Summarizing Discussion and Future Perspectives
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Summarizing Discussion

In this thesis, the reliability of minimally invasive monitoring in patients under general anesthesia was investigated. The main approach was to compare the agreement of “less” invasively derived variables with established, “more” invasively derived counterparts.

In the first part of this thesis, the focus was at the monitoring of the three traditional modalities of hemodynamics, being blood pressure, blood flow and blood volume and at the noninvasive monitoring of hemoglobin concentration.

In the second part of this thesis, the focus was at organ specific monitoring, i.e. the adequacy of assessing liver function in a minimally invasive manner using ICG elimination.

The Introduction section provides a summary of relevant cardiovascular physiology: the regulation of cardiac output, as well as the physiologic background and importance of (the determination of) fluid responsiveness, are discussed.

Furthermore, an outline and the clinical importance of basic, pressure-based hemodynamic monitoring and advanced, flow-based hemodynamic monitoring is presented. Also, the assessment and distribution of blood volume is described and discussed, as well as the noninvasive measurement of hemoglobin concentration and the minimally invasive assessment of liver function.

In Chapter 1, the agreement of volume clamp-derived continuous noninvasive measurement of mean arterial blood pressure (MAP\textsubscript{cNIBP}) with the gold standard (invasively derived mean arterial blood pressure; MAP\textsubscript{invasive}) is investigated and compared with that of the current clinical standard, intermittent noninvasive measurement of arterial blood pressure (MAP\textsubscript{iNIBP}). While many studies in which MAP\textsubscript{cNIBP} accuracy and precision were investigated previously\cite{1,2} solely focused on the comparison with the gold standard MAP\textsubscript{invasive}, we investigated whether MAP\textsubscript{cNIBP} and MAP\textsubscript{iNIBP} can be used interchangeably as the latter is the current clinical standard. We found MAP\textsubscript{cNIBP} to be non-inferior to MAP\textsubscript{iNIBP} when comparing both with the gold standard. Importantly, the investigation was performed in patients under general anesthesia at random moments during surgery in a hemodynamically stable phase. Therefore, the observed non-inferiority is applicable only to these circumstances but the obvious advantage is that continuous beat-to-beat monitoring of MAP could provide a faster identification of hemodynamic fluctuations, such as changes in arterial blood pressure during induction of anesthesia\cite{3}, or during short but hemodynamically challenging procedures like electroconvulsion therapy.\cite{4} Interestingly, both MAP\textsubscript{cNIBP} and MAP\textsubscript{iNIBP} failed to meet two different internationally standardized criteria set for the validation of blood pressure measurement devices.\cite{5,6} Although both these criteria are not specifically designed for the validation of continuous measurement methods, they do support the suggestion that the observed agreement of MAP\textsubscript{cNIBP} with MAP\textsubscript{invasive} was insufficient and that these two methods cannot be used interchangeably, a finding that is supported by other studies.\cite{3,7} Future studies should evaluate the influence of hemodynamic alterations and other factors such as the use of vasopressors, on the accuracy and precision of MAP\textsubscript{cNIBP}.

In chapter 2, we demonstrated in patients undergoing extensive liver surgery that the ability to predict fluid responsiveness using noninvasive, plethysmographic waveform derived dynamic preload variables, is comparable with that of invasive, arterial pressure waveform based dynamic
preload variables. For this comparison, almost all commonly available arterial pressure-based dynamic variables were studied: PPV and SVV, as well as systolic pressure variation (SPV). For the plethysmographic-derived variables, we investigated the “plethysmographic variability index” (PVI), which is calculated using a proprietary algorithm as the variation of the ratio between pulsatile and non-pulsatile blood flow over multiple respiratory cycles. Also, the variations in peak and pulse amplitude of the plethysmographic waveform, which were calculated using an own automated algorithm, were included in the analysis. Interestingly, no significant differences were found between any of the investigated arterial-pressure and plethysmographic-waveform based dynamic preload variables. To some extent, this observation might partly be caused by the relatively limited number of patients studied (n=30). Nevertheless, this finding does suggest that it is clinically not relevant which of the available dynamic preload variables is used to guide fluid management, as long as it is measured using any form of an automated algorithm, as clinical assessment using the scope of the anesthesia monitor is regarded inaccurate.8

The requirement of an arterial catheter – together with other limitations – has been shown to allow the use of dynamic preload variables in only 30% of surgical procedures.9 Though, the availability of noninvasively derivable dynamic preload variables extends both the potential use of these variables to patients only monitored noninvasively and reduces the need for arterial catheter placement.

In addition, the more recent development of the volume-clamp method (see above), also allows the calculation of both PPV and SVV in a completely noninvasive fashion with comparable adequacy for predicting fluid responsiveness to its semi-invasively derived counterparts.10

In chapter 3, we demonstrated that the ability to predict fluid responsiveness by noninvasively determined PPV and SVV, increases for higher thresholds for the definition of fluid responsiveness. In addition, the performed “grey zone analysis”11,12 allowed the calculation of a range of values of either PPV or SVV, which would give an inconclusive result regarding fluid responsiveness. This analysis showed that grey zones were smaller for higher thresholds values with a concomitantly smaller proportion of patients with PPV or SVV values within this inconclusive zone.

The observation that higher thresholds yield a better prediction, can firstly be explained by the fact that, for example when spontaneous physiologic variation causes an increase in stroke volume, lower threshold values will false positively identify such a patient as a fluid responder. Secondly, the ability to correctly identify fluid responders (“specificity”) will increase for higher thresholds, making that the findings are partly mathematically-dependent. Nevertheless, both factors are independent of the type of dynamic preload variable (e.g. PPV, SVV) and will therefore be applicable to all available dynamic preload variables.

The definition of fluid responsiveness largely determines the actual results. It is important to keep this in mind in the individual patient: e.g. administering fluid in a patient at risk of cardiac decompensation, requires the clinician to be absolutely sure that no inadvertent excessive fluid is administered, and requires a high specificity. The contrary is true for a patient in whom hypovolemia would be more deleterious, i.e. the clinician requires assurance that not administering fluid was appropriate. Therefore, these findings can directly be translated to clinical practice, especially if clinical decision-making algorithms regarding the definition of fluid responsiveness are to be made, as the definition of fluid responsiveness should be selected on the patient-category or co-morbidity.

While reliable in a controlled setting, the ability of dynamic preload variables in predicting fluid responsiveness can be substantially reduced under ‘routine’ clinical circumstances.13 Importantly,
the investigations in chapter 2 and 3 were also performed under more or less 'routine' clinical circumstances, which might explain why others found an even better ability to predict fluid responsiveness by dynamic preload variables under more strict study conditions. During volume-controlled positive pressure mechanical ventilation, inspiration induces an increase in intrathoracic pressure, which in turn decreases venous return. The result is a temporary reduction in stroke volume. In the expiration phase, the reduction of the intrathoracic pressure allows venous return to increase, with a resulting temporary increase in stroke volume. In preload-independent patients, this variation will lead to little alterations of stroke volume. The opposite is true for preload-dependent patients. As the above mentioned interaction between the heart and the lungs forms the basis of the calculation of dynamic preload variables, factors that influence the heart-lung interaction can reduce the applicability of dynamic preload variables. The factors limiting the applicability of dynamic preload variables in predicting fluid responsiveness can be divided in 1) factors inducing alterations of stroke volume other than preload-dependency and 2) factors that alter (the interpretation of) fluid responsiveness.

Regarding the first point: if a patient was not mechanically ventilated in a volume controlled mode, alteration in intrathoracic pressure would occur due to changes in tidal volume, which invalidates dynamic preload variables. The same is true for spontaneous breathing. Other well-known factors that have been identified are the presence of an open thorax (no generation of changes in intrathoracic pressure), mechanical ventilation with insufficient tidal volumes (i.e. 8ml kg⁻¹; too little generation of intrathoracic pressure differences and cardiac arrhythmia (spontaneous variations in stroke volume).

Regarding the second point: some factors have been identified that render a patient, who is actually not in need of fluid, to become a “fluid responder”. For example, in chapter 2, fluid responsiveness was investigated after completion of hepatic parenchymal transection but still, surgical manipulation of the inferior caval vein in some patients might have caused temporary alteration in venous return, which might incorrectly suggest fluid responsiveness. Though, this would be applicable to all investigated variables, thus not hindering the performed comparisons. A comprehensive checklist has been proposed that can be used clinically in an individual patient, to verify whether all conditions are met for a valid prediction of fluid responsiveness using dynamic preload variables.

It has not been very well studied previously, whether dynamic preload variables are actually able to track fluid-induced changes in hemodynamics. Based on the data available in this thesis (chapter 2), it seems as if all of the dynamic preload variables – both arterial pressure and plethysmographic waveform based – are able to track these changes, except for PVI. This finding is of clinical importance when fluid administration would be based solely on PVI: because one might be misled to administer too much fluid based on the PVI value, as changes in hemodynamics are not well tracked by this variable. The transcutaneous measurement of Hb (SpHb) was derived from the same plethysmographic signal as PVI and is likely to be processed using the same, proprietary algorithm. As we have demonstrated in chapter 6 that SpHb agreement with the reference standard decreased substantially during colloid administration – and not during crystalloid administration – it might be likely that PVI is, just like SpHb, also influenced by the intravascular presence of colloid solution, a finding that has later been confirmed by others in case of the latter.

Furthermore, the commercially available dynamic preload variables (PPV, SVV, PVI) can be described either as pressure-based (PPV), flow-based (SVV) and volume-based (PVI). From a theoretical
perspective, differences between these variables might therefore be used to assess the relationship between pressure, flow and volume. As such, it was previously suggested that the ratio of PPV and SVV might serve as a pressure-to-flow relation and represents arterial elastance \((Ea_{\text{dyn}})\). In that study, an increase in MAP after volume expansion could be predicted using \(Ea_{\text{dyn}}\). We could not confirm this in the present thesis, although we found that the value of \(Ea_{\text{dyn}}\) before administration of fluid, allowed an adequate prediction whether or not norepinephrine could be reduced following fluid administration. This finding suggests that \(Ea_{\text{dyn}}\) could reflect “intrinsic” arterial tone. The value of \(Ea_{\text{dyn}}\) in assessing arterial tone deserves further research, especially whether it can prove to be of value in the decision whether a patient requires additional vasopressor therapy.

In Chapter 4, we measured central blood volumes and circulating blood volume in spontaneously breathing, anesthetized dogs in order to provide a sound physiologic understanding of the effects of hypo- and hypervolemia on the distribution of blood volume. Here, CO was measured by an ultrasound flow probe with high precision. Circulating blood volume \((V_{\text{d circ}})\) – which has been shown to be a reliable estimate of total blood volume – was measured by ICG dilution. Pulmonary and intrathoracic blood volume (PBV, ITBV) were also measured, and the ratios between \(V_{\text{d circ}}\) and PBV or ITBV were used as an estimate of the distribution of blood volume. Surprisingly, these ratios remained constant for all induced alterations in blood volume (up to \(\pm 30\%\) of \(V_{\text{d circ}}\)). This observation contrasts the traditional belief that, especially in case of hypovolemia, blood volume in the central compartment is kept constant at the expense of the peripheral compartment. Obviously, the study was performed in dogs and the results cannot be directly translated to humans. Additionally, the dogs were anesthetized, which is associated with partial sympathicolysis, which in turn might play a role in the unaltered distribution of blood volume. Importantly though, many of our patients subject to hypovolemia also receive (some form of) sympathicolysis due to anesthetic drugs, and therefore this finding can be of direct clinical importance. For instance, goal-directed fluid therapy is aimed at optimizing blood flow. Yet, as demonstrated in this chapter, acute hypovolemia up to \(30\%\) of \(V_{\text{d circ}}\) during anesthesia, results in an equal relative reduction in both central blood volumes and \(V_{\text{d circ}}\). As such, even during a goal-directed fluid therapy approach, the decision to administer fluid could be influenced by the traditional belief of centralization, while the patient might suffer a reduction in central blood volume – and thus a reduction in venous return – sooner than expected. In anticipation to acute hypovolemia, one could chose to bring the patient into the more “safe”, non-responsive part of the Frank-Starling curve.

In Chapter 5, a recently introduced method to provide a surrogate quantification of (a constituent of) blood volume in humans, was investigated. The cardiovascular model is based on the elements of CO regulation as determined by Guyton. It does not allow the quantification of blood volume (compartments) directly, but the model allows the calculation of an analogue of a theoretical variable, the mean systemic filling pressure \(Pmsf\), which is the equilibrated vascular pressure after blood circulation has stopped. \(Pmsf\) is a major determinant of venous return (and hence CO) and is determined by total blood volume and vascular capacitance, i.e. the balance between vasodilation and vasoconstriction. The algorithm calculates \(Pmsf\) using CVP, MAP and CO and scales according to demographic variables for venous resistance. \(Pmsf\) and the resulting driving pressure for venous return \((Pvr = Pmsf - CVP)\) were found to reflect volume changes following fluid administration. Most importantly, \(Pvr\) was able to predict fluid responsiveness to a similar extent as simultaneously measured dynamic preload variables. Therefore, \(Pvr\) might be regarded an alternative
way for assessing fluid responsiveness in patients in whom dynamic preload variables cannot be used by a variety of reasons, e.g. spontaneous breathing activity, substantial cardiac arrhythmia (see above). The exact clinical role of measuring Pmsa and its derived variables is still subject of debate, although the ability of Pvr to predict fluid responsiveness seems promising. In addition, the calculation of cardiac performance ($E_H$; calculated as Pvr / Pmsf) allows a further differentiation of fluid responders and non-responders as we demonstrated that $E_H$ remains stable in responders but decreased in non-responders. The latter finding can be explained by the fact that in these patients, the heart was unable to handle the fluid administration-induced increase in Pmsa (which allowed CVP to increase), and hence, cardiac output could not increase as these patients were already on the “flat” part of the Frank-Starling curve. In short, the applied cardiovascular model can, in conjunction with CO and dynamic preload variables, allow a more complete picture of actual hemodynamics, possibly allowing individually tailored therapeutic interventions to improve patient outcome. This should be confirmed in future randomized trials.

In chapter 6, the accuracy and precision of measuring hemoglobin concentration noninvasively (SpHb) was compared with the clinical standard: invasive satellite-lab analysis ($Hb_{satlab}$) in patients undergoing liver surgery. During the first – long and stable – phase of major hepatic resection, the agreement of SpHb with $Hb_{satlab}$ was moderate, in accordance with multiple other studies performed in various clinical settings. After completion of surgical resection, patients received 15 ml kg$^{-1}$ of fluid in a 30-minute period. The administered type of fluid was based on randomized allocation of either crystalloids or colloids. SpHb remained stable during infusion of crystalloids but decreased during infusion of colloid solution. An important implication of these observations is that when an accurate assessment of Hb concentration is essential, e.g. in case of colloid administration during acute surgical blood loss, SpHb accuracy is substantially decreased. In addition, other factors such as the level of $FiO_2$ and changes in peripheral circulation have been found to influence SpHb accuracy. In a recent meta-analysis on SpHb accuracy – which included the investigation presented in this thesis – it was proposed that SpHb in its current form cannot yet replace $Hb_{satlab}$ and that – especially in case of planning interventions (blood transfusion), this should be based on the actual $Hb_{satlab}$ value.

In chapter 7, a review about the clinical applications of minimally invasive assessment of liver function by measurement of indocyanine green (ICG) elimination is presented. The review discusses the role of measuring ICG elimination for assessing liver function during hepatic surgery or in critically ill patients.

In patients scheduled for major hepatic resection, pre-operative assessment of ICG elimination might help in predicting adverse postoperative outcome and possibly aids in assessing the maximal extent of liver resection. In patients undergoing liver transplantation, studies suggest that it might allow an improved ability to prioritize those on the waiting list for transplantation. In the intra- and postoperative phase, it is suggested that it might adequately monitor graft function and can allow a quick identification of postoperative complications. In critically ill patients, the measured ICG elimination was shown to be of value in assessing the degree of intra-abdominal hypertension and in predicting overall mortality. Also of interest is the suggestion in some studies that ICG elimination might accurately reflect the degree of acute liver failure and might play a role in assessing whether liver transplantation is required or not. An important point for consideration in clinical interpretation is the dependency of the elimination of ICG on blood flow; therefore, its value should be interpreted within the context of actual hemodynamics.
In summary, chapter 7 provides argumentation that – despite numerous studies that have been performed about liver function monitoring using ICG – no randomized, high-quality studies are available yet in any of the investigated areas of interest, while this would be necessary before routine monitoring of liver function can be advised.

Finally, in chapter 8 we demonstrated that ICG elimination measured already intraoperatively during orthotopic liver transplantation, could allow an assessment of early graft function. We found that ICG elimination at the end of surgery provided an adequate prediction of absence of early postoperative complications. In other words: high values of ICG elimination measured during surgery can be predictive of a favorable short-term graft outcome. These findings are similar to previous studies\textsuperscript{48-50}, although in those studies ICG elimination was assessed postoperatively. Importantly, the ability to assess graft function intraoperatively might subsequently permit performing interventions aimed at optimizing graft function in an early stage. The threshold for predicting absence of early postoperative complications (i.e. a plasma disappearance rate of ICG 23.5 % min\textsuperscript{-1}) is much higher than thresholds determined in previous studies\textsuperscript{48-50}, although these were used for predicting serious graft dysfunction, which was not the aim of our study.

**Future Perspectives**

Advanced minimally invasive monitoring potentially offers a unique role for the anesthesiologist as it allows the opportunity to improve patient outcome in a broad population of patients scheduled for surgery. In addition, optimization of flow-related variables (e.g. CO) in an individual patient allows tailoring hemodynamic optimization in a goal-directed fashion.\textsuperscript{55-58} Multiple studies using such a goal-directed approach have shown that the likelihood of postoperative complications can be reduced, especially in high-risk patients.\textsuperscript{58} The majority of perioperative mortality occurs in a minority of patients: those assessed as high-risk patients or in patients undergoing high-risk procedures.\textsuperscript{59} Especially in these patients, hemodynamic monitoring with subsequent hemodynamic optimization improves patient outcome and reduces the incidence of (post-operative) complications as has been shown extensively.\textsuperscript{57}

The means by which goal-directed fluid therapy can be achieved is by choosing an appropriate flow-related hemodynamic variable with a subsequent appropriate treatment algorithm. Clinical reality in everyday work on the OR is however fairly different from using flow-based and goal-directed algorithms: nearly all decisions regarding fluid therapy and regarding the titration of inotropes and vasopressors, are solely based on (changes in) arterial blood pressure. Although monitoring MAP in the perioperative setting is without any doubt important, one should question whether relying solely on measurements of MAP is correct, as this hemodynamic variable is arguably the most appropriate variable for (sometimes) delicate interventions such as fluid administration, while the determination whether or not the patient is in need of (extra) fluid can be far more adequately predicted by dynamic preload variables, as demonstrated in this thesis. The main reason why arterial blood pressure monitoring is not the best modality for guiding fluid management is that is has been shown that arterial blood pressure values do not discriminate between survivors and non-survivors in critically ill patients\textsuperscript{56,60} and are not correlated at all with CO.\textsuperscript{61} Finally, changes in CO are not reflected in changes in arterial blood pressure.\textsuperscript{62} Rather, changes in arterial blood pressure resulting from fluid administration more likely result from changes in vascular tone than that they reflect actual volume status, for which Ea\textsubscript{dyn} might be a sensitive indicator. Obviously, pressure-based
hemodynamic monitoring is insufficient and inappropriate to adequately monitor flow-related variables. In healthy, ASA physical status 1 and 2 patients, basic (pressure-based) hemodynamic monitoring might suffice to allow the patient to undergo the surgical procedure as the a-priori risk for developing (post-operative) complications is low, although MAP_{cNIBP} might be preferred over MAP_{iNIBP} due to its continuous beat-to-beat character with associated advantages. However, for patients graded as ASA PS 3 or higher and for healthier patients undergoing major surgery (with substantial fluid shifts, for example), advanced hemodynamic monitoring aimed at optimizing CO (as a major determinant of DO_2) is more appropriate. Unfortunately, according to a recent survey among European and North-American anesthetists, CO monitoring is only performed in 34% of high-risk cases, as it is regarded too invasive by a majority of respondents and because there is a lack of either protocols or available devices. However, a recent survey showed that the enthusiasm for using advanced monitoring techniques and GDT algorithms is high in the absence of such existing barriers.

The emerging availability of minimally invasive or noninvasive methods for measuring fluid responsiveness allows goal-directed fluid management in a broad patient population and also an assessment of blood flow, even when CO itself is not directly monitored but surrogates are measured (e.g. dynamic preload variables). As such, multiple studies have already shown that outcome can be improved and that treatment costs can be reduced when arterial-pressure based hemodynamic variables (e.g. SVV, PPV) are used for guiding fluid therapy, despite the additional costs of monitoring and optimization. Future studies should be aimed at investigating the effects on outcome of noninvasively derived dynamic preload variables. Importantly, especially when CO is not measured and dynamic preload variables are used as the sole surrogate of the patient’s volume status, the limitations of these variables should be reckoned, yet in such situations Pvr might be used as a suitable alternative for dynamic preload variables. Of note, optimization, e.g. of CO, not necessarily means “maximization”: one study in aerobically fit patients undergoing general surgery demonstrated that postoperative outcome could be worse when striving for maximization of CO.

The studies we presented in this thesis regarding monitoring of macro-hemodynamics and hemoglobin concentration were not performed to investigate the effects on outcome, but to assess the reliability of “less” invasively derived variables with “more” invasively derived ones. The reason is that the validity of a new monitoring modality should be investigated sufficiently before the effects on outcome can be studied. Therefore, the derived knowledge obtained in this thesis about the adequacy of predicting fluid responsiveness by minimally and noninvasive dynamic preload variables as well as by Pvr, and the influence of the threshold for the definition of fluid responsiveness can aid in a sound interpretation of these variables and in developing appropriate goal-directed fluid therapy algorithms. As such, Ea_{dyn}, Pmsf and Pvr can potentially provide a further clarification of individual hemodynamics and might help in guiding fluid therapy and inotropie / vasopressor therapy as these variables reflect both preload (Pmsf, Pvr) and afterload (Ea_{dyn}).

While the adequacy and reliability of monitoring is highly important, a sound physiologic understanding is just as important. As such, we believe that the findings of the maintained blood volume distribution between circulating and central blood volumes during hypo- and hypervolemia, support the understanding of cardiovascular regulatory mechanisms during such circumstances. Additionally, it points out that cardiovascular collapse due to acute hypovolemia in anesthetized patients, might occur sooner than expected, which suggests that the patient should be kept or be brought in the “safe”, non-responsive zone of the Frank-Starling curve in anticipation to acute hypovolemia.
Finally, the availability of minimally invasive liver function monitoring using ICG elimination offers the potential for performing early interventions aimed at improving liver function. Nevertheless, despite the numerous studies that have been performed in recent years concerning this issue, all studies were retrospectively and no definitive impact of measuring ICG elimination on outcome can be established as of yet. Therefore, in order to assess whether ICG elimination measurements should be used routinely, prospective trials are required to elucidate the effects on outcome.

In conclusion, this thesis was aimed at comparing “less” invasively with “more” invasively derived variables as well as assessing the adequacy of minimally invasive monitoring of liver function. While the underlying (cardiovascular) mechanisms as well as the interpretation thereof are highly complex, the transition of monitoring from being pressure-based and sometimes highly invasive to being more minimally invasive and predominantly flow-based, offers the potential to improve patient outcome in a broad patient population or possibly, in all patients undergoing any form of anesthesia.