Fluid loading responsiveness

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PROEFSCHRIFT

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 25 mei 2011
klokke 13.45 uur

(3

door

Bart Franciscus Geerts
geboren te Amsterdam
in 1979

4)

Promotiecommissie

Promotor: Prof. dr. L.P.H.J. Aarts

Co-promotor: Dr. J.R.C. Jansen

Overige leden: Prof. dr. A.B.J. Groeneveld (Vrije Universiteit Amsterdam)
Prof. dr. W. Buhre (Universiteit Utrecht)
Prof. dr. A. Dahan

6)

This study was funded by institutional funds of the departments of intensive care and anaesthesiology of the Leiden University Medical Centre.

Cover: Kanagawa Oki Nami Uraby by Katsushika Hokusai 1831

Design: Boulogne Jonkers Vormgeving, Zoetermeer

Printed by Schulten, Zoetermeer

ISBN: 978-90-9026085-3

Typeset in Scala

The printing of this thesis was supported by the department of Anaesthesiology of the LUMC and the Centre for Human Drug Research.

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Introduction

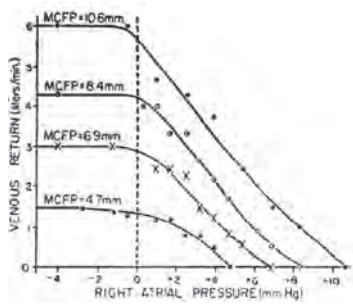
Patients in the intensive care unit (ICU) and in the peri-operative phase are dependent on physicians and nurses for their fluid intake. Moreover, alterations in volume status due to disease, co-morbidity, anaesthetic and surgical manipulations are to be compensated by inotropic support, additional fluid administration or diuretic therapy since sympathetic and hormonal auto-regulation are depressed and frequently myocardial dysfunction is present. Volume status optimization is required to maximize oxygen delivery to vital organs, like brain, kidneys and heart. Prolonged oxygen deficit can ultimately result in multi-system organ dysfunction [1]. On the other hand unnecessary fluid administration can lead to general and pulmonary oedema, cardiac failure, infections, prolonged hospitalization and death [2]. However, it is still not possible to directly determine volume status at the bedside. The quest for a method to directly or indirectly assess volume status continues.

Frank-Starling and Guyton physiology

Starling and Bayliss stated in 1894, that "the venous circulation was an important but disregarded chapter in physiology of circulation" [3]. Arthur Guyton, among others, tried to break with dominance of cardiac function in conceptual thinking about the circulation. In 1955, half a century later then Starling and Bayliss, Guyton postulated a conceptual model for flow in the (human) circulation [4]. In his model of flow, Guyton defines venous return, i.e. the flow towards the right atrium, to be largely dependent on the pressure gradient between central venous pressure (CVP) and mean systemic filing pressure (MSFP). MSFP was defined as the pressure that exists in the whole systemic circulation if flow is stopped and the blood volume is spread over the circulation at equal pressure. In their first experiments Guyton and co-workers arrested blood flow by heart defibrillation [5]. They avoided effects of circulatory control mechanisms by pumping blood from the arterial part to the venous part in a few seconds until blood pressures were equal. This pressure was called mean systemic filling pressure.

Using this technique as a reference technique they tested another technique in which right atrial pressure (or central venous pressure) was increased stepwise and the resulting decrease in venous return (VR) was measured (Figure 1).

Figure 1 The relationship of venous return and right atrial or central venous pressure at different mean systemic filling pressure (MSFP or here named MCFP) values in one normal dog from Guyton [4].



The relationship between CVP and VR was found to be linear. Extrapolation of the linear regression line to VR=zero, or the pressure were this line crosses the x-axis, gives mean systemic filling pressure (MSFP). The extrapolated value of CVP appeared to be equal to the value of MSFP determined with the method of cardiac arrest by defibrillation. The linear fit of the line through the data points is called the venous return curve and can be described according to:

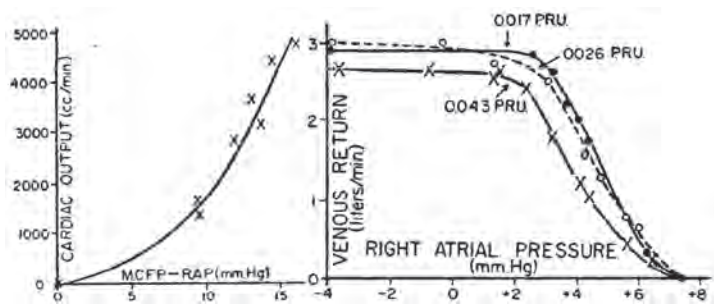
$$VR = (MSFP - CVP)/ Rsf$$

Were Rsf represent the flow resistance between MSFP and CVP. During steady state conditions VR becomes equal to cardiac output. In Figure 1 adapted from Guyton and co-workers, the effect of fluid loading on the venous return curve and MSFP is shown. Increasing circulatory volume shifted the venous return curve and increased MSFP. Different authors confirmed these findings in animal studies [6-8]. MSFP values between 7 and 20 mmHg were reported. Versprille and Jansen showed that these findings also hold for an intact circulation [6]. To arrange this they introduced inspiratory hold manoeuvres, i.e. inflations followed by and pause of 7 seconds. During such manoeuvres intra-thoracic pressure is increased, causing an increase in CVP and therefore a decrease in venous return and after a few heart beats in cardiac output. With seven different tidal volumes between 0 and 30 $ml \cdot kg^{-1}$ the resulting seven pairs of CVP and cardiac output (CO) values showed a linear relationship as mentioned above. Recently, we showed that MSFP can be determined in intensive care patients with an intact circulation with use of these inspiratory pause procedures, making estimations of circulatory compliance and serial measures of circulatory stressed volume feasible [9].

Analysis of cardiac output and right atrial pressure

Cardiac output is traditionally represented by the Frank-Starling heart function curves, which are dependent on heart rate, contractility and afterload. Another major contribution of Guyton and colleagues to the understanding of cardiac output regulation was that the venous return and heart function curve could be represented in the same graph (Figures 2-3).

Figure 2 Effect of the pressure gradient for venous return on cardiac output (MSFP is mean systemic filling pressure or named MCFP here; RAP is right atrial pressure equal to central venous pressure) and the effect of increasing peripheral resistance on venous return when the peripheral resistance is increased by occluding the small arteries with 250 micron glass beads in a normal dog [4]. The two graphs are the result of separate studies (points in the left and right graph do not correspond with the same measurement).



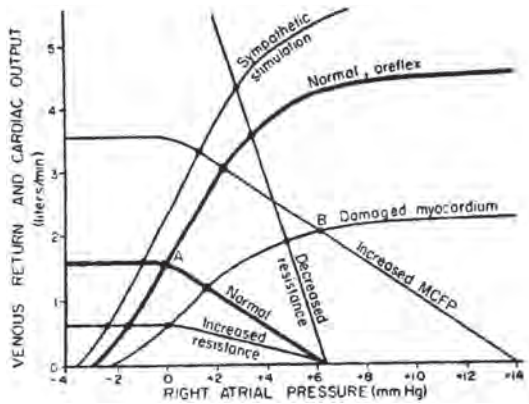
Indeed, in the complete circulation the heart and the systemic circulation must operate together. Thus, in steady state, VR and cardiac output are equal and the right atrial pressure is the same for both the heart and the systemic circulation. Therefore, actual cardiac output and right atrial pressure can be found at the intersection of the venous return curve and heart function curve as is shown in Figure 3. The two bold curves depict both the normal cardiac function curve and the normal function curve. The intersection is the working point of the circulation; venous return equals cardiac output at a certain right atrial pressure.

Effect of increased blood volume on cardiac output

A rapid volume loading of about 20% of total blood volume increases cardiac output to about 2.5 times normal [10]. The effect of increasing blood volume is depicted in Figure 3 by the venous return curve marked with increased MSFP. The intersection with the normal heart function curve shifted upwards increasing cardiac output and right atrial pressure. However

in the heart function curve damaged myocardium the intersection point B is on the flat part of the function curve. Additional fluid loading will not improve cardiac output. Furthermore, compared to the normal heart function curve, the change in right atrial pressure with volume loading is much greater.

Figure 3 Equilibration of various venous return curves with different cardiac response curves adapted from Guyton [4].



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In summary, the work of Arthur Guyton is an important step forward to the determination of volume status directly or at least the development of an accurate surrogate marker as will be discussed below and in the following chapters of this thesis.

Measurement of cardiac output

Besides signs like skin turgor, dieresis and skin colour, hemodynamic measurements like CVP and mean arterial pressure (MAP) are most often used for hemodynamic management. Organ perfusion is dependent on flow rather than pressure but flow is much more difficult to measure than pressure. CO is the amount of blood pumped through the circulation by the heart per minute. There are several reasons to use cardiac output in clinical practice. Cardiac output values, and trend, are often used as a substitute for volume status. The general conception is that an increase in cardiac output will improve perfusion of vital organs. Increased flow might also imply improved oxygen delivery to the tissues. This is the basis of the fluid loading responsiveness strategy that will be discussed later on in this introduction. Hence, an accurate determination of cardiac output is essential to allow not only for good patient assessment.

In the first chapter of this thesis we provide an overview of some of the most-often-used methods to measure cardiac output. We describe the Fick-method, ultrasound, indicator dilution techniques, arterial pulse contour analysis and bio-impedance. Characteristics like accuracy, precision, operator variability, invasiveness, interval of measurements, robustness and complications are reviewed. Thermodilution with a pulmonary artery catheter (PAC) is the de-facto gold standard for the measurement of cardiac output. The use of a PAC is however associated with several complications, like infection, pulmonary artery dissection, lung infarction, valvular lesion and pneumothorax [11]. In recent years, several less invasive methods have been developed. Pulse contour analysis is one of them and requires only a radial or femoral artery catheter [12]. In chapter two results are shown of an evaluation of the accuracy of the measurement of cardiac output using three methods (FloTrac–Vigileo, Modelflow and HemoSonic system) with thermodilution as the reference method [13]. Another parameter that can be estimated from the arterial pulse wave is stroke volume variation (SVV). Mechanical ventilation causes cyclic changes in venous return, pulmonary artery blood flow, and aortic blood flow. The changes in these parameters due to ventilation seem to be an indirect reflection of effective volume status [14]. SVV is the difference between the minimal and the maximum stroke volume divided by the mean stroke volume over a certain period of time. SVV is displayed as a percentage value. In some studies [15,16], stroke volume variation has been shown to have high sensitivity and specificity to predict of fluid loading responsiveness, i.e. the prediction of an increase in cardiac output with fluid loading. However, SVV requires full mechanical ventilation of the lungs and absence of arrhythmias when fluid loading responsiveness (FLR) is assessed [17]. Moreover, since stroke volume cannot be measured directly without a PAC, pulse contour methods are used. Different pulse contour methods are available but reports on their accuracy are rare. In chapter three, we present a comparison of the accuracy of SVV measured with the LiDCOplus and FloTrac-Vigileo system [18].

Parameters used in hemodynamic management in the ICU

Hemodynamic instability caused by relative or absolute intravascular volume deficiency are common in the ICU and OR. Physicians use several surrogate parameters to select patients who will benefit from fluid loading. We performed a survey to evaluate the use of these parameters by Dutch intensive care physicians. Results of this survey are shown in chapter four.

Fluid loading responsiveness

Traditional filling pressures like CVP often fail as a predictor [19-21]. Therefore, new methods are being developed or traditional parameters are used in a different setting to prevent fluid overloading by an accurate prediction of the response to fluid loading.

Relatively few strategies exist to assist the physician in hemodynamic management. One such strategy has recently received broad attention. This strategy is fluid loading responsiveness (FLR). FLR is used to predict whether cardiac output will significantly increase or not with fluid loading. A parameter that can accurately predict FLR has been sought for many years. New parameters like SVV have been developed and used in the FLR strategy. In chapter five we review the accuracy and limitations reported of the most frequently used methods in clinical practice to predict fluid responsiveness in patients undergoing mechanical ventilation. We provide a straightforward overview of determinants that can be used to predict a clinically significant effect of fluid administration on cardiac output.

Treating hypovolaemia

When hypovolaemia occurs and is diagnosed. Treatment is initiated. This will comprise the rapid administration of fluids. Fluid resuscitation is however not achieved immediately. The Trendelenburg position or head-down tilt, and passive leg raising (PLR) are routinely used in the initial treatment. In chapter six a meta-analysis is described into the hemodynamic effects of PLR and Trendelenburg. We asked ourselves which manoeuvre has the optimal effect on cardiac output (CO) while awaiting fluid resuscitation?

Mean systemic filling pressure

As we described above Arthur Guyton is responsible for some major steps in the development of a method to determine volume status directly. He defined mean systemic filling pressure as the mean pressure throughout the circulatory system under conditions of no flow. Together with the shape of cardiac output function curve, dimensions of the vascular system and blood viscosity, mean systemic filling pressure can be considered as a primary determinant of venous return and thus cardiac output. In chapters seven to nine, we present the results of three studies into mean systemic filling pressure. Ultimately, MSFP can be used to calculate stressed volume and, hence, quantify effective volume status in a specific patient [5].

However, in line with its definition determination of MSFP will require zero flow conditions throughout the circulatory system. Creating zero flow conditions at the bedside is unethical. We therefore developed a method to determine MSFP indirectly with two new methods; an arm model and a mechanical ventilator manoeuvre. In chapter seven, we studied the effect of dobutamine and hypovolemia on the circulation and tested the model of ventilatory holds with increasing airway pressure in pigs. In this model, CVP values can be used to extrapolate pressure at zero flow conditions. In chapter eight, we expanded on earlier work by Versprille and Jansen [6] to estimate MSFP with a ventilatory manoeuvre in humans. In chapter nine,

we use the second model (i.e. the arm model) to predict FLR in patients who underwent coronary artery bypass surgery.

Challenges to predict fluid loading responsiveness

In chapters ten to thirteen we study several challenges to predict FLR; +10 cmH_2O (chapter ten), the fluid challenge (chapter eleven), passive leg raising (chapter twelve) and the respiratory ventilator manoeuvre (chapter thirteen). New parameters like SVV and PPV are being developed to prevent fluid over-loading. But these parameters have their own limitations like inaccuracy in predicting FLR during low tidal volume ventilation [22] or in patients with arrhythmias [17]. In recent years traditional filling pressures like CVP often failed as a predictor for FLR [19-21]. We looked to re-use these traditional parameters, i.e. the changes induced by a challenge, to predict FLR.

A PLR-, fluid- or PEEP-challenge is aimed at determining the working point of the circulation on the Frank-Starling curve. It is assumed that when the patient is on the ascending portion of the Frank-Starling curve an (auto)transfusion will increase cardiac output. Once the heart is functioning near the ''flat'' part of the Frank-Starling curve fluid loading has little effect on cardiac output and central venous pressure will increase more. A PEEP-challenge on the other hand will give incrementally greater decreases in CO when the heart functions toward the flat part of the Frank Starling curve. We studied whether changes in parameters like CVP or CO as a result of a challenge can be used to estimate the working point on the Starling curve and consequently predict FLR.

In the discussion (chapter fourteen) of this thesis, we concentrate on the definition of fluid loading responsiveness and look for solutions and research directions for the future.

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Section 1

Accuracy of the measurement of cardiac output and stroke volume variation

Chapter 1

Methods in pharmacology: measurement of cardiac output

Bart Geerts, Leon Aarts and Jos Jansen
British Journal of Clinical Pharmacology 2011; 71(3): 316-330

"It is a source of regret that measurement of flow is much more difficult than measurement of pressure. This has led to an undue interest in blood pressure measurements. Most organs however, require flow rather than pressure." This statement by Jarisch in 1928 [1] is still fully valid. Many methods of cardiac output measurement have been developed, but the number of methods useful for human pharmacological studies is limited. Methods proposed to achieve this goal include; the Fick principle; ultrasound; indicator dilution techniques; arterial pulse contour analysis; and bio-impedance. To gain widespread acceptance, these methods should ideally be accurate, precise, operator independent, fast responding, non-invasive, continuous, easy of use, cheap and without complications. The methods may allow testing of circulatory changes on pharmacological interventions. In this review on cardiac output, the methods used in pharmacology are described.

Fick's cardiac output measurement

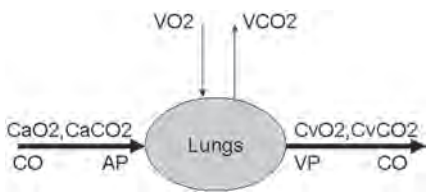
Direct Fick for oxygen

In 1870, Adolf Fick described a method to estimate cardiac output based on a mass balance for oxygen. He postulated that oxygen uptake in the lungs, i.e. the oxygen (O_2) consumption
20) in ml of pure gaseous oxygen per minute, is entirely transferred to the blood stream through the lung. With no consumption of oxygen in the lungs the oxygen consumption of the body is equal to the product of blood flow (cardiac output) and arterio-venous oxygen content difference. Therefore cardiac output can be computed as follows:

$$\text{Cardiac output (CO)} = \frac{\text{VO2}}{(\text{CaO2} - \text{CvO2})}$$

Where VO_2 is the oxygen uptake, CaO_2 and CvO_2 (ml $O_2 \cdot L^{-1}$ blood) are the oxygen content of arterial and venous blood respectively (also see Figure 1).

Figure 1 Graphical description of the Fick principle; oxygen enters the lungs (VO2) en is transported to peripheral tissue of the body (CvO2-CaO2), at the same time carbon dioxide produced by the rest of the body (CaCO2-CvCO2) is cleared by the lungs (VCO2). From these concentrations blood flow can be calculated using the formula described in the text.



At first sight the method seems simple to execute. VO_2 can be determined by breathing or mechanical ventilation within a spirometer incorporating a carbon dioxide absorber or, more conveniently, via an indirect calorimetry monitor. Also, the calculation of the arterial and venous oxygen content of the blood is a straightforward process and is readily available to physicians. However, the method is laborious and many variables need to be determined. During the acquisition of data the circulation needs to be stable. Considerations: 1; the large number of variables involved in the computation result in a large chance on permutation of errors, 2; ventilation of subjects with inspiratory O_2 fractions larger than 60% have been reported to decline the accuracy of the method [2], 3; the technique requires an invasive pulmonary artery catheter to sample mixed venous blood. Accurate measurement of VO_2 as well as reliable sampling of arterial and venous blood sample is labor-intensive. Nevertheless, in a laboratory with skilled researchers, the method is considered the most accurate method to which other methods are compared.

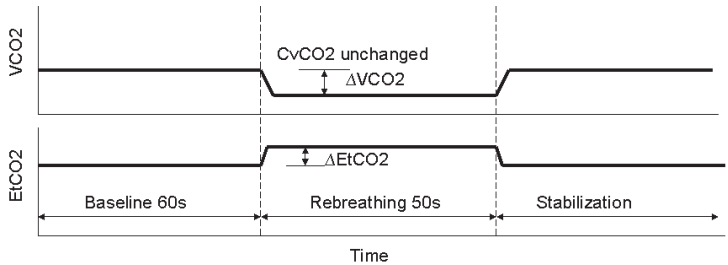
Partial carbon dioxide rebreathing

The Fick principle can be applied to all gasses that obey Henry's law and diffuse through the lungs, especially carbon dioxide (CO_2). The NICO (Novametrix Medical Systems Inc. Wallingford, CT, USA) is the most studied cardiac output monitor based on the Fick principle for CO_2 and uses intermittent partial rebreathing of CO_2. This monitor utilizes a specific disposable rebreathing loop in which a CO_2 infra-red light absorption sensor, a differential pressure transducer for air flow measurement and a pulse oximeter are placed. VCO_2 is calculated from the simultaneously measured minute ventilation by the differential transducer and its CO_2 concentration (Figure 2). The arterial content of CO_2 ($CaCO_2$) is estimated from end tidal CO_2 ($EtCO_2$) after a correction (S), i.e. the slope of CO_2 dissociation curve. Measurement of under normal and under rebreathing conditions allows elimination of measurement of $CvCO_2$. Fick's equation applied to carbon dioxide is:

$$CO = \frac{VCO2}{(CaCO2 - CvCO2)}$$

Where VCO_2 is the CO_2 production, $CaCO_2$ and $CvCO_2$ the arterial and mixed venous CO_2 content in blood.

Figure 2 The measurement of cardiac output with the use of carbon dioxide rebreathing.



Assuming cardiac output not changed by CO_2 rebreathing, $CvCO_2$ does not differ between normal and rebreathing conditions (CO_2 diffuses very fast in blood, 22x faster than O_2) and arterial $CaCO_2$ can be approximated by end-tidal CO_2 multiplied by the slope (S) of the CO_2 dissociation curve the equation above can be rewritten to:

$$CO = \frac{\Delta VCO2}{(S \times \Delta EtCO2)} \quad 22)$$

Where ΔVCO_2 is the change in VCO_2 and $\Delta EtCO_2$ is the change in end-tidal CO_2 between normal breathing and CO_2 rebreathing.
The method actually calculates effective lung perfusion. The effects of unknown ventilation/perfusion inequality and anatomic shunts may explain underestimation of CO and the method shows a lack of agreement with reference techniques [3]. To correct for shunt behaviour the subjects must be fully under mechanical ventilation and arterial blood samples are needed, making this method (less) invasive. However, clinically acceptable cardiac output estimation seems possible in intubated mechanically ventilated patients with minor lung abnormalities [4].

Indicator dilution techniques

Today four different modalities of the indicator dilution technique are commercially available, i.e. the pulmonary artery catheter (PAC) thermodilution method with bolus injection of cold fluid, the PAC continuous thermodilution method, the transpulmonary bolus thermodilution method and the transpulmonary lithium bolus dilution method. All these methods have in common that the computation of cardiac output is based on a mass balance:

$$mi = \int q(t) \bullet c(t) dt$$

Where; mi is the amount of indicator injected, q(t) is instantaneous blood flow and c(t) is concentration as function of time.
Application of this equation assumes complete mixing of blood and indicator, no loss of indicator between place of injection and place of detection. If we further assume blood flow to be constant than we found the well-known Stewart-Hamilton equation:

$$CO = \frac{mi}{\int c(t)dt}$$

Where ∫c(t)dt is the area under the indicator dilution curve. Errors made in the application of indicator dilution methods are primarily related to violation of the assumption mentioned above, inaccurate implementation of the method [5] and anatomic abnormalities [6].

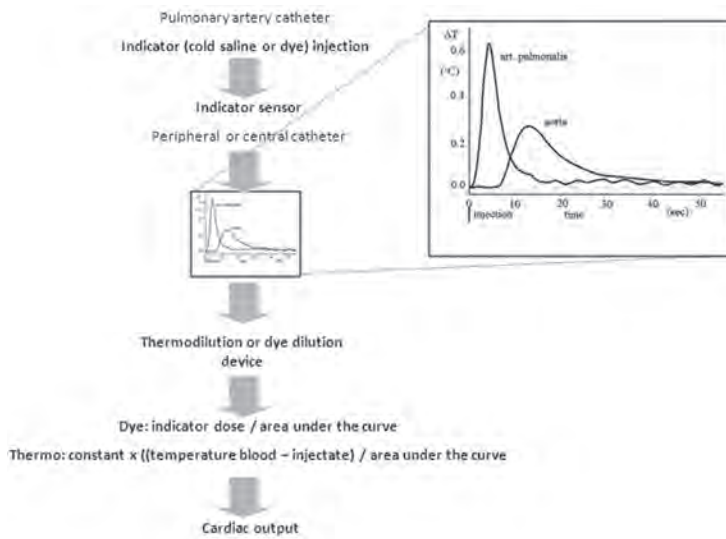
Intermittent Pulmonary Thermodilution

Since the introduction of the pulmonary artery catheter (PAC) equipped with a thermistor by Swan and Ganz in 1970 [7] the thermodilution method has become the standard method to determine cardiac output in patients. The thermodilution method is based on the law of conservation of thermal energy. With the intermittent thermodilution technique a certain amount of cold fluid is injected into the blood stream near the entrance of the right atrium and the resulting dilution curve is detected in the pulmonary artery. With temperature as indicator the Stewart-Hamilton equation can be rewritten as follows:

$$COtd = cc\frac{Tb - Ti}{\int \Delta Tb(t)dt}$$

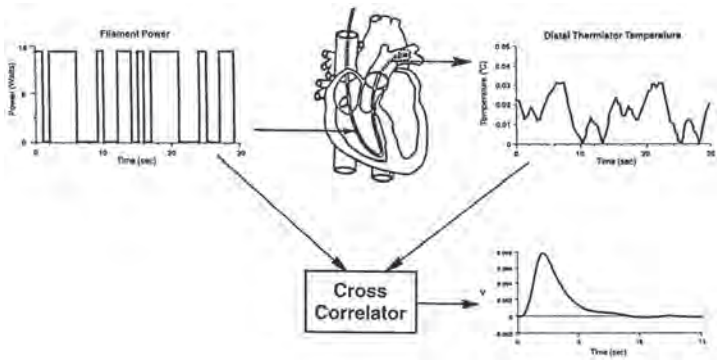
Where COtd is cardiac output by thermodilution, Tb is the temperature of blood in the pulmonary artery before injection of injectate, Ti the temperature of the injectate, and (∫ΔTb(t)dt the area under the dilution curve (Figure 3) and cc is the computation constant. The computation constant contains corrections for specific mass and heat of injectate and blood respectively, injected volume and loss of indicator in the PAC and has to be entered in the thermodilution cardiac output computer.

Figure 3 Indicator dilution to measure cardiac output. A dye solution or cold saline is injected and detected by a (dye or thermal) sensor downstream of the injection site. The dilution signal is fed to a cardiac output device. To compute cardiac output the dose injected is divided by the area under the indicator dilution curve. The inset shows the difference in temperature changes for two different locations of detection (see text).



Investigators have previously explored methods of minimizing the errors in the intermitted thermodilution technique [8-12]. The best method is to average the results of three or four thermodilution measurement with the injection of cold fluid equidistantly distributed over the ventilatory cycle. For such an approach injections of fluid must be done with an injector under computer control. Use of such a set-up results in a coefficient of variation or 1SD-precision of 3.5%. Whereas the averaged result of three randomly applied measurements have a 1SD-precision of about 10% and single measurements a 1SD-precision of 15%. After 40 years of clinical experience, the conventional thermodilution method has been generally accepted as the clinical standard to which all other methods are compared. However, some serious complications can arise from PAC insertion like arrhythmias, valvular lesions, rupture of the pulmonary artery and lung infarction.

Figure 4 Schematic diagram of the working principle of the continuous thermodilution method.



PAC continuous cardiac output

The Vigilance system, (Edwards Lifescience, Irvine, CA, USA) combines heat-dilution principles with stochastic system identification to measure cardiac output [13]. Small amounts of thermal energy (heat-indicator) are transported directly into the blood in a pseudo random on-off pattern to form the input signal (see Figure 4). The resulting blood temperature changes are detected with a thermistor in the pulmonary artery. This signal is small in proportion to the resident pulmonary artery thermal noise. To overcome this problem, a cross correlation is carried out on the input signal and the temperature data measured in the pulmonary artery, resulting in a thermodilution curve, as would have been found after a bolus injection. From this dilution curve, cardiac output is computed using the classical Stewart-Hamilton equation. The entire process is automated, requiring no user intervention. A detailed explanation of the technique is given by Yelderman *et al*. [13]. The "continuous" cardiac output measurement makes extensively use of averaging techniques, therefore, the displayed cardiac output number represents the averaged value of the previous 1 to 6 minutes [13]. Under extreme clinical situations this delay can run up to 12 minutes [14]. This property of the technique makes the method continuous but not instantaneous.

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Concerns for the pulmonary thermodilution techniques

Recently, the use of both pulmonary artery thermodilution cardiac output methods has been under discussion. Many physicians believe that the PAC due to its multi-purpose role is useful for the diagnoses, treatment and assessment of volume status in critical ill patients [15]. However, this is not confounded by studies. In contrast, different investigators raised doubts about the safety of the PAC. Indeed, most recent studies do not show a difference in morbidity and mortality between patients with and without a PAC [16-18]. On the other hand,

in these trials the introduction of the PAC could not be associated with an increase in morbidity and mortality. The inability to demonstrate the merit of the PAC in predicting outcome does not necessarily mean that our monitors using the PAC are not functioning [17]. It may also indicate a persisting lack of correct and consistent interpretation of PAC-derived data among physicians [19] or ineffectiveness of our current therapeutic options in reversing critical disease states. Thus, further investigation into the role of the PAC is feasible, likely safe, and should proceed forthwith [15,20].

Intermittent Transpulmonary Thermodilution

With this intermittent thermodilution technique a certain amount of cold fluid is injected into the blood stream near the entrance of the right atrium and the dilution curve is detected in the femoral artery [21-23]. CO is computed with the Stewart-Hamilton equation equal to the intermittent pulmonary thermodilution technique. In theory, the transpulmonary thermodilution technique should be less accurate due to unpredictable lost of indicator over the lungs, but more precise than pulmonary thermodilution [8,9] because the dilution curves are less affected by the respiration cycle. However the decreased signal-to-noise ratio of the dilution curve, i.e. a broader but smaller high of the curve (see Figure 3), may undo this advantage.

The transpulmonary thermodilution method is vulnerable to the same sources of error and variability as the pulmonary thermodilution because the two techniques rely on the same physical principles. But, CO by the transpulmonary method slightly overestimates the results of the pulmonary method due to a small extra loss of indicator between injection and detection site in the aorta or femoral artery. To gain sufficient precision the results of three measurements need to be averaged. These three measurements take approximately 3-10 minutes. Therefore, this transpulmonary thermodilution method lacks the ability to monitor cardiac output continuously, equal to the pulmonary method. The Intermittent Transpulmonary Thermodilution is incorporated in the PiCCO-system (Pulsion Medical Systems, Munich, Germany).

Transpulmonary Lithium dilution

The lithium dilution method is based on the venous bolus injection of a small dose (1-2 ml) of an isotonic lithium chloride (LiCl) solution (150-300 mmol) and the resulting arterial lithium concentration-time curve is measured by a lithium sensor in a pre-existing peripheral arterial line. Cardiac output is calculated by the Stewart-Hamilton equation:

$$COli = \frac{Li,dose \bullet 60}{(1 - PCV) \bullet \int \Delta c,li(t)dt}$$

Where Li,dose is amount of lithium injected, $\int \Delta c,li(t)dt$ the area under the lithium dilution curve and PCV the packed cell volume (calculated as the haemoglobin concentration ($g.dL^{-1}$) divided by 34). This correction is needed because lithium is only diluted in the plasma and not in the red and white cells of blood [24]. The pharmacokinetics of intravenous lithium administration is described [25]. No side effects have been reported. To achieve a good precision with this technique, the results of three measurements should be measured [26]. The lithium dilution method is incorporated in the LiDCO system (LiDCO, London, UK). Some of the concerns relate to the lithium dilution method are the need for repetitive blood draws. Furthermore, the lithium dilution technique is contraindicated in patients using high doses of neuromuscular blocking agents, because of interference with the sensing electrode. The technique can not be used in patients receiving lithium therapy and is not licensed in subjects weighing less than 40 kg.

Pulse contour cardiac output

The pulse contour devices are perhaps the most promising with respect to their ease of use. The estimation of cardiac output via pulse contour analysis is an indirect method; CO is computed from an arterial pressure pulsation on basis of a criterion or model. The origin of the pulse contour method for estimation of beat-to-beat stroke volume goes back to the classical Windkessel model described by Otto Frank in 1899 [27]. In principle the aortic pressure waveform is the input of the Windkessel models of the systemic circulation. In medical practice, the pressure waveform is not obtained from the aorta but from a peripheral artery (radial or femoral), which requires a backward filtering from the peripheral to aorta pressure. Not much is known about the algorithms applied. At present there are four commercial pulse-contour cardiac output computers available; PiCCO, PRAM, LidCO, Vigileo and Modelflow.

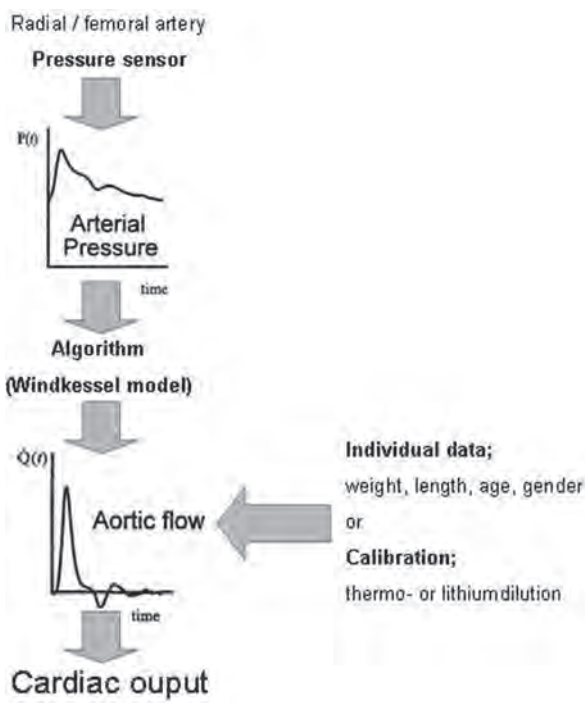
The PiCCO system

The PiCCO-system (Pulsion Medical Systems, Munich, Germany) uses a modified version of Wesseling's cZ algorithm [28,29]. It analyzes the actual shape and area under the pressure waveform and uses individual aortic compliance and systemic vascular resistance. The PiCCO algorithm is summarized in the following equation:

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

Where: COpi, cardiac output; K, calibration factor; HR, heart rate; P, arterial blood pressure; ∫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. The calibration factor (K) is determined with transpulmonary thermodilution and recalibration is needed after profound changes in SVR and at regular (≥ 1-hour) intervals [30-32]. Invasive catheterization is thus still required. For the PiCCO device both the radial and the femoral artery approach can be used [33]. A basic overview of the computation of pulse contour cardiac output is shown in Figure 5.

Figure 5 General working principle to estimate cardiac output by pulse contour analysis. A pressure signal is conducted from the pressure sensor to a pulse contour cardiac output device. Together with either calibration values obtained by transpulmonary thermodilution (PiCCO) or lithium dilution (LidCO), and personal patient data the algorithm estimates aortic flow over a certain interval. This is shown on the device as cardiac output.



The pressure recording analytical method (PRAM)

PRAM (Vytech Health, Padova, Italy) is a modified version of Wesselings cZ algorithm [28,29]. Stroke volume (SV) is proportional to the area under the diastolic part of the arterial pressure wave divided by characteristic impedance (Z). The proportionally factor is usually obtained by calibration with an independent SV measurement (for instant by intermitted thermodilution). However in contrast to other methods PRAM does not rely on calibration or demographic data. With PRAM characteristic impedance is obtained from morphological data of the pressure curve of a whole heart beat [34] and is calculated as $Z = (P/t) \cdot K(t)$. Stroke volume (SV) is therefore computed as:

$$SV = A/[(P/t) \cdot K(t)]$$

Where A is the area under the systolic part of the pressure curve, P/t is the analytical description of the pressure wave form of pressure (P) with time (t) for each heart beat and K(t) is a factor inversely related to the instantaneous acceleration of the cross sectional area of the aorta.

The value of K(t) is found from the ratio between expected and measured mean arterial blood pressure. This relationship approached an arctangent function (similar to that of Langewouters *et al.* [35]. The expected mean blood pressure which is constant depends on the site of measurement, i.e. for adults 100 mmHg for the aortic pressure and 90 mmHg for a peripheral pressure. With PRAM stroke volume is calculated for each beat and CO per beat is then derived by multiplying SV with heart rate of the same beat. CO is presented as the mean value of 12 beats.

As the internal calibration of PRAM is derived from the morphology of the pressure curve, this makes the method vulnerable to sources of errors related to signal quality and in patients with heart diseases that are suspected to affect the arterial pressure waveform (for instance in patients with aortic valve stenosis or valve insufficiencies).

The LiDCO's pulsco system

The LiDCO-system (LiDCO, London, UK) calculates continuous cardiac output by analysis of the arterial blood pressure trace. Using a non-linear relationship between arterial pressure and volume, given by Remington *et al.* [36], nominal changes in arterial volume within every cardiac cycle are calculated from the pressure waveform. These nominal changes are converted to actual stroke volume by multiplying the nominal stroke volume or nominal cardiac output by a calibration factor. This patient-specific calibration is derived from an independently measured cardiac output, for instance by the conventional thermodilution or by the transpulmonary lithium indicator dilution method. In this case invasive

catheterization with a PAC or an additional peripheral venous catheter is still necessary. Recent data suggest recalibration every eight hours or whenever major hemodynamic changes occur [37].

Vigileo/FloTrac system

The FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA, USA) is a pulse contour technique utilizing a dedicated pressure sensor (FloTrac) and a monitor to compute stroke volume and cardiac output (Vigileo). It does not require an independent calibration. The cardiac output algorithm is based on the principle that aortic pulse pressure is proportional to stroke volume and inversely related to aortic compliance. The system obtains the pressure signal from any standard peripheral arterial line. From the arterial pressure the standard deviation (σAP) around mean arterial pressure (MAP) is computed over a 20-second interval. This σAP is multiplied by a conversion factor Khi to calculated stroke volume. Khi incorporates a multivariate polynomial equation which assesses the impact of the patient's ever-changing vascular tone on pulse pressure. It is calculated by analyzing the patient's heart rate, standard deviation σAP, mean arterial pressure, pressure dependent arterial compliance estimated by patients demographics with the Langewouters equation [35], BSA body surface area calculated from weight and height, skewness (symmetry) and kurtosis (distinctness of a peak) of the beat-to-beat arterial waveform. Khi is updated and applied to the stroke volume algorithm on a rolling 60-second average:

$$\text{Stroke Volume } (ml \cdot beat^{-1}) = \sigma AP \text{ (mmHg)} \cdot \text{Khi } (ml \cdot mmHg^{-1})$$

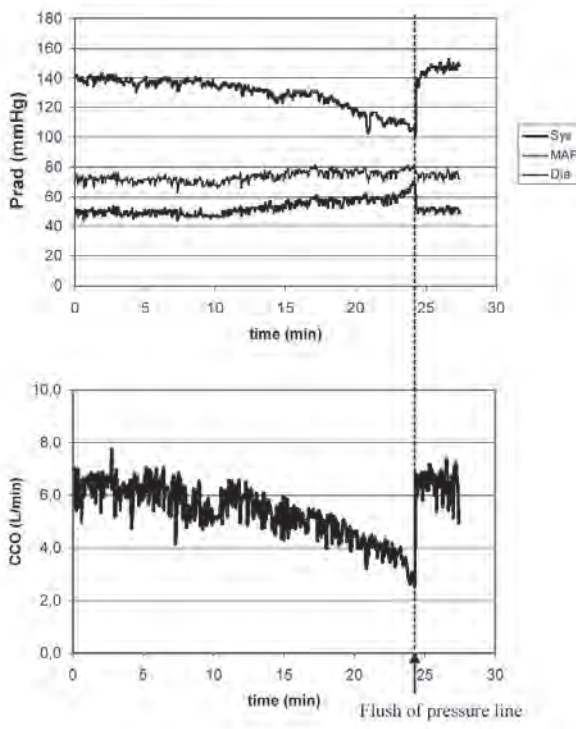
Cardiac output is calculated by multiplying stroke volume with heart rate. The extensive use of arterial pressure signal processing makes the FloTrac algorithm highly dependent upon a high fidelity pressure signal. Therefore, attention to the quality of the pressure monitoring signal by testing for optimal dampening and flushing of the arterial line is important.

Modelflow method

Fifteen years ago Wesseling and co-workers [29] discovered that a straightforward extension of the classical Windkessel model could be adequate for pulse contour analysis. Modelflow (FMS, Amsterdam, The Netherlands) is a three-element Windkessel model of the arterial circulation, 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 opposition of the aorta to volume increases, and peripheral resistance which represents the opposition of the vascular beds to the drainage of blood. Aortic compliance is not constant but depends besides demographic data of the patient

(gender, age, weight and height) on arterial pressure itself [35]. Aortic characteristic impedance, in contrast to compliance increases moderately with pressure. Systemic peripheral resistance depends on many factors including circulatory filling, metabolism, sympatic tone and the presence of vasoactive drugs. The Modelflow method simulates this behaviour. The modelflow method uses a peripheral arterial pressure and can be applied uncalibrated by using demographic data of the subject as well as calibrated. For calibration an independent measure of cardiac output [38] or a measure of the cross sectional area of the aorta can be used [39]. A more detailed description of the method can be found elsewhere [29,38].

Figure 6 Effects of damped radial artery pressure on LidCO pulse contour output of an individual patient. Upper panel systolic (Sys), diastolic (Dia) and mean (MAP) radial artery pressure (Prad). Bottom panel cardiac output by PulseCO (CCO).



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General concerns for pulse contour methods.
All pulse contour systems are based on a mathematical model and not on a mass balance as the indicator dilution and Fick method do. This implies that deviations of the model to the physiological reality have consequences for the estimated cardiac output. Growing knowledge of the arterial circulation and increasing computation possibilities has led to different software versions of the different methods. This complicates reviewing these methods. We selected only those papers that make use of recent software versions. Furthermore, with a peripheral arterial pressure as input of the model instead of aortic pressure, loss of signal quality may be crucial. An example of the effect of loss of signal quality on blood pressure and cardiac output is shown in Figure 6.

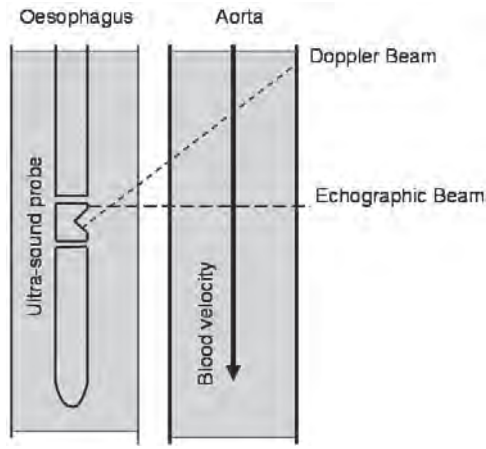
Echo-Doppler ultrasound methods

Transoesophageal Doppler
In the last decade the Transoesophageal Doppler (TOD) is most frequently used ultrasound method (Figure 7); a small ultra-sound transducer, mounted at the tip of a flexible probe, is orally or nasally positioned in the oesophagus along the descending aorta. Insertion depth is
32) typical 35 to 45 cm for adults, depending on the route of insertion (oral vs. nasal). The transducer is pointed towards the aorta by rotation to obtain the optimal aortic velocity signal. The blood flow velocity is calculated with the Doppler equation.

$$V = \frac{Fd \bullet c}{2 \bullet Fo \bullet \cos\theta}$$

Where V is the velocity of blood, Fo is the transmitted frequency, Fd is the change in frequency (Doppler shift), cosθ is the angle between the direction of the ultra-sound beam and blood flow and c is the velocity of ultra-sound in blood. Three different models of oesaphageal CO monitoring have been offered. Two of these systems i.e. the Deltex monitor (CardioQ, Deltex Medical, Chichester, UK) and the monitor of Medicina (TECO, Berkshire, UK), use a nomogram to obtain the cross sectional area (CSA) of the ascending aorta base on patient's age weight and height, whereas the Hemosonic (Arrow International, Reading, PA, *currently not available*) uses the M-mode echo for the measurement of the diameter of the aorta at the point of the velocity measurement. From aortic diameter cross section area is calculated assuming a circular aorta. Aortic blood flow ($L \cdot min^{-1}$) is found by multiplying velocity with heart rate and cross sectional area of the aorta at the insonation point. Cardiac output is calculated from aortic blood flow by assuming a constant distribution of blood between cephalic and caudal circulation.

Figure 7 Transoesophageal probe geometry. Blood flow velocity is measured by the Doppler beam using the well known Doppler principle. Aortic diameter is determined by the echographic beam by measuring the distance between the backward scatter of the proximal and distal aortic wall. From this distance the cross sectional area of the aorta is calculated.



It is however questionable whether this partitioning of blood streams is constant under a variety of patho-physiological circumstances [40,41]. Most obvious concerns with the technique are angle of insonation and the fixation of the transducer with respect to the blood flow, especially during subject movements. This has led to the conclusion that the method is operator dependent [42] and that additional training is required. Another point of concern is the use of a nomogram to estimated CSA. It is clearly that a nomogram for CSA is based on group averages with may include large individual difference. Also CSA has been found pressure dependent [35]. Lastly, the technique is poorly tolerated in awake non-intubated subjects and cannot be used in subject with an oesophageal disorder.
In a meta-analysis of Dark and Singer in 2004 [43], the authors concluded that the TOD estimates absolute cardiac output with minimal bias but limited agreement. However, the semi-invasive TOD technique enables trend monitoring of CO as long as the probe position is not changed.

Transthoracic Doppler
Transthoracic Doppler (TTD) is an entirely non-invasive method using a ultrasound probe positioned in the jugular notch to obtain blood velocity in the outflow of the left ventricle.

The method is in essence equal to oesophageal Doppler technique. Cardiac output is calculated by measuring the cross sectional area of the aortic valve together with the velocity profile in the outflow track. However, is may be very difficult to identify the aortic root in some subjects. In these cases the outflow over the pulmonary valve may be used. Although it is possible to orientate the ultrasound beam in the assumed 0 degree direction of blood flow and perpendicular on the valve, in practice this is difficult to realize. The alignment is affected by operator skill, anatomy and subject movements (for instance during breathing). Consequently the technique has a larger inter- and intra-observer variability and larger limits of agreement compared to reference methods than the transoesophageal method. The portable and non-invasive character of the method allows use in many settings with patients in supine position.

Thoracic electrical bioimpedance

Electrical bioimpedance was introduced five decades ago as an inexpensive and non-invasiveness cardiac output method. A high-frequency alternating electrical current with low amplitude is applied to the thorax via two electrodes. The resulting voltage is measured with two other electrodes, positioned in between the current electrodes. The measured changes in bio-impedance are thought to be related to changes in cardiac related blood volume. A mathematical conversion is used to translate the change in bioimpedance into cardiac output. Several formulas exist for this conversion. These formulas and their nuances go well beyond the scope of this review. A more detailed description can be found in a review of de Waal and co-workers [44]. The over-simplifications of physiological reality by mathematical equations, motion artefacts, abnormal thoracic anatomy, cardiac valve disease, thoracic shunts and arrhythmias contribute to the inaccuracy of this method. In a large meta-analysis of three decades of validation studies on thoracic impedance cardiography Raaijmakers *et al.* [45] concluded that a better physical-physiological model in combination with improvements on the impedance CO-equation are still needed.

We expect this aspect accounts also for the recently developed bio-reactance technology (Biorectance, Cheetah Medical Inc., Indianapolis USA). This method is based on the observation that blood volume changes induce small changes in frequency and phase of the electrical signal propagating across the thorax. These small changes have been shown to correlate with stroke volume [46].

How to evaluate the different cardiac output measurement methods?

Bland and Altman [47,48] proposed that bias (the mean difference between the techniques) ±2SD-precision is an appropriate indication of agreement between techniques. Here bias is the systematic error and the standard deviation (SD) of the differences is the random error

between methods. Thus the limits of agreement (bias ± 2SD) involve the combination of errors of each measurement technique.

In the present review on cardiac output methods a lack of consistency was found in the presentation of results. Regularly the method under study is compared to thermodilution by linear regression analysis also known as calibration statistic, presenting the regression coefficients of the line together with the correlation coefficient. Bland and Altman [47,48] in their statistical notes pointed out that it could be highly misleading to analyse data pairs by combining repeated observations from several patients and then calculating standard regressions and correlation coefficients.

Critchley and Critchley [49], in an effort to establish objective criteria for judging the accuracy and reproducibility of cardiac output measurement state that: if a 'new' method is to replace an older, established method, the new method should itself 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. In an example Critchley and Critchley [49] showed that if the reference technique has a 2SD-precision of ±20%, then a new method may have also a 2SD-precision of 20% to be acceptable. According to Pythagoras' law, the limits of agreement in the Bland-Altman plot should be less than ±28%, i.e. $\sqrt{(20^2+20^2)}$, to conclude for agreement between methods. This example has led to an oversimplification in comparison of methods and many authors conclude that the Bland-Altman limits of agreement should be less than ±30% to accept the new measurement technique. Based on the fact that the 2SD-precision of reference method may be less than 20%, the criteria of 30% derived from Bland-Altman analysis is highly misleading. Therefore, evaluation studies should provide the precision of the reference method. In addition to the above discussion about the evaluation of new methods, we should realize that a proper evaluation method of continuous cardiac output methods is still awaited [50].

In Table 1, we summarized results of different methods to estimate cardiac output against the results of the intermittent pulmonary thermodilution method as reference method. From each peer reviewed study we noted or recalculated the bias and limits of agreement for cardiac output, hereto cardiac index was converted to cardiac output. For each method we took the median results of the included studies. Furthermore, we calculated the 2SD-precision for the difference methods assuming the reference method having a 2SD-precision of 10%, 20% and 30% respectively. A 2SD-precision of 10% correspond to the averaged results of three thermodilution measurements equally spread over the ventilatory cycle whereas 20% correspond to the average result of three measurement randomly applied and 30% to single estimates [5]. The number of studies included in Table 1 are: CCO-vigilance

thermodilution method 13 [13,51-62]; transpulmonary thermodilution method 5 [62-66]; transpulmonary lithium dilution method 4 [67-70]; the Fick CO_2-rebreathing method 5 [3,71-75]; calibrated Modelflow method 5 [29,38,76-78]; uncalibrated Modelflow 4 [38,78-80]; PiCCOplus 7 [62,76,81-84], only results with software version 4.x and later are used; LiDCOplus 5 [69,70,85-87]; PRAM 3 [34,88,89]; FloTrack-Vigileo 9 [79,84,90-96], only results of software version 1.07 and later are selected. No data of ultrasound methods are included because not enough of these methods were compared to thermodilution cardiac output except for the HemoSonic [79,97-99] which is however out of production at the moment. Also, the results of the impedance method were excluded because Raaymakers *et al.* [45] in a meta-analysis concluded already for insufficient agreement with reference methods. From the data given in Table 1, we may learn that none of the methods can replace the averaged results of three measurement with pulmonary artery intermittent thermodilution equally distributed over the ventilatory cycle (2SD<10%). Transpulmonary thermodilution, transpulmonary lithium dilution both with the averaged results of three measurements, calibrated Modelflow and LiDCOplus pulse contour may replace the pulmonary artery thermodilution with the results of 3 randomly applied measurements. All methods can replace single thermodilution estimates with a 2SD-precision of 30%.

Table 1 Median results for different methods in comparison to intermitted pulmonary thermodilution cardiac output.

Method	N observations	Differences with COpa			Calculated 2SD-precision with Precision Limitations		
		Bias		2SD-precision	2SDpa =10%	2SDpa =20%	2SDpa =30%
		L·min^{-1}	%	%	%	%	%
Indicator dilution							
CCO-Vigilance	3439	0.03	0.55	27	25	18	6
transpulmonary TD	818	0.43	7.74	21	18	7	0
transpulmonary LiD	245	-0.03	-0.55	26	23	16	0
Fick							
CO_2-rebreathing	601	-0.25	-4.35	35	34	29	19
Pulse Contour							
Modelflow-calibrated	995	0.00	0.00	17	16	0	0
Modelflow-noncalibrated	924	0.31	5.63	31	29	23	7
PiCCOplus	1802	0.04	0.73	32	30	25	10
LiCCOplus	452	0.05	0.91	24	22	13	0
FloTrac-Vigileo	1777	0.25	4.55	41	40	36	29

N obs, total number of obersevation; COpa, cardiac output by intermittent pulmonary thermodilution

Table 2 Overview of characteristics for different methods to measure cardiac output.

CO method	Invasiveness	Response	Accuracy	Precision	Limitations
Fick O_2	+++	Intermittent	High	Moderate	Requires a PAC for venous O2 and spirometer or mechanical ventilator. Labor intensive technique
Fick CO_2	+	Slow	Low	Low	Subject must be on ventilator Errors due to shunts
PAC Td bolus	+++	Intermittent	High	High	Special precaution during mechanical ventilation Requires a PAC and triplicate measurement
PAC CCO	+++	Continuous	Moderate	Moderate	Requires a PAC and triplicate measurement
TP Td bolus	++	Intermittent	High	High	Requires a PAC and triplicate measurement
TP Li bolus	++	Intermittent	Moderate	Moderate	Requires only arterial catheter but needs triplicate measurement for sufficient agreement with reference methods
PiCCO	++	Beat-to-beat	Moderate	Moderate	Requires frequent calibration with independant (other) method
LiDCO	++	Beat-to-beat	Moderate	Moderate	Requires frequent calibration with independant (other) method or lithium indicator method
Vigileo	++	Beat-to-beat	Moderate	High	Needs specific sensor
Modelflow	++	Beat-to-beat	High	High	Needs femoral or radial arterial catheter
TOD	+	Continuous	High	Low	Not well tolerated in awake subjects and transducer position difficulty
TTE	-	Continuous	Moderate	Low	Large inter-operator variability
Bioimpedance	-	Continuous	Low	Low	Artifacts due to anatomic variations, shunt, movement, electrical noise

CO is cardiac output, CCO is continuous cardiac output, Li is Lithium, PAC is pulmonary artery catheter, Td is thermodilution, TOD is transoesophageal Doppler, TP is transpulmonary, TTE is transthoracic echography.

Conclusion

Many methods to measure cardiac output are available (see Table 2). None of the methods studied fulfil the criteria of accuracy, precision, operator independence, fast responding, non-invasiveness, continuous measurement, easy of use, low cost and without complications. The Fick for O_2, for instance, is labor intensive and invasive but highly accurate and precise. The continuous thermodilution method does not have a fast response, needs skilled physicians to introduce the PAC and is invasive. The pulse contour methods add no invasiveness give beat-to-beat cardiac output and are easy to use. The ultrasound methods have large inter-intra observer variability. The transpulmonary indicator dilution methods score better in accuracy and precision. The ultrasound methods are limited by large inter-intra observer variability. With respect to precision and accuracy, all methods can replace single thermodilution estimates with a 2SD-precision of 30%, most can replace the averaged result of three randomly applied intermittent thermodilution measurements but none can replace the averaged results of three estimates equally distributed over the ventilatory cycle.

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Chapter 2

Performance of three minimally invasive cardiac output monitoring systems

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Anaesthesia 2009; 64: 762–769

Ideally cardiac output monitoring is accurate, precise, operator-independent, rapid, non-invasive, continuous, easy to use, and cost-effective. Methods that follow changes in cardiac output may provide an early warning on changes in circulatory function or allow 'interrogation' of the circulation with interventions.

Cardiac output has perhaps traditionally been monitored by using a thermodilution pulmonary artery catheter (PAC) using intermittent bolus thermodilution (COtd) and this is still considered by some the best reference method. However, it may not be feasible to follow changes on interventions or applied challenges, due to its time delay [1,2]. Devices based on beat-to-beat assessment of stroke volume are better equipped to monitor changes in cardiac output and two technologies currently available are based on arterial pulse contour and transoesophageal 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 PiCCO™ (Pulsion Medical, Munich, Germany) and LiDCO™ (LiDCO Ltd, Cambridge, UK), does not require an independent calibration [3] and is thus relatively non-invasive using the pressure signal from a standard peripheral arterial line. The standard deviation (SD) of the pulse pressure is correlated to stroke volume based on the patient's age, gender, body height and weight after an automatic adjustment related to an estimate of vascular compliance. Early validation showed conflicting results, but after the introduction of newer software (version 1.07), results became more uniform [4-8].

In some respects the Modelflow method is similar, deriving 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. The Modelflow (or pulse contour) method can follow beat-to-beat cardiac output changes, both after calibration by thermodilution as well as in a non-calibrated setting [9-12].

The HemoSonic monitor (HemoSonic 100, Arrow International, Reading, PA, USA) comprises an ultrasound probe with both M-mode and pulsed Doppler transducers [13,14]. The former measures (in real time) the diameter of the descending aorta while the latter measures blood velocity in the aorta. From these, aortic blood flow (ABF) is computed which in turn enables estimation of cardiac output [15].

The aim of our study was to compare the accuracy, precision and monitoring ability of cardiac output measurements by FloTrac-Vigileo, Modelflow and HemoSonic with intermittent pulmonary artery thermodilution as the reference method.

Methods

Patients and anaesthesia

After ethical approval and written informed consent, 13 patients were studied after coronary arterial bypass grafting or mitral valve reconstruction. All patients had symptomatic coronary artery disease without previous myocardial infarction but patients with a history of abnormal ventricular function, aortic aneurysm, extensive peripheral arterial occlusive disease, aortic valve pathology, and pharyngeal or oesophageal 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).

Anaesthesia during surgery and ICU stay was generally with appropriate doses of propofol, sufentanil and vasoactive medication. 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 $ml \cdot kg^{-1}$ and a respiratory frequency of 12-14 $breaths \cdot min^{-1}$. The fraction of inspired oxygen was maintained at 0.4 and PEEP 5 cmH_2O. During the observation period ventilator settings, sedation and vasoactive medication, when used, were unchanged.

Monitoring techniques

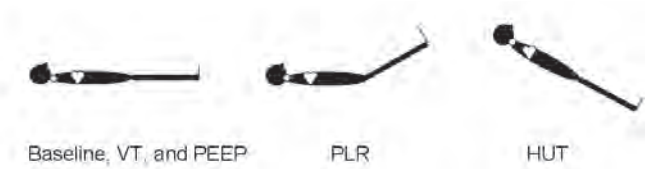
Before ICU admission, a radial artery was catheterized with a 20G catheter (Arrow, Reading, PA, USA) to monitor arterial pressure (Pa) and a pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) introduced into the right jugular vein to monitor central venous pressure (CVP), pulmonary artery 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 and measured in triplicate (10 ml saline solution at room temperature) in 2 minutes, with the measurements equally spread over the ventilatory cycle. These 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) from the radial artery catheter was also connected to a FloTrac pressure transducer (Edwards Lifesciences) with a bifurcated lead, one limb connected to the Vigileo system (Edwards Lifesciences) to measure pulse contour cardiac output (COed) and the other limb connected to a bedside monitor pressure module (Hewlett Packard model M1006A) whose output was used as the 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.
An ultra-sound probe (HemoSonic100, Arrow, Reading, Pa, USA) to monitor aortic blood flow (ABF) was inserted through the mouth and advanced in the oesophagus to the level of the 4th intercostal space and its position 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.

Figure 1 Different positions of the patient during the interventions. A: During supine position VT was increased with 50% and PEEP was increased with 10 cmH_2O. B: PLR, Passive legs 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 o) 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.



Study protocol
Measurements were carried out within 2 h of arrival in ICU and after hemodynamic stabilization post-surgery. Characteristics and treatment data of each patient were collected. During 'Baseline 1' (Figure 1) a series of measurements of HR, MAP, CVP, PAP, COtd, COed, COmf, and COhs were obtained. To change cardiac output, four interventions were applied. First, the tidal volume setting of the ventilator was increased by 50% for 5 minutes. Then 2 minutes later, the same series of measurements were repeated ('VT-series'). Then, 5 minutes after values returned to baseline another series of measurements were performed ('Baseline 2'). Next, positive airway pressure (PEEP) was increased by 10 cmH_2O for 5 minutes, and after 2 minutes the next series of measurements was taken ('PEEP-series').

Then, 5 minutes after return from increased PEEP, a 'Baseline 3' series of measurements was 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 later, 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. Lastly, a head up tilt was induced by raising head of the bed to 30°: 2 minutes later a series of measurements ('HUT-series') were made. Five minutes after return from HUT, during, the last series of ('Baseline 5') measurements were performed.

Statistical analysis

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 precision (i.e., standard deviation), with the limits of agreement (LOA) computed as the bias ±2SD [19]. The coefficient of variation was computed as [COV=100*(SD/mean)]. We also applied the method of Myles and Cui [20], and used a random effects model to calculate precision and limits of agreement. 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 ($p<0.05$) result in cardiac output between baseline and intervention, a post-hoc test (Tukey-HSD in multiple comparison, LSD in pairwise comparison) was used to identify the significant effect. The ability of the monitors to measure the change in cardiac output change (ΔCO) due to our interventions was calculated by subtracting the averaged cardiac output values during the relevant baselines from the mean cardiac output during the intervention (both as absolute and percentage changes). We regarded a 'positive trend' as being when the change in value of the new monitor was in the same direction as those found for COtd, whereas, a 'negative trend' was one where these changed in opposite directions. Ideally, only positive scores should be present. These scores were analysed using 2x2 tables and presented as percentages. Separate scores were counted for changes when thermodilution cardiac output values differed by at least a clinically relevant 5 and 10%.

Results

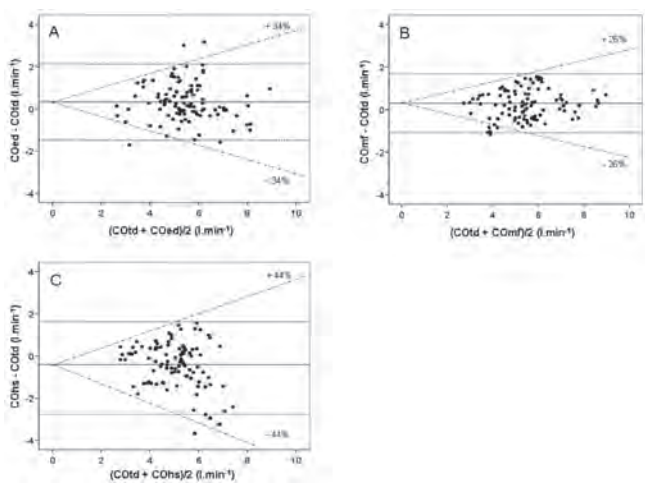
We included 13 cardiac surgical patients, 11 after coronary arterial bypass grafting and 2 after mitral valve reconstruction. A total of hundred seventeen paired CO data sets with COtd,

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 thermodilution cardiac output

Figure 2 shows Bland-Altman plots for difference between COtd and COed, COmf or COhs. Bias between COtd and COmf and between COed and 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}, $p < 0.001$). From Figure 2 it is observable that the distribution of errors is different among the methods. 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%, Figure 2B) whereas values of precision and limits of agreement for COed and COhs are larger (-1.47 to 2.13, 34%, Figure 2A and –2.62 to 1.80 L•min^{-1}, 44%, Figure 2C, respectively).

Figure 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.



Result based on the random effects model of Myles and Cui [20] are shown in Figure 3. The residual within-subject standard deviation was substantially smaller after adjustment 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 (Figures 2 and 3). Bias and precision of both, the original and modified Bland-Altman methods are presented in Table 1.

Figure 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

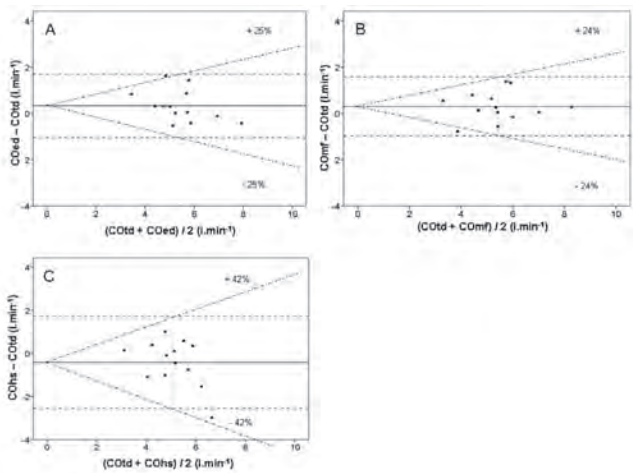


Table 1 Comparison of bias and precision between the original and modified Bland-Altman methods. COtd, intermitted thermodilution cardiac output (reference method); COed, CO measured with FloTrac-Vigileo; COmf, CO measured with non-calibrated Modelflow; COhs, CO measured with HemoSonic 100.

Method	Bias $L \cdot min^{-1}$	Precision $L \cdot min^{-1}$	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

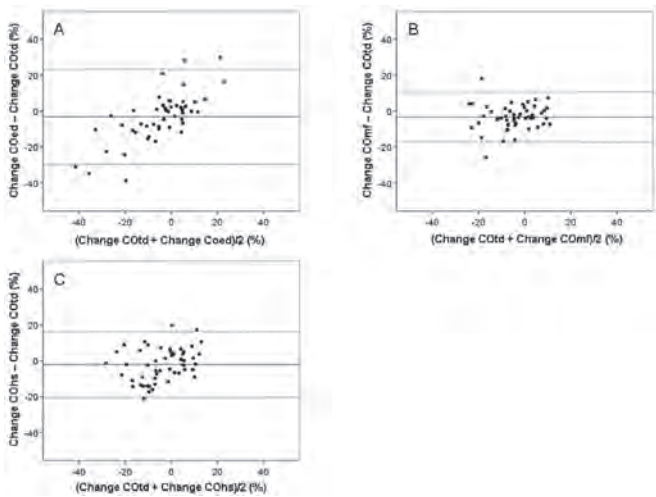
Effects of intervention on CO

The effects of the four applied interventions on our measures are shown in Table 2. Increasing tidal volume did not result in a change in cardiac output with any method. Other interventions did, however, change CO. 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 ($F = 0.19$, $p = 1.000$).

As expected, 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 01.01; COhs v COtd, slope 0.88, CI95% 0.62 to 1.15). COed significantly overestimates the change (compared with COtd) but changes in COmf and COhs were similar to COtd.

Regarding direction of change, the score for agreement was 86% for COmf and 81% for COed and COhs. These scores greatly 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.

Figure 4 Bland-Altman plots with percentage changes in cardiac output in three minimal invasive methods and percentage changes by conventional thermodilution. For abbreviations see Figure 2. Solid line presents bias and dotted lines limits of agreement.



The Bland-Altman plots for changes in cardiac output with LOA are shown in Figure 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 (Figure 4A).

Table 2 Changes in cardiac output (CO) related to increase of tidal volume, increase of PEEP, passive leg raising and head up tilt intervention. 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 ($F = 13.85$, $p < 0.001$).

	CO Baseline	CO Intervention	CO difference	
	Mean (SD) $L \cdot min^{-1}$	Mean (SD) $L \cdot min^{-1}$	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	5.34 (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

Discussion

Our main finding is that only Modelflow yields limits of agreement (26%) that are below the 30% criteria for limits of agreement for a theoretically acceptable alternative to thermodilution cardiac output [21]. Monitoring changes or trends in cardiac output can, however, be performed reasonably well with the non-calibrated Modelflow and HemoSonic (the auto-calibrated FloTrac-Vigileo performs less well in this regard).

Any error in our reference method (COtd) might influence the comparison between cardiac output by thermodilution and FloTrac-Vigileo, Modelflow or HemoSonic. Individual thermodilution cardiac output estimates show substantial scatter (10-15%) in value even under stable haemodynamic and ventilatory conditions [22]. An average of at least three measurements – over the respiratory cycle - is advised to obtain cardiac output estimate with acceptable precision [11,16] (this can require injections to be performed by a motor driven syringe under computer control) [23].

The results of the present study did not show conflicting results with respect to the results of previous reports, obtained with either the FloTrac-Vigileo system version 1.07 [4-8], the non-calibrated Modelflow method [11,12] or Hemosonic 100 system [24,25].
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 2 and 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 (Figure 2A) decreased considerably with the random effects model (Figure 3A). This is account for the overestimation of changes in cardiac output by the FloTrac-Vigileo system (Figure 4A).

Passive leg raising as an intervention in combination with oesophageal ultra-sound blood flow measurement has been used to identify those patients that likely beneficially respond to fluid challenge with an increase in cardiac output [26-28]. Monnet at al. [27] demonstrated that the HemoSonic device could reliably predict such responders. Our data suggests that this may also be the case with FloTrac-Vigileo and Modelflow.
One concern was that during passive leg raising (or even head up tilt), the oesophageal probe position may change. We were careful to reposition the probe regularly to obtain an optimal signal. However, the position of baroreceptors in relation to the heart is also changed by these manoeuvres and this may influence arterial blood pressure by auto-regulation (Figure 1). We would expect this effect to be constant across all methods and not bias any particular device.

Conclusions

The non-calibrated Modelflow method showed best performance in estimation of cardiac output. Changes in cardiac output by thermodilution were also tracked well by the non-calibrated Modelflow and also by the HemoSonic device, whereas the 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 suggest future work focuses on the Modelflow system.

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Chapter 3

A comparison of stroke volume variation measured by the LiDCOPLUS and FloTrac-Vigileo

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Anaesthesia 2009; 64(9): 1004-9

Since 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 have evolved in clinical practice. Most studies have shown SVV and PPV to be 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, such as occurs 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 seemed important.
The 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 five different interventions to the patients. These interventions were: increase of tidal volume, increase of positive end-expiratory pressure (PEEP), a head up tilt procedure, passive leg raising and fluid loading. In between these interventions patients returned to the baseline condition prior to undertaking the next intervention.

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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 prior to surgery. Patients were only selected if they were scheduled to receive a pulmonary artery catheter and a radial artery cannula for peri-operative monitoring and care. 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 a requirement for artificial pacing or cardiac assist devices were also excluded. The final inclusion of the patients was during their initial post-operative period in the ICU.
In the operating room, the radial artery was catheterized with a 20G catheter (Arrow, Reading, PA, USA) to monitor arterial pressure and a pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) was introduced into the right internal jugular vein to monitor central venous pressure (CVP), pulmonary artery pressure (PAP) and to estimate cardiac output (CO) by the intermittent thermodilution method (COtd).
Anaesthesia during surgery and the ICU-stay was maintained with propofol ($2.5\ mg \cdot kg^{-1} \cdot h^{-1}$), sufentanil ($0.06\text{-}0.20\ mg \cdot kg^{-1} \cdot h^{-1}$) 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·kg^{-1} and a respiratory frequency of 12-14 breaths·min^{-1}. The administered fraction of inspired oxygen was 0.4 with PEEP of 5 cmH_2O. During the observation periods, sedation and vasoactive medication, when used, were unchanged.

Measurements

Measurements started in the postoperative period. The radial artery pressure, 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, CA, USA) of which the output signal was used as input to the LiDCOplus (LiDCO Ltd, Cambridge, UK) 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]. Radial artery pressure, PAP and CVP were recorded online on computer disk for documentation and offline calculations. Radial artery pressure, PAP and CVP transducers were referenced to the intersection of the anterior axillary line and the 5th intercostal space. After changes in position of the patient the transducers were re-referenced. Airway pressure was measured at the proximal end of the endotracheal tube with an air-filled catheter connected to a pressure transducer. Airway pressure was balanced at zero level against ambient air.

COtd measurements were performed with an automated system under computer control and measured in triplicate (10 ml saline solution at room temperature) in 2 minutes, with the measurements equally spread over the ventilatory cycle. These three individual COtd measurements were averaged [10,11].

We calibrated the LiDCOplus system with thermodilution cardiac output measurements at the 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 radial artery pressure data.

Study protocol

Measurements were carried out within 2 hours of arrival in ICU and after hemodynamic stabilization. Characteristics and treatment data of each patient were collected. During the

'Baseline-1' period, a series of measurements of HR, COtd, PPVli, SVVli and SVVed were obtained. To change SVV, five interventions were applied. First, the tidal volume setting of the ventilator was increased by 50% for 5 minutes. Two minutes after onset of the increase tidal volume challenge, the same series of measurements were repeated ('VT-series'). Then, 5 minutes after the ventilation values were returned to baseline another series of measurements were performed ('Baseline-2'). For the second intervention, positive airway pressure (PEEP) was increased by 10 cmH_2O for 5 minutes, and after 2 minutes at the increased PEEP the next series of measurements was obtained ('PEEP-series'). Five minutes after return from increased PEEP to baseline, a 'Baseline-3' series of measurements was carried out. For the third intervention, passive leg raising was performed from the supine position by lifting both legs at a 30° angle and holding them there for 5 minutes. Two minutes after the onset of leg raising the series of measurements were repeated ('PLR-series'). Five minutes after return from passive leg raising, 'Baseline-4' measurements were performed. For the fourth intervention, a head-up-tilt was performed by raising head of the bed to 30°. After 2 minutes of head-up-tilt the next series of measurements were made ('HUT-series'). Five minutes after return from head-up, the last series of baseline measurements were performed ('Baseline-5'). Lastly, the fifth intervention, a fluid loading
64) with 500 ml Hydroxyethyl Starch (HES 130/0.4) over 15 minutes, was undertaken. Five minutes after ending fluid loading the last series of measurements were made ('FL-series'). Fluid loading was only performed in eight patients. In the other patients it was not indicated. The study protocol lasted about 75-90 minutes following which 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.

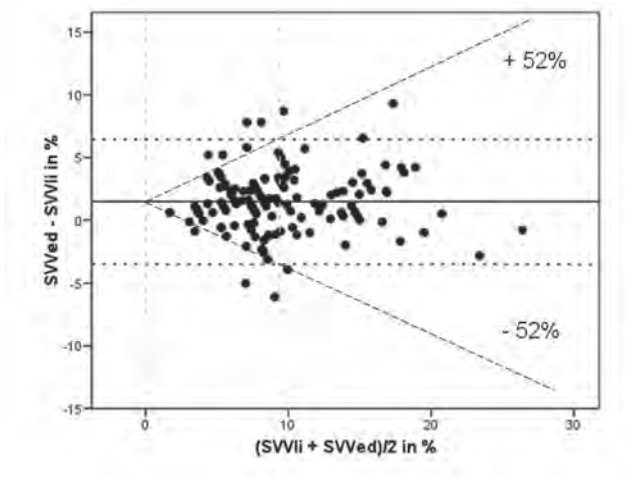
Statistical analysis

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, differences between SVVed and SVVli during baseline and interventions were analyzed using a paired t-test. Calculations of bias and precision and limits of agreement between SVVed and SVVli were performed using Bland and Altman analysis [12] in which bias was the difference between SVVli and SVVed and precision the standard deviation (SD) of this difference. The upper and lower limits of agreement were calculated as the bias ±2SD. The coefficient of variation was calculated as 100%·SD/mean. The percentage limits of agreement were calculated as twice the coefficient of variation. The differences in precision between the two methods were tested by using correlated variances in paired samples [13,14]. Repeatability of SVVli and SVVed was calculated using the data from the baseline measurements. A p-value of less than 0.05 was considered statistically significant. Unless otherwise stated, data are presented as mean ± SD.

Results

Fifteen postoperative cardiac surgery patients were included. Patient demographics were; male to female ratio of 12:3, mean age 66 (range 55 to 82) years, and mean body surface area (BSA) 1.98 ± 0.20 m^2. Only eight 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 $L \cdot min^{-1}$. Heart rate ranged from 54 to 92 (average 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%).

Figure 1 Bland-Altman plot, 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 agreements in percentage.



Agreement of SVVli and SVVed

The error diagram for difference between SVVli and SVVed is shown in Figure 1. Bland-Altman statistics are indicated in the Figure by bias and limits of agreement. The bias is significantly different from zero, at 1.5 ± 2.5%, < 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 was 26% giving a relatively large range for the percentage limits of agreement of 52%.

Interventions

Data on COtd, HR, PPVli, SVVli, SVVed and the differences between SVVli and SVVed for the different interventions and baseline conditions are shown in Table 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 interventions was ($F = 8.29$, $p < 0.001$). Differences between SVV measurement methods were consistent across all observations ($F = 1.54$, $p = 0.142$).

Table 1 Differences in cardiac output (CO), heart rate (HR), pulse pressure variation (PPV) and stroke volume variation (SVV) at interventions. The interventions are; increase of tidal volume with 50% (VT); increase in PEEP with 10 cmH_2O (PEEP); passive leg raising (PLR); head-up tilt (HUT) and fluid loading (FL); Method of measurement: CO thermodilution (COtd), PPV LiDCO system (PPVli), SVV LiDCO system (SVVli), SVV FloTrac-Vigileo system (SVVed). Statistic analysis paired t test (*).

Inter-vention	**COtd** ($L \cdot min^{-1}$) Mean ± SD	**Heart rate** (min^{-1}) Mean ± SD	**PPVli** (%) Mean ± SD	**SVVli** (%) Mean ± SD	**SVVed** (%) Mean ± SD	**SVVli** (%) Mean ± SD	**Coefficient of variation** (%)	**SVV** difference p-value*
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

One-way ANOVA statistics showed no significant difference between five baseline measurements for CO ($F = 0.203$, $p = 0.936$), HR ($F = 0.094$, $p = 0.984$), PPVli ($F = 0.184$, $p = 0.946$), SVVli ($F = 0.254$, $p = 0.906$) and SVVed ($F = 0.390$, $p = 0.815$), indicating no significant effects over time.

On average, the tidal volume challenge showed no change in COtd and an increase in PPVli, SVVli and SVVed. During the PEEP challenge we observed a decrease in COtd and an increase of PPVli, SVVli and SVVed. Passive leg raising resulted in increased COtd and decreased PPVli, SVVli and SVVed. The head-up challenge resulted in a decreased COtd

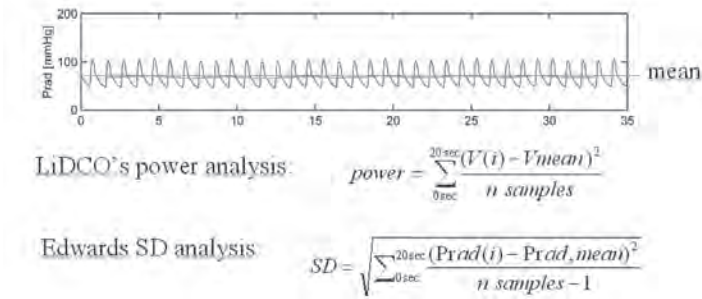
and increased PPVli, SVVli and SVVed. Fluid loading increased COtd and decreased PPVli, SVVli and SVVed. Heart rate did not change significantly during study interventions. The most significant result was the difference between SVVli and SVVed for the different interventions (Table 1). We considered the results obtained during the five baseline observations as repeated measures. Analysis of these repeated measurements showed the following coefficients of variation: SVVli = 21%, SVVed = 22% (no difference between SVVli and SVVed, = 0.024, = 0.779), and PPVli = 23%.

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 ambiguous as can be concluded from the high value of coefficients of variation (21 and 22%) for repeated measures. These findings underline Pinsky's warning to be careful in the clinical use of SVV by pulse contour techniques, and to be restrained in using SVV (as a solitarily variable) in the management of individual patients [4].

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 (where SVmax is the maximum, SVmin is the minimum and SVmean is the mean stroke volume). Therefore it is most likely explained by the difference in the calculation of SVmin, SVmax 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 [15] whereas the FloTrac-Vigileo uses Langewouter's equations [16]. There is a large similarity between the computations of SV (Figure 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.

Figure 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 (Prad) with Remington's equations. Edward's corrects cardiac output after SD calculation with Langewouter's equations.



In a recent paper Hofer *et al.* [17] compared the FloTrac-Vigileo and the PiCCOplus system
68) (Pulsion Medical Systems, Munich, Germany) for assessment of SVV to predict fluid responsiveness. The authors found SVV measured by the PiCCO system to be higher than the SVV by the FloTrac-Vigileo system. Besides this bias, we calculated from their Bland-Altman analysis percentage limits of agreement of approximately 40% between the two systems. The authors concluded that there was similar performance of the two investigated systems in terms of predicting fluid responsiveness although the SVV threshold level in predicting fluid responsiveness by the PiCCO system (12.1%) differed from the FloTrac-Vigileo system (9.6%). The differences in absolute SVV values were explained by the difference in signal detection sites (radial artery for FloTrac-Vigileo system and femoral artery for PiCCO system) as well as difference in signal analysis techniques. In our study we can exclude the influence of different detection sites because we used the same site for both techniques, i.e. the radial artery. Thus the difference between SVVli and SVVed was most probably related to differences in signal analysis. We did not calculate receiver operating curves to calculate differences in thresholds for predicting fluid responsiveness because we consider our number of fifteen patients too low. However, we expect different threshold levels for the LiDCO and FloTrac-Vigileo system as well.

A wide range for the percentage limits of agreement (approximately 40%) can also be observed in the study by de Castro *et al.* [18], in which SVV measured by the PiCCOplus system was compared with SVV measured by aortic Doppler echocardiography.

Given these margins of error, we conclude that none of the above mentioned systems is interchangeable with the other. It seems that the calculation of SVV is prone to propagation of errors [18]. This is supported by the high coefficients of variation for repeated measures, SVVli of 21% and SVVed of 22%, observed in our study. As the errors in the measurements of SVVli and SVVed are not completely independent we cannot estimate the coefficient of variation for the difference between the two techniques from the coefficients of variation of both systems [19]. The coefficient of variation for the difference may vary between 1% and 43%. In our study we observed a coefficient of variation for the difference of 26%, which lies within this range.

Nevertheless the changes in SVV induced by our interventions were in agreement with what was clinically expected (Table 1). During the increase in tidal volume we observed, in comparison to baseline, no change in cardiac output but an increase in SVV. A similar increase in SVV to the increase of tidal volume was observed by Kim and Pinsky [20] in a well controlled animal study. During both the increased PEEP and head-up-tilt manoeuvres, CO decreased and SVV increased. Following both passive leg raising and fluid loading we observed an increase in CO and decrease in SVV with both systems. However, the difference between SVVli and SVVed fluctuated considerably.

Despite these shortcomings, SVV still seems a variable of considerable interest. Several authors have shown that SVV can predict the effects of fluid loading on cardiac output, albeit using different thresholds (ranging from 9.5 to 12.5%) to separate responder and non responders [17,21-23]. Although there is no reason to doubt the general principle of SVV as a predictor of fluid responsiveness, we conclude from our results that some caution in the use of SVV in individual patients is justified. Indeed, based on Bland-Altman analysis for repeated measurements for SVV with percentage limits of agreement, the value of SVV may differ by up to 40% between measurements. Thus an initial observed SVV of 10% may subsequently change to 14% or 6% without any change in the patient's condition. This has important clinical implications: to improve cardiac output, a SVV of 14% may favour fluid loading, whereas a SVV of 6% may favour the use of catecholamines.

Conclusions

In this study, SVV measurements made by the LiDCOplus system (SVVli) and by the FloTrac-Vigileo system (SVVed) differed significantly. With percentage limits of agreement of 52% the two methods did not agree and should not be used interchangeably. Furthermore, the determination of SVVli and SVVed appeared to be ambiguous as illustrated by the high values of their respective coefficient of variation (21% and 22%) for repeated measures. These findings limit clinical usefulness in individual patients and limit the comparability of results on fluid loading responsiveness from different studies.

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Section 2

Hemodynamic management

Chapter 4

Hemodynamic assessment in Dutch intensive care units

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Netherlands Journal of Critical Care 2009; 13(4): 178-84

The prolonged presence of hypovolaemia seriously impairs oxygen delivery to vital organs, hence fluid loading is indicated [1]. However, unnecessary fluid administration can lead to general and pulmonary oedema and cardiac failure [1,2]. Therefore, the selection of patients that will benefit from fluid administration is critical.

This selection is traditionally based on clinical signs such as urine colour and production, as well as on filling pressures such as central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP). In 1998, Boldt and colleagues performed a survey and reported that 93% of all ICU physicians in Germany used CVP and 58% used PAWP to assess volume status [3]. Nevertheless, neither clinical signs nor filling pressures have unambiguously been shown to discriminate between those patients who benefit from fluid loading and those who do not [4-6]. In most studies, this beneficial effect was defined as a significant increase in cardiac output. Because, in principle, nearly all patients will experience an increase in cardiac output after fluid loading [7], there is a necessity to differentiate between an increase in measured cardiac output (CO) after fluid loading and a "clinically" significant increase in CO. In fluid-loading-responsiveness studies, responders and non-responders are divided by an increase of 10% in CO after approximately 500 ml of fluid loading. Furthermore, the presence of fluid-responsiveness does not imply the need for fluid loading. Not only the ability to accurately predict the effect on CO after fluid loading is important but, for instance, also tissue O_2 in the different organs and outcome need more attention.

In recent years, new variables based on heart-lung interaction, i.e. respiratory-induced stroke volume variation (SVV), pulse pressure variation (PPV) and systolic pressure variation (SPV), have been introduced [8]. These variables have been studied extensively but results regarding their predictive value in identifying responders and non-responders on fluid loading have been contradictory [9-11]. In addition, loading the circulation with small amounts of fluid (up to 500 ml) [12], or by passive leg raising (PLR) [7, 13-17] have become the subject of intense interest in assessing fluid loading responsiveness (or in other words to identify patients who will benefit from fluid loading).

We evaluated the impact of newly derived variables (SVV, PPV and SPV), fluid challenges and PLR, and new cardiac output devices in daily practice in Dutch intensive care units. Finally, we investigated the use of guidelines to monitor volume status and fluid responsiveness in the ICU.

Materials and methods

A questionnaire was sent via the Dutch Society of Intensive Care (NVIC) to 446 Dutch intensive care physicians (i.e. intensivists and fellows) working in one of the 99 hospitals with an ICU in the Netherlands. In the Netherlands, most intensive care physicians are members of the NVIC. A cover letter was included to provide background information and a

stamped addressed return envelope was added. The questionnaires were sent by regular mail in March 2008.
The questionnaire was designed to be answered within 10 minutes. The questionnaire was checked by a sociologist with experience in the design of surveys. The majority of questions were multiple choice. The questionnaire consisted of seventeen questions and covered three topics: 1. General characteristics of ICU physicians; prior specialty training, experience level, type of hospital; 2. Assessment of haemodynamic condition and treatment of patients; use of clinical signs, haemodynamic parameters and challenges to the circulation; 3. Guidelines used in the ICU; definitions of hypovolaemia and hypervolaemia, use of guidelines, date of guideline update. The questionnaire was in Dutch. A translation is shown in the appendix. Questionnaires were collected up to one month after being sent. The completed questionnaires were returned anonymously.
Because of the exploratory character of the data, analysis consisted of descriptive techniques and chi-square tests when appropriate (SPSS 14.0.1 for Windows, SPSS Inc., Chicago, IL). Results are expressed in frequencies. A p-value of ≤ 0.05 was regarded significant.

Results

General characteristic of ICU physicians
Altogether 176 of 446 (39%) questionnaires were returned. Respondents were predominantly specialized in internal medicine and anaesthesiology, the experience level within these two specialties was not significantly different (χ^2, p=0.079). Characteristics of respondents are shown in Table 1.

Table 1 Respondent characteristics (in % of all respondents).

Specialization	Anaesthesiology	45
	Internal Medicine	44
	Surgery	4
	Paediatrics	3
	Neurology	1
	Pulmonology	2
	Cardiology	1
Experience level	Fellow	7
	0-5 years	40
	5-10 years	14
	> 10 years	38
Type of hospital	Non-university	76
	University	24

Assessment of haemodynamic condition and treatment of patients

The clinical signs most often used by Dutch ICU physicians in their initial assessment are shown in Table 2. Urine colour and production as well as capillary refill were the most used. Combinations of clinical signs used were urine production and blood pressure (19%), capillary refill and blood pressure (10%), capillary refill and heart rate (8%). We requested respondents to circle up to two clinical signs, however, 10% of respondents marked more than five clinical signs. These respondents indicated to use a wide variety of clinical signs in their assessment.

To estimate the need for volume expansion, the haemodynamic status was further investigated using the parameters mentioned in Table 3. Clearly, CVP is the most used parameter (70%). Surprisingly, SVV, SPV or PPV were used by 47% of all respondents. MAP and CO were considered by 33% and 19% of the physicians to be the most important predictive parameters. At 31%, the combination of CVP and SVV or PPV or SPV was the most used (Table 4). Remarkably, CVP was mentioned in most combinations.

Table 2 Clinical signs used in the assessment of volume status.

Clinical signs	Frequency (in %)
Urine colour or production	39
Capillary refill	28
Blood pressure	7
More than five clinical signs	10
Skin turgor	7
Body temperature	5
Dry mouth	1
Fluid balance	2
Heart rate	1

Table 3 Parameters used in the assessment of volume status.

Parameter	Frequency (in %)*
CVP	70
SVV, PPV or SPV	47
MAP	33
Serum urea and creatinine	22
CO	20
SvO_2	20
Urine sodium	15
TEE	14
PAWP	12
Serum lactate	8
SAP	4
LVED	2
Shape of arterial wave	1

* Total frequency exceeds 100% since multiple parameters can be used by a respondent

Table 4 Most used combinations of parameters in the assessment of volume status.

Parameters	Frequency (in %)
CVP & SVV, PPV, SPV	31
CVP & MAP	22
CVP & Urea/ creatinine	17
SVV, PPV, SPV & CO	11
CVP & Urine sodium	11
CVP & CO	10
CVP & SvO_2	10
MAP & SVV, PPV, SPV	10
CVP & TEE	7
CVP & Lactate	6
MAP & Urine sodium	6
SVV, PPV, SPV & SvO_2	6
SVV, PPV, SPV & TEE	7
SVV, PPV, SPV & Urea/ creatinine	6

If cardiac output was monitored: the pulmonary artery catheter was used by 65%, PiCCO (Pulsion Medical Inc., NJ, USA) by 15%, trans-oesophageal echocardiography by 11%, Vigileo/ FloTrac (Edwards Lifesciences, CA, USA) by 5%, NICO (Novametrix Medical Systems Inc, CT, USA) by 4%, and trans-thoracic echocardiography by 2%. Forty-four percent of these respondents could choose from two or more devices to monitor cardiac output.
To predict which patients would benefit from fluid loading, the effect of passive leg raising (PLR) was used as an integral part of volume status monitoring by 2% of the respondents. Twenty-seven percent never used PLR, 21% seldom used PLR, 35% occasionally used PLR and 17% often used PLR. Interestingly, 10% of respondents always used a fluid loading challenge, 66% used it often, 21% sometimes and 3% seldom or never.
When a PLR or fluid challenge was applied, the majority of respondents monitored changes in heart rate, MAP and CVP to predict fluid loading responsiveness. Forty-two percent used one parameter, 34% used two parameters, and 24% used three or more parameters to make their assessment. In Table 5, an overview is given of the parameters used in the passive leg raising and fluid challenge.

Table 5 Eight most often used parameters during a fluid loading challenge or passive leg raising to predict fluid loading responsiveness.

Parameters	Frequency (in %)*
Heart rate	59
MAP	48
CVP	32
CO	21
Urine production	17
SVV, PPV or SPV	10
SAP	6
SvO_2	3

* Total frequency exceeds 100% since multiple parameters can be used by a respondent

Prior specialty training, experience level or type of hospital did not influence the selection of clinical signs or use of haemodynamic parameters to assess volume status. Exceptions were blood pressure and serum lactate which were used more often by physicians with less than five years of experience during initial assessment (10/ 84 vs. 3/ 92 with $p < 0.001$ and 10/ 84 vs. 12/ 92, $p=0.029$, respectively). Skin turgor was used less in the less-than-five-years experience group than in the group of physicians with more than five years experience (2/ 84 vs. 12/ 92 with $p<0.009$).

Guidelines used in ICU

A quarter (n=44) of all physicians have departmental guidelines to assess the hypo- or hypervolaemic status of a patient. Where guidelines were in place, 57% of respondents indicated that they almost always followed these guidelines, whereas 43% seldom followed them. The parameters used in the available guidelines are described in Table 6. Twenty-one percent used a single parameter from their guidelines 24% used two, 41% used three and 14% used four parameters.

Table 6 Frequency of use of haemodynamic parameters in active haemodynamic monitoring guidelines in Dutch intensive care departments.

Parameters	Frequency (in %)*
CVP	55
MAP	43
CO	33
SVV, PPV or SPV	21
Diuresis	36
Heart rate	21
Lactate	10
SvO_2	10
PAWP	7

* Total frequency exceeds 100% since multiple parameters can be used by a respondent

Eighty percent of these guidelines had been updated within the past year. Thirty-four percent of the respondents were unaware which authority was responsible for updating the guideline. A total of 48% of the guidelines were updated by a committee within the Intensive Care department, and 18% were updated by the head of the department. Surprisingly, none of the guidelines had been directly adapted from those of intensive care or anaesthesiology societies. The type of hospital did not influence whether a guideline for haemodynamic assessment was in place or not (p=0.092).

Discussion

In 2006, the Dutch Ministry of Health registered 238,022 adult-patient ventilation-days in ICUs in the Netherlands [18]. We may assume that these patients were continuously monitored and volume status was assessed regularly to optimize tissue perfusion. The aim of this survey was to evaluate the impact of recently introduced parameters and challenges in the daily practice of Dutch intensive care physicians. We mapped the current use of haemodynamic parameters in the assessment of volume status of intensive care patients. In addition, we researched the use of guidelines for haemodynamic monitoring.
Recent publications might have had a relatively high impact on the use of haemodynamic parameters in the assessment of volume status. Although the use of CVP measurement is still high (70%), 47% of physicians use SVV, PPV or SPV and 76% regularly use fluid

challenges in their assessment. There is no uniformity or consensus on the use of parameters in evaluating volume status. This is supported by the low number of ICUs with guidelines for haemodynamic monitoring of volume status and fluid loading. In addition, 43% of physicians reported that they barely used the available guidelines.

The incidence of use of SVV, PPV or SPV is remarkable for several reasons. First, we found that pulse contour devices are used less than thermodilution devices to measure CO. This contrasts the finding that SVV, PPV and SPV are used by 47% and CO by 19%. Second, the use of these parameters in haemodynamic monitoring has primarily been studied in cardiac surgery patients [10, 19, 20]. Third, the use of these parameters is restricted to sedated patients fully dependent on mechanical ventilation [21]. Moreover, the average duration of mechanical ventilation is decreasing due to fast track protocols [22]. Fourth, arrhythmia, a common phenomenon in ICU patients, hampers the use of SVV, PPV and SPV. Fifth, variations in stroke volume and arterial pressure are found to be reliable only when ventilation with larger tidal volumes (> 8 $ml \cdot kg^{-1}$) are used [8] while ventilation with lower tidal volumes (< 6 $ml \cdot kg^{-1}$) are advocated in the ARDSnet study for ARDS/ALI patients.
CVP is still frequently used although its use is controversial. In a recent review the authors calculated a pooled area under the receiver operating curve to predict fluid loading responsiveness for CVP of 0.56. They proposed the discontinuation of the routine measurement of CVP to monitor volume status of the patients in the ICU or operating room [23]. Moreover, several studies have shown SVV to be a better predictor of fluid loading responsiveness than CVP [10, 24, 25].
Passive leg raising has been studied for a number of years, and in this survey its use was limited to 17% of the responding intensivists. Although one advantage of PLR over fluid challenge could be the reversibility of the fluid challenge, 76% of respondents indicate using a fluid challenge. These findings become less surprising when we consider that the fluid challenge as well as SVV, PPV or SPV have been the subject of investigation since the 1990's. We hypothesize that considerable time has to elapse before experimental findings become a routine part of clinical care. Nevertheless, it can also be argued that the difference in use of PLR and fluid challenge is explained by the robustness of the fluid challenge.
When a challenge to the circulation is used to assess volume status, heart rate, MAP and CVP are most often used parameters to monitor and predict fluid loading responsiveness. Several of the most-often-used parameters, however, do not concur with recent literature. Change in CVP due to PLR for instance, has been shown to be an unreliable predictor [15]. The reliability of other parameters such as urine production and SvO_2 has not been studied during a challenge. This could also imply that some of the respondents performed another type of fluid challenge.

It must also be noted that the use of lactate is mentioned by only 8% of respondents even though "surviving sepsis" and "early goal directed therapy" clearly advocate the use of lactate [26,27]. This could be explained by the limitation of the number of answers that could be given in this survey. However, SvO_2 is used by 19% of respondents and this parameter is also advocated in both guidelines [26,27].

Other surveys

In Germany in 1997, Boldt and colleagues performed a survey to assess fluid loading strategies in ICUs [3]. In this survey CVP was used by 93% of respondents and PAWP by 58%, while the dynamic parameters SVV, PPV or SPV were barely used [3]. We assume that similar strategies have been used in haemodynamic management in Dutch and German ICUs. In the current survey, the incidence of use of CVP and especially PAWP, is lower and a large group of ICU physicians used SVV, SPV or PPV as parameter.

More recently, in 2006, Kastrup and colleagues sent a questionnaire to the leading physicians of 80 cardiac surgery ICUs in Germany [28]. In this subgroup, CVP, MAP and PAWP were used more frequently (89%, 84% and 33% respectively), while SVV, SPV or SPV was used by only 15% [28]. We attribute differences in Kastrup's and our findings to differences in the surveyed subgroup, time, and/or the country in which the survey was performed, and concomitant differences in the setup of post-registration education programmes.

Considerations

Firstly, although an acceptable return rate of 39% was achieved, inherent to this type of survey, it must be noted that it may not represent all physicians. In contrast, Boldt [3] and Kastrup [28] achieved return rates of around 60%. Secondly, the completed questionnaires were returned anonymously. Hence, we could not determine a no-response bias. Thirdly, some answers could have been 'desired' answers. The finding that 47% of respondents use SVV, PPV and/or SPV to evaluate volume status seems to be at odds with the actual use of pulse contour methods (20% of respondents). Lastly, the group of physicians with an academic position seems overrepresented as we got 24% respondents from academic hospitals whereas actually only 8% of ICU physicians have an academic position [18]. However, we could not detect a difference in response, for any of the questions (including usage of guidelines), between the two groups. Therefore, we do not regard this overrepresentation as a significant bias.

Conclusions

The present survey shows that CVP is still the most often used parameter to guide fluid loading. However, Dutch ICU physicians are remarkably compliant in using recently developed and published dynamic parameters as SVV and PPV as well as fluid challenges.

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Appendix Questionnaire volume status assessment and fluid loading

1. What is your specialty training, besides intensive care medicine? **Circle your choice:**
   a. Anaesthesiology
   b. Cardiology
   c. Cardiac surgery
   d. Surgery
   e. Internal medicine
   f. Pulmonology
   g. Neurosurgery
   h. Neurology
   i. Other, _____

2. How long have you been an intensive care physician? **Circle your choice:**
   a. Fellow
   b. 0-5 years
   c. 5-10 years
   d. > 10 years

3. In what type of hospital do you work? **Circle your choice:**
   a. University hospital
   b. Non-university hospital

4. Which clinical indicators do you use to decide on further analyses of a patient's volume status?
   Please circle a maximum of two choices:
   a. Skin turgor
   b. Dry mouth
   c. Dry axillae
   d. Urine colour and/or production
   e. Body temperature
   f. Capillary refill
   g. Colour of the extremities
   h. Fluid balance
   i. Blood pressure
   j. Heart rate
   k. Other, _____

5. Which indicator(s) do you use to determine the volume status of the patient?
Please circle up to three of your choices:
   a. Central venous pressure
   b. Mean arterial pressure
   c. Pulmonary arterial pressure
   d. Systolic arterial pressure
   e. Pulmonary arterial wedge pressure
   f. Dynamic parameters: SVV, PPV or SPV
   g. Cardiac output
   h. PaO_2
   i. SvO_2
   j. Trans-oesophageal Doppler echography
   k. Plasma urea, creatinine or electrolytes
   l. Urine sodium
   m. Serum lactate
   n. Other, _____

6. When you determine cardiac output, which device do you use? **Circle your choice(s):**
   a. None
   b. Pulmonary artery catheter (thermodilution bolus/ continue)
   c. Trans-pulmonary thermodilution
   d. Trans-oesophageal Doppler
   e. Pulse contour - PiCCO
   f. - LidCO
   g. - Vigileo/ Flotrac
   h. Other, _____

7. Do you use passive leg raising (PLR) to determine the volume status of your patients? **Circle your choice:**
   a. Never
   b. Seldom
   c. Once in a while
   d. Often
   e. Always

8. Do you use fluid challenges to assess the volume status of your patients? **Circle your choice:**
   a. Never
   b. Seldom
   c. Once in a while
   d. Often
   e. Always

9. If you use PLR and/or fluid challenges, which parameters do you use to determine the outcome?

   Parameter(s): _____

10. Are there guidelines or protocols in your ICU in which parameters for hypo- or hypervolaemia are used. If yes, which parameters? **Please circle your choice:**
    a. No
    b. Yes, the parameter(s) are: _____

11. If such guidelines exist, do you use the definition for hypo- or hypervolaemia?
    Please circle your choice:

Hypovolaemia:		Hypervolaemia:	
a.	Always	a.	Always
b.	Often	b.	Often
c.	Once in a while	c.	Once in a while
d.	Seldom	d.	Seldom
e.	Never	e.	Never
f.	Not defined	f.	Not defined

12. Are there guidelines in use in your ICU on how to perform fluid loading? **Please circle your choice:**
    a. Yes, please continue with the next question
    b. No, this is the end of the questionnaire

13. Do you use these guidelines for fluid loading in your treatment? **Please circle your choice:**
    a. Always
    b. Often
    c. Once in a while
    d. Seldom
    e. Never

14. If yes (question 12), when were these guidelines last updated? ____/____/____

15. Who is responsible for keeping these guidelines up to date? **Please circle your choice:**
    a. A committee related to the ICU
    b. A committee related to another department in the hospital
    c. A society or organization, namely; _____
    d. Head of the department

88)

Chapter 5

Fluid loading responsiveness: what parameter can we use?

Bart Geerts, Leon Aarts and Jos Jansen

On a daily basis physicians asses the volume status of individual patients. Volume status optimization is required to maximize oxygen delivery to vital organs, like brain, kidneys and heart. Prolonged oxygen deficit can lead to an inflammatory cascade resulting in multi-system organ dysfunction [1]. Conversely, unnecessary fluid administration can lead to anasarca, pulmonary oedema, cardiac failure, anastomotic leakage, infections prolonging hospitalization or even causing death [2]. In these cases, pharmacological support may be indicated instead of fluid replacement. Several studies have shown the beneficial effects of restrictive use of fluids during and after operations resulting in a reduction of hospital stay up to 10% [3]. Therefore, the selection of critically-ill patients that will benefit from fluid loading is essential. This selection can be made with the use of fluid loading responsiveness (FLR). In this review, we ask ourselves: "Which measurable determinant(s) can be used to predict a clinically significant effect of fluid administration on cardiac output (CO)?"

Methods

MEDLINE, EMBASE and CENTRAL databases were searched for all publications on prospective observational studies in adult patients in the intensive care unit (ICU) or operating room (OR) that assessed FLR up to 2010. To maximise the practical guidance for
90) the ICU clinician with this review, studies were included only when a specific cut-off value to predict FLR and its respective sensitivity and specificity derived from receiver operating curves (ROC) was reported. ROC curves describe sensitivity and specificity characteristics over a spectrum of cut-off points. An area under the ROC curve of 1.00 is optimal; both sensitivity and specificity are 100% [4].

Fluid loading responsiveness

The selection of patients that are likely to respond to fluid loading is traditionally based on clinical signs. Subsequently, other parameters are taken into consideration like central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) [5]. In recent years, new variables based on heart-lung interaction, i.e. respiratory-induced stroke volume variation (SVV) and pulse pressure variation (PPV) have been introduced in the ICU. Reversible autotransfusion by passive leg raising (PLR) has also become the subject of intense interest. In this review, a wide range of parameters is assessed for its value for the prediction of FLR.

Clinical signs and symptoms

The initial assessment of volume status is most often based on clinical signs and symptoms, like skin turgor, urine colour or production, fluid balance and the presence of peripheral oedema. Stephan *et al.* [6] measured circulating blood volume (CBV) with human-serum albumin in 36 patients. Hypovolaemia, defined as a 10% lower CBV compared to a control

population, was present in 53% of the patients. However, clinical signs did not prove to be useful to discriminate between hypovolaemic and normovolaemic individuals. For instance, the presence of skin mottling had a sensitivity of 28% and specificity of 78%, while absence of peripheral oedema had a sensitivity of 64% and specificity of 56% to predict hypovolaemia. The definition of hypovolaemia could be subject of critique in this study and fluid loading responsiveness was not measured. However, there is a clear indication that the use of isolated or combinations of clinical signs are unreliable to predict FLR.

Static/ filling pressures

Besides clinical signs, traditional hemodynamic parameters, like central venous pressure and pulmonary artery occlusion pressure (PAOP) are often used in the assessment of FLR [5,7]. Although multiple studies have reported positive results, the use of these parameters in patients with sepsis, trauma, acute respiratory failure, and in the per-operative phase of cardiovascular surgery is found controversial. Moreover, these studies could not show that changes in CVP and PAOP after volume loading are correlated with changes in stroke volume or cardiac output [8-13]. CVP was found to have clinical significance (i.e. it correlates to CBV) only for extreme values (<2 mmHg or >18 mmHg) [14]. PAOP studied by Lattik and Wyffels showed a poor predictive values for FLR in cardiac surgery patients with area under the ROC curves of 0.63 (95% CI between 0.44 and 0.82, n=15) and 0.58 (95% CI between 0.39 and 0.75, n= 32) respectively [15,16]. In Table 1 and 2 an overview is given of literature that reported on FLR and CVP and PAOP.

Table 1 Reliability of baseline central venous pressure to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Barbier, *et al.* [8]	20	Sepsis	12 mmHg	90%	30%	0.57 ± 0.13
Cannesson, *et al.* [9]	25	Cardiac surgery *	3.5 mmHg	77%	63%	0.75 ± 0.11
Osman, *et al.* [10]	96	Sepsis *	8 mmHg	62%	54%	0.58 (0.49-0.67)
Reuter, *et al.* [11]	12	Cardiac surgery *	6 mmHg	50%	90%	0.71 (0.50-0.92)
Reuter, *et al.*[11]	14	Cardiac surgery *	10 mmHg	71%	62%	0.71 (0.54-0.88)
Biais, *et al.* [12]	35	Circulatory failure	9 mmHg	61%	82%	0.68 (0.50-0.83)
Vistisen, *et al.* [13]	23	Cardiac surgery	8 mmHg	35%	100%	-
Muller, *et al.* [48]	33	Circulatory failure	7 mmHg	54%	100%	0.77 ± 0.10

* Multiple measurements in same patients

Table 2 Reliability of baseline pulmonary artery occlusion pressure to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Osman, *et al.* [10]	96	Sepsis	11 mmHg	77%	51%	0.63 (0.55-0.70)
Reuter, *et al.* [11]	12	Cardiac surgery *	7 mmHg	79%	70%	0.77 (0.58-0.96)
Reuter, *et al.* [11]	14	Cardiac surgery *	8 mmHg	59%	75%	0.70 (0.52-0.88)

* Multiple measurements in same patients

It seems that CVP and PAOP are not suitable for standard evaluation of FLR. This is most like due to the large differences in myocardial function. Especially in critically ill, myocardial function is oftentimes depressed. Since CVP and PAOP are directly related to the function of the heart as well as mechanical ventilation, the absolute magnitude of these parameters in itself are not reliable in predicting FLR.

Although mean arterial pressure (MAP) is a well-identified goal to maintain perfusion of vital organs, it has not been studied extensively for its value to predict FLR. There are only two studies available that report on the reliability of MAP to predict FLR; Preisman and Kramer studied the reliability of baseline mean arterial pressure to predict fluid responsiveness and found areas under the ROC curves of 0.73 (95% CI between 0.60 and 0.87, n=18) and 0.81 (95% CI between 0.62 and 1.00, n=21) respectively [17,18]. Preisman found MAP at a cut-off of 76.5 mmHg to have a sensitivity of 64% and a specificity of 77% to predict FLR in 18 post-elective CABG surgery.

The low predictive value of MAP is likely related to the influence of disease state, for instance vasoplegia in sepsis, and pre-existing differences in normotensive values in-between individuals. These differences also complicate consensus on target blood pressures to guarantee perfusion of the brain and other vital organs. The International Consensus Conference on Hemodynamic Monitoring in 2006 found moderate to low evidence to implement target blood pressures in the management of shock [19]. This because relevant clinical studies were absent.

Heart rate

Heart rate (HR) has been studied on a small scale. Kramer *et al.* [18] reported baseline HR to predict FLR with an area under the ROC curve of 0.81 (95% CI between 0.61 and 1.00) in coronary by-pass grafting surgery patients. Berkenstadt [20] reported an AUC of 0.59 (95% CI between 0.44 and 0.64) under the ROC curve to predict FLR in patients undergoing neurosurgery.

In theory, heart rate is considered to be a good predictor of FLR. For instance, in young spontaneous-breathing trauma patients, tachycardia is indicative of severe haemorrhage.

However, in patients fully under mechanical ventilation and anaesthesia, neuronal and humoral control seems completely blocked. Consequently a relation is lacking between baseline or change in HR and changes in CO due to fluid loading. Moreover, a large number of patients are receiving beta-blockade further complicating the possibility to use heart rate to predict FLR.

Cardiac output

CO has been used to predict FLR. However, results concerning the reliability of baseline cardiac output measurements to predict FLR are non-uniform. Baseline cardiac output to predict FLR has been predominantly studied in coronary by-pass surgery patients; AUC under the ROC curve vary from 0.52 ± 0.12 to 0.74 ± 0.07 [21,22]. In 30 septic patients, the AUC of the ROC of baseline triplicate trans-pulmonary thermodilution CO was 0.77 (95% CI between 0.60 and 0.94) to predict FLR [23]. Monnet *et al.* [24] reported a sensitivity of 78%, a specificity of 54% and a cut-off of 2.8 $L \cdot min^{-1} \cdot m^{-2}$. Although the predictive value of different cardiac output methods have not been directly studied, Biais *et al.* [12] found responder classification with CO Vigileo (Edwards Lifesciences, Irvine CA, USA) to correspond in 97% of the cases with pulmonary-artery-catheter thermodilution or trans-thoracic echography CO in liver-transplant patients. Research is needed that directly compares different cardiac output methods to determine their predictive value for FLR as accuracy of a CO method can vary between 3,5 and 25% [25,26].

Moreover, if we take in mind the Starling curve; a patient can be either on the upslope of the Starling curve, on the plateau or in-between. There is a large variability between patients for the maximum cardiac output that can be reached. This implies that a low baseline value for cardiac output does not necessarily mean that fluid loading will lead to an increase in cardiac output. Pharmacological or even mechanical intervention will probably have a similar chance to lead an improvement in CO.

Volumetric or echographic parameters

The above parameters represent an indirect estimate of preload, more direct estimation could be provided by ventricular volumes determined with echographic measurement for instance. Hemodynamic parameters determined with trans-thoracic or trans-oesophageal echography have been used in daily clinical care for decades. We highlight the results of the most studied parameters here; results for left ventricular end-diastolic area (LVEDA) [11,27-30] vary with sensitivity reported to be between 60 to 89%, specificity between 58 and 91% and the AUC of the ROC curve between 0.24 ± 0.11 and 0.78 (95% CI between 0.59 and 0.97) [11,28]. For global end-diastolic volume index (GEDVI) [26,31-33] the AUC of the ROC curves is between 0.23 and 0.70 (0.46-0.94) [32,33].

Other interesting parameters linked to echography are measurement of the inferior or superior vena cava. Vieillard-Baron and colleagues [34] reported that a superior vena cava collapsibility of 36% has a sensitivity of 90% and a specificity of 100% and an AUC of the ROC curve of 0.99 ± 0.01 in 66 patients after CABG surgery. Similar assessment of the inferior vena cava in 20 septic patients offered 90% sensitivity and specificity to predict FLR [8]. The vena cava diameter can only be properly assessed with the use transesophageal echography.

In theory, these echographically determined volume parameters of the heart are supposed to be highly reliable. The volume changes within the heart or vena cava are directly linked to cardiac function; when wall movement is limited inotropic assistance is warranted. And when filling of the ventricles is not optimal, fluid administration is indicated. Study results are very promising [35]. Several factors may frustrate these results. Operator-related factors, like level of experience, changes in probe position and intermittent application, greatly influence the reliability and robustness of echographic monitoring [36]. The predictive value for FLR of echographic parameters in patients receiving mechanical ventilation seems to outscore the results for these parameters in spontaneously-breathing patients [37].

Dynamic parameters: cyclic changes due to mechanical ventilation

In recent years dynamic parameters have been the focus of interest. Especially since more physicians use pulse contour methods that allow not only directly-available estimation of beat-to-beat cardiac output but also delivers stroke volume variation (SVV), pulse pressure variation (PPV) and systolic pressure variation (SPV) [38]. The results of literature review for the reliability of SVV to predict FLR is shown in Table 3.

Table 3 Reliability of stroke volume variation to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Hofer, *et al.* [26]	40	Cardiac surgery	12.5%	74%	71%	0.82 (0.68-0.97)
Reuter, *et al.* [11]	12	Cardiac surgery *,†	9.5%	71%	80%	0.76 (0.59-0.96)
Reuter, *et al.*[11]	14	Cardiac surgery *,†	9.5%	78%	85%	0.88 (0.77-0.99)
Preisman, *et al.* [17]	18	Cardiac surgery	11.5%	81%	82%	0.87 (0.79-0.96)
Hofer, *et al.* [31]	40	Cardiac surgery	9.6%	91%	83%	0.82 (0.68-0.97)
Hofer, *et al.* [31]	40	Cardiac surgery	12.1%	87%	76%	0.86 (0.75-0.97)
Berkenstadt, *et al.* [20]	15	Brain surgery	9.5%	79%	93%	0.87 (0.81-0.90)
Biais, *et al.* [12]	35	Liver transplant OR	10%	94%	94%	0.95 (0.81-0.99)
De Waal, *et al.* [33]	22	Cardiac surgery	8%	100%	78%	0.91 (0.78-1.00)
Cannesson, *et al.* [49]	25	Cardiac surgery	10%	82%	88%	0.87 ± 0.09
Biais, *et al.* [50]	30	ICU general	13%	100%	80%	-
Biais, *et al.* [50]	30	ICU general	16%	85%	90%	-
Derichard, *et al.* [51]	11	Major abd surgery	12%	86%	91%	0.95 (0.65–1.00)
Lahner, *et al.* [52]	20	Major abd surgery	8.5%	77%	43%	0.51 (0.32-0.70)
Monge Garcia, *et al.* [53]	38	Circulatory shock	13%	100%	80%	-

* Multiple measurements in same patients
† spontaneous breathing

(95

Pulse pressure (PP) is defined as the beat-to-beat difference between the systolic and the diastolic pressure. PPV is the amplitude of cyclic changes induced by mechanical ventilation. The variations in pulse pressure and stroke volume induced by mechanical ventilation have been linked to volume status [39]. PPV is thought to be directly proportional to stroke volume variation [40]. The reliability for SVV and PPV varies from lower sensitivity and specificity of 70% to over 90% to predict FLR (Tables 3, 4 and 5). Although SVV is a direct measure of variation in cardiac output, results for SVV are scattered. Even though PPV is used as an indirect measure for SVV, results for PPV seem superior which may be especially true in septic patients [23], where vasoplegia is less likely to cause a reliable SVV measurement result. We need to consider that the calculation of SVV requires beat-to-beat SV measurements using a pulse contour analysis algorithm whereas PPV is measured directly from the arterial waveform. SVV will require an ongoing validation in clinic conditions as algorithms are developing with time [41]. In that context it is noteworthy that more recent publications report lower area under the ROC curves than older publications. Whether this depends on publication bias, a decrease in the accuracy of newer pulse-contour methods to determine SVV or more frequent improper use remains uncertain.

Table 4 Reliability of pulse pressure variation to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Cannesson, *et al.* [28]	18	Cardiac surgery	12%	92%	83%	0.91 ± 0.07
Feissel, *et al.* [54]	20	Sepsis ‡	17%	85%	100%	0.96 ± 0.03
Kramer, *et al.* [18]	21	Cardiac surgery	11%	100%	93%	0.99 (0.96-1.00)
Feissel, *et al.* [55]	23	Sepsis ‡	12%	100%	70%	0.94 ± 0.05
Cannesson, *et al.* [21]	25	Cardiac surgery	11%	80%	90%	0.85 ± 0.08
Soubrier, *et al.* [56]	32	Circulatory failure †	12%	92%	63%	0.81 ± 0.08
Hofer, *et al.* [26]	40	Cardiac surgery	13.5%	72%	72%	0.81 (0.67-0.95)
Auler, *et al.* [22]	59	Cardiac surgery	12%	97%	95%	0.98 ± 0.01
De Backer, *et al.* [57]	60	Critically ill, Vt ≤ 8 $ml \cdot kg^{-1}$	12%	60%	74%	0.89 ± 0.07
De Backer, *et al.* [57]	60	Critically ill	12%	88%	89%	0.76 ± 0.06
Preisman, *et al.* [17]	18	Cardiac surgery	9.4%	86%	89%	0.95 (0.89-1.00)
Wyffels, *et al.* [16]	32	Cardiac surgery	11.8%	95%	92%	0.94 (0.79-0.99)
Michard, *et al.* [58]	40	Sepsis	13%	94%	96%	0.98 ± 0.03
Cannesson, *et al.* [9]	25	Cardiac surgery	12%	88%	100%	0.92 ± 0.06
Vieillard-Baron, *et al.* [34]	66	Sepsis	12%	90%	87%	0.94 ± 0.04
Feissel, *et al.* [55]	23	Sepsis	12%	100%	70%	0.99 (0.98-1.00)
Lafanachere, *et al.* [59]	22	Circulatory failure †	12%	70%	92%	0.78 ± 0.12
Huang, *et al.* [32]	22	ARDS	11.8%	68%	100%	0.77
Vistisen, *et al.* [13]	23	Cardiac surgery	7.5%	94%	83%	-
Derichard, *et al.* [51]	11	Major abd surgery	13%	88%	92%	0.96 (0.70–1.00)
Monge Garcia, *et al.* [53]	38	Circulatory shock	10%	95%	95%	0.97 ± 0.03
De Waal, *et al.* [33]	22	Cardiac surgery	10%	64%	100%	0.88 (0.74-1.00)
Hofer, *et al.* [26]	40	CABG	12.5%	74%	71%	0.82 (0.68-0.97)
Reuter, *et al.* [11]	12	Cardiac surgery *,†	9.5%	71%	80%	0.76 (0.59-0.96)
Reuter, *et al.* [11]	14	Cardiac surgery *,†	9.5%	78%	85%	0.88 (0.77-0.99)
Preisman, *et al.* [17]	18	CABG	11.5%	81%	82%	0.87 (0.79-0.96)
Hofer, *et al.* [31]	40	CABG, SVV flotrac	9.6%	91%	83%	0.82 (0.68-0.97)
Hofer, *et al.* [31]	40	CABG, SVV picco	12.1%	87%	76%	0.86 (0.75-0.97)
Berkenstadt, *et al.* [20]	15	Brain surgery	9.5%	79%	93%	0.87 (0.81-0.90)
Biais, *et al.* [12]	35	Liver transplant OR	10%	94%	94%	0.95 (0.81-0.99)
de Waal, *et al.* [33]	22	CABG	8%	100%	78%	0.91 (0.78-1.00)
Cannesson, *et al.* [49]	25	CABG OR	10%	82%	88%	0.87 ± 0.09
Biais, *et al.* [50]	30	ICU general	13%	100%	80%	-
Biais, *et al.* [50]	30	ICU general	16%	85%	90%	-
Lahner, *et al.* [52]	20	Major abd surgery	8.5%	77%	43%	0.51 (0.32-0.70)
Monge Garcia, *et al.* [53]	38	Circulatory shock	11%	79%	89%	0.89 + 006
Cannesson, *et al.* [21]	25	Cardiac surgery	10%	88%	87%	0.86 ± 0.08

† spontaneous breathing
‡ Semi-recumbent position

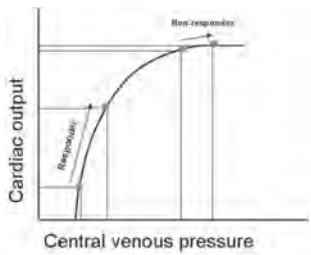
Several restrictions apply to the use of dynamic parameters. First, cardiac arrhythmias significantly decrease the reliability of SVV and PPV [36]. Second, the use of these dynamic parameters has been validated in sedated and mechanically ventilated patients without spontaneous breathing activity. Third, SVV, and probably PPV, is not only influenced by intravascular volume but also by the depth of the tidal volume used in mechanical ventilation of the lungs [11].

Table 5 Reliability of changes in parameters after a hemodynamic challenge to predict fluid loading responsiveness.

	N	Patients	Challenge	Parameter	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dPP	5%	87%	100%	0.96 (0.83-0.99)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dSP	4%	67%	82%	0.71 (0.53-0.86)
Perel, *et al.* [60]	14	Abd aorta surgery	RSVT	RSVT	0.24	88%	83%	0.90 (0.73-1.00)
Preisman, *et al.* [17]	18	CABG	RSVT	RSVT	0.51	93%	89%	0.96 (0.92-1.00)
Monge Garcia, *et al.* [53]	30	General ICU	10 s Valsalva	dPPV	52%	91%	95%	0.98 (0.84-0.99)
Monge Garcia, *et al.* [53]	30	General ICU	10 s Valsalva	dSPV	10%	73%	90%	0.90 (0.73-0.98)
Maizel, *et al.* [61]	34	Circulatory shock	Passive leg raising	dCO	5%	94%	83%	0.89 (0.73-0.97)
Monnet, *et al.* [24]	34	Circulatory shock	Passive leg raising	dCI	10%	91%	100%	0.94 (0.80-0.99)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dCI	5%	91%	100%	0.97 (0.85-1.00)
Maizel, *et al.* [61]	34	Circulatory shock	Passive leg raising	dSV	8%	88%	83%	0.90 (0.74-0.97)
Lamia, *et al.* [37]	24	Circulatory failure	Passive leg raising	dSV	12.5%	77%	100%	0.96 ± 0.04
Biais, *et al.* [50]	34	Circulatory shock	Passive leg raising	dSV TTE	13%	100%	80%	0.96 ± 0.03
Biais, *et al.* [50]	34	Circulatory shock	Passive leg raising	dSV	16%	85%	90%	0.92 ± 0.05
Thiel, *et al.* [62]	89	General ICU	Passive leg raising	dSV	15%	81%	93%	0.89 ± 0.04
Lafanechere, *et al.* [59]	22	Circulatory failure	Passive leg raising	dABF	8%	90%	83%	0.95 ± 0.04
Monnet, *et al.* [42]	71	General ICU	Passive leg raising	dABF	10%	97%	94%	0.96 ± 0.02
Monnet, *et al.* [42]	71	General ICU	Passive leg raising	dPP	12%	60%	84%	0.75 ± 0.06
Monnet, *et al.* [24]	34	Circulatory shock	Passive leg raising	dPP	11%	48%	91%	0.68 (0.50-0.83)
Monnet, *et al.* [42]	19	General ICU	Passive leg raising	dPP	8%	88%	46%	0.56 ± 0.14
Monnet, *et al.* [42]	30	General ICU	Passive leg raising	dPP	12%	88%	93%	0.91 ± 0.05
Cannesson, *et al.* [28]	18	Cardiac surgery	Passive leg raising	dSA	16%	92%	83%	0.91 ± 0.07

** Mixed spontaneous breathing and mechanical ventilation population
† Spontaneous breathing
‡ During surgery additional fluids were administered and measurements were repeated within individuals
dPP is change in pulse pressure, dSP is change in systolic pressure, RSVT is respiratory systolic variation test, dPPV is change in pulse pressure variation, dSPV is change in change in systolic pressure variation, dCO is change in cardiac output, dCI is change in cardiac index, dSV is change in stroke volume, dABF is change in aortic blood flow, dSA is variations in left ventricular stroke area

Figure 1 Cardiac function curve: a small fluid challenge or autotransfusion provocation with passive leg raising (PLR) is used to predict the effects of fluid loading. On the Y-axis cardiac output is shown and central venous pressure on the X-axis. The effects of fluid loading on central venous pressure (CVP) and cardiac output (CO) are shown. The heart of the non-responder will operate near or at the plateau of the Starling curve. A responder will show a larger change in CO when either PLR or a small fluid challenge are performed compared to a non-responder. The changes in CVP and CO caused by PLR or small fluid provocation will mimic changes of significant fluid loading.



Dynamic parameters: other challenges to the circulation

Another approach to determine FLR is a provocation method; the application of increased PEEP or an auto-transfusion with 30° to 45° passive leg raising (PLR). Particularly, the groups of Boulain, Monnet and Teboul studied the reliability of parameters during PLR to predict FLR [42,43]. The robustness and reliability of the "static parameters" during the challenge can be explained by the direct use of the Starling curve. These challenges change the working point on the Starling curve of the patient (Figure 1). The amplitude of the change in CO can be used to predict FLR. These challenges are reversible, standardized and easily performed. Results for these challenges are shown in Table 5.

Since the Starling-curve characteristics are different for each individual, with its own pathophysiological constitution, we can make use of challenge-induced changes to pinpoint the working point on the curve and answering the question: Will this patient be a responder?

Conclusions

Two adequate candidate parameters for FLR in everyday medical practise seem present. First, PPV and SVV in patients fully dependant on mechanical ventilation and secondly an auto-transfusion challenge with PLR using changes in CO, MAP or CVP. However, trials have to be performed to determine the effect of the fluid loading responsiveness strategy on hospital stay and mortality.

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Chapter 6

Comprehensive review: Is it better to use Trendelenburg or passive leg raising in the initial treatment of hypovolaemia?

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Submitted to Journal of Trauma

Hypovolaemia is a common problem in many clinical situations. The mortality of hypovolaemic shock is directly related to the severity and duration of organ hypoperfusion, which means that prompt volume replacement is the hallmark of success for managing the hypovolaemic patient [1] However, since fluid resuscitation will require some time to accomplish, manoeuvres like Trendelenburg position or passive leg raising (PLR) are commonly used as the initial treatment of shock and hypotension [2].

Trendelenburg position is the elevation of the pelvis above horizontal plane in the supine position. This position was originated by Bardenhauer of Cologne but a surgeon named Friedrich Trendelenburg popularized the position in the 19th century for facilitating surgery on the pelvic organs [3]. In World War I, the position was used as an anti-shock manoeuvre. In a survey by Ostrow and co-workers in 1997 99% of surveyed American nurses used the Trendelenburg position and approximately 80% had used PLR [4]. The Trendelenburg position is probably one of the most often used treatments in medicine.

Passive leg raising is straight passive elevation of both legs above cardiac level with the patient in a supine position. PLR is not only used to treat hypvolaemia but it is also used for its hemodynamic response to augment the murmur of heart valves and, to facilitate gynaecological and urological surgery.

104) Both manoeuvres are used either as a diagnostic tool to assess fluid loading response or as a therapeutic manoeuvre pending fluid resuscitation. It is the assumption that body inversion produces shifting of blood from the legs (and with Trendelenburg position also from the abdomen) towards the heart by gravitational displacement leading to an 'auto-transfusion' thereby increasing venous return to the heart and promoting cardiac output (CO) and ultimately increase perfusion of the vital organs [5,6]. With the advantage of auto-transfusion readily available both PLR and the Trendelenburg position are used for their expected instantaneous effect on cardiovascular performance.

The aim of the review is to evaluate whether PLR and Trendelenburg position supports the mechanism of auto-transfusion and to assess the effect of these manoeuvres on cardiac output.

Methods

This review was performed using the Cochrane Handbook for Systemic Reviews of Interventions [7]. We included prospective observational studies in normo- or hypovolaemic humans investigating the effects of hemodynamic parameters within 10 minutes after change from supine position.

The MEDLINE, EMBASE and CENTRAL databases were searched for relevant articles from 1960 up to 2010. We used (combinations of) the following search terms; passive leg raising, leg raising test, lower extremities elevation and passive leg elevation; Trendelenburg,

Trendelenburg position, head tilt-down, head-down; cardiac output and cardiac index (CI). Articles were collected by one reviewer and were crosschecked by another. This was supplemented by hand searching the reference lists for relevant articles.
Total-body head-down tilt of 5° to 60° was used as a definition for the Trendelenburg position and straight passive elevation of both legs of 10° to 90° in a supine position for PLR. Full text copies were obtained for all studies that were selected after reading title and abstract. Disputed articles or abstracts were included after arbitration by a third reviewer.

For all included studies the degree of tilt or elevation, number of patients, demographics, population pathology, CO or CI values, the CO measurement techniques and trends for mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), systemic vascular resistance (SVR), pulmonary artery pressure (PAP) and pulmonary artery occlusion pressure (PAOP) were tabulated.
Studies were excluded when fluid administration exceeded urinary loss or baseline measurement of CO or CI were missing. Other exclusion criteria were the presence of pregnancy, pneumoperitoneum, and epidural or spinal anaesthesia.

Statistical analysis into the effect of the different manoeuvres on cardiac output was performed. For all other hemodynamic data descriptive statistics were used. To enable comparative analysis cardiac output was calculated from cardiac index using a body surface area of 1.8 m^2 as an average converting factor. Mean change and standard deviation (SD) of CO after PLR and Trendelenburg was described in only a few studies. Also P-value of changes in CO or correlations with the baseline CO were scarcely reported. Therefore the standard error of the change from baseline was not available for the majority of the groups. Consequently a meta-analysis using traditional statistical techniques was not possible. Therefore we decided to perform an unweighted random effects meta-analysis. Under the usual random effects meta-analysis this is a valid approach, although not statistically optimal [8]. A paired t-test was used to calculate the overall mean changes and associated standard errors for both manoeuvres from baseline, up to one minute and between two and ten minutes. Due to the absence of most standard errors, forest and funnel plots could not be made, and random effect variance could not be determined. SPSS 17.0 was used for the analyses. All values are given as mean (SD). A p value < 0.05 was considered statistically significant.

Results

In total 624 articles were found after the first query in the three databases. For the Trendelenburg 500 hits were found after the first query and 47 were selected based on their abstract. Thirteen articles met the inclusion criteria and were included into the review. Three

articles were reviewed by arbitrage. 124 articles were found for PLR. 37 articles were selected after reading the abstract of which 21 remained after reading the full articles. An overview of all included studies and their characteristics are shown in Table 1 and 2.

Table 1 Characteristics of "Trendelenburg"-studies.

Authors	Population	N	Age	Hypo-volaemia	Tilt
van Lieshout, *et al.* [28]	Healthy	9	29	No	20°
Terai, *et al.* [5]	Healthy	8	19-26	No	10°
Reuter, *et al.* [29]	Cardiothoracic surgery	12	-	Yes	30°
Terai, *et al.* [30]	Healthy	10	21	No	20°
Ostrow, *et al.* [31]	Cardiothoracic surgery	18	55	No	10°
Sing, *et al.* [22]	Cardiothoracic surgery	8	60	Yes	15°
Dirschedl, *et al.* [32]	Coronary artery disease	10	-	No	6°
Reich, *et al.* [33]	Cardiothoracic surgery, EF >40%	18	62	No	20°
Gentili, *et al.* [34]	Mixed surgical	22	68	No	12°
Pricolo, *et al.* [35]	Cardiothoracic surgery, EF>50%	5	-	No	10°
Pricolo, *et al.* [35]	Cardiothoracic surgery, EF>50%	8	-	No	10°
Jennings, *et al.* [36]	Healthy	8	26	No	10°
Jennings, *et al.* [36]	Healthy	8	26	No	30°
Jennings, *et al.* [36]	Healthy	8	26	No	60°
Jennings, *et al.* [36]	Healthy	8	26	No	90°
Sibbald, *et al.* [9]	Mixed ICU	61	-	No	15-20°
Hong, *et al.* [37]	Gynaecological surgery	25	44	No	15°

Trendelenburg position

Thirteen studies were included that assessed the effects of the Trendelenburg position on cardiac output. In these studies 246 patients were studied (n ranged between 5 – 61 with an average of 14 subjects per study with an age of 40 ± 18 years). Sixty percent of the studied populations was male.

Overall, Trendelenburg position increased MAP and PAOP. CVP increased in three studies and did not change in four studies. Heart rate remained unchanged in the majority of studies during head-down tilt. Sibbald and Taylor looked into the difference in hemodynamic reactions between normo- and hypovolaemic subjects after Trendelenburg position [9,10]. This was defined either by kissing papillary muscles on echography or a PAOP smaller than 6 mmHg. Sibbald described a marked increase in CVP, MAP and PAP in normovolaemics [9]. In the hypovolaemic subjects there was no change in these parameters. However, the number of subjects in normovolaemic groups was three times larger than in the hypovolaemic groups (15 vs. 51 subjects).

Table 2 Characteristics of "passive leg raising" studies.

Authors	Population	N	Age	Hypo-volaemia	Tilt
Boulain, *et al.* [6]	Circulatory failure	15	65	Yes	45°
Tempe, *et al.* [38]	Cardiothoracic surgery, LVEF>50	10	57	No	45°
Tempe, *et al.* [38]	Cardiothoracic surgery, LVEF<35	10	52	No	45°
Reich, *et al.* [33]	Cardiothoracic surgery	18	62	No	60°
Reich, *et al.* [33]	Cardiothoracic surgery	20	36	No	-
Nelson, *et al.* [39]	Coronary artery disease	22	56	No	45°
Nelson, *et al.* [39]	Coronary artery disease	22	56	No	45°
Gaffney, *et al.* [40]	Healthy	10	30	No	60°
Paelinck, *et al.* [41]	Healthy	24	41	No	45°
Terai, *et al.* [5]	Healthy	8	19-26	No	60°
Bertolissi, *et al.* [42]	Cardiothoracic surgery, RVEF>45	10	56	No	60°
Bertolissi, *et al.* [42]	Cardiothoracic surgery, RVEF<40	6	67	No	60°
Schrijen, *et al.* [43]	Emphysema	16	53	No	30°
Schrijen, *et al.* [43]	Emphysema	13	56	No	30°
Carrère-Debat, *et al.* [44]	Respiratory failure	10	60	-	-
Schreuder, *et al.* [45]	Cardiothoracic surgery	6	-	No	45°
Schreuder, *et al.* [45]	Cardiothoracic surgery	6	-	No	45°
Dirschedl, *et al.* [32]	Coronary artery disease	10	-	No	45°
Ostrow, *et al.* [31]	Cardiothoracic surgery	18	55	No	30°
Lafanechere, *et al.* [12]	Circulatory failure	10	69	Yes	45°
Lafanechere, *et al.* [12]	Circulatory failure	10	69	Yes	45°
Albert, *et al.* [46]	Emphysema	30	52	No	35°
Maizel, *et al.* [11]	Circulatory failure	17	64	Yes	30°
Maizel, *et al.* [11]	Circulatory failure	17	58	Yes	30°
Jörgenson, *et al.* [47]	Emphysema	10	67	No	60-90°
Jörgenson, *et al.* [47]	Lung carcinoma	10	64	No	60-90°
de Wilde, *et al.* [48]	Cardiothoracic surgery	13	-	No	30°
de Wilde, *et al.* [49]	Cardiothoracic surgery	15	66	No	30°
Jabot, *et al.* [13]	General ICU	35	63	Yes	45°

Cardiac output showed a significant change in the overall population. Within one minute after head-down tilt: 9% or 0.35 $L \cdot min^{-1}$. The increase in CO declined to 4% or 0.14 $L \cdot min^{-1}$ after two to ten minutes of Trendelenburg application (see Table 3). The same trend was seen in the normo- and hypovolaemic subpopulations. However, only two studies focused on hypovolaemic patients. The degree of head tilt-down does not influence the occurrence of a significant change in CO except for a transient increase after one minute of 10° tilt-down.

Table 3 Meta-analysis of changes in cardiac output (CO) after Trendelenburg (after 1 and after 2-10 minutes) and after passive leg raising (PLR) (after 1 and after 2-10 minutes).

Authors	Studies (n subjects)	Baseline CO L·min^{-1}	CO after manoeuvre L·min^{-1}	Change in CO L·min^{-1} (%)	P-value
Trendelenburg, at 1 min [5,29,30,36]	4 (46)	2.81 ± 1.59	3.17 ± 1.97	0.35 ± 0.38 (9%)	0.111
Trendelenburg, at 2-10 mins [5,9,22,28-35]	11 (181)	3.04 ± 0.97	3.18 ± 1.04	0.14 ± 0.12 (4%)	0.004
PLR, at 1 min [6,32,33,38,40,42,43,45]	9 (140)	2.86 ± 0.39	3.05 ± 0.55	0.19 ± 0.23 (6%)	0.017
PLR, at 2-10 mins [5,11,12,31,33,38-41, 43,44,46,47,50,51]	15 (347)	2.91 ± 0.90	3.08 ± 1.01	0.17 ± 0.23 (6%)	0.005

CO is cardiac output; PLR is passive leg raising; $p < 0.05$ for change from baseline is considered significant

Passive leg raising

Twenty one studies were included that evaluated the hemodynamic effects of passive leg raising. In total 431 patients were studied with an average of 14 patients per study. In general, volume status was not clearly defined; four studies used hypovolaemic patients in their assessment. In these studies hypovolaemia was defined either as systolic pressure <90 mmHg, a drop in systolic blood pressure >50 mmHg, an increase in CO >12% after volume therapy [6,11-13]. The legs were raised with an average of 46° (ranging between 30° and 75°). Passive leg raising did not provide a general or unambiguous change in heart rate. Mean arterial pressure increased in 9 of 20 studies. CVP and PAP increased in all studies (n=8). Degree of PLR, volume status or pathological characteristics of the studied subjects did not influence the changes in either HR, MAP, CVP or PAP as a result of leg elevation.

CO increased significantly one minute after application of PLR with 6% or 0.19 L·min^{-1}. (see Table 3). In hypovolaemic populations CO is raised after one minute of leg elevation by 11% or 0.6 L·min^{-1}. This effect persists between two and ten minutes of application; 6% or 0.17 L·min^{-1}.

Table 4 Effects of PLR and Trendelenburg on cardiac output (CO in L·min^{-1}) in directly comparing studies.

		Trendelenburg				Passive leg raising			
Authors	N	Tilt	CO Base	CO 1–4 min	CO 5–10 min	Tilt	CO Base	CO 1–4 min	CO 5–10 min
Terai, *et al.* [5]	8	10°	3.0 ± 0.2	3.4 ± 0.3 *	3.1 ± 0.3	60°	2.8 ± 0.2	3.2 ± 0.2 *	3.1 ± 0.3
Ostrow, *et al.* [31]	18	10°	3.33 ± 0.77		3.63 ± 0.73	45°	2.6 ± 0.7	2.9 ± 0.9	
Dirschedl, *et al.* [32]	10	6°	2.6 ± 0.7		2.7 ± 0.7	30°	3.33 ± 0.77		3.61 ± 0.81
Reich, *et al.* [33]	18	20°	2.36 ± 0.79	2.52 ± 0.93 *		60°	2.36 ± 0.79	2.37 ± 0.73	

PLR is passive leg raising. All subjects are reported to be normovolaemic. * $p < 0.05$ for change from baseline

Direct comparison

Four studies directly compared the hemodynamic effects of Trendelenburg and PLR. Results of these studies are shown in Table 4. Although CO increases after both PLR and Trendelenburg within one minute after application with approximately 10% little can be said about the effect after 10 minutes. PLR seems to sustain this effect. However the amount of studies is low and the population sizes are small. More direct comparing studies are needed.

Discussion

The objective of this review was to compare the hemodynamic effects of the Trendelenburg position versus passive leg raising. We found that the Trendelenburg position and PLR increased cardiac output up to almost 10%. However, after several minutes Trendelenburg did not seem able to sustain this effect where PLR was still successful to maintain an increased CO. The reviewed studies nearly unanimously support the mechanism of autotransfusion as a way passive leg raising and Trendelenburg alters haemodynamics. Through elevation of the lower part of the body blood is translocated to the central circulation increasing cardiac output. The hypothesis of autotransfusion is supported by a nearly integral increase in reported central venous pressure and pulmonary artery occlusion pressure.

Trendelenburg vs. PLR

Cardiac output seems likely to be redirected to central parts of the circulation away from parts with increased resistance. Blood volume is shifted from the legs to the more central part of the circulation. The effect of PLR can be readily explained by auto-transfusion. Morgan and co-workers estimated that PLR of a single leg (30° angle) transfuses approximately 150 ml of blood to the central circulation [14]. This is confirmed by Boulain and colleagues who calculated, based on the results of radio-isotopic scans by Rutlen and co-workers, that PLR of both legs shifted 300 ml of blood from the legs toward the central compartment and subsequently confirmed this by showing no difference between changes in stroke volume after PLR and rapid fluid loading with 300 ml [6,15].

However, there is a discrepancy in the duration of this effect between PLR and the Trendelenburg manoeuvre. A first explanation can be found in the lower position of the baroreceptors in reference to the heart [10,16,17]. In the Trendelenburg position the baroreceptors are located below the level of the heart. The extra gravitational force or hydrostatic pressure is expected to cause a decrease in the baro-activity, leading to general vasodilatation, decreased heart rate and heart contractility. This is counterproductive to the desired effect. However, in the majority of studies heart rate did not change. Gravity and suppression of the baroreflex (or Bainbridge effect) during the Trendelenburg position will

cause blood to dam in the veins, atria and pulmonary circulation which will decrease venous return and cardiac output subsequently [18-21]. This is supported by Sibbald and co-workers who reported a rise in central venous pressure [9]. Additionally, Sing and co-workers found that the Trendelenburg position did not improve systemic tissue oxygenation in hypovolaemic subjects [22]. This can be explained by the cephalad movement of abdominal organs against the diaphragm, resulting in a higher thoracic pressure and central venous pressure thus decreasing venous return [19-21].

Considerations

Several issues need to be taken into consideration. The standard error of the mean change is underreported in PLR and Trendelenburg literature. Also the standard errors could not be indirectly extracted from other data given in the articles, such as P-values or correlations. Henceforth, the data was not suited for traditional meta-analysis. Therefore we did a straightforward unweighted meta-analysis, which is statistically valid but some power is lost. The quality of the results of this meta-analysis would improve if more data was available and direct comparison was performed in the same groups.

110) We have to realize that hemodynamic parameters were monitored with different techniques. For instance, arterial blood pressure was measured with the Riva-Rocci method in some studies or with invasive techniques in either aorta or radial artery. Cardiac output was measured with variety of techniques with accuracies between 8 and 15% [23,24]. Thermodilution is the most often used technique and can be considered the "gold standard". Only the techniques that show a high correlation or good agreement with the gold standard allowing to combine and to compare the results of the different studies [25]. The amplitude of the effect of CO with both maneouvers is well accepted in fluid loading responsiveness research and considered clinically significant [24,26].

The results of this review do not show a difference between normovolaemic and hypovolaemic patients in their response in CO after PLR or Trendelenburg. The amount of autotransfusion is likely to be less in a hypovolaemic state. However, this difference is likely compensated by the relative larger increase to a volume challenge in hypovolaemia compared to normovolaemia, i.e. when one is on a steeper slope of the Frank-Starling curve. A fluid loading challenge does not have to increase CO only in hypovolaemic patients but this will also occur during normovolaemia. In hypervolaemia, however, this is less likely since the heart will function on the flat part of the Frank Starling curve.

In this review differences exist between the studies such as mechanical ventilation or spontaneous breathing, level of sedation, beta blockade (i.e. cardiac surgery patients) and types of surgery. All these factors can influence the endogenous adrenergic response to

positional change and the magnitude of the effect on CO. Identification and consequent analysis of the influence of these confounders would be very complex and not in the scope of the present review.
We also have to consider the practical applicability of both manoeuvres. Trendelenburg can be performed in nearly every situation in a medical setting. Although PLR can be easy to perform it can be impossible during certain types of surgery. Trendelenburg will be relatively contraindicated in most head-trauma patients.
Finally, in hypovolaemia guarantee of sufficient cerebral blood flow is vital. Shenkin and co-workers observed cerebral flow velocity to decrease in normal humans during Trendelenburg position although carotid blood flow increased [27]. We cannot rule out that Trendelenburg position changes perfusion of the vital organs with or without coinciding changes in cardiac output. The absence of studies into the effects on regional blood flow or local oxygen delivery by these manoeuvres is a major limitation to hemodynamic assessment in clinical studies as a whole.

Conclusions

We compared the hemodynamic effects of the Trendelenburg and passive leg raising and found that both manoeuvres increased cardiac output by 6-9% within one minute. However, after several minutes PLR seemed more able to sustain this effect than Trendelenburg. This is possibly explained by the position of the baroreceptors and a cephalad movement of abdominal organs during Trendelenburg. Since fluid resuscitation during hypovolaemia is not achieved within minutes, we advocate the use of autotransfusion with PLR in the initial treatment of hypovolaemia if possible.

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Section 3

Mean systemic filling pressure

Chapter 7

Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation

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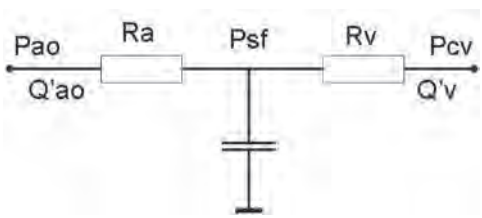
Journal of Clinical Monitoring and Computing 2010; 24: 377–384

The hemodynamic effects of therapeutic interventions have been extensively studied on isolated arterial, venous or heart models either in vitro or in vivo. Although, intact circulation models have been used before, they are often limited to only one study characteristic; i.e. heart function, venous capacitance, (un)stressed volume, vascular compliance, mean systemic filling pressure or venous resistance [1]. None of these models is applicable in ICU patients and none was used to determine the coherent characteristics of the venous and arterial vasculature and heart function. Since arteries, veins and heart operate in concert, we developed an integrated in vivo model, applicable in patients, based on Guytonian physiology.

We modelled the systemic circulation with one resistor upstream (Ra) and one resistor downstream (Rv) of mean systemic filling pressure (Pmsf) (Figure 1). At the site where the pressure is equal to Pmsf the large blood volume is indicated by a capacitor [2-4]. This site contains about 70% of total blood volume and has been reported to correspond with the location of the capillaries and post-capillary venules [5]. Resistance over the total systemic circulation (Rsys) and over the venous system (Rv) can be calculated from aortic pressure (Pao), central venous pressure (Pcv) and cardiac output (CO) values as (Pao-Pcv)/CO and Rv by (Pmsf-Pcv)/CO, respectively (Figure 1). Rsys reflects both arterial and venous resistance: Rsys = Ra +Rv. So, Ra = Rsys - Rv.

Figure 1 The circulation model to compute the resistances up-streams (Ra) and down-streams (Rv) of mean systemic filling pressure (Psf). The sum of Ra and Rv is equal to total systemic resistance (Rsys). Aortic pressure (Pao) and central venous pressure (Pcv) are measured. Mean systemic filling pressure is determined with inspiratory hold maneouvers.



In this study we used a hemodynamic condition of hypovolemia as well as dobutamine as a known cardiovascular stimulant to test our model in an intact anesthetized piglet model. In the vasculature, Ruffolo and colleagues [6] presumed that with dobutamine, the β_2 mediated

effects are counterbalanced by the α_1 activity leading a decreased total peripheral vascular resistance by a reduction of sympathetic tone and arterial vasodilatation. However, since local vascular effects may differ owning to local differences in receptor expression which varies in arteries and vein, one may see either local vasodilatation or vasoconstriction. Presently, no intact-circulation model exists to study differences in systemic arterial and venous resistance. Since we recently validated a bedside technique to estimate mean circulatory filling pressure (Pmsf) [7], we are now able to determine the venous resistance in patients. Thus, examining both total blood flow and the ratio of the systemic to venous resistance one can quantify the effect of different hemodynamic conditions and vasoactive agents on total systemic vascular resistance and venous resistance.

The aim of our study was to determine the reproducibility of Pmsf, Rsys and Rv in our intact *in vivo* piglet model and, secondly, we tested our model during dobutamine and hypovolemia. We hypothesize that dobutamine would increase CO by the combined actions of increasing inotropy, arterial vasodilation, with less evident venodilation. Furthermore, we expected both hypovolemia and dobutamine to decrease Pmsf and hypovolemia to not change in the site of Pmsf, i.e. the ratio Rv/Rsys to be constant.

Methods

All experiments were performed according to the ''Guide for Care and Use of Laboratory Animals'' published by the US National Institutes of Health and were approved by the local Animal Care Committee.

Surgery

Ten Yorkshire piglets were anesthetized with 30 $mg \cdot kg^{-1}$ sodium pentobarbital intraperitoneal, followed by a continuous infusion of 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$. After tracheostomy, the animals were ventilated at a rate of 10 breaths per minute at an I:E-ratio of 2.4:3.6 and with a tidal volume adjusted to maintain arterial PCO_2 of approximately 40 mmHg, while a positive end-expiratory pressure of 2 cmH_2O was applied. PCO_2, airway pressure and airflow were measured in the tracheal cannula. The animals were placed in a supine position on a thermo-controlled operating table (38° C). A catheter was inserted through the right common carotid artery into the aortic arch to measure Pao and to sample arterial blood. Two other catheters were inserted through the right external jugular vein. A pulmonary artery catheter was inserted to measure pulmonary artery pressure, to measure thermodilution cardiac output (COtd) and to sample mixed venous blood. A quadruple-lumen catheter was inserted into the superior vena cava to measure Pcv and to infuse sodium pentobarbital and pancuronium bromide (Organon N.V., Boxtel, the Netherlands). The catheters for vascular

pressure measurements were kept patent by an infusion of saline with 2.5 IE Heparin ml^{-1} at 3 $ml \cdot h^{-1}$. The bladder was cannulated trans-abdominally to check urine loss in order to maintain water balance. After an intercostal thoracotomy in the second left intercostal space, an electromagnetic flow probe (type transflow 601, model 400, Skalar, Delft, The Netherlands) was placed within the pericardium around the ascendant part of the aortic arch to measure aortic blood flow. Two suction catheters, one dorsal and one ventral, were inserted into the left pleural space. The thorax was closed airtight and both air and fluids were evacuated for 1-2 minutes with -10 cmH_2O suction while applying a PEEP of 10 cmH_2O. After surgery and while on continuous pentobarbital infusion, the animals were paralyzed with an intravenous infusion of pancuronium bromide (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$), after a loading dose of 0.1 $mg \cdot kg^{-1}$ in 3 minutes.

Measurements

The electrocardiogram (ECG), Pao, pulmonary artery pressure (Ppa), Pcv, flow probe signal and ventilatory pressure (Pvent) flow were simultaneously recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the pulmonary artery catheter during lateral-to-lateral radiography. The airway pressure transducer was balanced at
120) zero level against ambient air. During the observation periods, ECG, blood flow and pressure signals were sampled in real time for 30-s periods at 250 Hz. The mean of four thermodilution cardiac output measurements equally distributed of the ventilatory cycle was used to obtain the value of COtd [8,9]. Areas under the aortic blood flow curves were analyzed online and calibrated by COtd to estimate beat-to-beat cardiac output (COem). After the surgical procedure the animals were ventilated at a rate of 10 min^{-1} with an inflation time of 2.4 s and an expiration time of 3.6 s. Tidal volume was readjusted to an end-expiratory PCO_2 of approximately 5.33 kPa (40 mmHg), usually corresponding with a slightly higher arterial PCO_2. The ventilatory settings were kept constant during the observation periods.
We determined Pmsf using inspiratory pause procedures as previously described [5,10,11]. Briefly, during inflation of the lungs venous capacitance is loaded due to an increase in Pcv, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output (Figure 2). To avoid transiently effects on the relationship between venous return and Pcv, we measured Pcv and (CO) during short periods of end-inspiratory steady state following these initial non-steady state conditions. CO and Pcv are determined over the final 5 seconds for a set of seven 12-sec inspiratory hold procedures at seven randomly applied tidal volumes between 25 and 300 ml. The inspiratory hold manoeuvres are separated by 5-minute intervals to re-establish the initial hemodynamic steady state. From the steady state values of Pcv and CO measured by an electromagnetic flow probe (COem) during the seven inspiratory pause periods a venous return curve was

constructed by fitting a linear regression line according to the method of least square means through these data points (Figure 3). Pmsf is defined as the extrapolation of this linear regression to zero flow [5,10,11].

Figure 2 Effects of an inspiratory hold maneouver on aortic pressure (Pao), central venous pressure (Pcv), airway pressure (Pt) and beat to beat cardiac output (COem). Preceding the hold maneouver the effects of a normal ventilatory cycle are plotted.

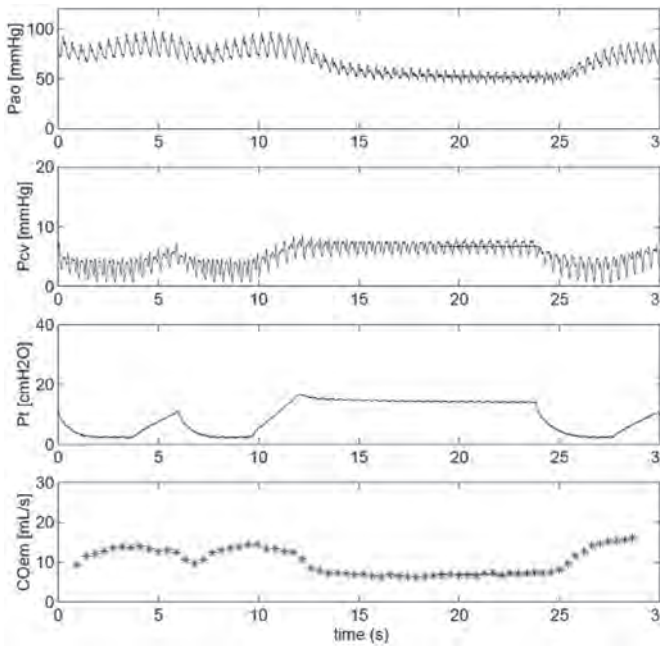


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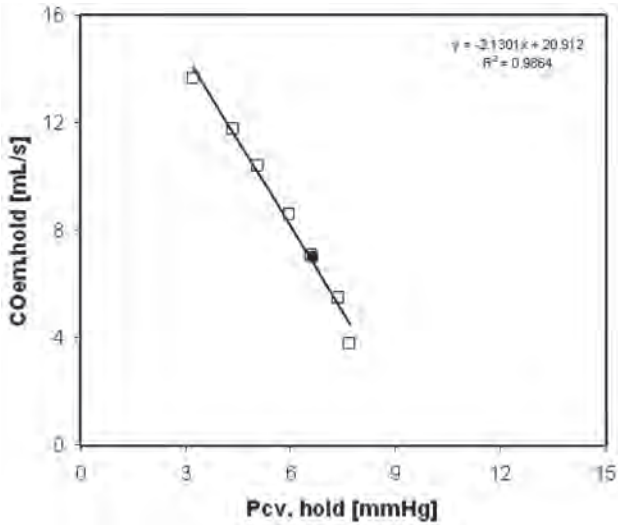
Figure 3 Venous return curve for an individual animal. The relationship between venous return (COem) and central venous pressure (Pcv) is plotted. Mean system filling pressure (Pmsf) is indicated by extrapolating the curve to COem=zero.



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Protocol

To eliminate the effects of surgery, opening of the pericardium, and applying mechanical ventilation on the hemodynamic measurements, the piglets were allowed to stabilize for 60 to 120 minutes after surgery. Data collection started once heart rate (HR), mean Pao and Pcv were stable for at least 15 minutes. After stabilization, baseline-1 measurements were performed. Next, continuous dobutamine infusion was started with 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and hemodynamic measurements were performed after 30 minutes. The dobutamine infusion was stopped and after 30 minutes baseline-2 measurements were obtained. The observations were continued 15 minutes after bleeding the animals with 10 $ml \cdot kg^{-1}$. The observations ended with baseline-3 measurements 15 minutes after giving back the withdrawn 10 $ml \cdot kg^{-1}$ blood.

Data analysis and statistics

We fitted the set of seven data points of Pcv and COem by linear regression for each condition to define the venous return curve. We defined Pmsf as the extrapolation of this

linear regression to zero flow (Figure 3), assuming that airway pressure does not affects Pmsf. We have previously validated this extrapolation in piglets [5,10,11]. Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pa and mean Pcv and COtd (Rsys = (Pa - Pcv)/COtd). The resistance downstream of Pmsf was taken to reflect the resistance to venous return (Rv) and was calculated as the ratio of the pressure difference between Pcv and Pmsf and COtd (Rv = (Pmsf-Pcv)/COtd). Systemic arterial resistance (Ra) was taken to be the difference between systemic and venous resistance. The ratio of Rv and Rsys describes the location within the circulation where Pmsf exists. A higher ratio implies a more upstream Pmsf location. After confirming a normal distribution of data with the Kolmogorov-Smirnov test, differences in parameters during baseline and interventions were analyzed using paired t-tests. Repeatability was calculated from the three baseline conditions using Bland-Altman analysis. Hereto, for each animal the mean and difference of the values of baseline-1 and 2 and of baseline-2 and 3 was determined. The upper and lower limits of agreement were calculated as bias ± 2SD. The coefficient of variation (COV) was calculated as 100% x (SD/mean). Effects of time on our data set were calculated by comparing baseline values. Changes induced by the interventions with dobutamine and hypovolemia were compared to the mean of the baseline values before and after the interventions to illuminate time effect. All values are given as mean ± SD. A p value < 0.05 was considered statistically significant.

Results

Ten 8–10 week old piglets (all females) bodyweight of 10.3 ± 0.7 kg were studied. Pooled data are shown in Table 1. A Kolmogorov-Smirnov test indicated normal distribution of all data. In 10 animals baseline-1, dobutamine, and baseline-2 data was obtained, in only 8 animals we were able to study the effects of bleeding by 10 $ml \cdot kg^{-1}$.

Table 1 Pooled results for 10 piglets at start (Baseline-1), 30 minutes after the start of 6 μg·kg^{-1}·min^{-1} IV dobutamine infusion (Dobutamine), 30 minutes after stopping the dobutamine infusion (Baseline-2), 15 minutes after bleeding 10 ml·kg^{-1} (hypovolemia) and 15 minutes after reestablishing normovolemia (Baseline-3).

	Baseline-1	Dobutamine	Baseline-2	Hypovolemia	Baseline-3
Pao (mmHg)	88.10 ± 17.24	87.51 ± 9.37	82.56 ± 17.02	83.05 ± 14.46	86.83 ± 18.30
Ppa (mmHg)	15.52 ± 3.51	19.77 ± 6.99	19.74 ± 7.39	17.10 ± 6.51	18.96 ± 5.97
Pcv (mmHg)	4.09 ± 1.33	4.10 ± 1.03	4.62 ± 1.38	3.75 ± 1.71 †	4.69 ± 1.47
HR (min^{-1})	146 ± 42	215 ± 33 ‡	152 ± 42	175 ± 47 ‡	150 ± 45
COtd (ml·sec^{-1})	24.15 ± 3.70	33.64 ± 3.94 ‡	24.53 ± 5.38	22.69 ± 3.87 †	24.57 ± 4.64
Pmsf (mmHg)	13.59 ± 1.04	12.02 ± 1.27 †	14.10 ± 1.37	10.94 ± 1.81 ‡	14.85 ± 1.28
Pvr (mmHg)	10.71 ± 1.21	7.88 ± 1.12 *	9.50 ± 1.72	7.19 ± 1.66 ‡	10.15 ± 1.75
Rv (mmHg·sec·ml^{-1})	0.401 ± 0.095	0.237 ± 0.037 ‡	0.406 ± 0.126	0.327 ± 0.104 †	0.465 ± 0.085
Rsys (mmHg·sec·ml^{-1})	3.474 ± 0.424	2.507 ± 0.271 ‡	3.379 ± 0.322	3.496 ± 0.352	3.359 ± 0.455
Rv / Rsys	0.117 ± 0.031	0.096 ± 0.019 †	0.127 ± 0.037	0.095 ± 0.035 †	0.129 ± 0.039
Hb (g·dL^{-1})	9.56 ± 1.02	10.34 ± 1.22 †	9.73 ± 0.99	9.67 ± 0.89	9.71 ± 1.05

Aorta pressure (Pao), pulmonary artery pressure (Ppa), central venous pressure (Pcv), heart rate (HR), cardiac output with thermodilution (COtd), mean systemic filling pressure (Pmsf), pressure gradient for venous return (Pvr), venous flow resistance (Rv), systemic flow resistance (Rsys), location of Pmsf (Rv/Rsys), and hemoglobin (Hb).
* $p < 0.05$, † $p < 0.01$ and ‡ $p < 0.001$ to the average of the baseline value before and after the intervention.

Repeatability

Bland-Altman analyses for repeated measurements of the main derived variables Pmsf, Pvr, Rsys, Rv and Rv/Rsys are given in Table 2. A remarkable low percentage coefficient of variation of 3.8% was found for Pmsf. The percentage coefficient of variation increases with the number of variables incorporated in the calculation and was highest for Rv/Rsys.

Table 2 Bland-Alman results for repeated measurements of mean systemic filling pressure (Pmsf), gradient for venous return (Pvr), systemic vascular resistance (Psys), the resistance for venous return (Rv) from Pmsf to central venous pressure and the quotient Rv/Rsys as a location of Pmsf in the circulation. Data of baseline-1, baseline-2 and baseline-3 are used (n=18).

	Mean	Bias	SD	COV	limits of agreement	
				%	lower	upper
Pmsf (mmHg)	14.17	-0.55	0.54	3.8	-1.63	0.53
Pvr (mmHg)	9.64	-0.18	0.78	8.1	-1.74	1.38
Rsys (mmHg·sec·ml^{-1})	3.422	0.078	0.348	10.0	-0.618	0.774
Rv (mmHg·sec·ml^{-1})	0.415	-0.023	0.059	14.2	-0.141	0.095
Rv/Rsys	0.12	0.01	0.02	16.7	-0.03	0.05

Interventions

The infusion of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine increased HR and COtd and decreased Pmsf, Pvr, Rv, Rsys and Rv/Rsys ratio. Whereas Pao, Ppa and Pcv did not change during the study. The decrease of Rv during dobutamine was larger than the decrease in Rsys, 52% and 28% respectively. Recovery baseline condition after dobutamine (baseline-2) did not show any significant changes from the initial baseline values (baseline-1), except for HR which decreased after dobutamine infusion was stopped but still was elevated compared to baseline-1. Bleeding the animals with 10 $ml \cdot kg^{-1}$ showed a decrease in Pcv, Pmsf, Pvr , Rv and Rv/Rsys. Recovery to baseline condition after bleeding (baseline-3) did not show any significant changes from baseline values before bleeding (baseline-2). Surprisingly, hemoglobin (Hb) increased during continuous dobutamine infusion and returned to baseline-1 values 30 minutes after the infusion was stopped. Hemoglobin did not changed by bleeding.

Discussion

Our data supports the feasibility to estimate Pmsf, Rsys and Rv. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. Our data on vascular resistance clearly shows that although both arterial and venous components of vascular resistance decrease, the primary peripheral vascular effects of dobutamine in the healthy animal model was to induce more venodilation than arterial dilation. Bleeding the animals showed Pmsf, Pcv, COtd and surprisingly Rv to decrease and Pao and Rsys to be constant. Evidently, there is some compensation for the loss of venous return by adaptation of Rv.

Repeatability

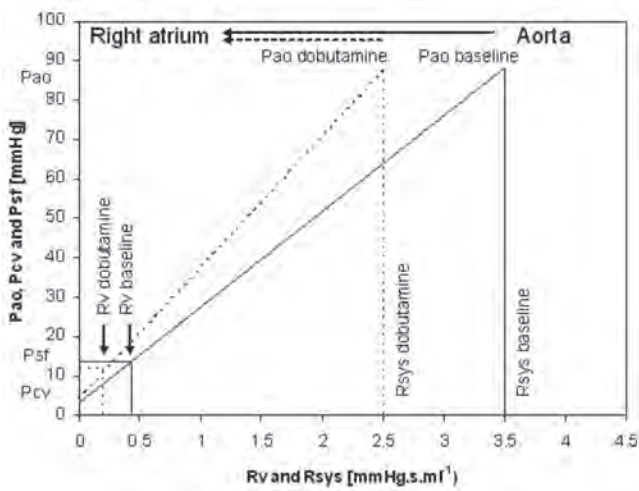
Comparison of baseline-1, -2 and -3 showed no differences, except for the observation of heart rate HR during baseline-2. Therefore, we conclude for a stable observation periods in our animals. We determined the precision of the main derived variables, i.e. Pmsf, Pvr, Rsys and Rv, by Bland-Altman analysis of repeated measurements (Table 2). Although, Pmsf is determined by extrapolation of the venous return curve to COem is equal to zero (Figure 3), the coefficient of variation appeared to be surprisingly low (3.8%). With the low coefficient of variation for Pmsf, Rv and Rsys changes by the intervention with dobutamine and hypovolemia can be monitored with precision. Therefore, we consider the data as presented in Table 1 as reliable.

Our estimated Pmsf values (11-15 mmHg) are in agreement with those described in highly instrumented animals, which are in dogs 7-12.5 mmHg [12-17], rats 7-9 mmHg [18,19], pigs 10-12

mmHg [5,10,11], and as high as 20-30 mmHg in conscious calves implanted with an artificial heart [20]. Furthermore, we report a baseline Pmsf value of 19 mmHg in cardiovascular surgical patients [7].

How can our data be explained? In a non-controlled circulation a decrease in effective blood volume (i.e. a change from stressed to unstressed volume) will be reflected by a decrease in Pmsf [21]. If dobutamine caused arterial vasodilation such that the number of perfused capillaries increased, then unstressed volume should also increase, decreasing Pmsf for a constant blood volume. The greater number of draining venous conduits would also decrease the resistance to venous return. We found that dobutamine decreased without altering Pcv, decreasing the pressure gradient for venous return. Despite this decrease in pressure gradient, cardiac output was increased. Thus, the decrease in Rv was more than inversely proportional to the increase in cardiac output or cardiac output would have remained constant. A decrease in Rv may be caused by four mechanisms; (1) a decrease of the length of the vascular bed between the sites were the pressure is equal to Pmsf and right atrium, (2) an increase in cross section of the vascular bed, (3) decrease blood viscosity of blood or (4) a combination of the three mechanisms. As we measure an increase in Hb during dobutamine infusion a decrease in viscosity is very unlikely. Thus, the observed decrease in Pmsf combined with the increased COtd requires that Rv decrease due to an increase in the venous flow cross-sectional area, presumably due to dobutamine-induced increased parallel vascular blood flow.

Figure 4 Conceptual model of the systemic circulation. Horizontally, the linear projection of vascular flow resistance (Rsys) between aortic valves (at the right) and right atrium (at the left) is plotted. In this linear projection the aorta takes about 2% , the arterioles about 55%, the remaining arterial system about 15% and the rest is distributed between capillaries and the venous system. The resistance (Rv) down-streams mean systemic filling pressure (Psf) and central venous pressure (Pcv) is indicated. Vertically, aortic pressure (Pao), central venous pressure (Pcv) and mean systemic filling pressure for baseline condition and during infusion of dobutamine are plotted. The values of Table 2 are used to construct the model. Further explanation is given in the text.



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The changes in Pao, Pcv, COtd, Rsys and Rv are illustrated schematically in Figure 4, in which flow resistance is projected on the x-axis. We have used this graphical model to analyze two different stationary conditions in circulation, i.e. baseline condition and during infusion of dobutamine. The numeric data for this model are taken from Table 1, columns baseline-1 and dobutamine. The lines between Pao and Pcv represent the pressure gradient (Psys) over Rsys and between Pmsf and Pcv; the pressure gradient (Pvr) for venous return over Rv. The slope of the lines represent blood flow, i.e. COtd=Psys/Rsys=Pv/Rv. During dobutamine infusion the Pao-Pcv difference was equal to baseline. However, COtd increased and both Rsys and Rv decreased significantly. The fall in Rv due to dobutamine was larger than the fall in Rsys, 52% and 28% respectively. From this difference in response to dobutamine we conclude that the primary peripheral vascular effect of dobutamine is on the venous side of the circulation as

shown in Figure 4. The larger decrease on the venous side can be explained mainly by the decrease in Pmsf due to dobutamine. If we had observed no change in Pao, Pcv or Pmsf despite an increase in COtd, then Rv must have changed proportional to Rsys, which is described by the intersection of dashed Pao-Pcv dobutamine line and solid Pmsf line. Importantly, our method to determine Pmsf has recently also been validated in mechanically ventilated patients [7], thus this approach can now to applied to humans as well. In addition, we confirmed the well-known positive inotropic effect of dobutamine as manifest by the increase in HR and stroke volume despite an unchanged Pcv and Pao. It is unclear from our data which factor plays a greater role in increasing COtd, increasing inotropy or decreasing Rv.
In our animals hypovolemia caused/produced Pmsf, Pcv, COtd and surprisingly Rv to decrease and Pao and Rsys to be constant. The gradient for venous return, Pvr=Pmsf-Pcv, decreased with 27%, so with a constant resistance for venous return, Rv, we expected a decrease in CO of the same order (CO=Pvr/Rv). However, Rv decreased by 16% leading to a decrease in COtd with only 9%. Thus, there appears to be compensation for the loss of venous return by adaptation of Rv, manifested by the significant increase in heart rate. Potentially, this occurred by shifting blood away from the splanchnic circulation with its higher Rv ro other systemic vascular circuits, as we have previously shown [22], but our study
128) does not allow us to confirm this speculation. However, since we observed that the location at which Pmsf exist (Rs/Rsys) shifted more into the direction of the venous site of the circulation, suggests that such a redistribution of blood flow did occur.

Limitations

Some limitations apply to our model. The technical set-up with a flow probe around the aorta is not general applicable in humans. A reliable less invasive beat-to-beat determination of cardiac output by trans-oesophageal ultrasound or arterial pulse contour allow similar studies to be done in humans [7].
We measured only Pao and Pcv and calculated Pmsf. Pmsf is a lumped variable of all the vascular beds. Thus, it is not clear, which specific or general vascular beds were affected by dobutamine infusion or hypovolemia. The difference in local adrenergic receptor (subtype) expression and overall expression of the receptors vary between different vascular beds and between species. Although the circulation of the pig bares macroscopic resemblance to the human physiology, a direct extrapolation of the results is precarious. This, however, also applies for previous studies [1,6]. Clearly, future human studies using less invasive means will need to be done to validate these findings in patient with normal vascular responsiveness and disease.

Conclusions

The use of our *in-vivo* animal model to assess the hemodynamic effects on Pmsf, Rsys, Rv and Rv/Rsys of a cardiovascular drug and of hypovolemia was successfully tested. The discrimination between arterial and venous resistance is possible because we can estimate Pmsf accurately. The higher cardiac output seen during dobutamine infusion was attributed to the combined increased cardiac function and decreased venous flow resistance despite a decrease in Pmsf. Hypovolemia decrease as expected Pmsf but this decrease was partly compensated for by a decrease in Rv to preserve venous return and thus cardiac output.

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Chapter 8

Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients

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Critical Care Medicine 2009; 37(3): 912-8

The cardiovascular system is a closed circuit with varying blood flow out of the heart into the arterial system (cardiac output) and flow back to the heart from the venous system (venous return) that may not be equal at any point in time owing to ventilation-induced changes in venous return, but which over time must be equal [1,2]. Thus, under steady state apnoeic conditions cardiac output (CO) and venous return (VR) equal. Guyton *et al.* [3,4] showed that the relationship between stepwise changes in right atrial pressure (Pra) and the resulting changes in venous return describes a venous return curve, which itself is a function of the circulating blood volume, vasomotor tone and blood flow distribution. Importantly, right atrial pressure at the extrapolated zero flow pressure-intercept reflects mean systemic filling pressure (Pmsf) and the slope of this relation describes the resistance for venous return (Rvr) [3,5]. This relationship between right atrial pressure and VR was well described in animal models with an artificial circulation [4], in patients during stop flow conditions [6] and in animals with an intact circulation using invasive hemodynamic monitoring [7-10]. However, it has never been evaluated in humans with an intact circulation. If such venous return curves could be easily calculated at the bedside, then complex cardiovascular analysis would be feasible thereby augmenting greatly our understanding of the dynamic determinants of circulatory insufficiency states and their responses to therapies. Intravascular blood volume
134) can be divided in unstressed volume (the blood volume necessary to fill the blood vessels without generating an intravascular pressure), and stressed volume (the blood volume which generates the intravascular pressure, which is mean systemic filling pressure in no flow conditions).

Previously, Pinsky [7] constructed instantaneous venous return curves based on the beat to beat changes in Pra and simultaneously measured right ventricular output during a single mechanical breath, neglecting possible transient effects of increasing Pra on venous return [1,2]. Versprille and Jansen [8] prevented these transient changes by measuring Pra and right ventricular output during steady state conditions generated by ventilator applied inspiratory pause periods at different inflation volumes. Unfortunately, it is difficult to measure pulmonary blood flow on a beat to beat basis at the bedside. We hypothesized that if inspiratory hold manoeuvres that increase right atrial pressure create a new steady state then venous return and cardiac output would again be equal and direct measures of left-sided cardiac output could be used to estimate steady state venous return.
Thus, we studied the effect of 12-second inspiratory hold manoeuvres on the relation between central venous pressure (Pcv), as a surrogate for right atrial pressure, and arterial pulse contour-derived cardiac output (COmf), as a surrogate for venous return, as Pcv was varied by inspiratory hold manoeuvres and intravascular volume status altered by a head-up tilt body position (relative hypovolemia) and intravascular volume loading (hypervolaemia).

Methods

Patients

Twelve post-operative patients after elective coronary artery bypass surgery or aortic valve replacement were included into the study after approval by the university medical ethics committee and patient's informed consent was obtained. All patients had symptomatic coronary artery disease without previous myocardial infarction and were on beta adrenergic blocking medication. Patients with congestive heart failure (NYHA class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiency, were not considered for this study. Patients with postoperative arrhythmia or the necessity for artificial pacing or use of a cardiac assist device were also excluded.

Anaesthesia during surgery was maintained with sufentanil and propofol and patients were ventilated in synchronized intermittent mandatory surgery was maintained with propofol and ventilation (SIMV) mode (Evita4 servo ventilator Draeger, Lubeck, Germany) adjusted to achieve normocapnia (arterial PCO_2 between 40 and 45 mmHg) with tidal volumes of 6-8 $ml \cdot kg^{-1}$ and a respiratory rate of 12-14 $breaths \cdot min^{-1}$. Fraction of inspired oxygen (FiO_2) was 0.4 and a positive end-expiratory pressure (PEEP) of 5 cmH_2O was applied. A hemodynamic stability was achieved using fluids and catecholamines. During the study interval all subjects were haemodynamically stable and no changes were made in their vasoactive drug therapy. Every patient experienced full recovery from anaesthesia within 8 hours following surgery and was discharged from intensive care unit on the first post-operative day.

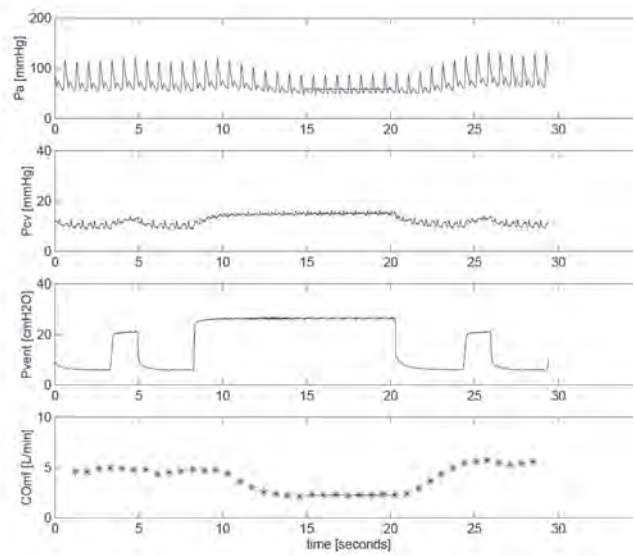
Measurements

Arterial blood pressure (Pa) was monitored via a 20 Gauge, 3.8 cm long radial arterial catheter inserted by Seldinger technique and connected to a pressure transducer (PX600F, Edwards Lifesciences). Pcv was measured with a central venous catheter inserted through the right internal jugular vein (MultiCath 3 venous catheter, Vigon GmbH & Co, Aachen, Germany) and connected to a pressure transducer (PX600F, Edwards Lifesciences). Both Pa and Pcv transducers were referenced to the intersection of the anterior axillary line and the 5^{th} intercostal space. Airway pressure (Pvent) was measured at the entrance of the endotracheal tube. Pvent was balanced at zero level against ambient air. Standard ECG leads were used to monitor heart rate (HR). Beat to beat cardiac output was obtained by modelflow (COmf) pulse contour analysis as previously described by us [11-13]. We calibrated the pulse contour cardiac output measurements with 3 thermodilution cardiac output measurements equally spread over the ventilatory cycle [12].

Experimental protocol

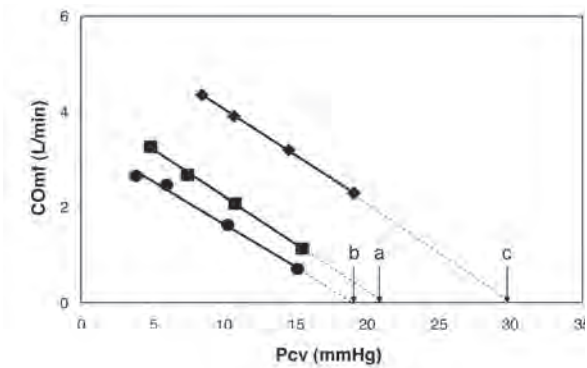
Before starting the protocol the mechanical ventilation mode was switched to airway pressure release ventilation (APRV) with the same rate, FiO_2, and PEEP level. Inspiration pressure was adapted to have the same gas exchange as in SIMV mode. This change in ventilation mode allowed external control of the ventilatory process. We developed a computer program to drive the ventilator. During the observation period ventilator settings, sedation and vasoactive medications remained unchanged. No spontaneous breathing movements were observed during the study. Pa, Pcv and Pvent were recorded on computer disk for offline data analysis at a sample frequency of 100 Hz and 0.2 mmHg resolution. We constructed venous return curves by measuring steady state Pa, Pcv and COmf over the final 3 seconds for a set of four 12-second inspiratory hold manoeuvres at Pvent plateau pressures of 5, 15, 25, 35 cmH_2O. The inspiratory hold manoeuvres were separated by 1-minute intervals to re-establish the initial hemodynamic steady state. An example of the hemodynamic changes during an inspiratory hold is presented in Figure 1.

Figure 1 Effects of an inspiratory hold manoeuvre on arterial pressure (Pa), central venous pressure (Pcv), airway pressure (Pvent) and beat to beat cardiac output (COmf). Preceding the hold manoeuvre the effects of a normal ventilatory cycle are plotted.



When Pvent increases, Pcv increases concomitantly, while COmf and Pa decrease with a delay of 3-4 beats, reaching a steady state between 7 and 12 seconds after start of inflation. From the steady state values of Pcv and COmf during the four inspiratory pause periods a venous return curve was constructed by fitting a linear regression line through these data points (Figure 2).

Figure 2 Relationship between venous return (COmf) and central venous pressure (Pcv) for an individual patient. Venous return curves are plotted for three conditions, baseline (a), hypovolemia (b) and hypervolaemia (c).



The four inspiratory hold manoeuvres were performed under three sequential volumetric conditions: initial baseline conditions (Baseline) with the subject lying supine, relative hypovolemia by rotating the bed to a 30° head-up (anti-Trendelenburg) position (Hypo), and after administration of 500 ml HydroxyethylStarch (HES 130/0.4) in supine position (Hyper). Measurements were done 2 minutes after head-up tilt and 2-5 minutes after the fluid bolus, which was given in 15-20 minutes.

Data analysis and statistics

We fitted the set of 4 data points of Pcv and COmf by linear regression for each volume state to define the venous return curve. We defined Pmsf as the extrapolation of this linear regression to zero flow (Figure 2), assuming that airway pressure does not affects Pmsf. We have previously validated this extrapolation in piglets [8-10].

Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pa and mean Pcv and COmf (Rsys = (Pa - Pcv)/COmf). The resistance downstream of Pmsf was taken to reflect the resistance to venous return (Rvr) and was

calculated as the ratio of the pressure difference between Pcv and Pmsf and COmf (Rvr = (Pmsf-Pcv)/COmf). Systemic arterial resistance (Ra) was taken to be the difference between systemic and venous resistance. The ratio of Rvr and Rsys describes the location within the circulation where Pmsf exists. A higher ratio implies a more upstream Pmsf location. Systemic compliance (Csys) was calculated by dividing the amount of fluid (Vload) administrated to induce the Hyper state by the Pmsf difference between Baseline and Hyper (Csys = Vload /($Pmsf_{Hyper}$ –$Pmsf_{Baseline}$). We assume systemic compliance to be constant for the three volaemic conditions studied. Stressed vascular volume (Vs) was calculated as the product of Csys and Pmsf. We calculated Vs for all three relative volume conditions.
Data are presented as mean ± SD. Linear regressions were fitted using a least-squares method. The changes between the three conditions were tested by a paired t-test, with differences corresponding to a $P < 0.05$ considered significant. We compared Baseline to both Hypo and Hyper.

Results

Sixteen patients were recruited into the study but 4 were excluded from analysis because they could not receive an additional volume challenge. We report in Table 1 the patient characteristics and in Table 2 the pooled data of the 12 subjects who completed all three steps of the protocol.

Table 1 Patient characteristics.

No.	Gender	Age (years)	Weight (kg)	Length (cm)	HR (min^{-1})	Pcv (mmHg)	CO ($L \cdot min^{-1}$)	MAP (mmHg)	Temp (°C)	Surgery	Inotropics ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Propofol ($mg \cdot h^{-1}$)	Sufentanil ($\mu g \cdot h^{-1}$)
1	M	60	80	172	85	8.2	4.6	72	36.8	CABG	-	300	15
2	M	57	78	169	119	9.9	5.7	73	36.9	CABG	Dobu 2	300	15
3	M	79	78	174	86	7.5	6.3	88	36.9	AVR	Dobu 5	200	10
4	M	50	90	190	93	7.4	3.2	138	36.3	AVR	NPN 0.25	300	15
5	M	80	90	172	99	8.0	6.1	80	36.7	CABG	Nor 0.01	200	10
6	F	64	83	167	76	7.1	5.8	88	37.4	CABG	Nor 0.04, Dobu 3	200	10
7	M	50	112	183	83	4.0	5.7	85	37.0	CABG	Nor 0.06	500	15
8	M	57	91	177	63	4.9	6.4	78	35.1	CABG	-	300	10
9	M	71	73	179	93	8.0	8.8	91	37.1	CABG	Nor 0.09, Dobu 4	120	5
10	M	66	88	178	69	3.0	7.4	71	35.8	CABG	Nor 0.02	200	10
11	M	75	95	173	77	9.0	4.4	130	36.5	CABG	-	300	10
12	F	60	74	158	89	3.7	5.3	86	36.6	CABG	Nor 0.04, Enox 2	150	5
mean		64	86	174	86	6.7	5.8	90	36.6			256	11
sd		10	11	8	15	2.3	1.4	22	0.6			101	4

HR, heart rate; Pcv, central venous pressure; CO, cardiac output; MAP, mean arterial pressure; Temp, body temperature; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; Dobu, dobutamine; NPN, nitroprusside sodium; Nor, norepinephrine; Enox, enoximone

Venous return curve analysis

Pcv and COmf decreased during Hypo and increased during Hyper. Similarly, Pmsf decreased during Hypo and increased during Hyper, whereas the slope of the venous return (conductance) was not significantly different for the three conditions of Baseline, Hypo and Hyper. The pressure gradient for venous return did not change with Hypo but increased with Hyper such that Rvr was unchanged by Hypo but increased with Hyper. Importantly, Rsys, did not change. Thus, the estimated location of Pmsf was unchanged by Hypo but migrated upstream with Hyper.

Table 2 Hemodynamic data of patients during baseline, hypo- and hypervolaemic condition.

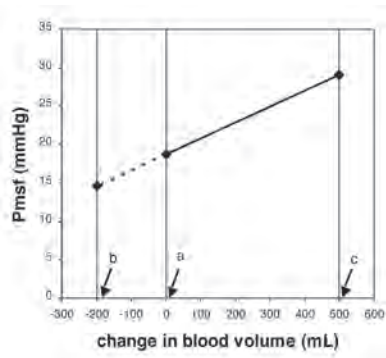
	Baseline mean	SD	Hypo mean	SD	p1	Hyper mean	SD	p2
Pa (mmHg)	89.9	21.6	75.7	17.3	0.001	96.5	14.9	0.17
Pcv (mmHg)	6.72	2.26	4.02	2.12	0.001	9.67	2.63	0.007
COmf ($L \cdot min^{-1}$)	5.82	1.44	4.76	1.3	0.001	6.83	1.36	0.002
HR (min^{-1})	86	14.7	85.7	15.1	0.456	84.3	10.7	0.401
Slope ($L \cdot min^{-1} \cdot mmHg^{-1}$)	-0.465	0.151	-0.429	0.16	0.388	-0.389	0.135	0.134
Pmsf (mmHg)	18.76	4.53	14.54	2.99	0.005	29.07	5.23	0.001
Pvr (mmHg)	12.04	3.70	10.52	2.27	0.106	19.40	6.88	0.003
Rvr ($mmHg \cdot min \cdot L^{-1}$)	2.18	0.86	2.41	1.14	0.184	2.91	1.10	0.037
Rsys ($mmHg \cdot min \cdot L^{-1}$)	15.89	9.00	16.95	10.27	0.379	13.52	5.60	0.122
Rvr/ Rsys (%)	14.94	5.00	14.84	2.37	0.931	22.62	8.07	0.006

Values are means ± SD; n=12 patients. Pa, arterial pressure; Pcv, central venous pressure; COmf, cardiac output; HR, heart rate; Slope, slope of venous return curve; Pmsf, mean systemic filling pressure; Pvr, pressure difference between Pmsf and Pcv; Rvr, resistance for venous return; Rsys, resistance of the systemic circulation. Statistical comparison, p1, paired t-test between baseline and hypovolaemic condition (hypo) and p2, paired t-test between baseline and hypervolaemic condition (hyper)

Systemic compliance and stressed volume

The change in stressed volume versus Pmsf is shown in Figure 3. Assuming a constant compliance the loss of stressed volume due to Hypo is approximately 200 ml. On average systemic compliance was 80 ± 62 $ml \cdot mmHg^{-1}$ (0.98 ± 0.82 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ body weight) and stressed volume during Baseline was 1677 ± 1643 ml (12.5 ± 12.1 $ml \cdot kg^{-1}$ body weight).

Figure 3 Relationship between change in blood volume and mean systemic filling pressure (Pmsf) for three conditions, baseline (a), hypovolemia (b) and hypervolaemia (c). See text for discussion.



Discussion

Our study demonstrates that by using a simple inspiratory hold manoeuvre while
140) simultaneously measuring Pcv and Pa one can generate venous return curves and derive their associated vascular parameters at the bedside. Our data suggest that volume altering manoeuvres (Hypo and Hyper) do not alter vascular conductance (slope of the venous return curve). These clinical data are concordant with the long-described experimental data introduced by Guyton and colleagues over 50 years ago [4,14]. Importantly, our novel approach to assessing venous return allows these analyses to be done at the bedside in patients after coronary artery bypass surgery or aortic valve replacement. Patients with congestive heart failure (NYHA class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, postoperative valvular insufficiency, postoperative arrhythmia or the necessity for artificial pacing or use of a cardiac assist device were excluded from this study. It will be interesting to see how these vascular parameters change in different disease states, such as septic shock and heart failure, and how treatments alter them further because these analyses allow for the repetitive estimation of circulatory vascular compliance and effective circulatory blood volume.

Methodological issues

During an inspiratory pause period a new steady state was attained, which can be concluded from the plateau phase in the COmf, Pa and Pcv (Figure 1). In this example the time needed to reach the plateau was approximately 7 seconds. This duration is too short to be associated with changes in autonomic tone which would otherwise occur owing to the decrease in Pa-induced baroreceptor-mediated increase in sympathetic tone. Samar and Coleman [15] showed in rats that a total circulatory stop, by pulmonary occlusion, caused a simultaneous

decrease of arterial pressure and a rise in central pressure to an equal plateau pressure within 4 to 5 seconds. This was followed by a second rise in Pcv after 10-12 seconds of circulatory arrest in rats [15,16] and after 12-15 seconds in dogs [17]. The second rise was seen in unanaesthetized rats and during methoxyflurane anaesthesia, however, seldom seen with pentobarbital and inhibited by hexamethonium or spinal-cord transaction [18]. Thus, any secondary increase in HR or Pcv was due to sympathetic reflex activation. We did not observe an increase in Pcv or HR during the last phase of our inspiratory pause, not even during pause pressures of 35 cmH_2O. Furthermore, all Pa values rapidly reached steady state conditions within 7 seconds, making our analysis relatively free of the confounding effects of varying autonomic tone. However, our subjects were also receiving neuro-suppressive agents (propofol and sufentanil) during the study interval, thus sympathetic responsiveness may have been blunted. Propofol depresses the baroreflex responses to hypotension and inhibits sympathetic nerve activity in healthy volunteers [19,20], whereas sufentanil might depress baroreceptor reflexes [21]. Thus, these studies will need to be repeated in non-anesthetized subjects to validate their usefulness in that population. Still, in the setting of general anaesthesia, these findings appear valid.

During inflation venous capacitance is loaded due to an increase in central venous pressure, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output [1,2]. To avoid this effect on the relationship between venous return and Pcv we measured Pcv and COmf during short periods of steady state following these initial non-steady state conditions (Figure 1). Our Pmsf estimation method by extrapolating the values of four pairs of Pcv and COmf obtained from four levels of inspiratory plateau pressures has several advantages. First, it allows the construction of Guyton-type venous return curves with an intact circulation, an opportunity not presently available. Second, Pmsf can be determined without creating stop flow conditions, such as stopping the heart by electrical fibrillation or injection of acetylcholine or by blocking the circulation. And thirdly, mean systemic filling pressure is not influenced by changes in lung or thorax compliance. Lung or thorax compliance effects the transfer of the applied airway pressures to intra-thoracic pressures. Thus, during an inspiratory hold the resulting Pcv depends on these compliances. But, indeed, the measured Pcv and CO will always be on the same line in the venous return plot. For instance, in a patient with stiffer lungs, during an inspiratory hold the transfer from airway pressure to intra-thoracic pressure will be less, resulting in a smaller increase in Pcv and a smaller decrease in CO.

We assumed a linear relation between Pcv and COmf to extrapolate to the condition of COmf is zero (Figure 2). This assumption is based on the observation of linearity of the

venous return curves presented by Guyton and co-workers [4,14] and is expressed by the mathematical relation VR=CO=(Pmsf – Pcv)/Rvr. Furthermore, this linearity has been confirmed in the intact circulation in several animal studies [7-10,22,23]. Our venous return curves were best fitted with straight lines allowing extrapolating the venous return curve to flow zero. This linearity was neither affected by Hypo or Hyper.

Our estimated Pmsf values are higher than those described in highly instrumented animals, which are in dogs 7-12.5 mmHg [4,7,14,17,24,25], rats 7-9 mmHg [15,16], pigs 10-12 mmHg [8-10], and as high as 20-30 mmHg in conscious calves implanted with an artificial heart [26]. We report Baseline Pmsf values of 18.8 mmHg in our cardiovascular surgical patients. A primary difference between the prior animal studies and our patient observations is the difference in baseline Pcv. In the animals studies this value is close to zero whereas Pcv in our patient population is on average 6.7 mmHg. If one assumes a similar Rvr, this Pcv pressure difference would extrapolate to a Pmsf of 12 mmHg for our subjects if their Pcv were zero (see Table 2). Thus, our Pmsf values are coupled with the increased Pcv.

142) Our present data seem to be in conflict with those of our previous study, wherein we demonstrated that inspiratory hold manoeuvres did not decrease blood flow, as estimated by thermodilution pulmonary artery flow [27] despite an increase in Pcv. There were no differences between the two studies in terms of Pa (75 ± 15 versus 88 ± 18 mmHg), Pcv (9 ± 4 versus 8 ± 2 mmHg) and cardiac output (5.7 ± 1.52 versus 5.6 ± 1.6 $L \cdot min^{-1}$, previous to present mean pooled data, respectively). However, two major differences in the protocols exist. First, the inspiratory hold manoeuvre used by van den Berg *et al.* [27] had a temporarily higher inflation pressure at the beginning of the manoeuvre which was decreased to the steady state plateau value, and second the bolus thermodilution method was applied during the inspiratory pause in the first study whereas we used the modelflow pulse contour cardiac output method to measure instantaneous flow in the present one. Re-examination of the data of van den Berg *et al.*[27] suggests that the thermodilution injections might have been performed before the plateau in blood flow had been reached. If this were the case, then the thermodilution cardiac output values would over-estimate steady state values, resulting in an underestimation of the slope of the venous return curve. Furthermore, in their study [27] plateau pressures from 0 up to 19 cmH_2O were used whereas we used plateau pressures from 5 up to 35 cmH_2O, which are comparable to those used by Versprille and Jansen [8] in their animal experiments. The limited range of applied plateau pressures in the van den Berg study [27] might have hampered the construction of proper venous return curves. Jellinek *et al.* [28] estimated in 10 patients during episodes of apnoea and ventricular

fibrillation, induced for defibrillator testing, and found a mean Pmsf value of 10.2 mmHg and Schipke *et al.* [6] estimated a mean Pmsf value of 12 mmHg in a similar group of 85 patients. However, both studies were done on highly anesthetized non-volume resuscitated subjects. Our method of estimation of Pmsf differs considerably from stopping flow by defibrillation of the heart and our method allows an estimation of Pmsf with intact circulation, applicable in the intensive care unit. Still, until paired comparisons of Pmsf are made using the two techniques (i.e. stop flow and our method) in the same subjects direct comparisons and interpretation of the data can not be made.

Using these manoeuvres to assess cardiovascular status

Moving patients from supine into a head up tilt position shifts blood from the central compartment to the legs, creating a relative hypovolaemic state as manifest by a decreasing Pmsf, Pcv and cardiac output. Potentially, other conflicting processes could also be occurring simultaneously. As the blood volume shifted to the legs increase femoral venous pressure, venous vascular diameter will increase decreasing vascular resistance from the legs. The impact of the intra-abdominal volume shift off the diaphragm is less clear but may increase hepatic resistance if chest wall movement compresses the sub-diaphragmatic liver. The results of these effects lead to no change in Rvr and a decrease in COmf, Pa, Pcv and Pmsf (Table 2).

Volume loading creates relative hypervolaemia which results in an increase of Pmsf, Pcv, CO and Pa. The higher CO can only be generated by a higher filling of the right atrium reflected in an increase of Pcv. Because the pressure gradient for venous return is increased more than Rvr, CO increases (Table 2).

Pmsf is the pressure at the mid-point of the vascular pressure drop from the aorta to the right atrium. In practice, it is usually locate in the venules and is less than arteriolar pressure and more than Pcv but close to capillary-venule tissue pressure [8,18]. The localization of Pmsf within the circulation is a conceptual model at best, since it reflects a lumped parameter of all the vascular beds. However, its position in the pooled vascular beds will shift depending on changes in arterial and venous resistances as was pointed out by Versprille and Jansen [8]. Our data suggests that the vascular site for Pmsf exists in the range of the capillary-venule pressures, i.e. Rvr/Rsys= 15% (Table 2). And, indeed, this site shifted upstream (Rvr/Rsys=23%) with Hyper, whereas Hypo had no effect on the site of Pmsf (Rvr/Rsys=15%). These data suggest that in the immediate post-operative period increased sympathetic tone keeps Pmsf in the venular side but with volume loading and a presumed reduction of vasomotor tone, this point shifts retrograde toward the arterial system. It will be interesting to see how this location changes with the use of vasoactive drug therapy and in patients with either sepsis or heart failure. We also saw that Rvr increased during

hypervolaemic conditions whereas conductance (conductance = 1 / Rvr) was constant. We are not sure why this would be the case, because anatomically and physiologically speaking, the same factors affect both resistance and conductance. Potentially, our technique systematically overestimated Pmsf, and thus pressure gradient for venous return under hypervolaemic conditions due to squeezing of blood volume out of the lung; or the associated increase in Pcv decreased the flow through the more dependent venous conduits. Our study design does not allow us to speculate further on these Rvr changes.

Whole body vascular compliance is calculated as the ratio of the change of volume to the change in estimated Pmsf (ΔV/ΔP). Using our inspiratory hold technique we found a vascular compliance, Csys, of 0.98 ml·mmHg^{-1}·kg^{-1} body weight. Because the administration of 500 ml of colloid can expand plasma volume with more than 500 ml, because of fluid recruitment of the extravascular space and because of fluid loss (urine and blood loss), the amount of 500 ml is an approximation of the actual volume expansion. Previous studies in instrumented anesthetized animals have reported a linear relation between Pmsf and blood volume over a Pmsf of 5 to 20 mmHg [18]. Thus, vascular compliance over this Pmsf range may be considered constant. From this constant total
144) systemic vascular compliance and the change in Pmsf from Baseline to Hypo we calculated an effective volume loss to be about 200 ml. This loss is due to a shift of blood from stressed to unstressed blood volume.

The stressed volume can be estimated from the compliance and Pmsf. In normovolemic patients in supine position we estimated an averaged stressed volume of 1677 ml or 19.5 ml·kg^{-1}. To our surprise this calculated stressed volume is close to the stressed volume of 20.2 ml·kg^{-1} reported by Magder and De Varennes [29] in patients undergoing hypothermic circulatory arrest for surgery on major vessels. They measured stressed volume as the volume that drained from the patient into the reservoir of the pump when the pump was turned off.

Previously reported values for Csys ranged from 1.4 to 2.6 ml·mmHg^{-1}·kg^{-1} in dogs [17,30-33] and from 1.5 to 2.4 ml·mmHg^{-1}·kg^{-1} in rats [15,16,34]. The lower compliance (0.98 ml·mmHg^{-1}·kg^{-1}) observed in our patients may reflect species differences or differences in methodology used. The main difference in methodology is related to the time between volume loading and the determination of Pmsf. In animal studies the Pmsf measurement is performed 30 seconds after volume loading, whereas we finished our measurements after more than 20 minutes following volume loading. According to Rothe [18] it is virtually impossible to measure the vascular capacitance characteristics, and thus passive V/P curves and stressed

volume of the total body in reflex-intact animals and humans. This limitation is because one cannot change blood volume and measure Pmsf in less than 7-10 seconds, which is the maximal delay before reflex venoconstriction normally becomes evident, unless these reflexes are blocked. In our patients the use of propofol and sufentanil might have blocked these reflexes [19-21] and might be the explanation for the corresponding stressed volume results of our study and the study of Magder and De Varennes [29].

Conclusions

Mean systemic filling pressure can be determined in intensive care patients with an intact circulation with use of inspiratory pause procedures, making estimations of circulatory compliance and serial measures of circulatory stressed volume feasible.

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Chapter 9

Is arm occlusion pressure a predictor of fluid responsiveness?

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Provisionally accepted by European Journal of Anaesthesia

Fluid therapy is an important tool in hemodynamic management of patients with suboptimal tissue perfusion. Excessive fluid resuscitation, however, can result in general and pulmonary oedema; increasing hospital stay and even mortality [1]. In ventilated patients with regular heart rhythm, stroke volume variation (SVV) and pulse pressure variation (PPV) perform well as predictors of a clinically significant increase in cardiac output (CO) after fluid administration (i.e. fluid loading responsiveness or FLR) [2,3]. In vasoplegic patients both indicators failed [4,5]. Furthermore, SVV and PPV have never been shown to perform as a measure of volume status. Therefore the search for a measure of volume status and a predictor of fluid loading responsiveness which can be used independent of respiratory settings and heart rhythm continues [6].

A physiological measure of effective volume status is mean systemic filling pressure (MSFP); the equilibrium pressure anywhere in the circulation under circulatory arrest. The pressure gradient between static filling pressure and central venous pressure is the driving force for venous return and thus for cardiac output. Consequently, increasing MSFP and thereby the pressure gradient for venous return by fluid expansion should improve cardiac output, assuming a constant resistance to venous return and adequate myocardial function.

In pharmacology research, upper arm occlusion pressure (Parm) has been used to determine (the effects of drugs on) venous capacitance and arterial resistance [7]. We hypothesize that Parm might function as an indicator of filling pressure and volume status. MSFP has never been studied as a predictor of fluid responsiveness. We determined Parm by measuring arterial pressure 30 seconds after stop-flow induced by inflating a cuff around the upper arm. The aim of this study was to explore the value of Parm as a predictor of fluid loading responsiveness. This approach is attractive, as it would provide the clinician with a simple, readily available and robust measure that can be obtained at the bedside. This method would be independent of sedation, arrhythmias and mechanical ventilation.

Methods

Twenty-four patients undergoing elective-cardiac surgery were included after approval of the institutional ethics committee (P06.149, chairmen Prof. Dr. F.C. Breedveld, approval date 5 december 2006) and personal informed consent was obtained. All patients had symptomatic coronary artery or valvular disease with preserved ventricular function. Patients with aortic aneurysm, extensive peripheral arterial occlusive disease, postoperative severe arrhythmia, postoperative valvular insufficiency or the necessity for artificial pacing or use of a cardiac assist device were excluded.

Prior to surgery, each patient received a pulmonary artery catheter (Intellicath; Edwards Lifesciences; Irvine, CA, USA) to measure thermodilution COtd and CVP and a 20 G radial artery catheter (Prad). Patient's anaesthesia was continued with propofol (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.06-0.20 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The lungs were mechanically ventilated (Evita 4, Draeger, Lubeck, Germany) in a volume-control mode with standard settings (12 $breaths \cdot min^{-1}$, tidal volume 8-10 $ml \cdot kg^{-1} \cdot min^{-1}$, FiO_2 0.4, PEEP 5 cmH_2O). Airway pressure (Paw) was measured at the proximal end of the endotracheal tube. During the observation period the patients maintained the supine position. Use of sedative and vascular medication remained unchanged. No fluids were administered during the observation period outside the study protocol.

An upper arm blood stop-flow was created with a rapid cuff inflator (Hokanson E20, Bellevue, Washington) and matching upper arm cuff. Duration of stop-flow was 35 seconds with a cuff pressure 50 mmHg above the patients' systolic blood pressure. Arm occlusion pressure (Parm) was calculated as the average arterial pressure during one second at 30 seconds after arm occlusion.

The arterial pressure Prad was analysed with the modelflow program (CO, FMS, Amsterdam, the Netherlands) to provide beat-to-beat values of CO. We calibrated the pulse contour cardiac output measurements with three thermodilution COtd measurements equally spread over the ventilatory cycle [8]. From these beat-to-beat cardiac output values, stroke volume variation (SVV) and pulse pressure variation (PPV) were determined. SVV and PPV were calculated for 5 ventilatory cycles and their values averaged.

Measurements of Parm, CVP, MAP, CO, SVV and PPV were done during baseline in supine position and 2-5 minutes after rapid fluid loading with 500 ml hydroxyethyl starch solution (Voluven®, Fresenius Kabi, Bad Homburg, Germany).

Statistical methods

A formal power analysis was not performed since relevant data was not available from literature. However, study sample size is similar to other fluid loading responsiveness studies. We used a Kolomogorov-Smirnov test and a paired t-test. Fluid responsiveness was defined as a >10% increment of modelflow cardiac output after volume expansion. The 10% cut-off corresponds with more than twice the reported precision of the Modelflow method (i.e. twice the SD for repeated measurements) [14,15]. Hence, responders will experience clinically significant changes in CO. Prediction of fluid responsiveness for Parm, CVP, PVR, SVV and PPV was tested by calculating the area under the receiver operating characteristic (ROC) curve. All values are given as mean ± SD. A p value < 0.05 was considered statistically significant.

Results

152) Twenty-four patients (19 males) of 64 ± 10 years with a BSA of 2.0 ± 0.2 m^2 started and finished the study protocol. Seventeen received straightforward coronary artery by-pass grafting, seven (also) had single or two valve repair. Data was distributed normally. Pooled results of hemodynamic variables at baseline and after 500 ml fluid administration are shown in Table 1. After 500 ml fluid loading CO, Parm, MAP and CVP increased. HR did not change. PPV and SVV decreased.

Table 1 Changes in hemodynamic parameters from baseline to after 500 ml fluid loading for all patients, responders and non-responders.

	All patients (n=24)			Responders (n=17)			Non-responders (n=7)		
Parameters	**Baseline**	**500 ml**	**P value**	**Baseline**	**500 ml**	**P value**	**Baseline**	**500 ml**	**P value**
CO ($L \cdot min^{-1}$)	5.2 ± 1.3	6.0 ± 1.4	< 0.001	5.1 ± 1.3	6.2 ± 1.4	< 0.001	5.5 ± 1.3	5.7 ± 1.3	0.148
Parm (mmHg)	18.6 ± 7.7	24.3 ± 8.7	< 0.001	16.2 ± 6.3	22.0 ± 7.6	< 0.001	24.3 ± 8.2	29.9 ± 9.1	< 0.001
MAP (mmHg)	82.3 ± 15.6	90.7 ± 16.1	< 0.001	78.9 ± 9.9	88.9 ± 11.2	< 0.001	90.4 ± 23.6	94.8 ± 25.2	0.056
CVP (mmHg)	9.0 ± 2.6	11.5 ± 2.9	< 0.001	8.6 ± 2.6	10.9 ± 2.5	< 0.001	9.9 ± 2.5	13.0 ± 3.4	0.004
PPV (%)	13.8 ± 9.0	8.0 ± 7.5	< 0.001	14.8 ± 7.8	8.1 ± 6.6	0.001	11.1 ± 11.5	7.7 ± 10.0	0.011
SVV (%)	15.5 ± 10.5	9.3 ± 9.3	0.001	16.5 ± 10.9	8.5 ± 6.5	< 0.001	13.0 ± 9.9	11.2 ± 14.6	0.627
HR (min^{-1})	83 ± 16	83 ± 14	0.908	83 ± 18	83 ± 16	1.000	81 ± 10	82 ± 11	0.860

CO is cardiac output, Parm is arm occlusion pressure, CVP is central venous pressure, MAP is mean arterial pressure and HR is heart rate

The population was divided into FLR responders (n=17) with an increase of at least 10% in COm after 500 ml fluid loading and non-responders (n=7). In the responder group CO, MAP, CVP increased and SVV and PPV decreased. Parm increased from 16 to 22 mmHg. In the non-responder group, Parm increased from 24 to 30 mmHg. CVP also increased. PPV decreased. CO, MAP, SVV and HR did not change significantly.

Receiver operating characteristic curves were used to qualify the prediction of fluid responsiveness for each parameter. The area under the curve (AUC) for prediction of fluid responsiveness for Parm was 0.786 (95% CI: 0.567 to 1.000). At a cut-off of 21.9 mmHg sensitivity is 71% and specificity 88% to predict FLR. The results for CO, Parm, MAP, CVP, PPV and SVV are in Table 2.

Table 2 Area under the receiver operating characteristics curve to predict fluid loading responsiveness from baseline values.

	Area	95% confidence interval	
		Lower	Upper
Cardiac output ($L \cdot min^{-1}$)	0.588	0.355	0.821
Arm occlusion pressure (mmHg)	0.786	0.567	1.000
Mean arterial pressure (mmHg)	0.588	0.399	0.853
Central venous pressure (mmHg)	0.353	0.105	0.601
Pulse pressure variation (%)	0.853	0.693	1.000
Stroke volume variation (%)	0.761	0.531	0.990

Discussion

Our study demonstrates that Parm was significantly lower in the responder group. Parm is a good predictor of fluid responsiveness in our studied group. We used Parm for the first time to study fluid loading responsiveness.

Both SVV and PPV have been reported to perform better as predictors of fluid responsiveness than static pressures (CVP and pulmonary artery occlusion pressure) [3,9-12]. However, SVV or PPV are influenced by ventilator settings as tidal volume [9,13], respiratory rate [14] and also to cardiac function. In patients with reduced cardiac function SVV is expected to be smaller, because stroke volume is obviously limited and consequently ventilator induced changes in stroke volume will be reduced [3,10] Reuter and co-workers showed that SVV could still perform as a predictor of fluid loading responsiveness in patients with reduced cardiac function, although SVV was indeed smaller in patients with impaired cardiac function [13]. Furthermore, for the determination of SVV and PPV it is essential that patients are fully dependent on mechanical ventilation, and a regular heart rate is obligatory. In spontaneous breathing patients [4,5] and in mechanically ventilated patients with tidal volumes smaller than 8 $ml \cdot kg^{-1}$ SVV and PPV failed to predict FLR accurately [9] In
154) our study patients, all after cardiac surgery, were mechanically ventilated with an averaged tidal volume of 9.1 $ml \cdot kg^{-1}$ (7-12 $ml \cdot kg^{-1}$) predicted body weight. Thus, for some of our patients SVV and PPV may be less reliable. The Parm technique does not require specific tidal volume or respiratory rate. To measure Parm with the arm occlusion method only a peripheral arterial catheter is required. These requirements allow measurement in almost all operating rooms and intensive care patients. Its application is not limited to sedated and ventilated patients with a regular heart rhythm. In our study, Parm was a good predictor of fluid loading responsiveness, at least equal to SVV or PPV. However, our study patients were a relatively homogenous group.

Definition of fluid loading responsiveness

There is no consensus on the amount of fluid or use of parameter to assess fluid loading responsiveness. Fluid amounts between 250-1000 ml are reported [3-5,15,16]. The outcome measures used were CO [4,5,16] and SV [15] or SV index [3]. A positive response was defined as a change in outcome parameter of more than 10%-25% [3,4,16]. We chose 10% change in pulse contour CO as cut-off level after fluid loading with 500 ml. The 10% increase in CO was chosen because this increase can be measured accurately with the modified Modelflow pulse contour method [17-20]. This value corresponds with the boundaries used in other studies where a 10% cut-off was used for 500 ml fluid loading responsiveness [4,21-23].

Considerations

The number of patients (n=24) included in our study is relatively low and the distribution of (non)reponders is unequal. Still with this low number of patients we were able to find highly significant results. Prediction of fluid loading responsiveness with baseline Parm was with a high sensitivity (71%) and specificity (88%). We theorise that these results can be explained by the similarity between Parm and mean systemic filling pressure. MSFP is the equilibrium pressure anywhere in the circulation under circulatory arrest, whereas Parm might be seen as the equilibrium pressure of the arm. We hypothesize that MSFP may be largely equal for different vascular compartments of the body because their venous outflow pressures and arterial input pressures are relatively similar. MSFP is a physiological measure of effective volume status [24,25]. The pressure gradient between MSFP and CVP is the driving force for venous return and thus for cardiac output. Increasing MSFP and thereby the pressure gradient for venous return by fluid expansion should improve cardiac output, assuming a constant resistance to venous return. If there is hypervolemia or a cardiac limitation, i.e. the heart operates on the flat part of the Frank-Starling curve, fluid loading will increase CVP along with MSFP, and venous return will not increase. It is important to stress that we excluded patients with previous myocardial infarction and patients with congestive heart failure (NYHA class 4). Therefore we must be careful to extrapolate to patients with heart failure. In our patients a low Parm (< 22 mmHg) could indicate fluid loading responsiveness. In the case of cardiac failure or tamponade, CVP will rise along with Parm during volume administration. This will result in an unchanged pressure gradient for venous return and thus will fail to induce an improvement in cardiac output. Therefore, we expect our results applicable to patients with uncompromised cardiac function. Rapid increments of CVP can than be seen as a warning of right ventricular limitation.

Conclusions

Arm occlusion pressure can be measured at the bedside. Unlike SVV, the measurement of Parm is relatively independent of heart rhythm, mechanical or spontaneous breathing or sedation. Parm seems to be a good predictor of fluid loading responsiveness, at least in cardiac surgery patients without severe heart failure.

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Section 4

Challenges and fluid loading responsiveness

Chapter 10

Predicting cardiac output responses to passive leg raising by a PEEP-induced increase in central venous pressure, in cardiac surgery patients

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Accepted for publication in British Journal of Anaesthesia

Changes in central venous pressure (CVP) are probably more useful in guiding fluid treatment of mechanically ventilated hypovolaemic patients than absolute pressure values which are confounded by concomitant positive end-expiratory pressure (PEEP) [1-3]. Furthermore, assessment of a reliable predictor prior to fluid loading would allow the physician to prevent harmful overloading. Ventilator-induced stroke volume variations (SVV) are commonly used to predict fluid responsiveness, i.e. an increase in cardiac output by fluid loading or passive leg raising (PLR). However, SVV is only applicable in mechanically-ventilated patients without spontaneous breathing efforts and with a regular heart rhythm. Furthermore, SVV depends on respiratory rates and tidal volumes [4-8]. Passive leg raising can be used as a reversible, endogenous fluid challenge of about 250-300 ml and, if correctly performed, the cardiac output response correlates well to that upon exogenous fluid administration in predicting fluid responsiveness [4,9-20]. However, repeated PLR is not practicable in all patients and all settings. Another manoeuvre to predict fluid responsiveness is an end-expiratory hold which produces an increase in pulse pressure and cardiac output. The magnitude of the change may be assessed by comparatively non-invasive pulse contour methods [19]. However, it is likely that the change depends on inspiratory pressure and thus on tidal volume and the resultant impediment in venous return. Taken together, current dynamic methods to predict fluid responsiveness have limitations and may not prevent harmful fluid overloading in mechanically ventilated, critically ill patients.

We hypothesized that the change in CVP produced by a change in PEEP of short duration can be used to predict the response of cardiac output to fluid loading, since an increase in PEEP is associated with an increase in CVP and a decrease in cardiac output, dependent on volume status [1,21-23]. To test this hypothesis, we measured the changes in CVP due to an increase in PEEP of 10 cmH_2O and defined fluid responsiveness by the response in cardiac output to subsequent PLR. We compared the predictive value of the change in CVP with those of absolute CVP and SVV.

Methods

The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent was obtained prior to surgery. Twenty consecutive patients undergoing elective cardiac surgery were enrolled into the study. During surgery, before admission to the ICU, each patient underwent pulmonary artery catheter insertion (Intellicath; Edwards Lifesciences; Irvine, CA, USA) to measure thermodilution cardiac output (CO) and CVP. A radial artery catheter was used to measure radial arterial pressure in all patients. In the ICU, anaesthesia was continued with propofol target control infusion (1.0 $\mu g \cdot ml^{-1}$) and sufentanil according to institutional standards. The lungs were mechanically

ventilated in a volume-control mode with standard settings to achieve normocapnia with a tidal volume of 8-10 ml·kg^{-1} and a respiratory frequency of 12-14 breaths·min^{-1}. The FiO_2 was 0.4 and baseline PEEP 5 cmH_2O. None of the patients suffered significant blood loss (> 50 ml·h^{-1}) during the data collection period.

Protocol and measurements

Blood pressure transducers were referenced to the level of the intersection of the anterior axillary line and the 5th intercostal space. CVP, mean arterial pressure (MAP) and heart rate (HR) were averaged over 30 second intervals. Bolus thermodilution CO was obtained, within 3 minutes with an automated system under computer control, by the mean of triplicate measurements equally spread over the ventilatory cycle [24]. SVV was determined from beat-to-beat CO values measured over 20 second intervals using the LiDCO (LiDCO Ltd, Cambridge, UK) radial artery pulse contour system. The system was calibrated by entering the mean value of the first series of 3 thermodilution measurements at the start of our protocol. All measurements were carried out following stabilization and within two hours of arrival on the ICU. During the observation period the patients remined supine and doses of sedative and vasoactive agents were unaltered. Measurements of CVP, SVV, CO, MAP and HR were made under five experimental conditions:

1) baseline 1;
2) PEEP increased with 10 cmH_2O (to a level of 15 cmH_2O);
3) baseline 2;
4) passive leg raising;
5) baseline 3;

Each condition was maintained for a five minute period and measurements were performed in the final three minutes of each period. Passive leg raising was performed by maintaining the patient supine position and raising the legs 30 degrees by using the facility to raise the lower end of the bed. The thorax and head (i.e. the heart and baroreceptors) were maintained at the same through all of the study periods and the pressure transducers did not have to be re-referenced.

Statistical analysis

Usually, fluid responsiveness is characterized by an increase of 10-15% in CO after rapid fluid loading with 500 ml [2]. Recently, Jabot and colleagues showed that PLR from the supine position induces lower increase in CO than PLR from the semi-recumbent position [17]. Based on their results and those of Lafanachere and colleagues [15] we reasoned that in responders PLR from the supine position should result in an increase of CO >7%. Our thermodilution technique with automated triplicate measurements equally spread over the respiratory cycle has a precision of

3.5% [24]. Therefore, this technique should detect changes in CO induced by PLR larger than 7% accurately, thereby allowing identification of responders. All data were normally distributed (Kolmogorov-Smirnov test P>0.05). The effects of PEEP and PLR were evaluated by subtracting the mean of the baseline value before and after the challenge from the value found during the challenge. Comparisons of different experimental conditions were performed using the paired t-test. The Pearson correlation coefficient was used to relate baseline variables to increases in CO upon PLR. Receiver operating characteristic (ROC) curves and 95% confidence intervals (95%CI) for the area under the curve (AUC) were computed. A p-value for the difference between the AUC and the reference value of 0.5 (i.e. prediction of responders and non-responders by chance) is calculated. From the ROC curves the optimum cut-off value with the greatest combined sensitivity and specificity were computed, using baseline SVV, absolute values and changes in CVP [25]. AUC's of the ROC curves (AUROC) of baseline SVV and PEEP induced change in CVP were compared. Data are summarized by mean and standard deviation (SD). A P<0.05 was considered statistically significant. Statistical calculations were performed by using SPSS for windows (V12; SPSS Institute, Chicago, IL, USA and MedCalc V9, Mariakerke, Belgium).

Results

162) Twenty patients were included in the study; patient characteristics are tabulated in Table 1. Twelve patients underwent coronary artery by-pass surgery (CABG) and, eight received either a single valve replacement or a combination of CABG and valvular repair surgery. Table 2 shows that, compared to baseline, an increase with 10 cmH_2O PEEP decreased CO increased CVP and SVV, but had little effect on MAP and HR. Passive leg raising increased CO, CVP and MAP but decreased SVV. All variables returned to baseline after the PEEP and PLR challenges. Whereas baseline CVP and baseline SVV related to the percentage change in CO due to PLR (Figure 1), the change in CVP due to PEEP correlated best to the change in CO due to PLR (Figure 1). Changes in CO upon PEEP moderately correlated to changes in CO by PLR (r=-0.47, P=0.036).

Table 1 Patient characteristics (n=20).

Age	**61 [range 35-80] years**
Sex m/f	16 [80%]/ 4 [20%]
Body surface area	2.00 (0.21) m^2
Type of surgery	
- coronary artery bypas grafting	11 [55%]
- valvular repair	9 [45%]
Dobutamine or dopamine	3 [15%]
Norepinephrine	2 [10%]
Tidal volume	752 (127) ml
Mean airway pressure	9 ± 1 cmH_2O
Positive end-expiratory pressure,	5 ± 0 cmH_2O
F_iO_2	0.4
P_aO_2	13.03 ± 0.13 kPa
P_aO_2/F_iO_2 ratio	31.0 ± 1.1

Data collected postoperative immediately before the study was performed. Data, except in the case of age, are shown as mean ± standard deviation

Table 2 Haemodynamics at baseline and after an increase in PEEP of 10 cmH_2O and after passive leg raising.

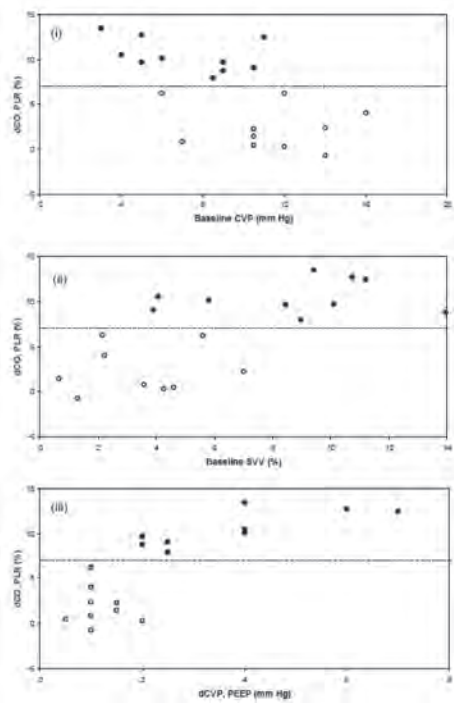
	Baseline PEEP	**+10 cmH_2O PEEP**	**Change**	**P**	**Baseline PLR**	**PLR**	**Change**	**P**
CVP (mmHg)	9.2 ± 3.6	11.5 ± 3.2	2.4 ± 1.8	<0.001	9.2 ± 3.6	11.6 ± 3.6	2.3 ± 1.3	<0.001
SVV (%)	6.2 ± 3.8	10.6 ± 6.5	4.7 ± 3.7	<0.001	5.8 ± 3.5	3.9 ± 2.7	-1.9 ± 1.8	<0.001
CO ($L \cdot min^{-1}$)	5.2 ± 1.3	4.6 ± 1.2	-0.6 ± 0.5	<0.001	5.5 ± 1.5	5.9 ± 1.7	0.4 ± 0.3	<0.001
MAP (mmHg)	83 ± 13	80 ± 14	-3 ± 10	0.054	84 ± 16	92 ± 14	8 ± 10	0.003
HR (min^{-1})	79 ± 13	78 ± 12	-1 ± 1	0.400	79 ± 12	77 ± 12	-2 ± 3	0.259

PLR is passive leg raising; CVP is central venous pressure; SVV is stroke volume variation; CO is cardiac output by thermodilution; MAP is mean arterial blood pressure; HR is heart rate. Baseline PEEP is the group average of the values before and after the PEEP-challenge; baseline PLR the group averaged value before and after PLR. The results are shown as mean (SD).

There were 10 PLR responders and 10 non-responders. Cardiac output values before and after the PEEP challenge were 5.1 ± 1.2 and 5.3 ± 1.5 $L \cdot min^{-1}$, in responders and non-responders (ns), respectively. Cardiac output values around PLR were 5.5 ± 1.6 and 5.5 ± 1.5 $L \cdot min^{-1}$ in responders and non-responders (ns), respectively. Baseline CVP values before and after the PEEP challenge were 7.1 ± 2.8 and 11.3 ± 3.1 mmHg in responders and non-responders, respectively (P=0.003). Baseline SVV values around the PEEP challenge were 8.7 ± 3.2 and 3.5 ± 2.1% in PLR responders and non-responders, respectively (P=0.001), but the PEEP-induced change in SVV did not differ. The PEEP-induced increase in CVP was less in non-responders to PLR than in

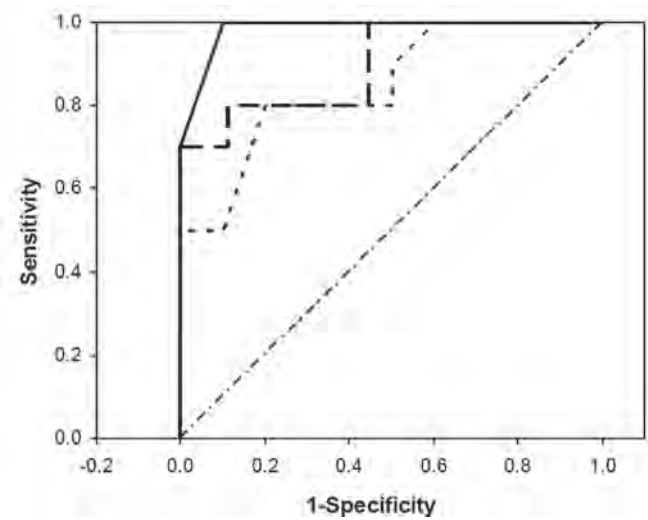
responders: 1.1 ± 0.4 and 3.6 ± 1.8 mmHg or 9 ± 7 and 62 ± 42% (P=0.001). Baseline values of CVP for responders and non-responders were 11.3 ± 3.1 and 7.1 ± 2.8 mmHg (P=0.006), respectively. Also, the decrease in CO upon the application of PEEP was less in PLR non-responders than responders (6 ± 7% versus 16 ± 10%, P=0.014).

Figure 1 In the first graph (i), the relationship between baseline central venous pressure (Baseline CVP) and change in thermodilution cardiac output (CO) by passive leg raising (dCO, PLR) is shown (r=-0.63, P=0.003); in the second graph (ii), the relationship between baseline stroke volume variation (Baseline SVV) and dCO, PLR (r=0.67, P=0.002). In the third graph (iii), relationship between the positive end-expiratory pressure (PEEP)-induced change in CVP (dCVP, PEEP) and dCO, PLR is depicted (r=0.77, P<0.001). Baseline values of CVP and SVV were the averaged results of baseline measurements before and after the PEEP-challenge. dCVP is the change in CVP due to PEEP compared to the averaged baseline value. The horizontal dashed line in the graphs indicate the cut-off between responders and non-responders. Closed symbols refer to responders.



The results of ROC curves analyses are shown in Figure 2. For baseline CVP, the AUC was 0.85 (95%CI 0.68 and 1.00, P=0.008) and the optimum cut-off value of 9.8 mmHg had a sensitivity of 80% and a specificity of 80% to predict PLR responsiveness. The AUC for baseline SVV was 0.90 (95%CI 0.76 and 1.00, P=0.003), and a baseline SVV cut-off of 7.3% had a sensitivity of 70% and a specificity of 100% to predict PLR responsiveness. For the predictive value of the CVP response (change) to PEEP, the AUC was 0.99 (95%CI 0.94 and 1.00, P<0.001) and a cut-off value of an increase of 1.5 mmHg had a sensitivity of 100% and a specificity of 90% for PLR responsiveness. The AUC of baseline SVV was not significantly different from the AUC for CVP response to PEEP (P=0.299), indicating that baseline SVV and the CVP response to PEEP can be used equally to predict responders and non-responders to fluid loading.

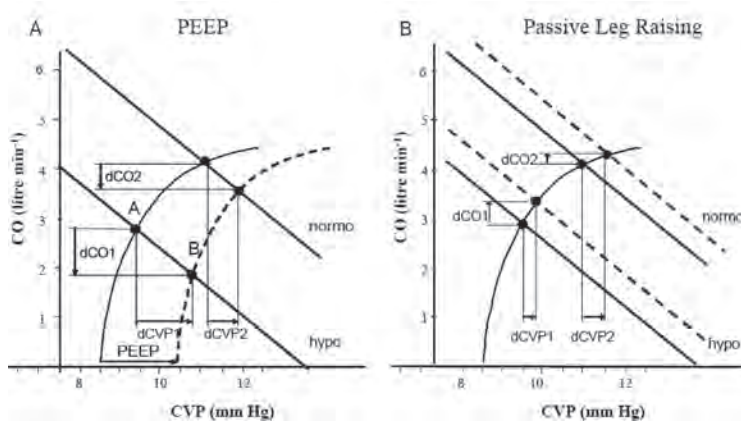
Figure 2 Receiver operating characteristics (ROC) curve of baseline CVP (dotted line), baseline stroke volume variation (dashed line) and change in central venous pressure (straight line) upon a PEEP challenge to predict responsiveness to passive leg raising. The area under the curve is 0.85 (with a 95% CI of 0.68 and 1.00) for baseline CVP, 0.99 (with a 95% CI 0.94 and 1.00) for changes in CVP and 0.90 (with a 95% CI 0.76 and 1.00) for baseline SVV.



Discussion

Our study shows that with higher baseline SVV values, lower baseline CVP values and greater rises in CVP upon a PEEP challenge the response of CO on an endogenous fluid loading by PLR can be predicted. Of these predictors, the rise in CVP with PEEP seems most robust to predict fluid responsiveness with least risk for confounding by ventilatory conditions.

Figure 3 A simplified model of the interaction of the heart function curve and venous return curve. On the left (A) the effects of positive end-expiratory pressure (PEEP) and on the right (B) the effects of fluid loading by passive leg raising (PRL) on central venous pressure (CVP) and cardiac output (CO) are indicated. From hypovolaemia (hypo) to normovolaemia (normo) the venous return curve (straight line) moves up and the intersection with the cardiac function curve (curved line) rises to a higher CO and CVP level. Left panel, addition of PEEP shifts the heart function curve to the right (dashed line) altering the intersection with the venous return curve to a lower CO and a higher CVP. With the application of PEEP the change in CVP (dCVP) and the change in CO (dCO) are larger during hypovolaemia ($dCVP^1$ and dCO^1) than during normovolaemia ($dCVP^2$ and dCO^2). Which suggest that the value of dCVP is an is an indicator for fluid loading responsiveness. Right panel, addition of PLR, dashed lines) results in an increase in CVP and CO. With fluid loading by PLR during normovolaemia a greater dCVP ($dCVP_2$) and a smaller dCO (dCO_2) is observable than during hypovolaemia ($dCVP^1$ and dCO^1). dCO with PLR have been shown to be an indicator of fluid loading responsiveness. For further explanation see text.



We based our study on the simplified Guytonian model of the circulation (Figure 3). We consider the effects of PEEP and of PLR in the hypo- and normovolaemic state. Many authors demonstrated that the venous return curve, i.e. the relationship between CO and CVP, moves up in parallel with increased blood volumes (Figure 3, lines hypo- and normovolaemia) [26-29]. We have previously constructed venous return curves using prolonged inspiratory hold manoeuvres in cardiac surgical patients and showed that the slopes were equal in hypo-, normo-, and hypervolaemic conditions [29]. Magder has shown that application of PEEP shifts the cardiac function curve to the right, altering the intersection with the venous return curve to a lower CO and a higher CVP (see Figure 3A, change from point A to point B) [1]. In patients with hypovolaemia, the increase in CVP and decrease in CO (dCVP1 and dCO1) is larger than in patients with normovolaemia (dCVP2 and dCO2), in line with experimental data [21]. Thus, the PEEP-induced change in CVP as well as the change in CO describes in which part of its function curve the heart operates. Fluid loading by PLR will move up the venous return curve (Figure 3B, dashed lines). In patients with hypovolaemia and in those with normovolaemia the intersection with the cardiac function curve will move towards its plateau [30]. Fluid loading in these two volaemic conditions results in an increasing change in CVP (see Figure 3B, from dCVP1 to dCVP2) and a decreasing effect on CO (see Figure 3B, from dCO1 to dCO2). Thus, with PEEP, dCVP and dCO should change inversely but proportionally, depending on the volume status whereas with fluid loading reverse effects of dCVP and dCO are predicted. We used PLR as a surrogate for fluid infusion since it well correlates with responsiveness to exogenous fluids [4,9-20]. Moreover, the use of PLR obviates unnecessary and potentially harmful fluid loading in non-responders.

We found, as predicted by the model, that the increase in CVP by PEEP directly relates to the increase in CO by PLR and thus may be of value to predict fluid responsiveness (Figure 1); second, that PEEP increases CVP and decreases CO, but that the increase in CVP as well as the decrease in CO is less in non-responders than in responders (normo- versus hypovolaemia). Our results imply that the predominant mechanism of the decrease in CO with PEEP is diminished venous return and a decrease in right ventricular preload, that in turn may limit the rise in CVP [1,21,22] We cannot judge from our data the effect of abnormal lungs and altered airway pressure transmission on the circulatory response to PEEP [22,23] Another limitation of the model is that it does not take circulatory control mechanisms into account. Therefore, we measured the effects of PEEP between 2 and 5 minutes after its application. Changes in myocardial contractility may change the position and shape of the heart function curve. Therefore, a deterioration of cardiac function may lead to a decrease in SVV and a decrease of in the change in CVP produced by PEEP as well as a less fluid-responsive patient. This was not examined in this study The fact that baseline CVP was also associated with changes in cardiac output can be explained by the relatively low PEEP we used

in our patients, but changes in filling pressures to guide fluid treatment are less confounded by PEEP than absolute levels [3,22]. The observation that the CO response to PEEP was of less predictive value than the CVP response for the CO increase upon PLR can be explained by a lesser decrease in CO for a given PEEP-induced rise in CVP in hypo- than in normovolaemic conditions, as shown in animal experiments [21]. We should also keep in mind that the PEEP challenge moves the work-point of the cardiac function and venous return curves downwards to the steep part of the curve (larger change in CO), whereas PLR moves the work point upwards into the flat part of curve (smaller change in CO, Figure 3). This may help explain why the PLR response of CO was of less predictive value for the PEEP-induced fall in CO than vice versa (data not shown). The decrease in CO with PEEP may lead to an unacceptably too low CO for several minutes. Thus, when there areclear signs of hypovolaemia the use of the PEEP-challenge may not be appropriate.

Our proposed challenge resembles the end-expiratory occlusion test [19] to predict fluid responsiveness but carries the relative advantage, of being independent of ventilatory conditions provided that PEEP can be increased by 10 cmH_2O. Since the PEEP challenge is easy to apply and CVP is measured routinely in the ICU, the PEEP-induced change in CVP may provide the physician with a robust and easy-to-use tool to assess fluid responsiveness.

168) The drawback of the PEEP challenge is its dependence on maintenance of a steady state during the challenge and potential worsening of hypotension. A SVV of about 10% or above, derived from non-invasive arterial pulse contour algorithms, has been used to predict an increase of 10% to 15% in CO in response to 500 ml fluid loading [4-8]. Our patients were subjected to a smaller preload challenge and the optimal cut-off to define responsiveness was somewhat lower. The SVV requires a regular heart rate and full mechanical ventilatory support, with predictive values dependent on respiratory rates and tidal volumes [7,8] Again, we may speculate that our PEEP challenge is less dependent on these prerequisites. Even though SVV had a similar predictive to the PEEP challenge, the latter may thus be preferable, particularly in case of arrhythmias. One might also argue that performing a PLR and looking at the CO response would render our PEEP challenge redundant. However, PLR is not always feasible and necessitates some CO measurement, while our PEEP challenge does not. (In contrast the PLR challenge does not require mechanical ventilation [14,18]. Finally, the relatively small changes in CVP evoked by PEEP can only be discerned at the bedside when accurately measured.

Conclusions

Our data suggest that brief PEEP-induced increases in CVP predict fluid responsiveness at least as well as absolute values of CVP and SVV, after cardiac surgery, and are less likely to be confounded by ventilatory conditions.

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Chapter 11

Vincent and Weil's fluid challenge: revisited and revised

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Submitted to Critical Care

Fluid overload and hypovolaemia can still not be accurately identified Hamilton recently concluded in an editorial [1]. Traditional filling pressures like central venous pressure (CVP) often fail as a predictor [2-4]. This complicates hemodynamic management since unnecessary fluid loading can lead to pulmonary and general oedema [5]. Therefore, new methods are being developed to prevent fluid over-loading by an accurate prediction of the response to fluid loading.

In 2006, Vincent and Weil (V&W) revisited the "fluid challenge". This protocol (see Figure 1) is largely based on their clinical experience and assessment of relevant publications [6]. It provides objectives for fluid management. In their approach, 500 ml of fluid is administered over 30 minutes and every 10 minutes the effect is evaluated. When a mean arterial pressure (MAP) of 75 mmHg is reached fluid administration is stopped. When a CVP of 15 mmHg is reached before this target is reached fluid administration is discontinued and the use of catecholamines may be considered.

Since flow-guided fluid therapy improves outcome in the ICU [1], we investigated the impact of adding pulse contour cardiac output to V&W's protocol to introduce a more sophisticated protocol to reduce the amount of unnecessary administered fluids (see Figure 1). We also compared the effects on unnecessary fluid loading and change in cardiac output (CO) of the original, and the altered, protocol of V&W with a straightforward fluid loading responsiveness protocol. In this third protocol (see Figure 1), we assessed the ability of changes in pulse contour cardiac output after 50 ml and 100 ml fluid loading to predict fluid loading responsiveness.

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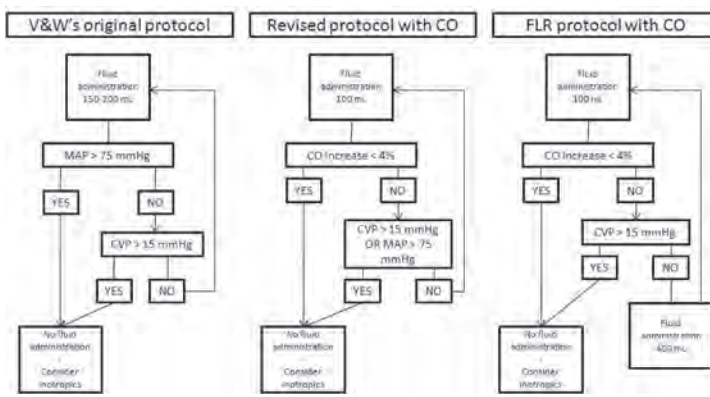
Figure 1 Vincent and Weil's original protocol and the protocol with the addition of pulse contour cardiac output.



Methods

Twenty-one patients undergoing elective coronary artery bypass grafting (CABG) or single valve repair were included into the study after approval of the institutional ethics committee and personal informed consent was obtained. All patients had symptomatic coronary artery disease without previous myocardial infarction and were on beta-adrenergic blocking medication. Patients with congestive heart failure (NYHA class 4), aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiency, were not considered for this study. Patients with the necessity for artificial pacing or use of a cardiac assist device were also excluded.

Before ICU admission, each patient had received a pulmonary artery catheter (Intellicath, Edwards Lifesciences; Irvine CA, USA) inserted into the pulmonary artery via the right jugular vein to measure CVP and thermodilution cardiac output (CO). In addition, all patients had received a 20 G radial artery catheter to measure arterial pressure (Prad). In the ICU, patient's anesthesia was continued with propofol-target-control infusion and sufentanil according to institutional standard. The lungs were mechanically ventilated in a volume-control mode with standard settings to achieve normocapnia (arterial PCO_2 between 40 and 45 mmHg) with tidal volumes of 8-10 ml·kg^{-1} and a respiratory frequency of 12-14 breaths·min^{-1}. Fraction of inspired oxygen was 0.4 and a positive end expiratory pressure (PEEP) of 5 cmH_2O was applied. During the study interval ventilator settings, sedation and vasoactive medication continued unchanged. No significant bleeding (<50 ml·h^{-1}) occurred during the study period.

Hemodynamic measurements

Both Prad and CVP pressure transducers were referenced to the level of the tricuspid valve and zeroed to atmospheric pressure. Prad and CVP data were continuously recorded with a resolution of 0.125 mmHg at a sample frequency of 200 Hertz and stored a personal computer for analysis and documentation. From Prad we calculated heart rate (HR), MAP, CO, pulse pressure variation (PPV), and stroke volume variation (SVV) over 30 second intervals using two different pulse contour methods; modified Modelflow (COm, FMS, Amsterdam, the Netherlands) and PulseCO (COli, LiDCO, LiDCO Ltd., London, UK). Both methods are extensively described elsewhere [7]. We calibrated both pulse contour devices with the same averaged value of three thermodilution measurements performed equally spread over the ventilatory cycle [8,9]. Over the same 30 seconds interval HR, CVP and MAP were calculated.

Study protocol

All measurements were carried out within two hours after arrival in the ICU. During the observation period patients maintained a supine position. At baseline, measurements of

MAP, HR, CVP, COm, COli, PPV, and SVV were performed. Following baseline measurements, a first out of ten 50 ml fluid loading boluses with a hydroxyethyl starch solution (Voluven®, Fresenius Kabi, Bad Homburg, Germany) was performed manually in 30 seconds and measurements were repeated one minute after fluid administration. Subsequently, two minutes after the start of the first fluid load, a second 50 ml fluid loading was performed. In 20 minutes a total of 500 ml of colloid was administered in 10 steps. After each 50 ml step measurements were repeated.

Statistical analysis

Statistical analyses were performed by a Kolmogorov-Smirnov test, paired t-test and linear regression analysis. A formal prospective power analysis was not performed since relevant data was not available from literature. However, study sample size is similar to other fluid loading responsiveness studies.

A 10% change in Modelflow cardiac output after 500 ml fluid loading was used to divide responders and non-responders [10-13]. The 10% cut-off corresponds with more than twice the reported precision of the Modelflow method (i.e. twice the SD for repeated measurements) [14,15]. Hence, responders will experience clinically significant changes in CO. The reliability
174) to predict responders (preload dependence) was analyzed by computing the area under the receiver operating characteristics (ROC) curve. Subsequently we used the optimal cut-off value for pulse contour CO after 100 ml fluid administration (to predict FLR after 500 ml of colloids) as a new step in our revised protocol. Both protocols were applied to all patients to analyse the total amount of fluid that would have been administered before goals were met (see Figure 1). All values are given as mean ± SD. A p value < 0.05 was considered statistically significant.

Results

Twenty-one patients (16 males) of 64 ± 11 years with a BSA of 1.99 ± 0.20 m^2 started and finished the study protocol. Fourteen received straightforward CABG, seven had single or two valve repair.

Kolmogorov-Smirnov analysis indicated normal distribution of all data. Pooled results of hemodynamic variables at baseline and after 50, 100 and 500 ml fluid administration are shown in Table 1. After 500 ml fluid loading COm, COli, MAP and CVP are increased. HR did not change. SVV and PPV of 8 patients could not be used because of heart beat irregularities and these variables were therefore not included for further analysis. An example of such irregularity is given in Figure 2.

Figure 2 An example of an irregular heart rhythm (patient 3) which causes variation in stroke volume variation (SVV) and PPV measurements over 5 sequential respiratory cycles. Prad is radial artery pressure and SV is stroke volume. The dots in the lower part of the graph show the variation in SV.

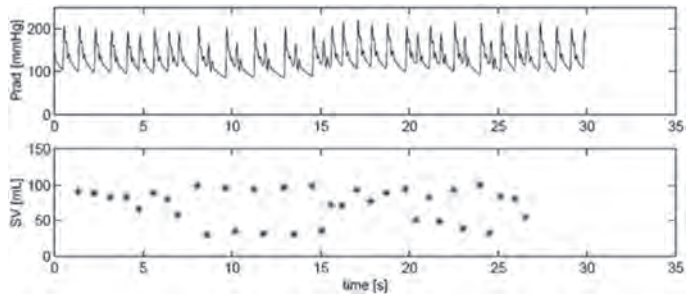


Table 1 Pooled data of hemodynamic variables before and after fluid loading.

Variable	Baseline	50 ml	p	100 ml	p	500 ml	p
MAP (mmHg)	81.8 ± 17.5	82.4 ± 18.0	0.207	83.9 ± 19.0	0.006	91.4 ± 17.4	<0.001
CVP (mmHg)	8.5 ± 2.7	8.7 ± 2.7	0.291	8.7 ± 2.8	0.446	11.5 ± 3.0	<0.001
HR (min^{-1})	82.9 ± 16.2	82.7 ± 15.6	0.420	82.9 ± 15.6	0.995	83.5 ± 14.6	0.490
COm ($L \cdot min^{-1}$)	5.2 ± 1.3	5.3 ± 1.2	0.014	5.4 ± 1.3	0.034	6.0 ± 1.4	<0.001
COli ($L \cdot min^{-1}$)	4.9 ± 1.3	5.1 ± 1.3	<0.001	5.2 ± 1.3	< 0.001	5.7 ± 1.3	<0.001

MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; COm, Modelflow cardiac output; COli, LiDCO cardiac output; p, p-value compared to baseline

The population was divided into responders (n=15) with an increase of at least 10% in COm after 500 ml fluid loading and non-responders (n=6). The average increase in COm after 500 ml was 18% in the responder group and <2% in the non-responder group. When V&W's original protocol would have been used approximately 200 ml fluid would have been administered in the responder group (14 of 15 responders reached a MAP of 75 mmHg and 1 of 15 a CVP of 15 mmHg). The average change in CO at this point was 7% compared to baseline. Around 100 ml fluid would have been administered in the non-responder group with an average change in CO of <1%.

Table 2 Area under ROC curves.

	Area	95% confidence interval	
		Lower	Upper
CVP, baseline	0.183	0.000	0.369
COm, baseline	0.478	0.234	0.721
ΔCOm, 50 ml	0.711	0.462	0.960
ΔCOm, 100 ml	0.856	0.647	1.000
COli, baseline	0.494	0.251	0.738
ΔCOli, 50 ml	0.456	0.193	0.718
ΔCOli, 100 ml	0.717	0.494	0.939
MAP, baseline	0.344	0.074	0.615
ΔMAP, 50 ml	0.278	0.025	0.530
ΔMAP, 100 ml	0.400	0.139	0.661
HR, baseline	0.467	0.214	0.720

dCVP is change in central venous pressure; dCOm and dCOli are change in cardiac output by Modelflow and LiDCO; dMAP is change in mean arterial pressure; HR is heart rate.

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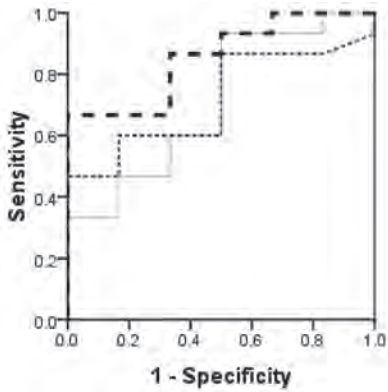
The area under the Receiver Operating Characteristics (ROC) curves for changes in CVP, MAP, HR, COm, COli after 50 and 100 ml are given in Table 2 and Figure 3. In general, the results of a fluid loading of 100 ml have a better chance to predict responders than results after a fluid loading with 50 ml. Best results are observed for changes in COm after 100 ml fluid loading (area under the ROC 0.86, 95% confidence interval between 0.65 and 1.00). A change in Modelflow CO of at least 4.3% has a sensitivity of 67% and a specificity of 100% after 100 ml of fluid loading. Sensitivity is 60% and specificity 83% for a similar cut-off in CO measured with the LiDCO device after 100 ml fluid loading. In our patient population, baseline CVP, MAP and COli did not predict responsiveness with more accuracy than mathematical chance.

Figure 3 Receiver Operating Curves (ROC) of changes in pulse contour cardiac output (COm 100 ml, dashed black line, COm 50 ml, thin gray line and COli 100 ml, dotted black line) in 15 cardiac surgery patients to predict a 10% increase in pulse contour cardiac output after 500 ml fluid loading. Both COm and COli have identical responders after 500 ml fluid administration.



When V&W's original protocol would have been used CO would have increased 7%. Addition of COm to the protocol would have lead to a mean administration of 100 instead of 200 ml fluid administration to non-responders and an increase of 18% in CO in responders (instead of 7%). Moreover, the use of pulse contour CO in the protocol would have prevented extra fluid loading in two (of 21) patients when a MAP of 75 mmHg was not yet reached.

Discussion

The objective of this study was to further refine Vincent and Weil's fluid-challenge protocol [5,6] by adding pulse contour CO and using smaller fluid-challenge steps. The use of changes in pulse contour CO (COm and COli) after 50 and 100 ml of fluid administration were assessed to predict the effects on CO after a fluid loading of 500 ml.

We found that changes in COm accurately predict fluid loading responsiveness even after a test administration of 50 ml. Accuracy is further improved after 100 ml of fluid loading. These findings concur with a previous report by de Wilde *et al.* [16] who showed in a comparative study of three pulse contour methods that COm had optimal correlation and highest Bland-Altman agreement with COtd. We also found that the addition of pulse contour CO to the strategy formulated by V&W would have led to less fluid being administered unnecessarily in non-responders. A fluid loading responsiveness protocol

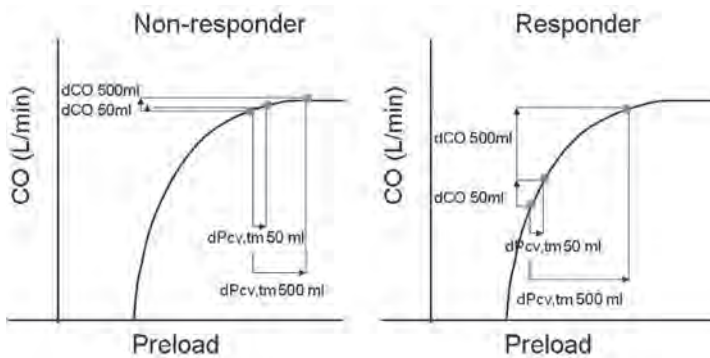
which uses with changes in pulse contour CO after a fluid challenge would have reduced unnecessary fluid loading and increased cardiac output further.
In general, reduced filling pressures, like CVP, are more likely to characterize hypovolaemia whereas high filling pressures are more likely in hypervolaemia or heart failure. Therefore absolute filling pressures are not reliable in predicting the effects of volume loading [17]. Volume deficit with low SV are commonly compensated for by an increase in HR to maintain CO (on a normal level). This compensatory mechanism may be absent in patients with intrinsic heart disease, and during treatments with anti-arrhythmic drugs or during deep sedation. Stress, fever, pain, anaemia or vaso-active drugs produce endogenous adrenergic stimulation with compensating increases in HR and vasoconstriction, limiting the value of HR and blood pressures for assessing the severity of hypovolaemia [18]. A protocol-based strategy is thus possible in sedated ICU patients, applicability in spontaneous breathing patients needs further evaluation. We, therefore, would like to advocate the use of CO to monitor hemodynamic improvements and use of CVP for safety limits.

Responders and non-responders

The 10% increase in CO was chosen because this increase can be measured accurately with the modified Modelflow pulse contour method [9,19]. This value corresponds with the boundaries used in other studies where a 10% cut-off was used for 500 ml fluid responsiveness [10-13].

Changes in COm due to the fluid challenge in responders and non-responders are different. COm increased 0.2 ± 0.1 $L.min^{-1}$ ($p<0.001$) after 50 ml, 0.3 ± 0.2 $L.min^{-1}$ ($p<0.001$) at 100 ml and 1.0 ± 0.3 $L.min^{-1}$ ($p<0.001$) after 500 ml fluid administration in the responder group. In contrast, COm did not change significantly in the non-responder group (-0.1 ± 0.1 $L.min^{-1}$ with $p=0.110$, 0.0 ± 0.2 $L.min^{-1}$ with $p=0.704$ and -0.3 ± 0.2 $L.min^{-1}$ with $p=0.054$, respectively). Also, pooled results for COli did show significant changes after 50, 100 and 500 ml fluid administration in responders.
Depending on the patient's condition the fluid challenge will achieve a significant increase in cardiac output. Fluid loading will shift the working point on the heart function curve to the right into the more flat part of the curve. We used changes in cardiac output due to a fluid challenge with 50 to 100 ml to predict the response to 500 ml fluid loading. This is shown graphically in Figure 4.

Figure 4 The cardiac function curve: a fluid challenge of 50 ml in a non-responder and a responder to predict a 500 ml fluid administration. On the vertical axis cardiac output (CO) is shown and on the horizontal axis preload by transmural central venous pressure (CVP,tm). In the left panel, the administration of 50 ml shifts the heart function curve of this non-responder to the right resulting in a small increase in CO and a relatively larger increase in CVP,tm. The increase in CO after adding 500 ml fluid is still small. For responder, right panel, the increase in CO is significant after 50 ml fluid loading and continues to increase after 500 ml.



Limitations of the technique

The use of small volumes to test fluid loading responsiveness could be valuable to decrease the chance of overloading the circulation to occur and at the same time correction of a suboptimal blood flow is initiated [5,6]. The findings of this study can provide a first step in the development of an adapted fluid-loading protocol. A larger randomized study is needed to test the effects of this protocol on morbidity and mortality.

The use of traditional parameters [2,4,20-23], dynamic parameters like SVV and PPV, have been studied extensively for their predictive value of fluid loading responsiveness. Other challenges, like the respiratory systolic variation test or passive leg raising, require either special techniques or depend on the method of execution for their quality (re-referencing of pressure transducers and bed-tilting for instance). The use of a test fluid administration is straightforward and can be used in everyday critical care.

Limitations of the study

Several limitations apply to this study. First, this is a proof of concept study. We studied 21 cardio-surgical patients. Although relations between the hemodynamic parameters and ROC

curves showed significance, a larger number of patients is needed to allow extrapolation of these results to a general ICU population.

Second, patients were sedated and lungs were mechanically ventilated. We agree with Vincent and Weil [6] that the fluid challenge is likely to be applicable to awake and spontaneous breathing patients. However, the predictive value of administering a test fluid and measurements of its response on pressures and CO has to be shown in spontaneous breathing patients.

Third, baseline SVV and PPV was not possible in 8 of our patients due to heart rhythm irregularities (see Figure 2). Hence, we were not able to study the value of SVV and PPV to predict FLR in this study or its possible value for the V&W's protocol. Several studies have reported on the effects of arrhythmias on SVV measurements [24]. Since changes in COli did not and COm did allow accurate prediction of FLR, we hypothesize that the heart rhythm irregularities also influenced the accuracy and precision of COli measurements. Nonetheless, COm measurements averaged over 30 second intervals remained reliable throughout this study. Because minor cardiac arrhythmias occur frequently (8 of 21 in this study alone) in the ICU and in cardiac surgery patients, this enhances the applicability and robustness of the pulse contour method strategy.

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Conclusions

Vincent and Weil's original fluid-challenge protocol reduces fluid loading in non-responders and leads to an increase in CO in responders. The addition of pulse contour cardiac output to the protocol can further reduce unnecessary fluid loading and enhances the improvement of CO in responders. When COm is increased by 4.3% after a 100 ml trial administration, a concomitant increase of at least 10% in COm after 500 ml fluid loading can be predicted accurately.

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Chapter 12

Pulse contour cardiac output and passive leg raising to assess fluid loading responsiveness in cardiac-surgery patients

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Journal of Cardiothoracic and Vascular Anesthesia 2011; 25(1): 48-52.

The selection of patients that will benefit from fluid loading is important since unnecessary fluid loading in a non-responsive subject may potentially cause pulmonary and general oedema. Passive leg raising (PLR) is a routinely-applied bedside method that accurately predicts volume responsiveness [1-6]. However, its clinical application requires dynamic assessment of cardiac output (CO). Transient increases in transthoracic and oesophageal Doppler CO and left ventricular stroke area by ultrasound during PLR predict preload responsiveness. However, ultrasound measurements are neither routinely performed, consistent among operators nor easy to perform continuously [7]. Furthermore, the HemoSonic ultrasound device most frequently used in PLR research [1-6] is currently withdrawn from the market. Recently, DeBacker and Pinsky hypothesized that other CO measurement techniques such as pulse power or pulse contour analysis could provide similar results and supplant Doppler ultrasound monitoring [8]. This approach is attractive, as it would provide the clinician with a simple, readily available and robust measure that can be obtained at the bedside.

The aim of our study is to evaluate the applicability of two different radial artery pulse contour CO devices, one using pulse power (COli, LiDCO, London, UK) and the other using Modelflow arterial pulse contour analysis (COm, FMS, Amsterdam, the Netherlands) in
184) prediction fluid loading responsiveness by tracking CO changes due to a PLR manoeuvre. The changes in cardiac output by these two methods are compared to changes in CO by thermodilution (COtd).

Methods

Twenty patients undergoing elective coronary artery bypass (CABG) and, or valvular reconstruction surgery were included into the study after approval of the University Medical Ethics Committee of the University of Leiden. All patients signed informed consent to be part of this study. Subjects were included in the study during their initial post-operative period once hemodynamically stable with a mean arterial pressure (MAP) > 70 mmHg, central venous pressure (CVP) between 5-10 mmHg and a cardiac index > 2.5 $L \cdot min^{-1}$. Exclusion criteria included severe arrhythmias, advanced congestive heart failure (ejection fraction <20%), intra-cardiac shunts, symptomatic peripheral vascular disease, symptomatic pulmonary disease, aortic aneurysm and significant valvular regurgitation after surgery.

Anaesthesia during surgery was with propofol and sufentanil infusions according to institutional standards. Upon arrival in the ICU sedation was continued. The lungs were mechanically ventilated 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·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 continued unchanged.

All subjects had a pulmonary artery catheter (Intellicath; Edwards Lifesciences; Irvine, CA, USA) inserted into the right jugular vein and a radial arterial catheter (20 G) inserted prior to ICU admission. COtd measurement was 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 [9]. Blood pressure transducers were referenced to the level of the tricuspid valve and zeroed to atmospheric pressure. Arterial pressure, heart rate (HR) and CVP data were continuously recorded with a sample frequency of 100 Hertz and stored on a personal computer for documentation and offline analysis. MAP, systolic arterial pressure (SP), pulse pressure (PP) and pulse pressure variation (PPV) were calculated from arterial pressure. Stroke volume variation (SVV) and CO was averaged over 30 second intervals using pulse power (SVVli and COli) and Modelflow (COm). The LiDCO system was calibrated. The Modelflow was used uncalibrated. A detailed description of the two methods can be found elsewhere [10-12].

Measurements were carried out within two hours after arrival in the ICU following MAP stabilization (85.0 ± 12.0 mmHg) and restoration of central body temperature (36.6 ± 0.7 °C). Characteristics and treatment data of each patient were collected. Passive leg raising was performed from the supine position by lifting both legs at a 30° angle and holding them there for 5 minutes. Measurements of HR, MAP, PP, SP, CVP, COtd, COm, COli, PPV and SVV were performed 5 minutes before, 2 minutes after initial elevation of the legs with legs still elevated, and 5 minutes after return from passive leg raising.

We used a Kolmogorov-Smirnov test, paired t-test and linear regression analysis. The reliability to track changes in CO was analyzed by computing the area under the receiver operating characteristics (ROC) curve, with responders related to 7% COtd increase during PLR [13]. Usually, responders are characterized by an increase of 10-15% in CO after rapid fluid loading with 500 ml [14]. Lafanechere *et al.* [3] showed that the effect of PLR on CO of patients in supine position was equal to 250 ml fluid loading. We reasoned that in the same group of responders a PLR-induced auto-transfusion of 250 ml should result in an increase of CO of 5 to 7.5%. Our thermodilution technique with automated triplicate measurements equally spread over the respiratory cycle has shown a precision of 3.5% [9,11]. Therefore, this technique should detect changes in CO induced by PLR larger then 7% (2SD precision) accurately and identifying responders by a >7% increase in CO by PLR reliable. All values are given as mean ± SD. Differences corresponding to a p value < 0.05 were considered significant.

Results

Twenty patients met the inclusion criteria and were enrolled in the study. All finished the study. Clinical patient data is shown in Table 1. An example of the effects of PLR on haemodynamics in one patient is given in Figure 1. Beat-to-beat systolic, mean and diastolic blood pressures increase and modulation of the variables by mechanical ventilation decrease during PLR, associated with no change in HR, an increase in SV and decrease in SVV.

Table 1 Demographic data of the patients.

Patient	Gender	Type of surgery	Age years	Weight kg	Length cm	Propofol $mg.h^{-1}$	Inotropic support $\mu g.kg^{-1}.min^{-1}$
1	m	AVR	52	80	160	250	0.25 nitroprusside
2	m	AVR	79	82	178	140	
3	m	AVR	61	73	186	150	4,0 dobutamin, 0,02 norepinephrine
4	m	CABG	72	97	178	200	
5	f	AVR	35	86	169	350	
6	m	CABG	65	69	170	220	
7	m	CABG	78	103	182	200	
8	m	CABG	56	118	178	250	
9	m	AVR	58	88	178	150	
10	f	CABG	69	73	158	200	3 dopamine
11	m	CABG	53	95	178	300	
12	m	CABG	67	83	175	200	2 dobutamine
13	m	CABG	75	88	178	250	
14	m	CABG, MVP, TVP	54	100	187	200	0.75 nitroprusside
15	f	CABG, AVR	59	59	158	150	
16	m	CABG	80	74	172	200	0.3 norepinephrine
17	m	CABG	66	72	183	200	
18	m	CABG	63	66	160	220	
19	m	AVR	62	106	176	250	0.25 nitroprusside
20	m	CABG, MVP, TVP	73	71	175	200	0.5 enoximone
Mean ± SD			64 ± 11	84 ± 15	174 ± 9	214 ± 52	

Abbreviations: CABG is coronary artery by-pass grafting; AVR is aortic valve replacement, TVP is tricuspid valve replacement; MVP; mitral valve replacement.

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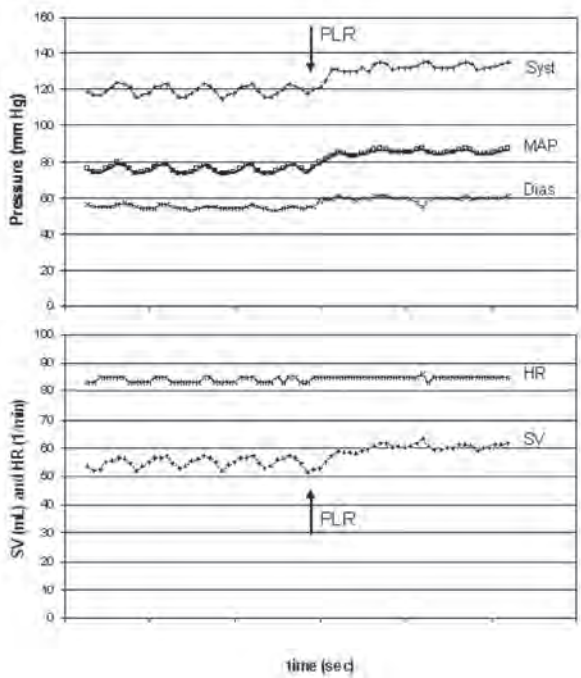
Figure 1 Beat-to-beat changes in hemodynamic variables by passive leg raising (PLR). Syst, MAP and Dias are systolic, mean and diastolic arterial blood pressure respectively; HR, heart rate; SV stroke volume



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A Kolmogorov-Smirnov test indicated normal distributions of all hemodynamic data. Compared to baseline (Table 2), PLR increased COtd, COm, COli, MAP, PP, SP and CVP, decreased SVV and PPV, and had no effect on HR. All 20 subjects behaved in a qualitatively similar fashion to the one subject's example, Figure 1. Although COtd increased in all patients, COm increased in 19 of 20, COli increased in 15 of 20. Furthermore, MAP increased in 19 of 20, SP in 19 of 20, PP in 18 of 20, CVP in 18 of 20, HR increased in 5 and decreased in 7 out of 20 subjects. SVVm and SVVli decreased in 16 and 17 out of 20, respectively whereas PPV decreased in 18 out of 20.

Table 2 Haemodynamic variables at baseline and after 30° passive leg raising (PLR) in all 20 patients.

Parameters	Baseline	PLR	P-value
COtd (L·min^{-1})	5.62 ± 1.66	5.91 ± 1.67	< 0.001
COm (L·min^{-1})	6.17 ± 1.75	6.28 ± 1.76	0.002
COli (L·min^{-1})	5.61 ± 1.39	5.85 ± 1.38	< 0.001
HR (min^{-1})*	79.1 ± 12.4	78.4 ± 13.2	0.256
CVP (mmHg)	9.2 ± 3.6	11.5 ± 4.0	< 0.001
PAP (mmHg)	19.9 ± 5.7	22.4 ± 5.8	< 0.001
MAP (mmHg)	84.7 ± 11.5	90.7 ± 13.4	< 0.001
PP (mmHg)	59.0 ± 10.3	65.2 ± 10.3	< 0.001
SP (mmHg)	124.8 ± 13.6	135.1 ± 17.2	< 0.001
SVVm (%)	5.8 ± 3.5	3.9 ± 2.7	< 0.001
SVVli (%)	7.3 ± 3.5	7,0 ± 2,1	< 0.001
PPV (%)	6.0 ± 4.2	4.3 ± 3.8	0.001
Rsys (dyne·sec·cm^{-5})	1115 ± 341	1140 ± 325	0.296

Abbreviations: Thermodilution cardiac output (COtd), radial artery pulse contour cardiac output (uncalibrated Modelflow, COm and LiDCO, COli), heart rate (HR), central venous pressure (CVP), pulmonary artery pressure (PAP), mean arterial pressure (MAP), systolic pressure (SP), pulse pressure (PP), stroke volume variation (SVVm and SVVli), pulse pressure variation (PPV) and systemic vascular resistance (Rsys).

188) Results of linear regression for all 20 patients are summarized in Table 3. A significant relationship between the change in COtd and the change in MAP, PP, SP, COm and COli was found. Noticeably, also baseline SVV and PPV related relatively well with the change in cardiac output due to passive leg raising.

Table 3 Slope of linear regression hemodynamic variables versus changes in thermodilution cardiac output due to PLR.

	Slope	95% Confidence Interval		P-value
		Lower	Upper	
ΔCOm	0.875	0.547	1.203	<0.001
ΔCOli	0.810	0.488	1.131	<0.001
ΔHR	-0.585	-1.318	0.147	0.109
ΔMAP	0.428	0.074	0.782	0.020
ΔSP	0.276	0.047	0.506	0.021
ΔPP	0.190	0.028	0.352	0.024
ΔCVP	0.060	-0.036	0.157	0.207
SVVm baseline	0.738	0.249	1.228	0.005
SVVli baseline	0.660	0.138	1,181	0.016
PPV baseline	0.656	0.238	1.074	0.004

Abbreviations: Uncalibrated Modelflow cardiac output (COm), LiDCO cardiac output (COli), heart rate (HR), mean arterial pressure (MAP), systolic pressure (SP), pulse pressure (PP), central venous pressure (CVP), stroke volume variation (SVV) and pulse pressure variation (PPV)

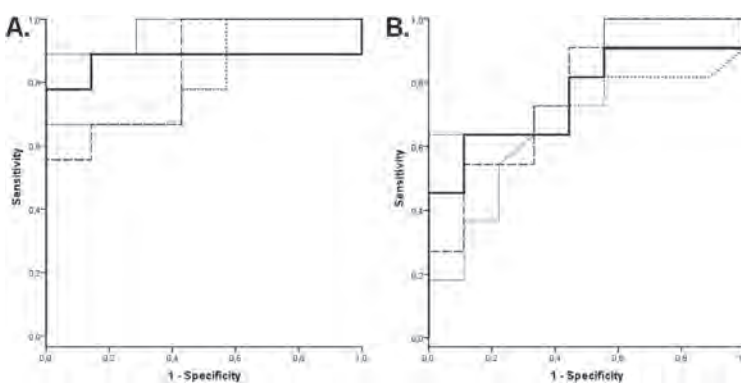
To construct Receiver Operating Characteristics (ROC) curves the population was divided into responders (n=10) and non-responders (n=10) based on an increase of at least 7% in COtd during PLR in responders. When COm increased by ≥2.5%, a concomitant increase of ≥5% COtd was predicted with 89% sensitivity and 100% specificity. The optimal cut-off for a change in MAP is 5.5% increase. The (area under the) ROC curves for ΔCOm, ΔCOli, ΔMAP, ΔPP, ΔSP and baseline SVV and PPV are given in Table 4 and Figure 2.

Table 4 Area under the ROC curves.

	Area	95% Confidence Interval	
		Lower	Upper
ΔCOm	0.968	0.890	1.000
ΔCOli	0.841	0.643	1.000
ΔMAP	0.873	0.694	1.000
ΔPP	0.714	0.434	0.995
ΔSP	0.778	0.535	1.000
PPV baseline	0.808	0.615	1.000
SVVm baseline	0.825	0.617	1.000
SVVli baseline	0.873	0.665	1.000

Responders are defined by an increase in thermodilution cardiac output of at least 7% as a result of PLR.
Abbreviations: Change in radial artery pulse contour cardiac output (uncalibrated Modelflow, ΔCOm and LiDCO, ΔCOli), change in mean arterial pressure (ΔMAP),), pulse pressure (ΔPP), change in systolic pressure (ΔSP), pulse pressure variation (PPV) and stroke volume variation (SVVm and SVVli)

Figure 2 Receiver operating characteristics curves comparing the ability of passive leg raising induced changes. In A: ΔCOm (thin line), ΔCOli (dashed line), baseline SVVm (dotted line), baseline SVVli (bold line). In B: ΔMAP (thin line), ΔPP (dotted line), ΔSP (bold line) and baseline PPV (dashed line) to predict ≥7% change in ΔCOtd.



Discussion

We showed that PLR with 30° of both legs produced a rapid increase of COtd associated with a proportional increase in COm, COli, MAP, PP and SP (Table 2). Furthermore, we found significant relationships between the change in COtd and the change in COm, COli, MAP, PP and SP. Our PP results confirm and extend the results of Boulain *et al*. and support their conclusion that PLR induced changes in PP predict the response to fluid loading [1]. Our results also support the hypothesis of DeBacker and Pinsky that changes in pulse contour derived cardiac output due to PLR can be used to assess preload in cardiothoracic surgery patients [8]. Changes in COm tend to a slightly better predictive value than changes in MAP and COli, or baseline SVV and PPV, these differences are not statistically significant.

Our findings concur with data previously reported by de Wilde *et al*. [10]. who showed that Modelflow pulse contour has lower limits of agreement and a better correlation coefficient for the regression of changes in CO with changes in thermodilution CO compared to the LiDCO's technique. Furthermore, in another report de Wilde *et al*.[15] showed superior results of uncalibrated Modelflow compared to auto-calibrated FloTrac-Vigileo and HemoSonic in tracking changes in cardiac output.

190) Continuous measurements of COm are more feasible than oesophageal Doppler CO and left ventricular stroke area since these methods are not routinely performed and the quality of measurement is dependant on the expertise of the observer. Also passive raising of the legs may interfere with the echocardiographic image.

To compare the effects of PLR on MAP, PP, SP, COm, COli and baseline SVVm, SVVli and PPV we separated responders from non-responders by setting the cut-off level for COtd change to 7%, considering the described effect of PLR from supine position [3] and the precision of our thermodilution method. Next, the reliability to predict preload dependency by changes in COm, COli, MAP, PP, SP due to PLR and baseline SVV and PPV was evaluated by calculating the area under the ROC curves. No statistical differences between the the AUC of the ROC curves for COm, COli, PPV and SVV were found. This uniformity might be explained by the fact that all predictors have the same radial arterial pressure source. However, the COm and COli techniques use different algorithms, therefore, some of the agreement must reflect similar accuracy of the two techniques.

In a large two-center study Monnet and co-authors [2] included 71 general ICU patients of which 31 had spontaneous breathing activity and/or arrhythmias. In the group of ventilator dependent patients they showed, by using the HemoSonic ultrasound system, that a PLR induced increase of aortic blood flow ≥ 10% predicted the effect of a 500 ml fluid load responsiveness with a 97% sensitivity and 94% specificity. Whereas a PLR induced increase in PP ≥ 12% had a 60% sensitivity and 85% specificity. In the patients with spontaneous

breathing activity the sensitivity and specificity were 88% and 93% for the aortic blood flow and as poor as 75% and 46% for PP. Other studies [3,5,6] confirmed that PLR predicts fluid responsiveness. Essential to the use of the PLR procedure to assess preload responsiveness is the need of a fast responding cardiac output method during the manoeuvre (Figure 1). The studies mentioned above used Doppler ultrasound techniques, however, these techniques may not be routinely performed or widely available. In addition, the quality of measurement is dependant on the expertise of the observer. Our results with beat-to-beat pulse contour cardiac output in patients after cardiac surgery agree with the results of Monnet *et al.* obtained with HemoSonic Doppler aortic blood flow (ABF) [2]. Therefore, measurement of pulse contour CO seems interchangeable with ultrasound ABF and may supplant it as was hypothesized by DeBacker and Pinsky [8].

We showed that various hemodynamic changes in response to PLR, such as COli, PP, MAP, COm can predict a positive CO response to PLR. The response to PLR can probably, in most circumstances, be used as a surrogate for response to fluid loading, because of its high sensitivity and specificity. We expected PLR to mimic a reversible fluid loading of approximately 250-300 ml. However, it is unsure whether the volemic status of a patient will change the volume of autotransfusion by PLR. We did not follow our initial measures with volume challenges because all the patients were deemed to be haemodynamically stable, and thus not needed further fluid resuscitation.

Our study confirms that baseline SVV and change in COm and COli by PLR can be used to predict preload dependence in patients receiving mechanical ventilation. Since COm and COli can also be measured in normal breathing patients, we expect that COm and COli are more appropriate candidates to predict preload dependence during PLR in these patients. However, further study is needed into the reliability in spontaneous breathing patients. Differences exist in the implementation of the PLR procedure between studies [2,3,6]. These differences could interfere with a direct comparison of our results with beat-to-beat pulse contour and Doppler ultrasound cardiac output measurements. In our study, patients remain in a supine position throughout the protocol and only the legs are raised. The heart and baroreceptors are in-level and do not change, thus, blood pressure transducers do not have to be re-referenced resulting in a constant quality for pulse contour cardiac measurement. In half of the Doppler ultrasound studies [2,5,6], the patient moved from a semi-recumbent position (45°) to a position with the lower limbs raised to 45° while the patient's trunk was lowered to supine position. This approach was probably chosen to keep the ultrasound probe in position but it changes the position of the baroreceptors in relation to the heart. Since heart rate was unchanged, this change in position may be considered as unimportant. Although, these differences may influence the comparability between studies we did not observed large differences.

Conclusions

In stable CABG patients under mechanical ventilation after cardiac surgery a correlation was observed between changes in method of the arterial pulse contour and thermodilution techniques. Preload reserve or responsiveness could therefore be determined. Further studies are necessary to determine the usefulness of these techniques in situations of shock or hemodynamic instability.

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Chapter 13

The Respiratory Systolic Variation Test to predict fluid loading responsiveness

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Especially in cardiac surgery patients, unnecessary fluid loading can lead to general and pulmonary oedema, and prolong hospitalization [1]. Several traditional and dynamic parameters have been studied for the predictive value to fluid loading responsiveness (FLR, i.e. an increase in CO) but no gold standard exists.

Preisman and colleagues studied a Respiratory Systolic Variation Test (RSVT) in 18 mechanically-ventilated patients undergoing cardiac surgery to predict FLR with a increase in CO of at least 15% after 250 ml fluid loading [2]. The RSVT consists of three successive incremental-pressure-controlled inspiratory breaths (10, 20 and 30 cmH_2O) of 1.5 seconds [2]. The lowest systolic blood pressure for each breath is plotted against their respective airway pressure, Figure 1. The slope of this plot is the RSVT-value, and is suggested to increase with hypovolaemia and decrease with fluid loading [2,3]. RSVT is reported to predict FLR with high sensitivity and specificity [2]. However, the RSVT were applied manually and no control group was used. We developed a semi-automated RSVT procedure and tested transferability of the RSVT with a threshold of 0.51 $mmHg \cdot cmH_2O^{-1}$ in independent group of patients to predict FLR.

Methods

196) Fourteen patients undergoing elective-cardiac surgery were included after approval of the institutional ethics committee and personal informed consent was obtained. Prior to surgery, each patient received a pulmonary artery catheter (Intellicath; Edwards Lifesciences; Irvine, CA, USA) to measure CO and CVP, and a 20 G radial artery catheter to measure arterial pressure (Prad).

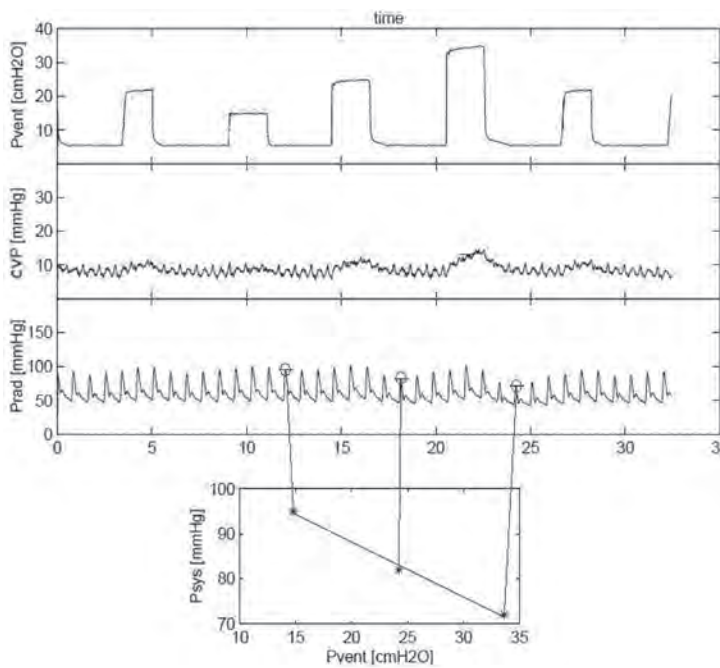
Patient's anaesthesia was continued with propofol-target-control infusion and sufentanil in the ICU. The lungs were mechanically ventilated (Draeger, Evita 4, Lubeck, Germany) in a pressure-control mode with standard settings (12 $breaths \cdot min^{-1}$, tidal volume 8-10 $ml \cdot kg^{-1} \cdot min^{-1}$, FiO_2 40%, PEEP 5 cmH_2O). To perform the RSVT semi-automatic we putted the ventilator under computer control. Airway pressure (Paw) was measured at the proximal end of the endotracheal tube.

The radial artery pressure (Prad) was analysed with the Modelflow program (FMS, Amsterdam, the Netherlands) to provide beat-to-beat values of systolic blood pressure (Psys), MAP, HR and to determine pulse pressure variation (PPV) over 30 second intervals [4]. Thermodilution cardiac output (COtd) was obtained as averaged value of three thermodilution measurements performed equally spread over the ventilatory cycle [5]. During the observation period the patients maintained the supine position. Use of sedative and vascular medication remained unchanged. No fluids were administered during the observation period outside the study protocol.

The 1.5 second RSVT procedure and COtd, MAP, Psys, PPV, HR and CVP measurements

were semi-automatically performed before and five minutes after a 500 ml administration of colloid in 15 minutes. Responders were characterized by a ≥10% increase in COtd with 500 ml fluid loading five minutes after fluid was administered.
Statistical analyses were performed with a Kolmogorov-Smirnov test and (un)paired t-test. Reliability to predict fluid loading responsiveness was assessed using the threshold of 0.51 for RSVT from the report of Preisman and co-workers [2]. Study size was similar to the study of Preisman and co-workers. The accuracy of the test is unknown hence no power analysis was performed.

Figure 1 An example of the Respiratory Systolic Variation Test (RSVT). Upper graph; three successive 1.5 seconds incremental-pressure-controlled inspiratory breaths of 10, 20 and 30 cmH_2O are applied with a PEEP of 5 cmH_2O (Pvent is airway pressure). Second graph; a linear transfer of Pvent to central venous pressure (CVP) can be observed. Third graph; radial artery pressure (Prad) is plotted and lowest systolic blood pressure (Psys) for each RSVT breath is indicated. Lower graph; Psys against Pvent is given. The slope of this plot is the RSVT value.



Results

Fourteen patients (10 male) of 63 ± 10 years, 86 ± 15 kg and 175 ± 9 cm were included. Eleven patients received straightforward CABG and three received single valve repair with or without CABG.

Data was normally distributed. CO, CVP and MAP increased due to fluid administration. HR did not change and PPV and RSVT-values decreased (Table 1). CO increased with 34% in responders (n=9) and did not change in non-responders (n=5). An RSVT with a threshold of 0.51 predicted responders and non-responders correctly in 78% of the patients (sensitivity 78%, specificity 60%, positive predictive value 78%, and negative predictive value 60%). A PPV of 10% (conform Preisman's 9.4%) would have missed one responder; sensitivity 90%, specificity 100%, positive predictive value 100% and negative predictive value 80%.

Table 1 Changes in hemodynamic parameters from baseline to after 500 ml fluid loading for all patients, responders and non-responders.

Parameters	All patients			Responders			Non-responders		
	Baseline	500 ml	*P value*	Baseline	500 ml	*P value*	Baseline	500 ml	*P value*
COtd ($L \cdot min^{-1}$)	5.6 ± 1.5	6.8 ± 1.6	0.002	5.3 ± 1.1	7.0 ± 1.4	0.001	6.3 ± 1.9	6.4 ± 2.1	0.384
MAP (mmHg)	84.1 ± 22.3	94.3 ± 18.1	0.021	86.0 ± 27.0	97.3 ± 21.1	0.074	80.7 ± 11.7	89.0 ± 10.6	0.187
HR (min^{-1})	81 ± 16	78 ± 14	0.075	86 ± 16	82 ± 12	0.120	72 ± 14	71 ± 15	0.313
CVP (mmHg)	9.2 ± 3.2	11.4 ± 2.8	0.001	9.6 ± 1.8	11.6 ± 1.6	0.007	8.4 ± 5.0	11.0 ± 4.4	0.107
RSVT ($mmHg \cdot cmH_2O^{-1}$)	0.96 ± 1.02	0.57 ± 0.80	0.003	0.86 ± 0.47	0.41 ± 0.33	0.007	1.15 ± 1.69	0.86 ± 1.30	0.229
PPV (%)	14.8 ± 9.2	7.2 ± 4.9	0.004	17.4 ± 8.5	7.0 ± 3.4	0.007	10.0 ± 9.3	7.6 ± 7.4	0.136

Thermodilution cardiac output (COtd), mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), Respiratory Systolic Variation Test (RSVT) and pulse pressure variation (PPV).

Discussion

In response to earlier publications of Preisman and co-workers [2], we evaluated the RSVT in an independent group of post cardiac surgery patients and found RSVT with a threshold of 0.51 reliable in predicting responders and non-responders. To perform semi-automated RSVT manoeuvres we put the ventilator under computer control. Preisman and colleague's characterized responders by a ≥15% change in CO after 250 ml of fluid loading [2]. We used 500 ml since this is more broadly used in FLR research [6-9]. Apparently, this difference in characterizing responders has no impact on the RSVT threshold of 0.51.

Several considerations have to be mentioned. First, RSVTs can only be measured in patients on mechanical ventilation with an arterial catheter and without arrhythmias [10]. Second, it is not unimaginable that pathologic states of the lung like COPD or ARDS influence the reliability of the test because the change in lung compliance may have an impact on the

transmission of alveolar to intra-thoracic pressure [11]. Third, changes in vasomotor tone during progression of sepsis, brain injury and peripheral vascular disease could influence clinical use of the RSVT as a hemodynamic monitoring tool. Fourth, one can imagine that during very low cardiac output states application of an RSVT can cause a brief reduction in venous return and hence further reduce CO. Fifth, only a small number of patients have been studied. The RSVT technique has to be further evaluated in other subgroups.

Conclusions

We showed that the RSVT procedure is transferable and feasible to predict fluid loading responsiveness. The advantage of the RSVT is that it is not affected by tidal volume and breathing frequency like PVV.

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Section 5

Discussion and conclusions

Chapter 14

Discussion; fluid loading responsiveness and how can we use it?

Bart Geerts, Johan Groeneveld, Leon Aarts and Jos Jansen

A wide array of variables is available to the ICU and OR physician to assess the hemodynamic state of a patient. Urinary output, skin colour, capillary refill, mean arterial pressure, central venous pressure, heart rate, mixed venous oxygen saturation and pulse pressure are just a few of these variables and their number keeps rising [1,2]. However, it is still not possible to accurately detect hypovolaemia or hypervolaemia [3]. Overzealous fluid administration can increase the incidence of infections, anastomosal leakage, general and pulmonary oedema. This complicates hemodynamic management since unnecessary fluid loading can increase hospital stay and even mortality [4,5] Several strategies exist to decrease the likelihood of hypervolaemia and at the same time select patients that may require fluid loading, pharmacological support or both.

Fluid loading responsiveness

No gold standard exists to guide hemodynamic management. Fluid loading responsiveness (FLR) is a relatively novel strategy and has received wide attention. In general, fluid loading responsiveness can be described as the response of cardiac output (CO) on an intra-vascular administration of a certain amount of fluid. Responders are defined as those patients that increase their cardiac output above a threshold value after this volume loading [6]. It is assumed that increasing cardiac output will lead to an increase in flow and oxygen transport to vital organs consequently. Thus, FLR aims to optimize perfusion and oxygen delivery to vital organs like brain, heart and kidneys. FLR does not specifically lead to the diagnosis of strict hypovolaemia or normovolaemia. Fluid loading responsiveness is more likely to signal that a patient is functioning on or near the flat part of the Frank Starling curve. Identifying a responder with FLR indicates that fluid will likely cause an improvement of the hemodynamics of the patient with less chance of overfilling.

The working point of the circulation of an ICU patient can be described by the intersection of both the venous return curve and the Frank Starling curve. The venous return curve of a patient shifts upward during hypervolaemia and shifts parallel downwards during hypovolaemia. Whereas, the Frank Starling curve is influenced by neurological and humoral control mechanisms, vascular and cardiac function. Hence, the working point of the circulation changes continuously due to changes in the administration of parenteral fluids, airway pressure and changing renal, cardiac and vascular function [7]. This stresses the need for a continuous or repeated determination of fluid-requirements.

However, a practical consensus over the definition of fluid loading responsiveness is missing and therefore the definition of FLR differs widely in the available literature. Even more important is the ability to predict FLR, i.e. responders and non-responders without the administration of fluids. The idea behind predicting FLR is that overall fluid administration will decrease. To our knowledge no study exists to date that studies the impact of FLR or

prediction of FLR on outcome. Thus, more elaborate research is needed. But first we have to develop a uniform definition of FLR to be able to compare the results of FLR research. Second, we will need to come up with a workable algorithm to predict FLR and to guide fluid management in a patient followed by a study of its effect on outcome. In this manuscript we will discuss different dimensions to fluid loading responsiveness and its possible use in everyday practice.

Pitfalls in Determining Fluid Loading Responsiveness

No consensus exists how to assess FLR. The amount of fluid used to assess FLR varies between 7 ml·kg^{-1} [8] and 20 ml·kg^{-1} [9], or 250 ml [10] and 1000 ml [11]. It is easy to imagine that if instead of 250 ml 1000 ml is administered the change in CO can be expected to be larger. The amount of fluid administrated to determine FLR should be weight adjusted to allow for comparison of inter-individual and inter-study results. A 5 ml·kg^{-1} bolus should illicit a significant change in CO in responders. For instance this would be a 500 ml bolus in a 100 kg man or a 250 ml in a 50 kg fragile elderly lady.

Directly related to this, is the type of fluid that is used for administration. The composition of a fluid does not only determine the time that it will be present in the intravascular compartment but also the amount of fluid recruited from the extra-vascular compartment. Prather *et al*. [12] showed that colloids remain in the intravascular compartment for more than two hours and even attract fluids from the extravascular compartments where crystalloids tend to disappear within 80 minutes in dogs. Consequently, we have to point out the importance of the duration of the administration of fluid and timing of the measurement of CO. This directly influences the number of responders, i.e. the number of responders is expected to be larger if CO is measured directly after fluid bolus administration instead of 60 minutes after a 60 minute infusion. This issue will be less relevant when fluids are administered within 5 minutes and CO is measured within several minutes.

Different parameters are used to define (non)responders; cardiac output, stroke volume, stroke volume index, left ventricular end-diastolic area index, cardiac index and aortic blood flow velocity. The effect of fluid loading can be described as a move of the working point to the right on the Frank-Starling curve. When the heart operates on the ascending part of the curve cardiac output will increase more in response to fluid loading (responder) than if the heart already operates near the flat part of the curve. We advocate the use of the change in cardiac output to determine (non)responders since it is one of few parameters likely to correlate to (vital) organ perfusion, it is a robust parameter, and CO is one of two factors to describe the Frank-Starling curve. The Frank Starling principle is based on the fiberlength-contractility relationship within the ventricle. If ventricular end-diastolic volume (preload) is increased ventricular fiberlength is also increased, resulting in an increased 'tension' of the

muscle and an increased contraction length.

Another factor directly influencing the number of responders is the cut-off value. The cut-off to discriminate between responders and non-responders after a fluid challenge varies between 5% and 25% change in CO [10,13]. Since the precision and accuracy of cardiac output measurement technique directly determines the clinical significance, we would like to relate the technique to measure CO to the cut-off value and the amount of administered fluid [14]. Previously, Critchley and Critchley [15] concluded that a new method was allowed to replace the gold standard when repeatability was within twice the standard deviation (2SD) of the gold standard method. Cecconi *et al.* discussed that the coefficient of variance (CV) was to be used [16]. They advised only to use a new CO method clinically when CV is below 10% (or clinically significant in their words). However, studies on the accuracy of different CO methods to determine changes (after an intervention) are scarce or lacking. Moreover, it is disputable that the assessment of agreement of CO methods as put forth by Critchley and Cecconi can be used for this purpose. Data by de Wilde and co-workers suggest that pulse contour methods (Modelflow and possibly LidCO) track changes in thermodilution cardiac output more accurately than suggested by earlier repeatability data [17]. We found that a 4.3% change in Modelflow CO after 100 ml fluid administration accurately predicts fluid loading responsiveness.

Jansen *et al*. reported a precision of 3.5% for thermodilution cardiac output to determine (genuine) CO [18]. Henceforth, a cut-off for triplicate thermodilution CO would be between 3.5% and 7%. Thus, our data indicates that lower cut-off values can be used (or more fluid has to be administered than with thermodilution) than the previously used 20%. We, therefore, advocate the use of different cut-off values based on the methods used to assess CO and their accuracy to track changes in cardiac output. We also advocate the use of a limited number of CO measurement techniques in FLR research. Only those measurement techniques that (have) prove(n) to be precise and accurate can be used.

Prediction of FLR

The aim of predicting FLR is to achieve the most adequate or optimal cardiac output with the least amount of fluids. In the prediction of FLR three major shortcomings are to be solved. First, an unambiguous definition of FLR is needed (see the discussion above). Second, errors related to the calculation and use of various predictors like LVEDA, SVV, PVV and changes on challenges like PLR and PEEP need to be quantified. Third, patient characteristics have to be taken into consideration to select a suitable parameter for FLR prediction. Forth, reliability of statistical analysis to compute the sensitivity, specificity and the threshold value to define responders and non-responders must be defined.

Echographic and Dynamic Parameters to Predict FLR

In theory, echographically determined volume parameters of the heart are supposed to be highly reliable predictors of FLR. The volume changes within the heart or vena cava are directly linked to cardiac function; when wall movement is limited inotropic assistance is warranted. And when filling of the ventricles is not optimal, fluid administration is indicated. Study results are very promising [19]. Several factors may, however, frustrate these results. Operator-related factors, like level of experience, changes in probe position and intermittent application, greatly influence the reliability and robustness of echographic monitoring [20]. The predictive value for FLR of echographic parameters in patients receiving mechanical ventilation seems to outscore the results for these parameters in spontaneously-breathing patients [21].

These operator- and patient-bound factors influence the accuracy to predict FLR. We highlight the results of the most studied parameters here; results for left ventricular end-diastolic area (LVEDA) [22-26] vary with sensitivity reported to be between 60 to 89%, specificity between 58 and 91% and the AUC of the ROC curve between 0.24 ± 0.11 and 0.78 (95% CI between 0.59 and 0.97) [23,26]. For global end-diastolic volume index (GEDVI) [13,27-29] the AUC of the ROC curves is between 0.23 and 0.70 (0.46-0.94) [28,29].

In recent years, new variables based on heart-lung interaction, i.e. respiratory-induced stroke volume variation (SVV) and pulse pressure variation (PPV) have been introduced in the ICU. Pulse pressure (PP) is defined as the beat-to-beat difference between the systolic and the diastolic pressure. PPV is the amplitude of cyclic changes induced by mechanical ventilation. The variations in PP and stroke volume induced by mechanical ventilation have been linked to volume status [30]. PPV is thought to be directly proportional to stroke volume variation [31]. The reliability for SVV and PPV varies from lower sensitivity and specificity of 70% to over 90% to predict FLR. Although SVV is a direct measure of variation in cardiac output, results for SVV show a wider spread [13,32,33]. Even though PPV is used as an indirect measure for SVV, results for PPV seem superior which may be especially true in septic patients [34], where vasoplegia is less likely to cause a reliable SVV measurement result. We need to consider that the calculation of SVV requires beat-to-beat SV measurements using a pulse contour analysis algorithm whereas PPV is measured directly from the arterial waveform. SVV will require an ongoing validation in clinic conditions as algorithms are developing with time [35]. In that context it is noteworthy that more recent publications report lower area under the ROC curves than older publications. Whether this depends on publication bias, a decrease in the accuracy of newer pulse-contour methods to determine SVV or more frequent improper use remains uncertain. Several restrictions apply to the use of dynamic parameters. Cardiac arrhythmias significantly decrease the reliability of SVV and PPV [20]. The use of these dynamic parameters has been validated in sedated and mechanically ventilated patients without

spontaneous breathing activity. Third, SVV, and probably PPV, is not only influenced by intravascular volume but also by the depth of the tidal volume used in mechanical ventilation of the lungs [26].

Patient Characteristics, Challenges and FLR

When FLR is assessed patient (co)morbidity is of importance to select the most reliable parameter. For SVV, PPV and LVEDA determinations the limitations are reasonably well described (see above). For several disease states, however, we do not know yet how they influence the reliability of a parameter to predict FLR. For instance, we do not know what the influence of right ventricular dysfunction has on the accuracy of dynamic variables to predict FLR. In these cases, the use of a challenge could be helpfull.

Reversible autotransfusion by passive leg raising (PLR) and a provocation method with the application of increased PEEP have also become the subject of intense interest. Particularly, the groups of Boulain, Monnet and Teboul studied the reliability of parameters during PLR to predict FLR [36,37]. The robustness and reliability of the "static parameters" during the challenge can be explained by the direct use of the Starling curve. The working point on the Frank Starling curve of each individual patient (with its own pathophysiological constitution) is determined and FLR can be assessed. The amplitude of the change in CO after the challenge can be used to predict FLR. These challenges are reversible, standardized and easily performed.

Statistical Testing

Overall receiver operating characteristics (ROC) are used to describe the precision of the prediction of fluid loading responsiveness. Sensitivity and specificity and threshold values to identify responders and non-responders on fluid loading are determined for several variables in a specific population. However, the application of ROC curves also requires secondary testing in a control population with the earlier found cut-off values in order to determine reproducibility in similar and different sub-populations. Since reproducibility is only rarely assessed, straightforward extrapolation of study results is not possible. This also hinders formulation of a department protocol for bedside use.

A second issue related to statistical analysis in FLR research is related to the size of the study populations; population size varies between 8 [38] and 60 [39] in reports up to 2010. However, no study reports on power analysis. Moreover, rarely the significance of the found area under the ROC curve (AUROC) is reported. Hanley *et al*. demonstrated the value of statistical testing between ROC curves [40]. We advocate the use of this test to compare AUROC with mathematical chance (Test: AUROC $\neq$ 0.500) and to allow comparison of ROC curves for different parameters, especially when power analysis are absent.

Conclusions

The restricted use of fluids in the intensive care and operating theatre reduces risk of complications like pulmonary edema. Targeted infusion strategies have shown to benefit patients. Fluid loading responsiveness is a novel strategy that aims to optimize perfusion and oxygen delivery to vital organs. This strategy is likely to signal that a patient is functioning on or near the flat part of the Frank Starling curve. Predicting fluid loading responsiveness is described as the use of a hemodynamic variable to predict the effect of a fluid bolus administration.

FLR research has shown promising results but no consensus exists on the exact definition of FLR. The amount of fluid, type of fluid, the parameter used to define responders, timing of the measurement of CO after fluid loading, the cut-off value to define responders and the cardiac output measurement technique vary widely. Based on these pitfalls and current knowledge, we propose to define FLR is the use of (a set of) baseline hemodynamic variables (or a change in a variable after a challenge manoeuvre) to predict a clinically significant change in cardiac output within 5 minutes after a 5 $ml \cdot kg^{-1}$ bolus of a crystalloid or colloid fluid is administered within 5 minutes. Moreover, the use of an accurate and precise cardiac output measurement technique to assess FLR is desirable. We advise a cut-off for triplicate thermodilution CO of 3,5% and for pulse contour CO around 5% change. Consequently, we can use this explicit classification to define responders and integrate results of different FLR studies. Until major morbidity and mortality studies have been performed into the LFR strategy, we advise the use of pulse pressure variation and challenges like passive leg raising to assess FLR in critically ill patients. Baseline PPV and changes in static filing pressure after PEEP and PLR challenges have repeatedly shown to predict FLR with high sensitivity and specificity in different patient populations. However, it remains important to recognize a patients specific pathophysiology to select the most reliable parameter to predict FLR.

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Chapter 15

Summary

Patients in the intensive care unit (ICU) and in the peri-operative phase are dependent on physicians and nurses for their fluid intake. Volume status optimization is required to maximize oxygen delivery to vital organs. Unnecessary fluid administration can, however, lead to general and pulmonary oedema, cardiac failure, infections, prolonged hospitalization and death. Besides signs like skin turgor, diuresis and skin colour, hemodynamic measurements like central venous pressure (CVP) and mean arterial pressure (MAP) are most often used for hemodynamic management. These parameters, however, often fail to accurately predict the response of a patient to fluid loading.

Cardiac output (CO) is the amount of blood pumped through the circulation by the heart per minute. The general conception is that an increase in cardiac output will improve perfusion of vital organs. Increased flow might also imply improved oxygen delivery to the tissues. This is the basis of the fluid loading responsiveness strategy (FLR). This strategy aims to prevent fluid overloading by an accurate prediction of the response in cardiac output to fluid loading. Arthur Guyton's work provided an important step forward to the determination of volume status directly. Together with the shape of cardiac output function curve, dimensions of the vascular system, blood viscosity and mean systemic filling pressure (MSFP) can be considered as a primary determinant of venous return and thus cardiac output. Ultimately,

MSFP can be used to calculate stressed volume and, hence, quantify effective volume status in a specific patient.

In this thesis, we review literature on fluid loading responsiveness research, we try to assess the impact of literature on hemodynamic management in Dutch ICU's, we discuss a novel method to assess mean systemic filling pressure and last we discuss studies performed to assess the reliability of several challenges to predict FLR; +10 cmH_2O PEEP, the fluid challenge, passive leg raising, the respiratory ventilator manoeuvre and the measurement of baseline MSFP. The manoeuvres are aimed at determining the working point of the circulation on the Frank-Starling curve. It is assumed that when the patient is on the ascending portion of the Frank-Starling curve an (auto)transfusion will increase cardiac output.

Chapter 1

Many methods of cardiac output measurement have been developed, but the number of methods useful for human studies is limited. The "holy grail" for the measurement of cardiac output would be a method that is accurate, precise, operator independent, fast responding, non-invasive, continuous, easy to use, cheap and safe. This method does not exist today. In chapter one, we reviewed methods to measure cardiac output; the Fick principle, indicator dilution techniques, arterial pulse contour analysis, ultrasound and bio-impedance.

Chapter 2

We evaluated cardiac output using three new methods – the auto-calibrated FloTrac–Vigileo (COed), the non-calibrated Modelflow (COmf) pulse contour method and the ultra-sound HemoSonic system (COhs) – with thermodilution (COtd) as the reference. In 13 postoperative cardiac surgical patients, 104 paired CO values were assessed before, during and after four interventions: (1) an increase of tidal volume by 50%; (2) a 10 cmH2O increase in positive end-expiratory pressure; (3) passive leg raising and (4) head up position. With the pooled data the difference (bias (2SD)) 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) $L \cdot min^{-1}$, 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.

Chapter 3

The aim of this study was to compare the accuracy of stroke volume variation (SVV) as measured by the LiDCOplus system (SVVli) and by the FloTrac-Vigileo system (SVVed). We measured SVVli and SVVed in 15 postoperative cardiac surgical patients following five study interventions; a 50% increase in tidal volume, an increase of PEEP by 10 cmH_2O passive leg raising, a head-up tilt procedure and fluid loading. Between each intervention, baseline measurements were performed. 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 was found to be significantly different from zero at 1.5% ± 2.5%, $p < 0.001$, (95% confidence interval 1.1-1.9). The upper and lower limits of agreement were found to be 6.4% and 3.5% respectively. The coefficient of variation for the differences between SVVli and SVVed was 26%. This results in a relative large range for the percentage limits of agreement of 52%. Analysis in repeated measures showed coefficients of variation of 21% for SVVli and 22% for SVVed. 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 measures. These findings underline Pinsky's warning of caution in the clinical use of SVV by pulse contour techniques.

Chapter 4

Selection of patients who will benefit from fluid loading is critical since unnecessary fluid administration can lead to parameters and challenges in daily practice in Dutch intensive care units. We sent 446 questionnaires to ICU physicians in the Netherlands. 39% of questionnaires were returned. In the initial assessment of pulmonary oedema and cardiac

failure. Filling pressures such as CVP, MAP, cardiac output and clinical signs have traditionally been at the centre of haemodynamic monitoring. We performed a survey to evaluate the impact of recently introduced volume status urine production and capillary refill were found most important. To estimate need for volume expansion; CVP was used by 70%, stroke volume variation (SVV) or pulse pressure variation (PPV) by 47%, and CO by 20%. Seventy-five percent used a fluid challenge to predict responsiveness. Changes in heart rate, MAP, CVP and CO were used most in characterizing responders and non-responders. The presence of guidelines to characterize hypo- or hypervolaemia was indicated by 25% and only half of these respondents indicated they used these guidelines. Many Dutch ICU physicians use the recently developed variables SVV and PPV as well as fluid challenges to predict the effects of fluid loading on CO, although, CVP is still used by the majority.

Chapter 5

Unnecessary fluid administration increases morbidity, mortality and intensive care stay. Fluid loading responsiveness (FLR) is a strategy used to select patients that will benefit from fluid administration. We summarized recent publications on FLR to provide the physician working with critically-ill patients with an overview of parameters most frequently used in FLR and we evaluated their reliability to predict the response in cardiac output to fluid loading. Measurements of dynamic parameters, like pulse pressure variation (PPV) and stroke volume variation, have consistently shown to be more reliable than central venous pressure and pulmonary artery occlusion pressure (PAOP) to predict FLR. Changes in MAP, CVP or CO as a result of different challenges (passive leg raising) are also more accurate predictors of FLR. However, the definition of FLR lacks consensus as the quantity of administered fluids and the cut-off to discriminate (non)responders vary largely. Dynamic parameters, and especially PPV, are likely candidates to predict FLR in an everyday ICU setting in different patient populations. Moreover, changes in CVP, MAP and CO after passive leg raising can be used with equal reliability.

Chapter 6

Hypovolaemia is a common clinical problem. The Trendelenburg position and passive leg raising (PLR) are routinely used in the initial treatment awaiting fluid resuscitation. We evaluated the hemodynamic effects of PLR and Trendelenburg. Which position has the optimal effect on cardiac output (CO)? Databases were searched for prospective studies in normo- or hypovolaemic humans investigating the hemodynamic effects within 10 minutes after postural change from supine position published between 1960 and 2010. 21 studies were included for PLR (n=431) and 13 for Trendelenburg (n=246) position. Trendelenburg position increased mean arterial pressure (MAP). CO increased 9% or 0.4 $L \cdot min^{-1}$ after one

minute of head down tilt. Between two to ten minutes this increase in CO declined to 4% or 0.1 $L \cdot min^{-1}$. PLR showed no increase in MAP or heart rate. Central venous pressure increased. CO increased after one minute of leg elevation with 6% or 0.2 $L \cdot min^{-1}$. This effect persisted after this period with 6% or 0.2 $L \cdot min^{-1}$. We found that although both Trendelenburg and PLR significantly increase cardiac output only PLR seems able to sustain this effect after one minute. Since fluid resuscitation during hypovolaemia is not achieved within minutes, we advocate the use of autotransfusion with PLR. Studies that directly compare effects of the two manoeuvres that are still needed for one of the most often used therapies in medicine.

Chapter 7

We presented a new physiological model that discriminated between changes in the systemic arterial and venous circulation. To test our model, we studied the effects of dobutamine and hypovolemia in intact pentabarbitol- anesthetized piglets. Aorta pressure (Pao), central venous pressure (CVP), mean systemic filling pressure (MSFP) and cardiac output were measured in 10 piglets, before, during and after dobutamine infusion (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), as well as during hypovolemia (-10 $ml \cdot kg^{-1}$), and after fluid resuscitation to normovolemia. Venous (Rv) and total systemic (Rsys) resistance were determined from Pao, PCV, MSFP and CO. The quotient of Rv/ Rsys was used to determine the predominant location of vascular changes (i.e. vasoconstriction or dilatation on either venous or arterial side). Administration of dobutamine increased heart rate and CO, whereas it decreased MSFP, Rsys, Rv and Rv/Rsys. The decrease in Rv was significantly greater than Rsys. Pao and Pcv did not change. Hypovolemia decreased CO, CVP, MSFP, Rv and Rv/Rsys, but kept Rsys constant and increased heart rate. Hypovolemia and dobutamine differentially alter MSFP, Rsys, Rv and Rv/Rsys ratio. The increase in CO during dobutamine infusion was attributed to the combined increased cardiac function and decreased Rv. The decrease in CO with hypovolemia was due to a decrease MSFP but was partly compensated for by a decrease in Rv tending to preserve venous return and thus CO.

Chapter 8

We aimed to measure the relationship between blood flow and central venous pressure and to estimate mean systemic filling pressure (MSFP), circulatory compliance, and stressed volume in twelve mechanically ventilated postoperative cardiac surgery patients in the intensive care unit. Inspiratory holds were performed during normovolaemia in supine position (baseline), relative hypovolemia by placing the patients in 30° head-up position (hypo), and relative hypervolaemia by volume loading with 0.5 L colloid (hyper). We measured the relationship between blood flow and CVP using 12-second inspiratory-hold

manoeuvres transiently increasing CVP to three different steady state levels and monitored the resultant blood flow via the pulse contour method during the last 3 seconds. The CVP to blood flow relation was linear for all measurements with a slope unaltered by relative volume status. MSFP decreased with hypo and increased with hyper (18.8 ± 4.5 mmHg, to 14.5 ± 3.0 mmHg, to 29.1 ± 5.2 mmHg [baseline, hypo, hyper, respectively, $p < 0.05$]). Baseline total circulatory compliance was 0.98 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ and stressed volume was 1677 ml. Conclusions: MSFP can be determined in intensive care patients with an intact circulation with use of inspiratory pause procedures, making serial measures of circulatory compliance and circulatory stressed volume feasible.

Chapter 9

Arm occlusion pressure (Parm) is used to study the hemodynamic effects of drugs. It might serve as an indicator of static filling pressure. We hypothesized that Parm could be used to predict fluid loading responsiveness (FLR) in 24 patients after cardiac surgery. Fluid loading increased cardiac output (CO), Parm, mean arterial pressure (MAP) and central venous pressure (CVP). In responders (n=17), CO, Parm, MAP, CVP increased and, stroke volume variation (SVV) and pulse pressure variation (PPV) decreased. In non-responders (n=7), Parm and CVP increased, PPV decreased. CO, MAP, SVV and heart rate did not change significantly. The area under the curve to predict FLR for Parm was 0.786 (95% CI: 0.567-1.000), at a cut-off of 21.9 mmHg sensitivity is 71% and specificity 88% to predict FLR. Parm seems to be a good predictor of FLR in our group of cardiac surgery patients.

Chapter 10

Changes in central venous pressure (CVP) rather than absolute values may be used to guide fluid therapy in critically-ill patients undergoing mechanical ventilation. We conducted a study comparing the changes in the CVP produced by an increase in positive end-expiratory pressure (PEEP) and stroke volume variation as indicators of fluid responsiveness. Fluid responsiveness was assessed by the changes in cardiac output produced by passive leg raising. In twenty fully mechanically-ventilated patients after cardiac surgery, PEEP was increased +10 cmH_2O for 5 minutes followed by PLR. CVP, SVV and thermodilution cardiac output (CO) were measured before, during and directly after the PEEP challenge and 30ffl PLR. The cardiac output (CO) increase >7% upon PLR was used to define responders. Twenty patients were included of whom 10 responded to PLR. The increase in CO by PLR directly related ($r=0.77$, $P<0.001$) to the increase in CVP by PEEP. PLR responsiveness was predicted by the PEEP-induced increase in CVP (area under receiver-operating characteristic [AUROC] curve 0.99, $P<0.001$) and by baseline SVV (AUROC 0.90, $P=0.003$). The AUROC's for dCVP and SVV did not differ significantly ($P=0.299$). Our data in mechanically-ventilated, cardiac-

surgery patients suggest that the newly defined parameter, PEEP-induced CVP changes, like SVV, appears to be a good parameter to predict fluid responsiveness.

Chapter 11

In 2006, Vincent and Weil (V&W) reintroduced the fluid-challenge protocol. We studied the value of adding pulse contour cardiac output to V&W's protocol to reduce the amount of unnecessary administered fluid and compared it to a fluid loading responsiveness protocol with pulse contour CO. We measured the effects of the administration of 10 sequential 50 ml bolus colloid infusions on CO [Modelflow (COm) and LiDCO (COli)], central venous pressure (CVP) and mean arterial pressure (MAP) in twenty-one patients on mechanical ventilation after elective cardiothoracic surgery. COli and COm increased after 50, 100 and 500 ml fluid loading. When COm is increased ≥4.3% after a 100 ml trial administration, fluid loading responsiveness with a 10% increase in CO after 500 ml fluid administration can be predicted with a sensitivity 67% and specificity of 100%. Addition of COm to V&W's original protocol would have lead to a mean administration of 100 instead of 200 ml fluid to non-responders and an increase of 7% in CO. A fluid responsiveness protocol would have lead to a 18% increase in CO. The addition of pulse contour CO can improve the reliability and robustness of the V&W's fluid-challenge protocol. It resulted in an increase of cardiac output in responders and a decrease of unnecessary fluid loading in non-responders.

Chapter 12

We evaluated the ability of two pulse contour cardiac output techniques to track cardiac output changes during 30° passive leg raising (PLR) to assess fluid loading responsiveness in twenty mechanical-ventilated post-operative cardiac surgery patients. We estimated cardiac output by three techniques: thermodilution (COtd), arterial pulse power (COli, LiDCO) and pulse contour method (COm) based on uncalibrated Modelflow. We measured heart rate (HR), central venous pressure, arterial pulse pressure (PP), systolic pressure (SP) and mean arterial pressure. Stroke volume (SV), SP, PP and SV variation (PPV and SVV, respectively) were calculated over 5 breaths. SVV was measured by both LiDCO (SVVli) and Modelfow (SVVm) devices. PLR-induced changes in COtd correlated with COli ($p<0.001$) and COm ($p<0.001$). Preload dependence was predicted with an area under the ROC curve of 0.968 for ΔCOm, 0.841 for ΔCOli, 0.825 for SVVm, 0.873 for SVVli, 0.808 for PPV, 0.778 for ΔSP, 0.714 for ΔPP and 0.873 for ΔMAP. Changes in COm, COli, SVV and PPV track COtd changes during PLR with a high degree of accuracy in sedated ventilated post-operative cardiac surgery patients. Changes in pulse contour CO after PLR can be used to predict fluid loading responsiveness.

Chapter 13

In response to publications by Preisman and co-workers, we evaluated transferability of an automated ventilator manoeuvre of successive incremental-pressure-controlled 1.5-second breaths, Respiratory Systolic Variation Test (RSVT), in an independent group of 14 patients after cardiac surgery to predict fluid loading responsiveness (FLR). Cardiac output, central venous pressure and mean arterial pressure increased after 500 ml colloid administration. Pulse pressure variation and RSVT-values decreased. CO increased 34% in responders (n=9) and did not change in non-responders (n=5). An RSVT-threshold of 0.51 predicted FLR correctly in 78% of the patients. Prediction of FLR with an automated RSVT is feasible and reliable.

Discussion

No gold standard exists to guide hemodynamic management. Fluid loading responsiveness is a relatively novel strategy. In general, fluid loading responsiveness can be described as the response of CO on an intra-vascular administration of a certain amount of fluid. Even more important is the ability to predict FLR, i.e. responders and non-responders without the administration of fluids. This strategy could reduce unnecessary fluid administration
220) henceforth decreasing related complications and mortality. The idea behind predicting FLR is that overall fluid administration will decrease. To our knowledge no study exists to date that evaluates the impact of FLR (prediction) on fluid administration or outcome. More elaborate research is needed. Consequently a workable algorithm needs to be developed to predict FLR and to guide fluid management in a patient followed by a study of its effect on outcome. We advocate the use of a single definition to allow comparison of different studies in order to ultimately formulate a FLR-protocol and to assess the effect of FLR on mortality and morbidity. Moreover, statistical testing needs to improve; receiver operating curve characteristics alone are not sufficient and secondary testing in a control population or reproducibility testing is necessary.

The most important issue, however, is the lack of a practical consensus over the definition of fluid loading responsiveness; the amount of fluid, type of fluid, timing of the measurement, the choice of parameter to define responders, the technique to measure this parameter and its cut-off value vary widely in literature. We propose to define fluid loading responsiveness. as a clinically significant increase in cardiac output within 5 minutes after a bolus 5 $ml \cdot kg^{-1}$ administration of a colloid or crystalloid solution.

Chapter 16

Samenvatting

Patiënten op een intensivecare-afdeling en in de periode gedurende en rondom een operatie, zijn afhankelijk van medisch personeel voor hun vloeistofinname. Het optimaliseren van de vullingtoestand is noodzakelijk voor een maximaal zuurstofaanbod aan vitale organen. Overmatige toediening van vloeistof leidt tot gegeneraliseerd oedeem, longoedeem, hartfalen, infecties, verlengde ziekenhuisopnames en zelfs overlijden. Symptomen als huidturgor, urineproductie, kleur van de huid, en hemodynamische metingen, zoals centraal veneuze druk (CVD) en gemiddelde slagaderlijke bloeddruk (MAP), worden meestal gebruikt in het beleid. Deze parameters zijn echter in veel situaties onbetrouwbare voorspellers van de effecten van het toedienen van vloeistof.
Cardiac output (CO) is de hoeveelheid bloed die door het hart per minuut in de bloedsomloop wordt rondgepompt. Men is er van overtuigd dat een toename in cardiac output ook een verbeterde doorbloeding van de vitale organen geeft. Een toegenomen doorbloeding houdt in dat het zuurstofaanbod aan deze organen waarschijnlijk verbetert. Dit is de basis van de vloeistofresponsiviteitstrategie (FLR). Deze strategie heeft als doel cardiac output te optimaliseren, de hoeveelheid vloeistoftoediening te minimaliseren en de kans op overvulling te verkleinen.
In het verleden heeft Arthur Guyton een belangrijke stap gezet waardoor het direct meten van
 de vullingtoestand mogelijk zou moeten worden. De weerstand van de bloedvaten, centraal veneuze druk (CVD) en statische vullingdruk (MSFP) zijn de primaire determinanten van veneuze terugvloed van bloed naar het hart en dus ook cardiac output. Uiteindelijk kan MSFP gebruikt worden om het (actieve of) circulerend bloedvolume te bepalen in patiënten. MSFP is de druk die in de bloedvaten (aders en slagaders) ontstaat als er geen bloed stroomt dus als het hart stil zou staan.
In dit proefschrift, hebben we een overzicht gemaakt van de publicaties over FLR en we hebben getracht het effect van deze publicaties op de Nederlandse intensivecarepraktijk in kaart te brengen. Wij bespreken de resultaten van twee onderzoeken naar de nauwkeurigheid van pulscontouranalyse om CO en slagvolumevariatie (SVV) te bepalen. Vervolgens presenteren we de resultaten van een nieuwe methode om MSFP in mensen te kunnen bepalen zonder dat stilstand van het hart noodzakelijk is. Als laatste bediscussiëren wij vijf studies waarin de betrouwbaarheid is onderzocht om FLR te voorspellen door middel van een manoeuvre met +10 cmH_2O piek eind-expiratiedruk (PEEP), een proeftoediening van vloeistof, passief benen heffen, een mechanische beademingmanoeuvre en het meten van baseline MSFP. De manoeuvres hebben als doel het werkpunt op de hartfunctiecurve te bepalen en te kijken of er “ruimte” is voor toediening van vloeistof.

Hoofdstuk 1

Er zijn meerdere technieken ontwikkeld om de pompkracht van het hart, ofwel cardiac output, te meten. Het aantal technieken dat voor onderzoek in mensen is te gebruiken, is

echter beperkt. De 'heilige graal' voor het meten van cardiac output zou een techniek zijn die nauwkeurig, precies, gebruikeronafhankelijk, snel reagerend, continue, makkelijk in gebruik, goedkoop en veilig is. Zo'n methode bestaat momenteel nog niet. In hoofdstuk één van dit proefschrift hebben wij een overzicht gemaakt van de meest gebruikte en de bruikbare technieken om cardiac output te meten: de Fick, indicatorverdunning, puls-contouranalyse (waarbij de pulscontour wordt gebruikt om CO te berekenen), echografie en bio-impedantiemethoden.

Hoofdstuk 2

We hebben de nauwkeurigheid en precisie van drie methoden om cardiac output te meten bestudeerd - autogekalibreerde FloTrac–Vigileo (COed) en niet-gekalibreerde Modelflow (COmf) drukgolfmethoden en een echografische (HemoSonic, COhs) techniek - in vergelijking met de thermodilutietechniek (COtd). Bij 13 postoperatieve, mechanisch beademde, cardiochirurgische patiënten werden 104 gepaarde CO-waarden beoordeeld voor, tijdens en na vier interventies (1) een 50% toename in teugvolume; (2) een 10 cmH_2O toename in PEEP; (3) 30° benen heffen en (4) hoofd-omhoog-positie. Het verschil (bias (2SD)) tussen COed en COtd, COmf en COtd, en COhs en COtd was 0.33 (0.90), 0.30 (0.69) en (0.41 (1.11) $L \cdot min^{-1}$, respectievelijk. Modelflow had de laagste gemiddelde fout, wat suggereert dat deze techniek de meest precieze prestaties levert. COed overschat de veranderingen in cardiac output terwijl COmf- en COhs-waarden niet significant verschillen van COtd. De richting van de veranderingen in thermodilutie cardiac output komt in zeer hoge mate overeen met de richting van veranderingen waargenomen met de drie methoden.

Hoofdstuk 3

Het doel van de studie beschreven in hoofdstuk drie is het vergelijken van de nauwkeurigheid van stroke volume variatie gemeten door het LiDCOplus-systeem (SVVli) en het FloTrac-Vigileo-systeem (SVVed). We hebben SVVli en SVVed in 15 postoperatieve cardiochirurgische patiënten geregistreerd tijdens vijf interventies; (1) een 50% toename in teugvolume; (2) een 10 cmH_2O toename in positieve eind-expiratoire druk; (3) 30° benen heffen, (4) hoofd-omhoog-positie en (5) toediening van vloeistof. Tussen de interventies door zijn basismetingen uitgevoerd. 136 gepaarde SVV-waarden werden verzameld. SVVli-waarden varieerden van 1.4% tot 26.8% (gemiddeld 8.7% ± 4.6%); SVVed van 2.0% tot 26.0% (gemiddeld 10.2% ± 4.7%). De gemiddelde bias bleek significant te verschillen van nul met 1.5% ± 2.5%, $p < 0.001$, (95% betrouwbaarheidsinterval 1.1–1.9%). De bovenste en onderste grenzen van het betrouwbaarheidsinterval waren 6.4% en 3.5% respectievelijk. De variatieco-efficiënt voor de verschillen tussen SVVli en SVVed was 26%. Dit resulteert in een relatief grote spreiding van de betrouwbaarheidsintervallen van 52%. Analyse van de herhaalde

metingen liet een variatiecoëfficiënt van 21% voor SVVli en 22% voor SVVed zien. De SVV-waarden van de LiDCOplus en FloTrac- Vigileo-systemen zijn niet uitwisselbaar. Daarnaast zijn de metingen van SVVli en SVVed niet eenduidig. Dit kan geconcludeerd worden uit de hoge variatiecoëfficiënt bij herhaalde metingen. Deze bevindingen onderstrepen de waarschuwing van Michael Pinsky om voorzichtig te zijn om SVV-waarden die via pulscontouranalyse verkregen zijn in de kliniek te gebruiken.

Hoofdstuk 4

De selectie van patiënten die baat zullen hebben bij het toedienen van vloeistof is essentieel voor een verantwoord vullingbeleid. Het onnodig toedienen van vloeistof kan leiden tot het ontstaan van longoedeem en hartfalen. Vullingdrukken zoals CVD en MAP, cardiac output en klinische symptomen hebben altijd centraal gestaan bij de hemodynamische bewaking van patiënten. Wij hebben een enquête afgenomen om de gevolgen van publicaties over nieuwe parameters op de dagelijkse praktijkvoering in Nederlandse intensivecareafdelingen te bekijken. Enquêtes werden verstuurd naar alle (446) intensivecare-artsen in Nederland. 39% Van de enquêtes werd ingevuld en teruggezonden.

In de eerste beoordeling van de vullingtoestand worden de productie van urine en capillary refill als meest belangrijk gevonden. De CVD wordt door 70% van de artsen gebruikt om de behoefte aan extra vloeistof in te schatten. SVV werd door 47% van de respondenten gebruikt, en CO door 20%. 75% Procent gebruikt een proeftoediening van vloeistof om vloeistofresponsiviteit in te schatten. Veranderingen in hartslag, MAP, CVD en CO na vloeistoftoediening worden vaak gebruikt om vloeistofresponsiviteit te beoordelen. Slechts een kwart van alle respondenten geeft aan dat er een protocol beschikbaar is in het ziekenhuis om onder- of overvulling te beschrijven/behandelen en slechts de helft van deze respondenten zegt dat protocol ook te gebruiken. Relatief veel intensivecare-artsen gebruiken recent ontwikkelde variabelen als SVV en polsdrukvariatie (PPV) evenals een proeftoediening van vloeistof om te trachten de effecten van vloeistoftoediening te voorspellen. Daarentegen wordt door de meerderheid nog een ‘ouderwetse’ variabele als CVD gebruikt.

Hoofdstuk 5

De onnodige toediening van vloeistof verhoogt de kans op complicaties en sterfte, en verlengt het verblijf op de intensive care. FLR is een strategie om patiënten te selecteren die baat zullen hebben bij het toedienen van vloeistof. Wij hebben recente publicaties over dit onderwerp op een rij gezet. We hebben een overzicht gemaakt van de meest gebruikte parameters voor FLR en we hebben de nauwkeurigheid om het effect van vloeistoftoediening op CO van deze parameters bekeken. Dynamische parameters zoals PPV en SVV hebben

veelvuldig en consequent laten zien dat zij meer betrouwbare voorspellers van FLR zijn dan centraal veneuze druk en pulmonaal arterie wiggedruk. Veranderingen in MAP, CVD en CO ten gevolge van verschillende manoeuvres zoals passief benen heffen (PLR), zijn ook voorspellers van FLR. Dynamische parameters, en met name PPV, zijn aan te raden om in de praktijk te gebruiken om FLR te voorspellen. Tevens zijn veranderingen in CVD, MAP en CO na benen heffen met een zelfde mate van betrouwbaarheid te gebruiken.

Hoofdstuk 6

Ondervulling is een veelvoorkomend klinisch probleem. De Trendelenburg (i.e. bed gekanteld met hoofd omlaag en benen omhoog) positie en benen heffen worden routinematig gebruikt in afwachting van definitieve behandeling van het probleem en het toedienen van vloeistof of bloedproducten. Wij hebben de hemodynamische effecten van PLR en de Trendelenburgpositie onderzocht door een literatuur studie over de periode 1960 tot 2010 naar prospectieve onderzoeken in mensen gedurende de eerste 10 minuten na positieverandering. Welke positie heeft het meest effect op CO? 21 Studies over PLR waren relevant (n patiënten=431) en 13 over Trendelenburg (n patiënten=246). Trendelenburgpositionering deed MAP toenemen. CO steeg 9% of 0.4 $L \cdot min^{-1}$ na 1 minuut Trendelenburg. In de periode hierna (2-10 min) daalde deze toename tot 4% of 0.1 $L \cdot min^{-1}$. PLR deed noch MAP noch de hartslag veranderen. CVD nam toe. CO steeg met 6% of 0.2 $L \cdot min^{-1}$ na één minuut. Alhoewel zowel Trendelenburg als PLR CO significant doet stijgen, is het alleen PLR dat dit effect langer dan enkele minuten laat duren. Wij zouden dus het gebruik van PLR willen aanraden voor de eerste behandeling van ondervulling

Hoofdstuk 7

Wij introduceren een nieuw fysiologisch model dat onderscheid mogelijk maakt tussen de slagaderlijke en aderlijke bloedsomloop. Om ons model te testen hebben we de effecten van dobutamine en ondervulling in biggen onder barbituratennarcose onderzocht. Lichaamsslagaderdruk (Pao), CVD, MSFP en CO werden gemeten in 10 biggen voor, tijdens en na dobutamine-infusie (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), tijdens hypovolemie (-10 $ml \cdot kg^{-1}$), en na herstel van normale vullingstatus. Aderlijke (Rv) en systemische (Rsys) vaatweerstanden werden bepaald uit Pao, CVD, MSFP en CO. Het quotiënt van Rv/Rsys werd gebruikt om de voornaamste verandering van vaatweerstanden te bepalen (verwijden of vernauwen van de aderlijke of slagaderlijke kant van de bloedsomloop). Infusie van dobutamine verhoogde de hartslag en CO. MSFP, Rsys, Rv en Rv/Rsys daalden. De daling in Rv was significant kleiner dan Rsys. Pao en CVD veranderden niet. Ondervulling verminderde CO, CVD, MSFP, Rv en Rv/Rsys, maar Rsys bleef onveranderd en de frequentie van de hartslag nam toe. Ondervulling en dobutamine veranderen MSFP, Rsys Rv en de Rv/Rsys-ratio variërend. De stijging in CO

tijdens dobutamine-infusie wordt geweten aan de gecombineerde verhoging van hartfunctie en afgenomen Rv. De afname in CO tijdens ondervulling wordt veroorzaakt door een afname in MSFP maar wordt ook deels gecompenseerd door de afname in Rv.

Hoofdstuk 8

Het doel van deze studie was de relatie tussen CO en CVD te bepalen, en om statische vullingdruk en effectief circulerend bloedvolume te berekenen in twaalf mechanisch beademde, postoperatieve, cardiochirurgische patiënten. Inademingpauzes met verschillende drukken werden verricht bij normale vulling (rugligging, baseline), relatieve ondervulling door 30° hoofd-omhoog-positie (hypo) en relatieve overvulling (500 ml colloid toediening, hyper). De relatie tussen CO en CVD werd gemeten m.b.v. deze twaalf seconden durende inademingpauzes die de CVD verhoogde en CO verlaagde. De cardiac output werd middels pulscontouranalyse gemeten gedurende de laatste drie seconden van de adempauze. De relatie tussen CVD en CO was lineair voor alle metingen met een helling die gelijk bleef voor de verschillende vullingtoestanden. MSFP verminderde van baseline naar hypovolemie en nam toe tijdens hypervolemie (van 18.8 ± 4.5 mmHg naar 14.5 ± 3.0 mmHg, naar 29.1 ± 5.2 mmHg ($p < 0.05$)). De baselinecompliantie van de bloedsomloop was

0.98 ml·mmHg^{-1}·kg^{-1} en het effectief circulerend bloedvolume was 1677 ml. Concluderend: statische vullingdruk kan bepaald worden bij ic-patiënten met een intacte bloedsomloop door gebruik te maken van de inademingpauzeprocedure met het beademingsapparaat. Deze procedure maakt het mogelijk de compliantie van de bloedsomloop en het effectief circulerend bloedvolume te volgen bij beademde patiënten.

Hoofdstuk 9

De druk gemeten met de armocclusiemethode is in het verleden gebruikt om de effecten van medicijnen op de bloedsomloop te bestuderen. Wij stellen dat deze armocclusiedruk (Parm) ook gebruikt zou kunnen worden als een indirecte indicatie van de vullingstatus. We hebben de waarde van Parm bestudeert om FLR te voorspellen in 24 patiënten na cardiochirurgie. Vloeistoftoediening vergrootte CO, Parm, MAP en CVD. In responders (n=17) namen CO, Parm, MAP en CVD toe en SVV en PPV af. In non-responders (n=7), namen alleen Parm en CVD toe. PPV daalde. CO, MAP, SVV en hartslag veranderden niet significant. De oppervlakte onder de voorspellingcurve (AUROC) voor Parm was 0.786 (95% betrouwbaarheidsinterval 0.567-1.000). Een Parm < 21.9 mmHg had een sensitiviteit van 71% en een specificiteit van 88% om FLR te voorspellen. Hiermee lijkt Parm een goede voorspeller van FLR in onze bestudeerde groep van patiënten na cardiochirurgie.

Hoofdstuk 10

Niet de absolute waarde maar de verandering in CVD zou wel eens een goede basis kunnen zijn voor het vloeistofbeleid bij kritisch zieke patiënten. We hebben een studie uitgevoerd om de CO-verandering ten gevolge van 30° PLR te voorspellen op basis van veranderingen in CVD na verhoging van PEEP. Twintig mechanische beademde patiënten na cardiochirurgie werden bestudeerd. PEEP werd verhoogd met 10 cmH_2O gedurende vijf minuten gevolgd door vijf minuten benen heffen. CVD, SVV en thermodilution CO werden bepaald voor, gedurende en na de PEEP-manoeuvre en PLR. Een toename in thermodilutie CO van >7% na PLR werd gebruikt om responders te identificeren. De toename in CO door PLR was direct gerelateerd aan de toename in CVD na +10 PEEP ($r=0.77$, $P<0.001$). PLR-responsiviteit werd voorspeld door de +10 PEEP veranderingen in CVD (AUROC 0.99, $P<0.001$) en door baseline slagvolumevariatie (AUROC 0.90, $P=0.003$). De resultaten van ons onderzoek suggereren dat door PEEP geïnduceerde veranderingen in CVD FLR met ongeveer dezelfde betrouwbaarheid als baseline SVV kan voorspellen.

Hoofdstuk 11

In 2006, herintroduceerde Vincent en Weil (V&W) de proeftoediening van vloeistof in een protocol voor hemodynamisch beleid. In ons onderzoek hebben wij de waarde van de toevoeging van CO (middels pulscontourmeting) aan het V&W-protocol geëvalueerd om onnodige vloeistoftoediening te reduceren. We hebben in 21 mechanisch beademde patiënten na electieve cardiochirurgie de hemodynamische effecten gemeten van de toediening van een serie van 10 achtereenvolgende toedieningen van 50 ml colloïde oplossing op CO (Modelflow (COm) en LiDCO (COli)), CVD en MAP. COli en COm namen toe na 50, 100 en 500 ml vloeistoftoediening. Indien COm ≥4.3% toenam na 100 ml proeftoediening dan werd vloeistof responsiviteit (CO > 10% gestegen na 500 ml vloeistoftoediening) met een sensitiviteit van 67% en specificiteit van 100% voorspeld. Toevoeging van COm aan het V&W protocol zou hebben geleid tot een gemiddelde toediening van 100 in plaats van 200 ml vloeistof in non-responders en een toename van 18% in CO bij responders (i.p.v. 7%). De toevoeging van pulscontour-CO zal de betrouwbaarheid en robuustheid van het V&W-protocol verbeteren. Samenvattend: de toevoeging resulteerde in een grotere stijging in CO in responders en een verminderde onnodige vloeistoftoediening bij non-responders.

Hoofdstuk 12

We hebben de mogelijkheid van twee pulscontourtechnieken onderzocht om veranderingen in CO door 30° PLR om vloeistofresponsiviteit te beoordelen in twintig beademde post-cardiochirurgie patiënten. CO werd gemeten met thermodilutie COtd, pulscontourpower

(COli, LiDCO) en pulscontouranalyse (ongekalibreerde modelflow, COm). Verder zijn gemeten: hartslag, CVD, slagaderlijke polsdruk (PP), systolische bloeddruk (SP), diastolische bloeddruk (DP) en MAP. Slagvolume (SV), SP, PP, PPV, SVV werden berekend over vijf ademhalingcycli. SVV werd bepaald met de LiDCO (SVVli) en Modelfowapparaten (SVVm). PLR geïnduceerde veranderingen in COtd correleerden met veranderingen in COli ($p<0.001$) en COm ($p<0.001$). COtd-verandering werd voorspeld met een AUROC van 0.968 door ΔCOm, 0.841 door ΔCOli, 0.825 door SVVm, 0.873 door SVVli, 0.808 door PPV, 0.778 door ΔSP, 0.714 door ΔPP en 0.873 door ΔMAP. Dus: veranderingen in COm, COli, SVV en PPV volgen de veranderingen in COtd gedurende PLR met een hoge graad van nauwkeurigheid in gesedeerde en beademde patiënten na cardiochirurgie. Veranderingen in pulse contour CO na PLR kan worden gebruikt om vloeistofresponsiviteit te voorspellen.

Hoofdstuk 13

Als reactie op de publicaties van Preisman *et al*. hebben wij de herhaalbaarheid onderzocht van een beademingsapparaatmanoeuvre met drukgecontroleerde 1.5 seconde durende ademteugen met toenemende druk. Deze 'Respiratory Systolic Variation Test (RSVT)' hebben wij bovendien geautomatiseerd. In een onafhankelijke groep van 14 patiënten na cardiochirurgie hebben wij de waarde van RSVT om vloeistofresponsiviteit te voorspellen onderzocht. CO, CVD en MAP namen toe na 500 ml colloïdeoplossing was toegediend. PPV- en RSVT-waarden daalden. CO steeg 34% in responders (n=9) en veranderde niet in non-responders (n=5). Een RSVT-drempelwaarde van 0.51 voorspelde FLR in 78% of de patiënten. Voorspellen van FLR met de RSVT lijkt betrouwbaar, herhaalbaar en geautomatiseerd goed uit te voeren.

Discussie

Er is geen goudstandaard voor hemodynamisch beleid. Vloeistofresponsiviteit is een relatieve nieuwe strategie. In het algemeen kan FLR beschreven worden als het effect van cardiac output op een intraveneuze toediening van een bepaalde hoeveelheid vocht. Nog belangrijker is het om dit effect te kunnen voorspellen. Dit betekent dat men responders en non-responders op een vloeistoftoediening van tevoren zou kunnen onderscheiden. Deze strategie heeft als doel onnodige vloeistoftoediening te voorkomen en dientengevolge de kans aan overvulling gerelateerde complicaties en sterfte te verminderen. Tot op heden bestaat er nog geen studie die de gevolgen op een systematische toepassing van FLR in de praktijk op totale vloeistoftoediening of complicaties heeft onderzocht. Meer onderzoek is nodig. Het nog niet gelukt om een praktisch en uitvoerbaar protocol vast te stellen om FLR te voorspellen en als leidraad te dienen voor vloeistofbeleid. Bovendien dient de analyse van FLR studies meer diepte te krijgen. Het bepalen van de AUROC lijkt niet afdoende. Ook

dient de herhaalbaarheid van studieresultaten onderzocht te worden in een controlegroep. Het belangrijkste probleem blijft dat er geen consensus is over de definitie van vloeistofresponsiviteit; de hoeveelheid vloeistof, de samenstelling van de vloeistof, het tijdstip van de metingen, de parameter om responders te definiëren, de techniek om deze parameter te meten en de afkapwaarde voor responders variëren enorm in de literatuur. Wij willen de definitie van vloeistofresponsiviteit definiëren als een klinisch relevante toename in cardiac output (afkap waarde dus gerelateerd aan de nauwkeurigheid van de meetmethode) binnen vijf minuten na een snelle toediening van 5 $ml \cdot kg^{-1}$ van een colloïde (zetmeel) of fysiologische zoutoplossing (crystalloïde).

List of abbreviations

A	Area under the systolic part of the pressure curve
ABF	Aortic blood flow
ARDS	Adult respiratory distress syndrome
AUC	Area under the curve
AVR	Aortic valve replacement
BP	Blood pressure
BSA	Body surface area
C	Velocity of ultra-sound in blood
CABG	Coronary artery bypass grafting
$CaCO_2$	Arterial carbon dioxide content in blood
CaO_2	Oxygen content of arterial blood
CBV	Circulating blood volume
Cc	Computation constant
CCO	Continuous cardiac output
CI	Cardiac index
CO	Cardiac output
CO_2	Carbon dioxide
COed	Cardiac output measured with the Flo-trac Vigileo system
COem	Cardiac output measured with an electromagnetic flow probe
COhs	Cardiac output measured with the hemosonic syste
COm	Cardiac output measured with the modelflow system
COmf	Cardiac output measured with the modelflow system
COpi	Cardiac output measured with the PiCCO system
COPD	Chronic obstructive pulmonary disease
Cosθ	Angle between the direction of the ultra-sound beam and blood flow
COtd	Thermodilution cardiac output
C(P)	Pressure dependent arterial compliance
C(t)	Concentration as a function of time.
CSA	Cross sectional area
$CvCO_2$	Mixed venous carbon dioxide content in blood.
CvO_2	Oxygen content of venous blood
CVP	Central venous pressure
Dia	Diastolic arterial blood pressure
Dobu	Dobutamine
ECG	Electrocardiogram

Enox	Enoximone
$EtCO_2$	End-tidal carbon dioxide
Fd	Change in frequency (i.e. Doppler shift)
FLR	Fluid loading responsiveness
Fo	Transmitted frequency
GEDVI	Global end-diastolic volume index
Hb	Haemoglobin
HR	Heart rate
HUT	Head-up tilt
ICU	Intensive care unit
K	A calibration factor
Khi	Conversion factor
LiCl	Lithium chloride solution
LVEDA	Left ventricular end-diastolic area
LVEDAI	Left ventricular end diastolic area index
MAP	Mean arterial pressure
Mi	Amount of indicator injected
MSFP	Mean systemic filling pressure
MVP	Mitral valve plastique
Nor	Norepinephrine
NPN	Nitroprusside sodium
NVIC	Dutch Society of Intensive Care
NYHA	New York Heart Association
O_2	Oxygen
OR	Operating room
P	Pressure
Pa	Arterial pressure
PAC	Pulmonary artery catheter
$PaCO_2$	Arterial carbon dioxide pressure
PAP	Pulmonary artery pressure
Pao	Aorta pressure
PAOP	Pulmonary artery occlusion pressure
Parm	Arm equilibrium pressure
Paw	Airway pressure
PAWP	Pulmonary artery wedge pressure
PEEP	Positive end-expiratory pressure
PLR	Passive leg raising

	MSFP	Mean systemic filling pressure
	Prad	Radial artery pressure
	PRAM	Pressure recording analytical method
	PP	Pulse pressure
	Ppa	Pulmonary artery pressure
	PPV	Pulse pressure variation
	PPVli	Pulse pressure variation with LiDCO system
	Pra	Radial artery pressure
	Pvent	Ventilator pressure
	Pvr	Pressure difference between MSFP and CVP
	Q(t)	Instantaneous blood flow
	Ra	Arterial resistance
	ROC	Receiver operating curve
	RSVT	Respiratory systolic variation test
	Rsys	Total systemic resistance
	Rv	Venous resistance
	RVEDAI	Right ventricular end diastolic area index
232)	Rvr	Resistance for venous return
	S	A constant
	SA	Left ventricular stroke area
	SD	Standard deviation
	SE	Standard error
	SV	Stroke volume
	SVI	Stroke volume index
	SVR	Systemic vascular resistance
	SVV	Stroke volume variation
	Sys	Systolic arterial blood pressure
	SP	Systolic arterial pressure
	SPV	Systolic pressure variation
	SVVli	Stroke volume variation measured with LiDCO system
	SVVed	Stroke volume variation measured with FloTrac-Vigileo system
	Temp	Body temperature
	T_b	Temperature of blood in the pulmonary artery before injection of injectate
	T_i	Temperature of injectate
	TI	Tricuspid insufficiency
	TOD	Transoesophageal Doppler
	TTD	Transthoracic Doppler

TVP	Tricuspid valve plastique
V	Velocity of blood
VCO_2	Carbon dioxide production
VO_2	Oxygen production
Vt	Tidal volume
V	Arterial volume
V&W	Vincent and Weil
Vload	Amount of fluid administrated
VR	Venous return
V(s)	Stressed vascular volume
V&W	Vincent and Weil
Z	Characteristic impedance

Curriculum vitae

Bart Franciscus Geerts was born on August 29th 1979 in Amsterdam. He attended the dr. Rijk Kramerschool and the Fons Vitae Lyceum in Amsterdam. He obtained his Atheneum high school diploma at the Leeuwenhorst College in Noordwijkerhout in 1997. From 1997 he attended Biomedical Sciences at Leiden University and received his master in 2006. From 1999 he also attended medical school and received his medical degree in 2005. As a student, he worked one year full-time for the board of directors of the Leiden University Medical Centre. He was an advisor to the dean of the medical faculty, prof. dr. Vermeer, on student and educational affairs. He also performed extra-curricular internships at the Catholic Hospital in Battor Ghana and at the department of Health Action in Crises at the World Health Organisation in Geneva Switzerland. In 2011, he was certified in clinical pharmacology after attending a training program and working as a project leader in diabetes research at the Centre for Human Drug Research of prof. dr. Adam Cohen in Leiden. From 2006 to 2011 he performed several studies with dr. Jos Jansen, dr. Rob de Wilde and Jacinta Maas in the department of intensive care in the LUMC and worked on this dissertation. In 2008, he started specialty-training in the department of anaesthesiology of prof. dr. Leon Aarts at the Leiden University Medical Centre.

Dankwoord

Een heleboel mensen ben ik dank verschuldigd voor hun hulp bij het tot stand komen van dit proefschrift. Hierbij wil ik speciaal bedanken en aandacht besteden aan:

Jos Jansen voor de ontelbare uren corrigeren, becommentariëren, reviseren, discussiëren, motiveren en het aandragen van ideeën; kortom de inhoud van dit boekje. Betty Jansen voor het dulden dat haar man ondanks zijn pensioen praktisch fulltime is blijven werken.

Rob de Wilde voor alle hulp en de goede samenwerking. Er zijn weinig mensen die zoveel over hebben voor anderen.

Leon Aarts voor de goede begeleiding, adviezen en het bieden van alle mogelijkheden.

Jacinta Maas, Micheal Pinsky en Johan Groeneveld voor hun medewerking en kritische commentaren.

De maatschap anesthesie van het Rijnland ziekenhuis voor het bieden van tijd om naast klinisch werk aan dit proefschrift te kunnen werken.

Abbott Pharmaceuticals en Philips Healthcare N.V. voor hun financiële steun.

De medewerkers van het secretariaat van de afdelingen intensive care en anesthesiologie; Ingrid van Leijden, Anneke Vuijk, Simone Langezaal-de Groot, Margo Donkers-Jagers en Monique Mauer.

Willem Bisseling voor zijn hulp en adviezen.

Mijn paranimfen Geerten Geerts en Ward van Beers.

Ik wil mijn vader Jo, mijn moeder Frederike en mijn broertjes en zusje danken voor alles. Altijd een thuis, een warm “nest”.

In het bijzonder wil ik mijn verloofde Charlotte danken voor haar liefde. Ik wil haar danken voor haar geloof in mij en mijn kunnen.

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