CHAPTER 10

General discussion and Summary
General discussion

Often, the first therapeutic intervention in the intensive care unit is fluid loading. The ultimate goal of fluid resuscitation is the maintenance of adequate oxygen delivery to vital end organs. It is well established that patients with significant impairment of oxygen delivery and oxygen extraction have greater morbidity and mortality. However, fluid loading will cause an increase in interstitial fluid due to cellular injury and extravascular leakage of fluid. Therefore, the cost of aggressive fluid resuscitation is fluid accumulation in the lungs and abdomen with consequently impaired oxygen exchange and abdominal compartment syndrome, respectively, eventually contributing to multi-organ failure and death. Therefore, it is important that overresuscitation is prevented and oxygen delivery and extraction is optimized. Oxygen delivery to cells is determined by several factors including cardiac output, arterial oxygenation and haemoglobin level.

To measure cardiac output, several invasive and less-invasive monitoring devices are available, since vital signs have been shown to be inaccurate markers of tissue perfusion. Particularly in the course after cardiac surgery, optimal monitoring of cardiac preload and output is paramount for precise hemodynamic management. The effects of extracorporeal circulation together with the underlying cardiac pathology are often associated with substantial changes in intravascular volume and hemodynamic status. Maintenance of adequate preload remains the primary target to optimize left ventricular performance and thereby global oxygen delivery.

In this thesis, we outlined the advantages and limitations associated with the different available hemodynamic monitoring systems. In the following table a overview is given of the different devices used in this thesis and their properties and measured variables and gives a framework for choosing among techniques for patient-tailored hemodynamic monitoring in the ICU.
FEATURES OF THE HEMODYNAMIC MONITORING DEVICES USED IN THIS THESIS

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary artery catheter (PAC)</th>
<th>Transpulmonary thermodilution technique + pulse contour technique (PiCCO)</th>
<th>Arterial pressure waved-derived technique (FloTrac/Vigileo and HemoSonic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration of device</td>
<td>-</td>
<td>+</td>
<td>HemoSonic needs calibration FloTrac/Vigileo does not need calibration</td>
</tr>
<tr>
<td>Invasiveness</td>
<td>Invasive</td>
<td>Less invasive</td>
<td>Minimally invasive</td>
</tr>
</tbody>
</table>

### Preload parameters

#### Static

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAC</th>
<th>PiCCO</th>
<th>FloTrac/Vigileo</th>
<th>HemoSonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PAOP</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GEDV</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ITBV</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EVLW</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Dynamic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAC</th>
<th>PiCCO</th>
<th>FloTrac/Vigileo</th>
<th>HemoSonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVV/PPV/SPV</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Afterload parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAC</th>
<th>PiCCO</th>
<th>FloTrac/Vigileo</th>
<th>HemoSonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\text{SvO}_2$</td>
<td>Intermittent or continuous</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\text{ScvO}_2$</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuously with special PreSep® catheter or intermittent with CVC</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac output

<table>
<thead>
<tr>
<th>Method</th>
<th>PAC</th>
<th>PiCCO</th>
<th>FloTrac/Vigileo</th>
<th>HemoSonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus</td>
<td>Continuous</td>
<td>Thermodilution based</td>
<td>Thermodilution based Based on pulse contour analysis</td>
<td>- Based on pulse contour analysis</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Usefulness in the presence of arrhythmias

<table>
<thead>
<tr>
<th>Condition</th>
<th>PAC</th>
<th>PiCCO</th>
<th>FloTrac/Vigileo</th>
<th>HemoSonic</th>
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</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Partly useful</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations:

- CVP: central venous pressure; PAOP: pulmonary artery occlusion pressure; GEDV: global end-diastolic volume; ITBV: intrathoracic blood volume; EVLW: extra vascular lung water; SVV: stroke volume variation; PPV: pulse pressure variation; SPV: systolic pressure variation; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; $\text{SvO}_2$: mixed venous saturation; $\text{ScvO}_2$: central venous oxygen saturation; CVC: central venous catheter.

### CONSIDERATIONS FOR PATIENT-TAILORED HEMODYNAMIC MONITORING.

The PAC can help to guide fluid resuscitation in the critically ill, since the device gives information about right atrial and ventricular preload and afterload (central venous
pressure (CVP), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), right ventricular stroke work), the left ventricular preload and afterload (pulmonary artery occlusion pressure (PAOP), systemic vascular resistance (SVR), cardiac performance by means of the cardiac output (CO) and mixed venous oxygen saturation (SvO2) (Table).

Even so, the catheter can be used in patients with atrial fibrillation or other arrhythmias, which frequently occurs in the critically ill. Another benefit is that CO can be measured continuously, by means of the thermodilution technique, like SvO2, so almost instant information of the patients’ hemodynamic performance is available. For instance, in patients with pulmonary artery hypertension, sepsis or potentially reversible systolic heart failure the PAC can be helpful to guide fluid resuscitation and inotropic or vasodilator support. Since the technique is invasive, adverse events occur. However, according the literature, the most common catheter related adverse event is the occurrence of non-lethal arrhythmias. Nevertheless, the question remains why the use of the PAC, does not decrease morbidity or mortality in the critically ill. Many studies reported no clear benefit by managing critically ill patients with pulmonary artery catheterization.4,5,6,7 Furthermore, prospective clinical trials failed to demonstrate any better outcome with maximizing oxygen consumption by hemodynamic monitoring.8,9 The major criticisms of these studies are that misinterpretation of the hemodynamic data obtained frequently led to inappropriate therapy and no “early goal-directed-therapy” protocols were used. Despite the literature is unanimous about the fact that PAC-guided therapeutic strategies do not benefit mortality or morbidity, less invasive hemodynamic monitoring tools are developed, since intensive care specialists want to monitor hemodynamic effect of fluid resuscitation and other therapeutic interventions in the critically ill and vital signs have shown not to be accurate. The majority of these new techniques are based on arterial pressure waveform analyses or the so called pulse contour techniques with or without the need for calibration. The PiCCO device (Pulsion Medical Systems, Munich, Germany) needs central venous access and the cannulation of a large artery. Manual invasive calibration by transpulmonary thermodilution is required to compensate for interindividual differences in arterial compliance. When calibrating, the transpulmonary thermodilution CO, global end-diastolic volume (GEDV), intrathoracic blood volume (ITBV) and extravascular lung water (EVLW) values become available (Table). In the literature these volume based preload parameters seem to correlate better with CO in response to fluid loading than pressures (CVP and PAOP). Furthermore, EVLW measurements can be helpful to guide fluid resuscitation in preventing or escalating pulmonary oedema, especially in patients with an adult respiratory syndrome. However, no outcome studies are available and most studies are done in patients after coronary artery bypass surgery with a good left ventricular function. In patients with diminished left ventricular function preload pressures seem to predict fluid responsiveness better than changes in volumes (this thesis). Moreover, mathematical coupling between the calibrated CO and
volume based preload parameters is not unlikely (this thesis) and therefore the obtained values should be interpreted with care. After calibration of the device, pulse-contour CO and stroke volume variation (SVV) value, a dynamic preload parameter, are displayed continuously (Table). However, SVV is only useable in fully sedated and ventilated patients, which nowadays is rare in a modern ICU. Even more, both pulse contour CO and SVV are useless in patients with arrhythmias or during IABP counterpulsation, which is also the case in the subsequently discussed Flotrac/Vigileo device (Edwards Lifesciences, Santa Ana, CA, USA).

The newest device on the market is the FloTrac/Vigileo device. It calculates the dynamic preload parameter SVV and continuous CO from arterial pressure waveform characteristics but does not require external calibration. Both CO and SVV are displayed continuously. If CVP is available, by means of a central venous catheter, systemic vascular resistance can be displayed. The device is simple to use, it only needs standard arterial access which is available in every critically ill patient. Studies indicate that the CO values provided by FloTrac/Vigileo show acceptable agreement with intermittent thermodilution. However, the FloTrac/Vigileo has been shown to overestimate CO in the setting of significant aortic regurgitation; like all pulse contour based techniques, it will not function during IABP counterpulsation; and appears to underestimate the CO in high-output, vasodilatory states and thus appears to be vascular tone dependent. Despite this, the FloTrac might be useful as a trending device, especially in spontaneous breathing patients, such as in patients with aneurysmal subarachnoid hemorrhage in which early hemodynamic monitoring for adequate cerebral circulation and for preventing overhydration during triple-H therapy for vasospasm, is important but is often precluded by the invasiveness and complexity of the intermittent thermodilution CO technique. The potential use of the FloTrac/Vigileo for “early goal-directed therapy” defines its niche, perhaps as a device that can assist in preventing gross hemodynamic instability.

Another less invasive hemodynamic arterial-wave based monitoring system, is the non-calibrated and calibrated modified ModelFlow techniques which calculates CO and the dynamic preload parameters SVV, pulse pressure variation (PPV) and systolic pressure variation (SPV) from a computed aortic flow waveform, derived from the radial artery pressure curve. The major limitation of the usefulness of these dynamic preload parameters is that patients must be fully sedated and heart rhythm must be regular. Moreover, the value of dynamic preload indices to predict fluid responsiveness, depend on, among others, ventilatory settings and thoracic compliance. By increasing positive end-expiratory pressure (PEEP), and not tidal volume, biventricular preload decreases and as a result ModelFlow CO falls and appears even more sensitive than a rise in SVV, in tracking a fall in intermittent thermodilution CO (this thesis). This finding underscores
the value of non-calibrated modified ModelFlow and probably other pulse contour
methods to track circulatory changes during changes in ventilatory settings.

The arterial waveform based devices PiCCO, FloTrac/Vigileo and modified ModelFlow
do not provide data about mixed venous saturation (\(S_vO_2\)), although \(S_vO_2\) measurement
is considered “the gold standard of defining global adequacy of cardiovascular perfor-
mance”. An alternative parameter is central venous saturation (\(S_cvO_2\)), which can be
obtained intermittent, by means of an ordinary central venous catheter, or continuous
by means of a special designed central venous catheter (PreSep®, Edwards Life Sciences,
Santa Ana, CA, USA) which can be connected to the Vigileo computer. However, the dif-
fferences between mixed and central venous saturation can vary greatly according to the
pathophysiological status. Clinical trials have demonstrated that \(S_cvO_2\) can consistently
over-estimate \(S_vO_2\) in critically ill patients.\(^{15-17}\)

**CONCLUSION**

There is no uniformly applicable hemodynamic monitoring tool that helps predicting
fluid responsiveness and cardiac output in every critically ill patient. Which hemody-
namic monitoring device to choose in which patient, remains a decision of the treat-
ing physician, who must be aware of the drawbacks and flaws of each of the available
systems.
REFERENCES


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Summary

In this thesis, we explored confounders of measurements by the transpulmonary thermodilution technique, in patients with intrathoracic pathology (chapter 3) or valvular insufficiencies (chapter 5). The possible role of mathematical coupling explaining the superiority of volumes over pressures as indicator of preload and the influence of cardiac function on preload parameters is described in chapter 4 and 6, respectively. Furthermore, we evaluated whether two non-calibrated pulse contour cardiac output techniques track thermodilution cardiac output changes during altering preload and afterload, in patients after cardiac surgery (chapter 8 and 9).

CHAPTER 1

In the critically ill, hemodynamic monitoring is usually performed with a pulmonary artery catheter (PAC), allowing assessment of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), both which are assumed to be reliable guides for fluid therapy. Moreover, cardiac output can be measured via thermodilution. However, CVP and PAOP measurements are influenced by lung compliance and intrathoracic pressures. Moreover, the PAC is invasive with inherent risks. To bypass these flaws, a less invasive technique was developed which is able to measure volumes instead of pressures, not influenced by positive pressure ventilation. However, there are some drawbacks of the transpulmonary thermodilution method, inherent to technique. Indeed, in patients with valvular insufficiencies or intrathoracic pathology, measurements can be confounded. Moreover, the contribution of mathematical coupling to the superiority of volumes over pressures as indicators of preload is unclear, when both cardiac output and cardiac volumes are derived from the same thermodilution curve. These doubts form the basis of the first aim of this thesis: to clarify some issues associated with the transpulmonary thermodilution technique in assessing cardiac output, preload and fluid responsiveness.

In the critically ill both preload and afterload conditions of the heart change over time, due to altered cardiac compliance, volume status, change of inotropic or vasodilator doses and ventilator settings, which will result in CO changes. In the second part of this thesis we evaluate whether two minimally invasive, non-calibrated arterial waveform based techniques, the modified ModelFlow and FloTrac/Vigileo, track these CO changes.
CHAPTER 2

We give a summary of the literature of the role intrathoracic blood volumes determined by transpulmonary thermodilution, in the monitoring of critically ill patients, with respect to assessing volume status, heart function and response to fluids in the treatment of hypovolemia and shock. We concluded that functional hemodynamic monitoring of intrathoracic volumes with double or single indicator dilution is a useful tool to assess preload and fluid responsiveness in critically ill patients. However, the effect of volumetric (rather than pressure) monitoring on morbidity and mortality of critically ill patients is lacking, although the method is less invasive compared to the PAC.

CHAPTER 3

We describe two patients, one with severe haemorrhage and one with a partial anomalous pulmonary vein in which cardiac output measurements were performed simultaneously by means of the single-indicator transpulmonary thermodilution technique and continuous pulmonary artery thermodilution method. In both cases, the methods revealed clinically significant different cardiac output values based upon the site of measurement and the underlying pathology. In the first patient with excessive blood loss, cold indicator could be lost due to the accumulation of blood in the thorax. Vliers et al.\(^1\) demonstrated the leave and re-entrance of indicator from the vascular bed into the lungs by recording the intrabronchial air temperature changes during the passage of the cold indicator through the pulmonary vascular bed. This will lead to a reduction and distorted thermodilution curve, resulting in overestimation of the cardiac output. However, in the second patient a persistent anomaly was present. In this patient, both techniques, for cardiac output measurement, seem to measure the real-time cardiac output of, respectively, the left and right ventricle, since the amount of blood passing the thermistor of the pulmonary artery catheter is the sum of the shunt flow and of the vena cava inferior and superior flow.

CHAPTER 4

This study investigated the role of mathematical coupling of shared measurement error when cardiac volumes and cardiac output are obtained from the same thermodilution curve. Eleven consecutive and mechanical ventilated patients with hypovolemia after coronary artery surgery and a pulmonary artery catheter in place, allowing continuous cardiac index (CCIp) measurements, received a femoral artery catheter for transpulmo-
Summary

nary thermodilution measurements (PiCCO™, Cltp). A total 48 fluid loading steps of 250 mL were done. We found that central venous pressure and volumes equally related to Cltp and CClp and that fluid responses were predicted and monitored similarly by Cltp and CClp. However, during fluid loading, changes in volumes related better to changes in Cltp when derived from the same curve than to changes in Cltp of an unrelated curve or changes in CClp. These data suggest that the superiority of volumes as indicator of fluid responsiveness over filling pressures can be caused, at least in part, by mathematical coupling of shared measurement error when cardiac volumes and output are derived from the same thermodilution curve.

CHAPTER 5

This study investigated whether residual left-sided valvular insufficiencies after valvular surgery confound transpulmonary thermodilution cardiac output (COtp) technique. We compared the technique with the continuous right-sided thermodilution technique (CCO) after valvular and coronary artery surgery. After valvular surgery, there was minimal aortic insufficiency in 4 patients and minimal to moderate mitral valve insufficiency in 6. 5 Fluid loading steps (250 mL) were done in each patient. We found a lower cardiac output after valvular than coronary artery surgery but responses to fluid loading steps were similar among surgery types and techniques. We also found that after valvular and coronary artery surgery, cardiac output was lower prior to responses than in non-responses to fluids, by either technique. After valvular surgery, COtp and CCO correlated but fluid-induced changes did not. After coronary artery surgery, COtp and CCO correlated and changes also did. At fluid-induced CCO increases <20%, the r for changes in cardiac output measured by both techniques was similar after valvular and coronary artery surgery. These data imply that COtp and CCO are of similar value in predicting and monitoring fluid responses after both surgery types, therefore arguing against left-sided valvular insufficiencies, severely confounding COtp.

CHAPTER 6

In this chapter we compared the value of cardiac filling pressures and volumes in patients after valvular (VS) and coronary artery surgery (CAS) patients, since cardiac function may differ after both types of surgery and therefore may effect assessment of fluid responsiveness. Eight patients after VS and 8 after CAS were included. In each patient, five sequential fluid loading steps of 250 mL of colloid were done. Fluid responsiveness was defined by a cardiac index (CI) increase >5% or ≥10% per step. We found a lower global
ejection fraction and a higher pulmonary artery pressure (PAOP) after VS compared to CAS. In responding steps after VS, PAOP and volumes increased, while central venous pressure (CVP) and volumes increased in responding steps after CAS. After VS, baseline PAOP as well as changes in PAOP and volumes were of predictive value and PAOP and volume changes equally correlated to CI changes. After CAS, CVP and volumes were of predictive value and changes in CVP and volumes correlated to those in CI. These data suggests an effect of systolic cardiac function on optimal parameters of fluid responsiveness and superiority of the pulmonary artery catheter over transpulmonary dilution for hemodynamic monitoring of VS patients.

CHAPTER 7

In this chapter we summarize the physiology of static indicators used to predict and monitor preload responsiveness in critically ill patients on mechanical ventilation. First, we explain the definitions preload and fluid responsiveness used in the literature. Secondly, we discuss filling pressures and volumes of the heart and the influence of positive pressure mechanical ventilation on both measurements. In the last part, we describe the influence of contractility and afterload of the heart on the cardiac function curve relating cardiac output to end-diastolic filling pressure. We also explain the relative predictive value of volumes versus pressures for changes in cardiac output, depending on the position on the compliance curve and the position and shape of this curve. Furthermore, we illustrate the clinical implications of these physiological considerations. We concluded that the relative predictive value of static filling pressures and volumes for the cardiac output response to preload changes depends on biventricular systolic and diastolic function. Overall, this implies that both pressures and volumes may be needed to predict and monitor fluid responses. However, the ultimate guide to fluid therapy may be frequently intermittent or continuous cardiac output monitoring to prevent fluid overloading by discontinuing fluid infusion when cardiac output does not further increase.

CHAPTER 8

This chapter reports on our prospective study to investigate whether changes in less invasive, non-calibrated pulse-contour cardiac output (by modified ModelFlow, COmf) and derived stroke volume variation (SVV), as well as systolic and pulse pressure variations predict changes in bolus thermodilution cardiac output (COtd), induced by continuous and cyclic increases in intrathoracic pressures by increases in positive
end-expiratory pressure (PEEP) and tidal volume (Vt), respectively. We found that SVV increased at PEEP 10cmH₂O and 15 cmH₂O, concomitantly with a decrease in COmf and COtd. In contrast, systolic and pulse pressure variation did not increase. We also found that changes in COmf correlated with those in COtd, whereas changes in SVV did not. Remarkably, variables did not change when Vt was increased up to 50%. Thus, in mechanically ventilated patients after cardiac surgery, during continuous increases in intrathoracic pressure, tracking a fall in COtd by COmf is more sensitive than a rise in SVV, which is more sensitive than systolic pressure variation and pulse pressure variation. These result suggest that PEEP causes a reduction in biventricular preload and is the main factor in decreasing cardiac output and increasing SVV.

CHAPTER 9

In this prospective study we investigated whether cardiac output and its postoperative course by a new non-invasive pulse-contour technique of radial artery pressure waves, without need for calibration (FloTrac™/Vigileo™ [FV], Edwards Lifesciences) conforms with the standard bolus thermodilution method via a pulmonary artery catheter. Fifty-six simultaneous measurement sets were obtained, in 20 patients up to 24 h after cardiac surgery. We found that cardiac output measured by the non-invasive pulse-contour FV method reasonably well compares to that measured by bolus thermodilution via pulmonary artery catheter, in cardiac surgery patients, over a relatively wide range of cardiac output. Moreover, for clinical purposes the concordance of detected changes in cardiac output over time was satisfactory. Thus, the FV pulse-contour method is a clinically applicable non-invasive pulse-contour method for cardiac output assessment without the need for calibration, after cardiac surgery.
REFERENCES