Dynamic haemodynamics
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Chapter 13

Summary and general discussion

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Summary
The focal point of this thesis centres around three main elements of dynamic haemodynamics: fluid responsiveness, ventilator-induced dynamic parameters and ventilator-induced myocardial dysfunction (VIMD). Haemodynamically unstable mechanically ventilated patients are often initially treated with fluid administration. Although rapid fluid loading can serve as an important part of the resuscitation bundle, one must realise that both insufficient as well as overzealous fluid administration increases morbidity and mortality. To make matters worse, a positive response to fluid administration termed fluid responsiveness is hard to predict as it equals a coin flip in critically ill patients. Therefore, a thorough understanding of the underlying physiological principles is of the utmost importance for correct prediction of fluid responsiveness. The remarkable absence of a formal definition of fluid responsiveness further hampered the ultimate goal of patient-tailored volume titration and needed to be resolved. While ventilator-induced dynamic parameters can be helpful in assessing fluid responsiveness when certain requirements are met, their reliability during changes in arterial compliance and positive end-expiratory pressure remained unknown. Moreover, mechanical ventilation by itself might negatively affect myocardial function, fuelling the search for alternative ways to assess fluid responsiveness. Several more recent methods such as passive leg raising and the mini-fluid challenge circumvent the necessity of mechanical ventilation, yet their reliability in predicting fluid responsiveness needed to be established. All these topics on the three elements of dynamic haemodynamics were investigated and described in the following chapters divided in four parts covering physiological principles, experimental studies, clinical studies and future perspectives.

Part I  Physiological principles

Chapter 2 provides a review of the complex physiology of cardiopulmonary interactions in the critically ill during spontaneous breathing and mechanical ventilation. An important difference concerns the intrathoracic pressure, being negative with spontaneous breathing and predominantly positive with mechanical ventilation. The positive intrathoracic pressure reduces right ventricular preload while
the applied positive airway pressure has the potential to increase right ventricular afterload as can be depicted from Figure 2.5. These changes in right ventricular loading conditions serve as the main determinants of the subsequent decrease in cardiac output frequently observed during mechanical ventilation, leading to the belief that effects of mechanical ventilation on left ventricular function are mostly secondary. However, it remains crucial for clinical decision-making to reveal whether the haemodynamic compromise is driven by preload, afterload and/or ventricular dysfunction. Using low tidal volume ventilation may reduce intrathoracic pressures and the need to apply high inspiratory airway pressures potentially ameliorating ventilator-induced haemodynamic compromise, while the effect on myocardial function needs to be further elucidated.

In Chapter 3 we present the potential of fluid responsiveness to enable tailor-made fluid titration in the treatment of haemodynamically unstable critically ill patients. Although the cornerstone of resuscitation is often considered to be fluid administration, assessing one’s volume status can be challenging especially when realising that both too little and too much fluid loading can be deleterious. The relation between the venous return curve and the cardiac function curve, graphically illustrated by Guyton, improves our understanding of the fluid responsiveness concept. It is instrumental to imagine a patient’s position on the combined curve to assess whether an increase in cardiac output is to be expected from fluid loading (Figure 3.3). Furthermore, the curve offers an explanation for the observed superiority of ventilator-induced dynamic parameters, namely stroke volume variation and pulse pressure variation, in predicting fluid responsiveness compared to static parameters such as central venous pressure (Table 3.1). However, the clinical use of ventilator-induced dynamic parameters are limited by several requirements including controlled mechanical ventilation with tidal volumes > 8 ml/kg as well as a regular heart rhythm. Unsurprisingly, these conditions are seldom encountered on the Intensive Care Unit. Passive leg raising could serve as an attractive alternative to predict fluid responsiveness at the bedside in a broad population of critically ill patients creating a temporary increase in biventricular preload. The subsequent effect on cardiac output is preferably tracked continuously to allow the evalu-
iation of repeated fluid administrations facilitating patient-tailored volume titration.

**Part II  Experimental studies**

**Chapter 4** describes the relationship between centrally measured stroke volume variation and peripherally derived pulse pressure variation during increased arterial compliance in the setting of normovolaemia and hypovolaemia. To induce a change in arterial compliance, rats were randomised to receive nebulised lipopolysaccharide or saline. To create a hypovolaemic state, a balloon positioned in the inferior vena cava was inflated for a maximum of 30 seconds. Stroke volume was measured directly in the left ventricle using an intraventricular conductance catheter, while pulse pressure was derived from the carotid artery. Stroke volume variation and pulse pressure variation were calculated over three controlled mechanical ventilator cycles. The rats subjected to lipopolysaccharide demonstrated increased arterial compliance calculated by stroke volume divided by pulse pressure. All rats showed increased stroke volume variation and pulse pressure variation upon balloon inflation suggestive of hypovolaemia. Although stroke volume variation and pulse pressure variation were correlated during normovolaemia and hypovolaemia in untreated rats, there were no such correlations during increased arterial compliance. The data from this experimental animal model suggest that pulse pressure variation may not be used as an indicator of stroke volume variation in the setting of a changed arterial tone such as in sepsis.

In **Chapter 5** we used a two-hit animal model to investigate if high tidal volume ventilation causes left ventricular dysfunction and whether this is augmented during acute lung injury. Rats were randomised to two ventilation strategies: a low tidal volume strategy using a tidal volume size of 6 ml/kg vs. a high tidal volume strategy with tidal volumes of 19 ml/kg. Acute lung injury was created through the administration of intrapulmonary lipopolysaccharide. Left ventricular systolic and diastolic function were assessed by pressure-volume loops obtained within seconds following vena cava occlusion to acquire parameters which are relatively load-independent. Left ventricular function, both systolic as diastolic, decreased during
acute lung injury and high tidal volume ventilation. The combination of high tidal volume ventilation plus lipopolysaccharide aggravated left ventricular dysfunction probably contributing to the death of all rats in this group, while all rats in the other groups survived till the end of the experiment. The data supports the existence of VIMD, in particular in the setting of acute lung injury. Low tidal volume ventilation has the potential to ameliorate left ventricular dysfunction, yet needs to be confirmed in clinical studies.

Part III Clinical studies

Chapter 6 attempts to validate the experimental findings of Chapter 5 in critically ill patients investigating whether low tidal volumes are protective against VIMD compared to high tidal volumes. Since a mechanical ventilator strategy incorporating low tidal volumes is already considered standard care in patients with the acute respiratory distress syndrome (ARDS), myocardial function was assessed in non-ARDS patients ventilated > 24 hours in the Intensive Care Unit. Left and right systolic and diastolic parameters were measured using transthoracic echocardiography in 42 patients. The myocardial performance index was chosen as primary parameter for myocardial function as it combines systolic and diastolic function. Patients subjected to high tidal volumes averaging 9.5 ml/kg demonstrated decreased left and right myocardial function compared to patients following a low tidal volume strategy with a mean tidal volume size of 6.5 ml/kg. Systolic parameters were higher in the group receiving low tidal volumes, but no difference in diastolic parameters was observed between both groups. This clinical study advocates the use of low tidal volumes to reduce systolic VIMD in patients without ARDS.

In Chapter 7 we examined whether right ventricular stroke volume variation is affected by positive end-expiratory pressure (PEEP) in controlled mechanically ventilated patients. Stroke volume variation was obtained through thermodilution using a pulmonary artery catheter with a rapid-response thermistor during different levels of PEEP. Right ventricular stroke volume variation and the coefficient of variation of all other thermodilution-derived parameters remained unaltered upon PEEP changes. This may be explained by cyclic counteracting changes in preload and afterload during the ventilatory cycle.
independent of PEEP. The unchanged variation in right ventricular stroke volume implies that the policies regarding the number and timing of pulmonary artery catheter measurements remain unaltered with changing PEEP. This is clinically relevant since thermodilution is still commonly used as the gold standard for cardiac output measurements.

Chapter 8 presents a prospective clinical study investigating whether a mini-fluid challenge can be used as a predictor of fluid responsiveness in postoperative cardiac surgery patients. Since the volume that is minimally required is dependent on the measurement technique of the subsequent change in cardiac output, we compared two different pulse contour analysis methods: the un-calibrated modified Modelflow® and calibrated PulseCO®. Patients received 500 ml of fluids, albeit in 10 consecutive fluid boluses of 50 ml with cardiac output measurements following each bolus. The Modelflow® could correctly predict fluid responsiveness following a mini-fluid challenge of 150 ml, while the PulseCO® required 50 ml more. This data shows that the mini-fluid challenge can reliably predict fluid responsiveness assessed by pulse contour analysis, reducing unnecessary fluid loading.

In Chapter 9 we explored whether the ventilator-induced dynamic parameter central venous pressure variation (CVPV) could predict fluid responsiveness in contrast to the static parameter central venous pressure, yet similar to the other ventilator-induced dynamic parameters stroke volume variation and pulse pressure variation. Therefore, the study was performed in postoperative patients subjected to controlled mechanical ventilation with tidal volumes of 8-10 ml/kg without cardiac arrhythmia to fulfil the requirements for dynamic parameters to predict fluid responsiveness. CVPV was obtained from a central venous catheter calculated as $100 \times \frac{(CVP_{max} - CVP_{min})}{[(CVP_{max} + CVP_{min}) / 2]}$. Stroke volume variation and pulse pressure variation were measured using the modified Modelflow®. Most patients were fluid responders, in whom CVPV decreased upon fluid loading in contrast to non-responders. CVPV was correlated with the change in cardiac output in contrast to central venous pressure. Moreover, CVPV could identify all fluid responders and non-responders correctly at a cut-off value of 12% with no difference in the area under the receiver
operating characteristic curve (AUROC) compared to stroke volume variation and pulse pressure variation. So despite the fact that central venous pressure is generally useless to determine fluid responsiveness, detailed analysis of the variation in central venous pressure induced by mechanical ventilation can be useful serving this purpose.

**Part IV  Future perspectives**

**Chapter 10** focused on a novel definition of fluid responsiveness as a generally excepted definition was still lacking. Through a comprehensive literature search the different amounts, timing and type of fluids were reviewed as well as the best physiological parameter and measurement technique. This resulted in the following definition of fluid responsiveness: “an improvement in a physiological parameter preferably cardiac output within 15 minutes superseding twice the error of the measuring technique following a 15-minute administration of 6 ml/kg crystalloids”.

In **Chapter 11** we performed a meta-analysis to ascertain whether passive leg raising can be used in future clinical protocols to reliably assess fluid responsiveness in different clinical settings and patient groups. Although passive leg raising creates an increase in venous return, the amount of recruited volume may vary in various clinical settings. Moreover, the preferred measurement techniques and outcome parameters upon passive leg raising were systematically reviewed. Twenty-three clinical trials were analysed combining 1013 patients resulting in a pooled sensitivity of 86%, specificity of 92%, and summary AUROC of 0.95. Different modes of ventilation, type of fluids, or measurement techniques did not affect the diagnostic performance of passive leg raising. A passive leg raising-induced change in pulse pressure as outcome parameter demonstrated a lower diagnostic performance compared to a change in a flow parameter such as cardiac output. This meta-analysis provides proof that passive leg raising can be used as a substitute of the classic fluid challenge to predict fluid responsiveness in various clinical settings. Nonetheless, the effect of passive leg raising needs to be determined by a rapid and direct assessment of cardiac output or its derivative.
Finally, in **Chapter 12** we extend our research on VIMD to a patient with severe ARDS in whom low tidal volume ventilation was not achievable due to respiratory acidosis. Additionally, marked right ventricular dysfunction and haemodynamic instability was present. An extracorporeal lung assist device primarily eliminating carbon dioxide was initiated enabling a reduction in applied tidal volume. A marked improvement of right ventricular function with restoration of haemodynamic stability was noted during simultaneous improvement in oxygenation, decarboxylation and acidosis. This case report shows that the recent emergence of extracorporeal lung assist devices in the Intensive Care Unit may facilitate a low tidal volume strategy potentially protecting against the development and/or progression of VIMD.

**General discussion**

The results of the studies presented in this thesis demonstrate the clinical importance of dynamic haemodynamics. However, it is imperative to have a thorough understanding of the underlying physiological principles (**Chapter 2 and 3**). One famous example of misinterpretation of dynamic haemodynamics is embedded in the term pulsus paradoxus. Normal inhalation can account for a decrease up to 10 mmHg in systolic blood pressure, so the inspiratory decline in systolic blood pressure of more than 10 mmHg observed in pulsus paradoxus is hardly ‘paradox’ and can better be described as an exaggeration of ordinary cardiopulmonary interaction. Kussmaul should not be faulted for this rather innocent erroneous terminology as he described this phenomenon almost 150 years ago. On the other hand, the unwarranted and potentially deleterious use of central venous pressure to guide fluid titration has persisted over the last 50 years, retaining recommendation in current international guidelines. From the combined venous return curve / cardiac function curve shown in **Figure 3.3**, it can easily be depicted that a given central venous pressure cannot predict fluid responsiveness. Furthermore, the figure explains that unwarranted fluid loading not only fails to generate a significant increase in cardiac output, but may cause a sharp increase in cardiac filling pressures instead. It is therefore of no surprise that both insufficient as overzealous fluid loading has the propensity to
increase morbidity and mortality (Figure 13.1). In two recent meta-analyses, Marik et al. has convincingly demonstrated that central venous pressure barely beats a coin flip in various clinical settings (Table 10.1). Interestingly, the one study describing the usefulness of central venous pressure to predict the volume status was performed in a haemorrhagic model of standing horses. Left ventricular end-diastolic area has been viewed as a superior marker of left ventricular preload compared to central venous pressure and its assessment using echocardiography is increasingly employed in the peri-operative setting. Nevertheless, left ventricular end-diastolic area does not establish a patient’s position on the combined venous return / cardiac function curve either and is therefore not able to reliably predict fluid responsiveness (Table 3.1), rather similar to the global end-diastolic volume index obtained by transpulmonary thermodilution. Even baseline cardiac output, generally regarded as the ultimate physiological parameter, demonstrates only a moderate diagnostic performance to predict fluid responsiveness. We must conclude that static haemodynamic parameters cannot lead to a proper prediction since a single value simply does not discriminate a patient’s position on the curve. Ideally, multiple cardiac output measurements are obtained during changes in preload for this purpose.

Mechanical ventilation can cause cyclic impediment of biventricular preload and can thus serve as a vehicle to predict fluid responsiveness. Indeed, ventilator-induced changes in stroke volume and pulse pressure have shown the capability to predict fluid responsiveness, confirmed by another meta-analysis of Marik et al. The predictive value of these ventilator-induced dynamic parameters largely depend on a predictable and sufficient change in preload to assess the patient’s location on the curve. This explains the numerous requirements such as a regular heart rhythm and controlled mechanical ventilation with tidal volumes > 8 ml/kg severely limiting the use of ventilator-induced dynamic parameters in the Intensive Care Unit. Nevertheless, these conditions are more often present in the operating room enabling the clinical applicability of ventilator-induced central venous pressure variation to predict fluid responsiveness described in Chapter 9.
stroke volume variation in the setting of changing arterial compliance ([Chapter 4]) frequently encountered in the operating room, for example upon the use of anaesthetics. This observation further emphasised the need for a more clear statement on the preferred outcome parameter ([Chapter 10]).

Although our proposed gold standard for fluid responsiveness consists of the administration of fluids, a random fluid challenge has generally a 50/50 chance to unveil a fluid responder.17,23 This generates a paradox, in which half of patients will receive potentially deleterious fluid loading to determine their fluid responsiveness. The mini-fluid challenge can serve as an alternative method minimising the amount of fluid necessary to predict fluid responsiveness ([Chapter 8]). A reversible fluid challenge would be ideal, which can be accomplished at the bedside through passive leg raising. Our meta-analysis shows that passive leg raising retains a high diagnostic performance in various patient groups ([Chapter 11]). This holds true for certain clinical settings in which patients breath spontaneously, where ventilator-induced dynamic parameters cannot be used. Moreover, even in the setting of controlled mechanical ventilation with tidal volumes > 8 ml/kg enabling the use of ventilator-induced dynamic parameters, one should realise that high tidal volume ventilation carries the risk of inducing VIMD ([Chapter 5, 6 and 12]). Mechanical ventilation with high tidal volumes had already demonstrated the potential to contribute to lung injury,28,29 previously regarded as the primary explanation for the observed increased morbidity and mortality in ARDS patients.30 Recent experimental studies have shown the release of inflammatory mediators upon high tidal volume ventilation resulting in extrapulmonary injury as well,31,32 probably contributing to the aforementioned decline in survival. We observed that the development of VIMD correlates with tidal volume size, while the effect is magnified in the setting of acute lung injury. This may explain the absence of diastolic VIMD in the non-ARDS patients ventilated with a high tidal volume strategy of 9.5 ml/kg in [Chapter 6], in contrast to the acute lung injury model with tidal volumes of 19 ml/kg in [Chapter 5]. Low tidal volume ventilation is thus an important component of a lung protective strategy, with growing evidence for a proverbial “the lower, the better” approach,33,34 potentially further mitigating VIMD as well. Although a lung protective ventilation strategy is now considered standard care
in ARDS patients,\textsuperscript{35} as it has confirmed to improve survival,\textsuperscript{36,37} this is not always attained in the real world.\textsuperscript{33,38} Novel technologies such as extracorporeal lung assist devices may help to achieve ‘supra-low’ tidal volume ventilation in this patient group to reduce additional lung injury.\textsuperscript{39,40} We demonstrate that an extracorporeal lung assist device enabling the application of these very low volumes has the potential to decrease VIMD as well (\textbf{Chapter 12}).

\textbf{Future research}

The research performed in this thesis demonstrates the relative merits of dynamic haemodynamics to assist clinicians caring for critically ill patients in their decision whether or not to administer fluids. However, robust randomised controlled trials using a valid fluid responsiveness protocol in the Intensive Care Unit are regrettably still lacking. Furthermore, no studies have been done to investigate whether fluid responsiveness can aid in ‘deresuscitation’: accomplishing a negative fluid balance while preserving adequate perfusion. These strategies need to be tested in sufficiently powered trials to investigate their impact on hard clinical endpoints.

\textbf{Conclusion}

“To fill or not to fill”, that is the question this thesis has primarily aimed to answer. Although ventilator-induced dynamic parameters may be helpful in this assessment, the required high tidal volumes carry the risk of inducing myocardial dysfunction. Several alternative methods to assess fluid responsiveness are available to accomplish the ultimate goal of tailor-made fluid titration in critically ill patients.
References


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