CHAPTER 1

General introduction
Hemodynamic monitoring and interpretation is a fundamental but difficult task in intensive care medicine. Usually, monitoring is performed with fluid filled catheters such as the pulmonary artery catheter, allowing assessment of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), both of which are assumed to reflect end diastolic pressure and therefore to be reliable guides to fluid therapy. Moreover, cardiac output can be measured via thermodilution. However, the pressures are indirect volume indicators at best, and are influenced by lung compliance and intrathoracic pressures, particularly in ventilated patients. Moreover, because of its invasiveness and inherent risks, the pulmonary artery catheter is met with criticism and, as a consequence, a re-evaluation of the use of the catheter and derived parameters is considered. Based on this background, new monitoring devices and parameters are investigated.

**FIRST PART: TRANSPULMONARY THERMODILUTION.**

The arterial double-indicator thermal dye dilution method was developed in the 1990s by a German company, using a fiberoptic and thermistor-equipped 4-Fr femoral artery catheter. This technique involves the intravascular determination of the dye and the thermal signal (COLD machine z-021, Pulsion Medical Systems, Munich, Germany) after central venous injection. The mean transit time of the dye (detected in the aorta via femoral artery catheter) multiplied by cardiac output yields the intrathoracic blood volume (ITBV), whereas the mean transit time of the thermal signal multiplied by cardiac output yields the intrathoracic thermal volume. The transpulmonary cardiac output is derived from the thermal indicator dilution curve based on the Stewart-Hamilton formula. Combining the ITBV and thermal volume, additional parameters like extravascular lung water (EVLW), global end diastolic volume (GEDV), which represents the sum of volumes in all chambers of the heart at the time of end-diastole can be computed. The ITBV consists of GEDV plus the pulmonary blood volume. However, the COLD method, although enabling bedside assessment of ITBV, GEDV and EVLW, is time consuming and expensive. Sakka et al. and Buhre et al. compared ITBV measured by the double-indicator technique (COLD) with that estimated from GEDV that can be derived from the transpulmonary single-indicator dilution (PiCCO) and found sufficient accuracy of the latter method. The linear relationship between ITBV and GEDV enables the estimation ITBV from GEDV. In addition, the PiCCO device provides continuous cardiac output measurement by pulse contour analyses. Despite its potential, there are some drawbacks of the transpulmonary thermodilution method, inherent of the technique and some questions remain. Indeed, in patients with valvular insufficiencies or intrathoracic pathology cardiac output measurements may be confounded. Moreover, mathematical coupling may contribute to the superiority of volumes over pressures as indicator of preload as...
a consequence of shared measurement error,\textsuperscript{6,7,8} when both cardiac output and cardiac volumes are derived from the same thermodilution curve. Finally, the superiority of volumes may depend on cardiac function.\textsuperscript{9}

Objectives and outline

In the first part of our thesis we aim to clarify some issues associated with the transpulmonary thermodilution technique in assessing cardiac output, preload and fluid responsiveness.

In \textit{chapter 2} we give a summary of the literature of intrathoracic blood volumes determined by transpulmonary thermodilution, in the monitoring of critically ill patients, with respect to assessing volume status and heart function and response to fluids in the treatment of hypovolemia and shock.

In \textit{chapter 3} we describe two patients with intrathoracic pathology in which simultaneous cardiac output measurements were performed by means of the single transpulmonary thermodilution technique and the continuous pulmonary artery thermodilution method. In both cases, the methods revealed clinically significantly different cardiac output values based upon the site of measurement and the underlying pathology.

In \textit{chapter 4} we studied the effect of fluid loading on cardiac output and its relationship with filling pressures and volumes in the early postoperative period following coronary artery bypass surgery. We hypothesized that mathematical coupling of shared measurement error partly accounts for the supposed superiority of volumes over pressures in assessing fluid responsiveness, when cardiac volumes and cardiac output are derived from the same thermodilution curve.

In \textit{chapter 5} we studied the influence of residual valvular insufficiency on transpulmonary thermodilution and continuous pulmonary artery thermodilution cardiac output, in patients after valvular surgery. We hypothesized that the value in predicting and monitoring fluid responses by both techniques would not differ between patients after coronary artery bypass or heart valve surgery.

In \textit{chapter 6} we studied the value of transpulmonary thermodilution derived cardiac volumes and pulmonary artery derived filling pressures in assessing fluid responsiveness in patients after coronary artery and valvular surgery, by virtue of differences in cardiac systolic and/or diastolic function.
In chapter 7 we review the value of volumes and pressures as preload indicators used to predict and monitor fluid responsiveness in critically ill patients. In depth, we describe the goals and effects of fluid loading. Furthermore, the differences between pressure and volume measurements in assessing fluid responsiveness and the influence of mechanical ventilation on these measurements are discussed. In the last part, physiological considerations and clinical implications are described.

SECOND PART: PULSE-CO\-UNTUR

In view of rapid change of hemodynamic status of critically ill patients, continuous monitoring of cardiac output will provide information allowing rapid adjustment of therapy. Moreover, instead of the invasive pulmonary artery catheter (PAC), less invasive techniques are preferred. The estimation of cardiac output based on pulse contour analysis is an indirect method, since cardiac output is not measured directly, as with an electromagnetic flow probe, but is computed from a pressure curve and a model. The origin of the pulse contour method for estimation of beat-to-beat stroke volume goes back to the classic Windkessel model, first described by Otto Frank in 1899. Most pulse contour methods are, explicitly or implicitly based on that model. They relate an arterial pressure or pressure difference to a flow or volume change. The pressure waveform is not obtained from the aorta itself but rather from a peripheral artery (radial or femoral), which requires assumptions to be made regarding the changes in pulse shape between these different locations. The values attributed to model parameters (resistance, compliance and characteristic impedance) are initially estimated according to the patients’ sex and age and from the pressure waveform. They are then refined following a calibration of mean cardiac output using an indicator dilution technique. Nowadays, at least three pulse contour methods are available; PiCCO (Pulsion), PulseCO (LiDCO) and Modelflow (TNO/BMI). All these three pulse contour methods utilize an invasively measured arterial blood pressure and need to be calibrated to increase the accuracy of flow prediction. Recalibrating every 4 hours (or at least before any important data acquisition) may augment the accuracy of pulse contour estimated cardiac output in critically ill patients, who are likely to exhibit frequent changes in vascular tone. PiCCO is calibrated by transpulmonary thermodilution, LiDCO by transpulmonary lithium dilution and Modelflow by the mean of 3 or 4 conventional thermodilution measurements equally spread over the ventilatory cycle. Output of these pulse contour systems is based on calculating stroke volume from the contour of the systolic portion of the arterial pressure waveform and therefore a good waveform is crucial in obtaining accurate data for cardiac output measurements. Several studies have compared cardiac output as measured using thermodilution and pulse contour and fair agreement between values obtained
using the two techniques.\textsuperscript{10,14-16} However, there are some major concerns about pulse contour analysis. First, the aorta's compliance at low distending pressure is substantial but at higher pressures compliance progressively decreases, resisting overstretching of the aortic wall. This ‘non-linear’ behaviour increases with age and prevents any simple approach to pulse contour estimates of stroke volume. To our knowledge, the variables have been taken into account fully when measuring aortic flow by the Modelflow method only.\textsuperscript{17} Second, intra-arterial pressure is measured predominantly with fluid filled catheter-transducer systems. Nevertheless, damped waveforms are a major concern. Therefore, patients with poorly defined arterial waveforms or with arrhythmias are excluded from studies, since pulse contour methods cannot provide reliable results in such conditions. To overcome the issue of (re-) calibration, a new arterial pressure waveform analysis has been introduced (FloTrac\textsuperscript{TM} sensor and Vigileo\textsuperscript{TM} monitor; Edwards Lifesciences, Santa Ana, CA). To work, it just needs an arterial catheter. Compliance and resistance are derived from the analysis of the arterial waveform. The hypothesis is that in order to calculate the effects of compliance and peripheral resistance on flow all the necessary information can be obtained by the analysis of the arterial pressure waveform. Age, weight and sex of the patient are the only information that the clinician needs to insert into the Vigileo\textsuperscript{TM} monitor. The transducer (Flotrac\textsuperscript{TM}) can be connected to whatever arterial catheter. The algorithm recalculates continuously the compliance, thereby bypassing the need of calibration.

Another issue is the influence of controlled positive pressure ventilation on changes in cardiac output due to intermittent changes in preload of the heart. During inspiration the venous return to the right heart decreases thereby lowering preload of the right and seconds later of the left heart. Whereas heart-lung interaction has a negative influence on the measurement of static cardiac filling pressures, since measurements are affected by transmitted airway pressure, this interaction is the basis of the left-sided dynamic indices to predict fluid responsiveness. These left-sided dynamic indices, include stroke volume variations (SVV) and systolic and pulse pressure variations (SPV, PPV), which can be derived from the arterial pressure curve by pulse contour analyses and are evoked by ventilation induced alterations in cardiac loading conditions.\textsuperscript{18-24} The value of dynamic indices thus depends on ventilatory settings and thoracic compliance.\textsuperscript{20,21,24} Increases in positive end-expiratory pressure (PEEP) and tidal volume (Vt), for instance, will result not only in decreased right ventricular preload but also in increased right ventricular afterload and may thereby affect left ventricular loading, stroke volume and arterial pressure variability.\textsuperscript{25}
Objectives and outline

In this part of the thesis we evaluate whether two minimally invasive, non-calibrated pulse contour cardiac output techniques track thermodilution cardiac output changes during altering preload and afterload conditions, in patients after cardiac surgery.

In chapter 8 we examined whether the non-calibrated Modelflow® cardiac output and stroke volume variation, as well as systolic pressure variation and pulse pressure variation track thermodilution cardiac output changes during altered ventilatory settings in mechanical ventilated patients after cardiac surgery. Responses to continuous and cyclic intrathoracic pressures by stepwise increases in positive end-expiratory pressure and tidal volume were compared.

In chapter 9 we evaluated the performance of a new non-invasive pulse contour cardiac output method (FloTrac™/Vigileo™ [FV], Edwards Lifesciences) in patients up to 24 hours after coronary artery surgery and/or valvular surgery.
REFERENCES


