD			
Baseline 1	4.9 ± 1.0	76 ± 7	7.9 ± 4.3	7.8 ± 3.4	9.4 ± 3.9	1.6 ± 1.7	20	0.003
VT	4.9 ± 1.0	78 ± 9	11.2 ± 5.6	10.6 ± 5.8	12.9 ± 6.5	2.3 ± 2.9	24	0.009
Baseline 2	5.1 ± 0.9	74 ± 8	7.5 ± 3.6	7.6 ± 3.0	8.5 ± 3.3	1.0 ± 2.4	30	0.134
PEEP	4.3 ± 1.1	75 ± 8	12.4 ± 5.8	12.4 ± 5.6	13.3 ± 5.0	0.9 ± 2.4	19	0.171
Baseline 3	5.2 ± 0.9	75 ± 7	7.7 ± 3.7	7.6 ± 2.9	8.9 ± 3.4	1.7 ± 1.9	34	0.010
PLR	5.4 ± 1.0	74 ± 8	6.5 ± 3.3	5.9 ± 2.8	8.7 ± 3.1	2.9 ± 3.2	44	0.004
Baseline 4	5.2 ± 1.0	75 ± 8	8.5 ± 3.9	8.3 ± 4.2	10.0 ± 4.1	1.7 ± 1.9	21	0.004
HUT	4.9 ± 1.0	75 ± 9	9.7 ± 5.0	10.8 ± 4.5	11.6 ± 8.3	0.8 ± 2.9	26	0.287
Baseline 5	4.9 ± 1.3	75 ± 11	8.6 ± 4.0	9.0 ± 6.1	10.1 ± 5.4	1.2 ± 1.9	20	0.009
FL	5.6 ± 1.2	74 ± 12	6.7 ± 4.0	5.9 ± 2.9	6.5 ± 3.3	0.7 ± 1.0	15	0.095

The interventions are; increase of tidal volume with 50%(VT); increase in PEEP with 10 cm H_2O (PEEP); passive leg raising (PLR); head-up tilt (HUT) and fluid loading (FL); Method of measurement: SVV LiDCO system (SVVli), SVV FloTrac-Vigileo system (SVVed). Statistic analysis paired T-test (*).

From the results of Hofer et al. [13] we calculated percentage limits of agreement of 40% during 30^{o} head up-position and 42% during 30^{o} head-down position. Also in the paper of de Castro et al. [14], comparing SVV measured by the PiCCOplus system with SVV measured by aortic Doppler echocardiography, a wide ranged for the percentage limits of agreement of approximately 40% can be observed. Given these margins of error, we concluded that none of these systems is interchangeable with one of the others. Furthermore, it seems that the calculation of SVV is prone to propagation of errors in the calculation of SVV [14]. This is supported by the high coefficient of variation for repeated measurements of SVVli of 21% and SVVed of 22% in our study. This fluctuation can also be seen on the display of both monitor systems by the frequent changes in SVV value. The reason for these fluctuations is still unclear. As the errors in the measurements of SVVli and SVVed are not completely independent we cannot estimate the coefficient of variation for the difference from the coefficient of variations of both systems. The coefficient of variation for the difference may vary between 1 and 43%. The coefficient of variation found for the difference of 26%, is in range with these numbers.
Nevertheless the above, the changes in SVV induced by our interventions are in concordance with what was expected (Table 8.1). During the increase in tidal volume we observe, in comparison to baseline, no change in cardiac output but an increase in SVV. A similar increase in SVV to the increase of VT was observed by Kim and Pinsky [15] in a well controlled animal study. During PEEP and head up position CO decreased and SVV increased and during passive leg raising and after fluid loading we observed an increase in CO and decrease in SVV with both systems. However, the difference between SVVli and SVVed fluctuates considerably.
Despite these shortcomings, SVV seems a variable of considerable interest. Several authors have shown that SVV can predict the effects of fluid loading on cardiac output, however with different thresholds ranging from 9.5 to 12.5% to separate responder and non responders [13, 16-18]. Although there is no reason to doubt about the general principle of SVV as predictor of fluid responsiveness, we conclude from our results that some precaution in the use of SVV in an individual patient is justified. Indeed, based on Bland-Altman analysis for repeated measurements for SVV with percentage limits of agreement, the value of SVV may differ up to approximately 40% between measurements. Taking in mind a stable condition with at a certain moment in time we measure a SVV of 10%, a moment later in time this value may be 14% and an at another moment 6%. With SVV = 14% one may conclude for fluid loading to improve cardiac output, whereas with 6% one may conclude for catecholamines.

Conclusions

SVVli and SVVed differ significantly. With a percentage limits of agreement of 52% the two methods do not agree and cannot be used interchangeably. Furthermore, the determination of SVVli and SVVed appeared to be ambiguously as can be concluded from the high value of coefficient of variation (21 and 22%) for repeated measurements. These findings limit clinical use in individual patients and limit the comparability of fluid loading responsiveness results between different studies.

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Chapter 9

Summary and conclusions

Samenvatting en conclusies

Summary

Chapter 1
Accurate clinical assessment of the circulatory status is particular desirable in critically ill patients in the intensive care unit (ICU) and patients undergoing cardiac, thoracic, or vascular interventions. As the patient's haemodynamic status may change rapidly, continuous monitoring of cardiac output will provide information allowing rapid adjustment of therapy.
Aim of this thesis is an overview and evaluation with respect to less invasive cardiac output measurement and monitoring systems, especially the pulse contour technique.
The introduction highlights historical and physiological aspects of cardiac output measurement and effect of respiratory changes on blood flow and pressure. Secondly it introduces methodological aspects of measurement, with attention to the reference method and analysis of agreement.

Chapter 2
Because pulse contour cardiac output is derived from on the input signal from the arterial blood pressure, it can be deduced that the place of measurement could be of major interest to the results found. The shape of the arterial blood pressure signal depends on the location of measurement. In this context, it is useful to investigate whether and how cardiac output differs when radial or femoral blood pressure signals are used.
The first commercially available cardiac output monitoring systems based on the pulse contour method is the PiCCO-system. This system is prior to measurement to be calibrated (by transpulmonary thermodilution), requiring a central venous for bolus infusion and a thermistor tipped femoral catheter. Our study was performed to determine the interchangeability of femoral artery pressure and radial artery pressure as input of the PiCCO-system (Pulsion Medical Systems, Munich, Germany).
We studied fifteen intensive care patients after cardiac surgery. A five second averages of the cardiac output derive from the femoral artery pressure (COfem) were compared to 5 second averages derived from the radial artery pressure (COrad). The equality of the two PiCCO devices (A and B), used in this study, was confirmed in dataset of 1243 comparative cardiac output values (COfem), Figure 9.1a.
One patient was excluded from our study because of problems in the pattern recognition of the arterial pressure signal. In the remaining fourteen patients, 14734 comparative cardiac output values were analysed. The mean sample time was 88 min, range [30 - 119 min]. Mean (SD) COfem was 6.24 (1.1) $l.min^{-1}$ and mean COrad was 6.23 (1.1) $l.min^{-1}$.
We concluded that femoral artery pressure and radial artery pressure are interchangeable as input of the PiCCO device, allowing change to the radial artery pressure line if the preferred femoral artery pressure line is no longer available for use.

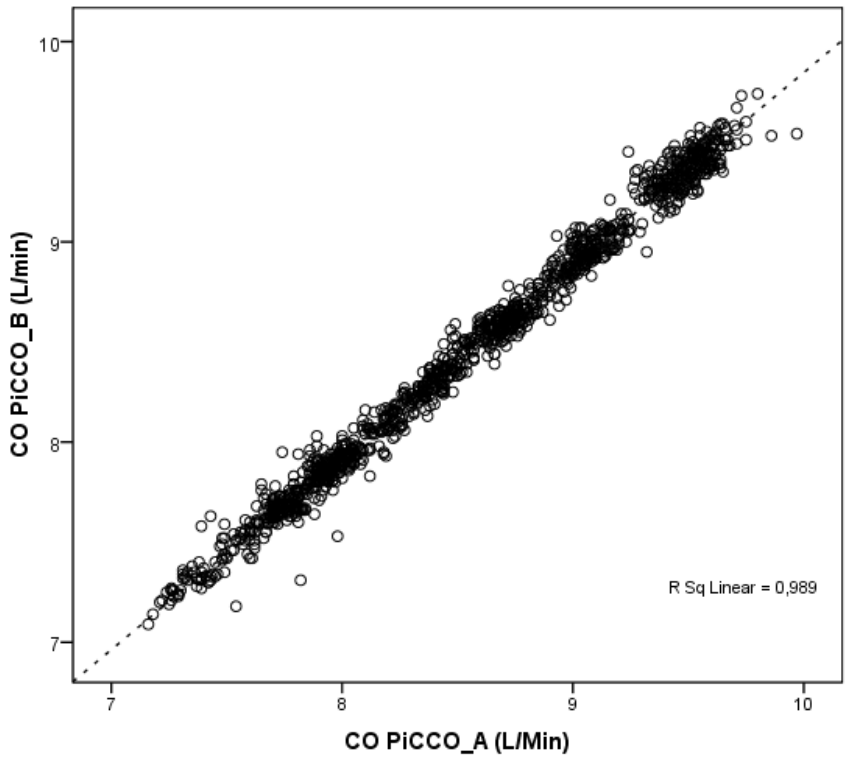

Fig. 9.1a. Analysis of two used PiCCO devices with linear regression. In analysis one data set used (N 1243) Values on X and Y axis are CO in L/min. Equation of linear regression is y = 0.99x, $r^2 = 0.99$

Chapter 3

Bias, precision and tracking ability of five different pulse contour methods were evaluated by simultaneous comparison of cardiac output values with that of the conventional intermittent thermodilution technique (COtd). The five different pulse contour methods enclosed in this study were: Wesseling's method (cZ); the Modelflow method; the PulseCO system (LiDCO Ltd., UK); the PiCCO system (Pulsion Medical Systems, Germany) and a recently developed Hemac method.

We studied twenty-four cardiac surgery patients undergoing uncomplicated coronary arterial bypass grafting. In each patient, the first series of COtd values was used to calibrate the five pulse contour methods. All pulse contour techniques need a reliable invasive calibration. After calibration, most methods may replace the thermodilution method with a precision of ≈ 10% (i.e. the averaged result of three randomly performed measurements). The Modelflow and Hemac technique even, might replace the thermodilution estimates based on the averaged result of four measurements done equally spread over the ventilatory cycle i.e. a precision of ≈ 5%. The slightly lower precision of the continuous pulse contour cardiac output techniques may compared to COtd, in clinical settings, be outweighed by the advantages of being automatic and continuous. However, under research conditions the use of conventional thermodilution method with four measurements equally spread over the ventilatory cycle remains the method of choice.

Due to the character of the examined study population, we need to emphasize that the findings of this study are restricted to patients without congestive heart failure, with normal heart rhythm and reasonable peripheral circulation.

Chapter 4

In a review we focus on the PiCCO device: the first widely available commercial system for measuring and monitoring of cardiac output by arterial pulse contour analysis. We described the basic principle of the device and the monitoring approach. Furthermore, we reviewed the main parameters and discussed the use as well as the limitations of this device in the light of our own experience.

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, stroke volume variation (SVV) or pulse pressure variation (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 literature, that measurement of global end diastolic volume index (GEDVI) and intrathoracic blood volume index (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.

Chapter 5

In 2006 a new pulse contour monitoring system was introduced by Edwards Lifesciences, (Irvine, CA USA), the FloTrac-Vigileo-system. Unlike the PiCCO and the PulseCO system this new monitoring system don't need to be calibrated, with an external calibration method. Because the challenging prospects in clinical practice, this un-calibrated pulse contour method, gained our interest and was entered in a study. In a first evaluation, we studied twenty-eight cardiothoracic surgical patients, after ICU admission**.** The performance of the new un-calibrated FloTrac-Vigileo system was compared with simultaneously obtained cardiac output values with Vigilance continuous pulmonary artery thermodilution, the calibrated PiCCOplus, and LiDCOplus. All systems were evaluated with the intermittent pulmonary artery thermodilution as reference method.

The number observation periods varied between 4 and 8 per patient. Data was collected during standard care. Data was analyzed with respect to bias and precision (classical Bland - Altman statistics), cardiac output changes and stability of calibration (drift). We concluded that the performance of pulse contour methods is significantly increased the last few years, which makes comparisons with older

publications invalid. The auto-calibrated FloTrac-Vigileo system can replace the ones calibrated LiDCO and PiCCO system. The Vigilance continuous thermodilution method agreed the best with bolus thermodilution and had the highest score in following slow changes in cardiac output. The auto calibrated FloTrac-Vigileo and the ones calibrated LiDCO system showed best performance in detecting beat-to-beat cardiac output changes.

Chapter 6

New developed cardiac output (CO) methods are preferred to be minimal invasive, or at least do not add supplementary invasive procedures for external calibration.

The only two candidate methologies available, compliance concordant with this demand are the ultrasound and pulse contour methods. In this chapter we evaluated the transesophageal ultrasound, HemoSonic 100 monitorsystem (ARROW International, USA), the un-calibrated Modelflow and the auto-calibrated FloTrac-Vigileo, from which the last two are both pulse contour systems.

In thirteen postoperative cardiac surgical patients paired CO values of these un-calibrated cardiac output monitoring methods were compared with intermittent pulmonary thermodilution cardiac output before, during and after four study interventions. These interventions were: tidal volume increase of 50%, increase of positive end expiratory pressure (PEEP) by 10 cmH_2O, passive leg raising (PLR) and head-up position (HUT) of the patient.

The un-calibrated Modelflow method showed best performance in estimation of cardiac output. Changes in cardiac output by thermodilution were tracked significantly by HemoSonic and un-calibrated Modelflow whereas auto-calibrated FloTrac-Vigileo overestimated the changes in cardiac output. Directional changes in cardiac output by thermodilution were detected with a high score by all three methods.

Chapter 7

Cardiac output by Modelflow pulse contour method can be monitored quantitatively and continuously only after an initial calibration, to adapt the model to an individual patient. The Modelflow method (COmf) computes beat-to-beat cardiac output from the radial artery pressure, by simulating a three-element model of aortic impedance with post-mortem data from human aortas. In an improved version of Modelflow (COmfc) we adapted this model to a real time measure of the aortic cross-sectional area (CSA) of the descending aorta just above the diaphragm, by a transoesophageal echo device (HemoSonic 100). The COmf and COmfc were compared with intermittent pulmonary thermodilution cardiac output in twenty-four patients in the intensive care unit. Each COtd value was the average cardiac output value of four intermittent pulmonary thermodilution cardiac output measurements equally spread over the ventilatory cycle.

After diameter-calibration, the improved Modelflow pulse contour method reliably estimates cardiac output without the need of a calibration with thermodilution, leading to a less invasive cardiac output monitoring method.

Chapter 8

With the introduction of continuous cardiac output measurement by arterial pulse contour analysis, real time measurement of stroke volume, and stroke volume variation (SVV) during mechanical ventilation was introduced in clinical practice. Studies showed, SVV to be a good indicator of fluid responsiveness. Only one study reported a lack of correlation between SVV and the response of the cardiac output to fluid loading. Pinsky, in two separate publications advised caution in the clinical use of SVV, he stated; "although validation of mean SV is adequate by the pulse contour technique, it is not been validated to monitor rapid changes in SV, which will occur over a single breath". This is further complicated by the fact that different algorithms are been used by different monitoring systems. In this light, clinical validation studies of SVV by various pulse contour monitoring systems seem important.

In this chapter we reported on a study aimed to compare left ventricular stroke volume variation measured by PulseCO (LiDCO) and FloTrac-Vigileo system (Edwards Lifesciences). After informed concent, all measurements were collected during standard clinical care in fifteen postoperative cardiac surgical patients. Clinical relevance of SVV was evaluated by enforced changes in left ventricular preload. Applied study interventions included an increase of tidal volume and the level of PEEP, passive leg raising (PLR), a tilt procedure of the patient (HUT), and volume loading (500 ml Voluven).

At baseline and study interventions SVV(LiDCO) and SVV(Edwards) differ significantly. With percentage limits of agreement of 52% (pooled data) the two methods do not agree and cannot be used interchangeably. Furthermore, the determination of SVV(LiDCO) and SVV(Edwards) appeared to be ambiguously as can be concluded from the high value of the coefficient of variance (21 and 22%) for repeated measurements. These findings limit clinical use in individual patients and limit the comparability of fluid loading responsiveness results between different studies.

Conclusions

- Intermittent pulmonary thermodilution cardiac output with pulmonary artery catheter was used as reference measurement in all studies without complications.
- The average value of cardiac output using four equally spread measurements over the ventilatory cycle, the error of measurement (calculated as coefficient of variation), was < 5%.
- Of the cardiac output measurement and monitoring systems, the arterial derived pulse contour, Modelflow performed best. The Modelflow and Hemac technique, can replace the thermodilution estimates based on the averaged result of four intermittent pulmonary thermodilution cardiac output measurements, equally spread over the ventilatory cycle.
- Considering stability of calibration or drift in time, the PulseCO system performed better than the than the PiCCO system and FloTrac-Vigileo system.
- In our studies, we included only cardiac surgical patients. Therefore study results may not be valid for other patient categories or an entire adult ICU-population. Validation studies using other groups of patients are warranted.

Samenvatting

Hoofdstuk 1
Nauwkeurige klinische beoordeling van de hemodynamische conditie is bijzonder wenselijk bij de ernstig zieke patiënten op de Intensive Care (IC) en patiënten in de direct postoperatieve fase. Deze hemodynamische conditie kan snel veranderen en zich openbaren als daling in bloeddruk en/of afname van de hoeveelheid bloed die door het hart per minuut uitgepompt kan worden (cardiac output). Continue bewaking van de cardiac output kan informatie verschaffen die aanpassing van de therapie mogelijk maakt.
Doel van dit proefschrift is een overzicht en evaluatie te geven van de minder invasieve cardiac output meet- en monitorsystemen, in het bijzonder de verschillende puls-contourmethoden die momenteel op de IC-afdelingen worden gebruikt.
In de introductie zullen historische en fysiologische aspecten van het meten van de cardiac output en de hart-longinteractie voor het voetlicht gebracht worden. Tevens wordt ingegaan op methodologische aspecten van de meting, met extra aandacht voor de referentiemethode en de analyse van de mate van overeenkomst tussen cardiac-outputmethoden.

Hoofdstuk 2
Puls contour cardiac output wordt afgeleid van het arteriële bloeddruksignaal (inputsignaal). Hierdoor zal de plaats van meten in de bloedsomloop van groot belang kunnen zijn voor de waarden van gevonden resultaten. De vorm van het arteriële bloeddruksignaal is immers afhankelijk van de plaats van meten. In dit kader is het zinvol om te onderzoeken of en hoe groot de cardiac-outputverschillen zijn als bloeddruksignalen van verschillende meetplaatsen gebruikt worden.
In dit hoofdstuk wordt de uitwisselbaarheid van arteria-femoralis- en arteria-radialisbloeddruk als inputsignaal van het PiCCO-systeem (Pulsion Medical Systems, München, Duitsland) getest.
We bestudeerden dit in vijftien IC-patiënten na een openhartoperatie. Gemiddelden van vijf opeenvolgende cardiac-outputwaarden van de arteria-femoralisdruk (COfem) werden vergeleken met waarden afgeleid van de arteria-radialisdruk (COrad). Voorafgaand aan het onderzoek werden de twee gebruikte monitoren met elkaar vergeleken door een identiek inputsignaal (COfem) te gebruiken. Met een testset van 1243 cardiac-outputwaarden vonden we een goede correlatie (Figuur 9.1b). Hieruit bleek dat de twee PiCCO-monitoren (A en B) de cardiac-outputwaarden identiek meten. Gegevens van één patiënt werden niet meegenomen in de evaluatie.
Bij de overgebleven veertien patiënten werden in totaal 14734 gelijktijdig opgenomen cardiac-outputwaarden (COfem en COrad) geanalyseerd. Hieruit bleek dat het bloeddruksignaal van de arteria femoralis en de arteria radialis als inputsignaal voor de PiCCO-monitor, uitwisselbaar zijn. Waarmee gesteld mag worden dat, indien de druklijn van de arteria femoralis niet (meer) beschikbaar is, cardiac output ook via de arteria radialis bepaald kan worden.

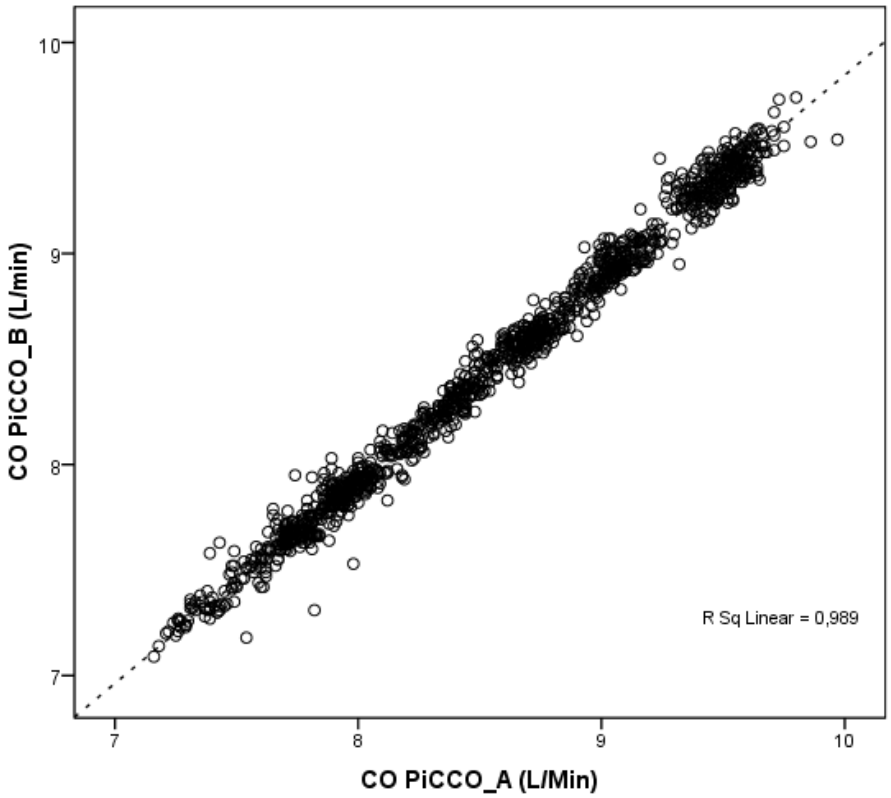

Fig. 9.1b. Analyse van de twee gebruikte PiCCO-apparaten met lineaire regressie. Analyse van een testset van 1243 cardiac-outputwaarden. De cardiac-outputwaarden (CO) van de X en Y-as worden weergegeven in L/min. Lineaire regressie $y = 0.99x$, $r^2 = 0.99$.

Hoofdstuk 3

Dit hoofdstuk beschrijft een studie waarbij de nauwkeurigheid en precisie van verschillende puls-contourmethoden van cardiac-outputmeting onderzocht werden. In deze studie werden gelijktijdig gemeten cardiac-outputwaarden vergeleken met de waarden van de conventionele thermodilutietechniek (COtd). De vijf verschillende puls-contourmethoden in deze studie waren: Wesseling-methode (cZ); de Modelflow-methode; het LiDCO-systeem; het PiCCO-systeem en een recent ontwikkelde puls-contourmethode, Hemac. We onderzochten cardiac-outputdata in vierentwintig patiënten die een ongecompliceerde coronaire arteriële bypassoperatie (CABG) hadden doorstaan. Bij elke patiënt werd de eerste reeks van COtd-waarden gebruikt voor kalibratie van de vijf bestudeerde puls-contourmethoden. Na kalibratie hebben we 199 gelijktijdig opgenomen cardiac-outputwaarden kunnen analyseren.

Uit onderzoek bleek dat na kalibratie de meeste onderzochte meetmethoden de referentiemethode (bolusthermodilutie, COtd) met een nauwkeurigheid van 10% konden vervangen. De Modelflow en Hemactechniek hadden een grotere precisie dan de andere puls-contourmethoden. Beiden konden de thermodilutiemethode, overeenkomend met het gemiddelde meetresultaat van vier metingen die gelijkmatig over de ademcyclus verdeeld zijn, vervangen. In het kader van onderzoek blijft de conventionele thermodilutiemethode, met vier gelijkmatig over de ademcyclus verdeelde metingen, de meetmethode van keuze. Echter de iets lagere nauwkeurigheid van de continue puls-contourtechniek wordt in de klinische setting mogelijk gecompenseerd door de voordelen van een automatische en continue waarneming.

Uitgaande van de eigenschappen van de onderzoekspopulatie, beklemtonen we dat de resultaten van deze studie beperkt kunnen zijn tot patiënten die leiden aan chronisch hartfalen met een normaal hartritme en zonder uitgebreide aandoeningen van het perifere vaatbed.

Hoofdstuk 4

In dit overzichtsartikel beschrijven we onze ervaringen met het PiCCO-systeem. Het PiCCO-systeem is het eerste commerciële systeem, gebaseerd op puls-contouranalyse, dat klinisch gebruikt werd voor het meten en monitoren van de cardiac output. We beschrijven de fundamentele beginselen van de meetmethode en de follow-up benadering. Bovendien bespreken we, in het licht van onze eigen ervaring, de belangrijkste secundaire parameters die naast arteriële bloeddruk en de cardiac output worden weergegeven. Uit de literatuur en uit onze eigen vergelijkende studies naar de verschillende puls-contourmeetmethoden van cardiac output zijn we tot de slotsom gekomen dat de nauwkeurigheid (bias), precisie (SD), als mede het volgen van veranderingen in de cardiac output van het PiCCO-systeem de mindere is in vergelijking met haar concurrenten. Tijdens het gebruik van het PiCCO-systeem werden een aantal technische en patiëntgerelateerde beperkingen blootgelegd. De technische beperkingen zijn in verband te brengen met i) een onjuiste indeling van de hartslag, ii) een verkeerde detectie van de ejectiefase van de hartcyclus, iii) dat geen oplossing geboden wordt ten aanzien van eventuele demping van het arteriële bloeddruksignaal, wat leidt tot onjuiste berekening van de cardiac output. Ook omdat slagvolumevariatie (SVV) en variatie van polsdruk (PPV) als dynamische parameters voor vulling alleen betrouwbaar gemeten kunnen worden bij beademende patiënten, zijn deze van beperkte waarde bij de groep postoperatieve thoraxchirurgische patiënten die wij onderzochten. Deze groep patiënten wordt immers na operatie vrij snel ontwend van de beademing. Tevens beschrijven we enkele patiëntgerelateerde problemen. Bij patiënten met uitgebreide perifere vaatafwijkingen en patiënten waarbij de hartfunctie tijdelijk ondersteund moet worden met een intra-aorta-ballonpomp, is bewaking met het PiCCO-systeem niet mogelijk en is de introductie van een arteriële katheter in de arteria femoralis zelfs gecontra-indiceerd. Naar onze ervaring en in overeenstemming met de literatuur, is het meten van volumetrische parameters als ‘Global Eind Diastolische Volume Index’ (GEDVI) en het ‘Intra Thoracaal Bloedvolume Index’ (ITBVI) bij patiënten met een vergroot hart, zoals het geval is bij ernstige cardiomyopathie, niet relevant. Bovendien hebben we, op basis van de achterliggende theorie, de indruk dat de nauwkeurigheid van deze parameters afhankelijk is van SVV. Uit het voorgaande zijn wij van mening dat het PiCCO-systeem van beperkte waarde is tijdens de postoperatieve bewaking bij de groep van thoraxchirurgische patiënten op de IC.

Hoofdstuk 5

In 2006 werd een nieuw puls-contourmethode geïntroduceerd welke niet geijkt hoeft te worden, met een externe kalibratiemethode. Ook deze ongekalibreerde puls-contourmethode, FloTrac-Vigileo (Edwards Lifesciences, Irvine, CA, USA) werd in het onderzoek betrokken.

Wij vergeleken de gelijktijdig continu gemeten cardiac-outputwaarden van het FloTrac-Vigileo-monitorsysteem, de LiDCOplus (LiDCO Ltd. UK), het PiCCOplus monitorsysteem (Pulsion Medical Systems, Duitsland), en de continue cardiac output

(CCO) met intermitterende bolusthermodilutie cardiac-outputwaarden (COtd), gemeten met Swan-Ganzkatheter en de Vigilance-monitor (Edwards, Lifesciences, Irvine, CA, USA). Cardiac-outputgegevens werden tijdens standaard klinische zorg verzameld. Hiervoor werden achtentwintig patiënten geïncludeerd die na een open-hartoperatie op de IC werden opgenomen. Het aantal observaties varieerde tussen de 4 en 8 per patiënt.
We stelden vast dat de betrouwbaarheid van de puls-contourmethoden de laatste jaren dermate is toegenomen dat vergelijking met oudere publicaties niet langer gerechtvaardigd is. Uit de gevonden resultaten konden we ook concluderen dat de cardiac-outputwaarden gemeten met het FlowTrac-Vigileo-systeem uitwisselbaar zijn met die van het LiDCO- en PiCCO-systeem. Voorts stelden we vast dat de cardiac-outputwaarden met de continu gemeten cardiac output (CCO) het meest overeenkwamen met de waarden die we vonden met bolusthermodilutiemethode. Ook stelden we vast dat CCO de hoogste score had in het volgen van langzame veranderingen in de cardiac output. Alle puls-contoursystemen, met uitzondering van de LiDCO, toonden een significante drift in relatie met de tijd. Het FloTrac-Vigileo systeem en de eenmalig gekalibeerde LiDCO-systeem presteerden het best bij snelle veranderingen in de cardiac output (veranderingen in slagvolume).

Hoofdstuk 6
De nieuw te ontwikkelen meetmethoden van de cardiac output moeten bij voorkeur minimaal invasief zijn of moeten in ieder geval toegepast kunnen worden zonder aanvullende invasieve procedures voor externe kalibratie. Tot op heden zijn slechts twee methoden beschikbaar. Deze meetmethoden zijn gebaseerd op de Doppler-ultrageluidtechniek en de puls-contourmethode. In dit hoofdstuk beschrijven we een studie waarbij gelijktijdig verzamelde cardiac-outputwaarden met het HemoSonic 100-systeem (Doppler-ultrageluid), de ongekalibreerde Modelflow en het FloTrac-Vigileo-systeem vergeleken werden met de cardiac-outputwaarden die met bolus-thermodilutietechniek waren gemeten.
Bij dertien postoperatieve thoraxchirurgische patiënten werden veranderingen in cardiac output gegenereerd door vooraf afgesproken interventies uit te voeren. De cardiac-outputwaarden werden voor, tijdens en na de interventies geregistreerd. De interventies waren verandering van het opgelegde slagvolume van de beademing (toename van 50%), verhoging van de positieve eindexpiratoire druk (PEEP) met 10 cm H_2O, autotransfusie door de benen 45° op te tillen (passive leg raising, PLR) en houdingsverandering door de patiënt 30° in anti-Trendelenburg te leggen (head up tilt, HUT).
De ongekalibreerde Modelflowmethode bleek de beste in het schatten van de cardiac output. De mate van de cardiac-outputverandering (ΔCO) was identiek tussen de pulmonale thermodilutietechniek en HemoSonic 100 en ongekalibreerde Modelflowmethode. Het automatisch gekalibreerd FloTrac-Vigileo-systeem bleek de veranderingen in de cardiac output te overschatten.

Hoofdstuk 7
Met de Modelflow-puls-contourmethode kan men pas na aanpassing van het model voor een individuele patiënt (geslacht, lengte en gewicht) een kwalitatief goede cardiac output meten. De Modelflowmethode (COmf) berekent slag-op-slag cardiac output uit het signaal van de arteria-radialisbloeddruk door het nabootsen van een

(drie-elementen) model van de aorta-impedantie met postmortemgegevens van menselijke aorta's.
In de verbeterde versie van Modelflow (COmfc) wordt de waarde van de aortadiameter (CSA) meegenomen in het model. In deze studie werd de CSA met een HemoSonic 100 bepaald om de cardiac output te berekenen. Na diameterkalibratie bleek de verbeterde Modelflow puls-contourmethode in staat om een betrouwbare schatting van de cardiac output te berekenen. Zonder de noodzaak van een op thermodilutietechniek gebaseerde kalibratie leidt dit tot een minder invasieve methode van cardiac-outputmeting.

Hoofdstuk 8
Met de invoering van puls contour cardiac output werd het mogelijk in 'real-time' het linkerventrikelslagvolume en slagvolumevariatie (SVV) tijdens mechanische ventilatie te meten. Uit studies is gebleken dat SVV een goed voorspellende waarde heeft hoe een patiënt op vloeistof/volumetoediening zal reageren. Slechts een enkele studie maakte melding van een gebrek aan correlatie tussen de waarde van SVV en veranderende cardiac output bij volumeexpansie. Pinsky stelde terecht vast dat SVV niet gevalideerd is om verandering in het linkerventrikelslagvolume (binnen één ademcyclus) te meten. Voorts zou de beoordeling verder gecompliceerd kunnen worden doordat in de monitorsystemen (PiCCO, LiDCO en FloTrac-Vigileo) verschillende algoritmes gebruikt worden. In dit licht bezien, zijn klinische validatiestudies van SVV, waarbij verschillende puls-contourmonitorsystemen gebruikt worden, belangrijk.
In dit hoofdstuk doen we verslag van een studie waarin we waarden van de slagvolumevariatie, gemeten met de PulseCO (LiDCO) en het FloTrac-Vigileo systeem (Edwards Lifesciences), met elkaar vergelijken. Alle SVV-waarden werden bij vijftien patiënten na openhartoperatie tijdens het verblijf op de Intensive Care verzameld. De klinische waarde van SVV werd geëvalueerd door bij de patiënten vooraf gedocumenteerde interventies uit te voeren.. Deze interventies waren: toename van het opgelegde beademingsvolume, toename van de eindexpiratoire beademingsdruk (PEEP), passief optillen van de benen (PLR), een kantelprocedure (HUT) en intraveneus toedienen van 500 ml Voluven (volume). Door de interventies uit te voeren konden we verschillende klinische condities bij de patiënten nabootsen. In onze studie bleken de waarden van SVV(LiDCO) en SVV (Edwards) te verschillen. Met een gemeten overeenstemming van 52% tussen de twee meetmethoden zijn de methoden niet uitwisselbaar, zoals kan worden opgemaakt uit de hoge waarde van de variatiecoëfficiënt (21 en 22%) voor herhaalde metingen. Uit deze bevindingen bleek dat gemeten SVV-waarden, als enkelvoudige parameter, geringe waarde heeft voor de individuele patiënt. Tevens beperken deze bevindingen de vergelijkbaarheid van studiesresultaten met betrekking tot de response van de hemodynamisch instabiele IC-patiënt op volumetherapie.

Conclusies

- Als referentiemethode voor de onderzochte cardiac-outputmeetmethoden hebben we de bolus-thermodilutiemethode (COtd) met de Swan-Ganzkatheter gebruikt. Wij hebben tijdens de studies geen complicaties gevonden in relatie tot het gebruik van deze katheters.
- De meetfout van de Cotd-methode (de variatiecoëfficiënt), berekend op basis van vier metingen die gelijkmatig over de ademhaling verdeeld zijn, was < 5%.
- Van de geëvalueerde puls-contoursystemen bleek de Modelflow- en Hemac-methode de beste meetresultaten te geven. Deze resultaten van de Modelflow- en Hemac-methode kwamen overeen met de cardiac-outputwaarden die gevonden werden met de referentiemethode (COtd). De gemiddelde cardiac-outputwaarde was berekend op basis van vier metingen met de intermitterende thermodilutiemethode, waarbij de metingen gelijkmatig over de ademcyclus verdeeld waren.
- De stabiliteit van de kalibratie en drift van het PiCCO- en LiDCO-systeem verschillen.
- In ons onderzoek hebben we alleen cardiochirurgische patiënten bestudeerd. Daardoor kunnen onze studieresultaten niet zonder voorbehoud worden gegeneraliseerd naar andere categorieën van patiënten. Validatiestudies waarin andere groepen patiënten worden onderzocht blijft belangrijk.

Curriculum Vitae

The author was born on January 27, 1955 in Geleen, where he grew up. In 1972 he graduated from secondary school the Princess Margriet MAVO in Haarlem. From 1973 to 1977 was the author was trained as a nurse, at the hospital named Mariastichting in Haarlem. After his military service in 1978 the author worked until this date at Leiden University Medical Center, where in 1980, he graduated in intensive care nursing. In 1984, the management training for nurses was completed. In 2000, he graduated the post-HBO training in scientific research at Rotterdam.
From 1982 to 1985, the author was director and chairman of the Dutch Association for Neuro- Surgical Nurses. ("Het Beterschap", Utrecht).
Since 1980, the PhD student continuously worked at the Neurosurgical Intensive Care. In this period, the first steps in scientific research were made. Since 1990, the author, did research focused on the changes in cerebral blood flow velocity due to and recognition of cerebral vasospasm after subarachnoid haemorrhage, using transcranial Doppler sonography.
In 2000, after the merger of the different specialized intensive care units into one Department of Intensive Care, the author became a staff member, assigned to contribute into clinical research. Results of this research are regularly presented at medical congresses and are published in the medical literature.

De promovendus werd op 27 januari 1955 in Geleen geboren. De middelbare schooltijd werd in 1972 afgesloten met het behalen van het MAVO-examen op de Prinses Margriet MAVO te Haarlem. Van 1973 tot 1977 werd opleiding tot Verpleegkundige-A, gevolgd in de Mariastichting in Haarlem. Na militairedienst trad de promovendus in 1978 in dienst van het Academisch Ziekenhuis Leiden, waar hij in 1980 het diploma van Intensive Care verpleegkundige haalde. In 1984 werd de middenkader opleiding voor verpleegkundig leidinggevende afgesloten met het behalen van het diploma. In 2000 werd de post-HBO opleiding "Wetenschappelijk onderzoek" behaald aan de Hoge School Rotterdam.
Van 1982 tot 1985 is de promovendus bestuurslid en voorzitter geweest van de Nederlands Vereniging voor Neurochirurgisch Verpleegkundigen. (vallend onder de verpleegkundige beroepsorganisatie "Het Beterschap", te Utrecht)
Sinds 1980 is de promovendus onafgebroken werkzaam geweest op de Intensive Care van het Leids Universitair Medisch Centrum. Op de Intensive Care Neurochirurgie werden de eerste stappen in het wetenschappelijk onderzoek gezet. Vanaf 1990 nam de promovendus, de taak op zich om patiënten, na een door gemaakte subarachnoideale bloeding, met transcraniele Doppler te gaan monitoren.
Na samenvoegen van de verchillende intensive care afdelingen kreeg de promovendus de functie van verpleegkundig wetenschappelijk onderzoeker. In deze functie heeft de promovendus een wezenlijke bijdrage gegeven aan het wetenschappelijk onderzoek op de afdeling Intensive Care. Resultaten van onderzoek zijn regelmatig op medische congressen gepresenteerd. Daarnaast heeft de pomovendus meerdere publicaties in de medische vakliteratuur.