Optimizing fluid management in critically ill patients

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Summary,

general discussion

and future perspectives
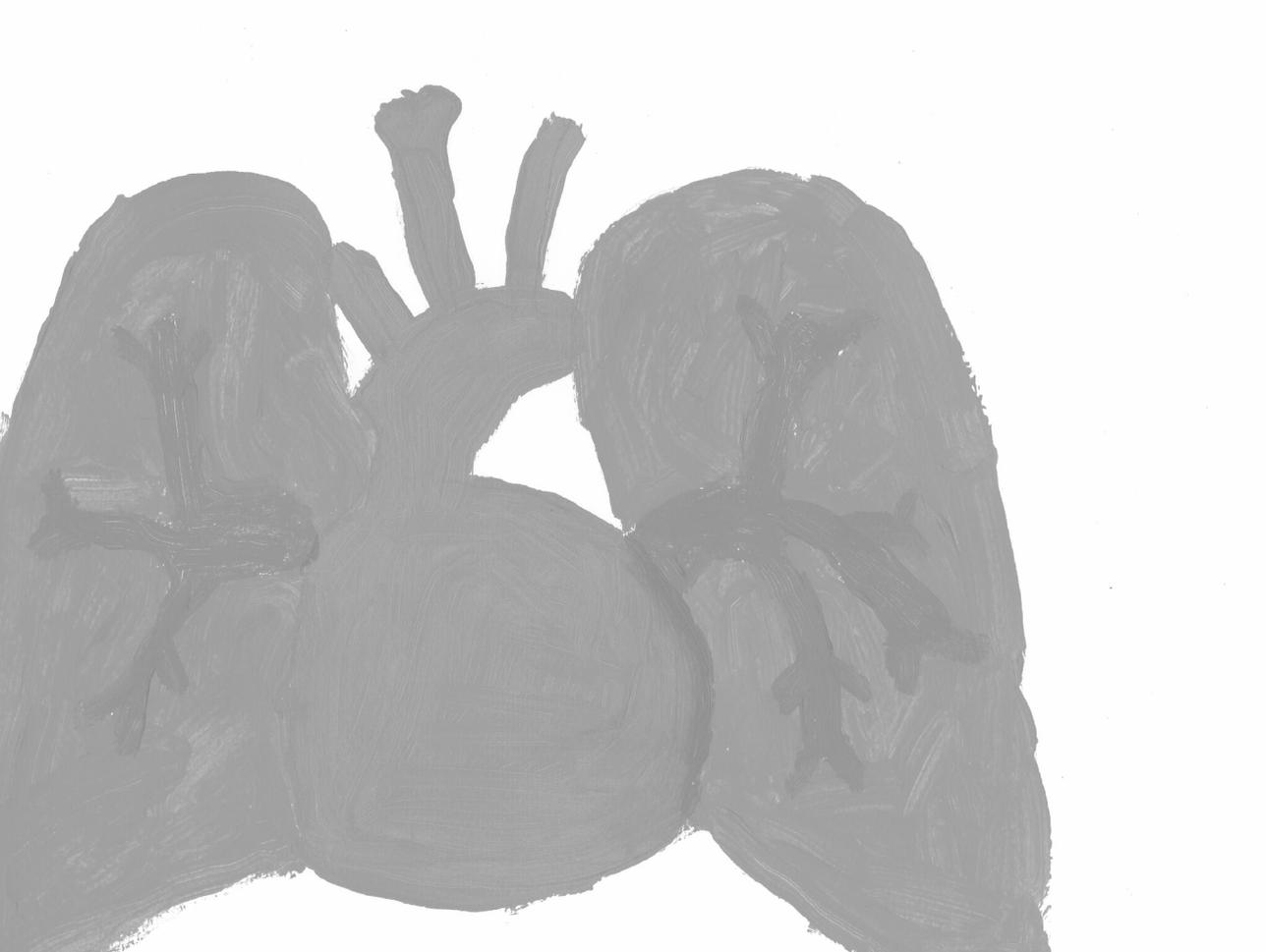
In the first part of this thesis we focused on the benefits and detriments of (synthetic) colloids versus crystalloids for fluid resuscitation in circulatory shock. We explored whether cardiac response depends on the type of fluid administered, and critically reviewed the literature on the crystalloid-colloid volume ratio in determining hemodynamic effects and discussed current views on the potential hazards of synthetic colloids in sepsis. The second part of this thesis was aimed at monitoring of fluid therapy. We compared the transpulmonary (thermo)dilution technique with filling pressure based hemodynamic monitoring in critically ill patients with different disease etiologies in order to improve understanding and interpretation of transpulmonary (thermo)dilution derived indices versus filling pressures, which is of importance because of its potential diagnostic and therapeutic implications.

PART I
Fluids: type, dosing and timing

Chapter 2

In chapter 2 we hypothesized that fluid loading with colloids results in a greater increase in preload-recruitable cardiac output and stroke work than saline loading. We assumed that this effect would be more pronounced in nonseptic than in septic patients because of differences in cardiac function and vascular permeability. Indeed we demonstrated that fluid loading with colloids resulted in a greater increase in cardiac filling, cardiac output and stroke work than with saline. However, we also found that the hemodynamic response to fluid loading in sepsis was similar to that in nonsepsis. This may suggest that myocardial depression and presumably increased vasopermeability, as seen in sepsis, are subordinate to the effect of colloids, at least within the time window of 90 minutes we used for our study. The most likely explanation for this mechanism is maintaining or even increasing the plasma colloid oncotic pressure (COP), even when accompanied by increased vasopermeability, as often seen in sepsis. We found that the volume ratio for reaching similar hemodynamic endpoints was approximately 1 colloid to 3 crystalloids, based on the difference in cardiac output increase multiplied by the difference in volume infused.

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Chapter 3

In this chapter we performed an in-depth exploration of the crystalloid-colloid volume ratio and reviewed the available clinical data order to determine the differences in hemodynamic effects. The increase in cardiac output after fluid loading is commonly believed to be caused by increasing the plasma volume. However, this relationship may not be as straightforward when infused fluids are differently partitioned in stressed and unstressed volume compartments. Fluid loading may also affect blood viscosity and may thereby lower cardiac afterload and increase contractility. Furthermore, baseline cardiac loading and the function of both ventricles may affect mechanisms of cardiac output increase upon fluid loading. Based on the reviewed data, we found that the volume ratio is approximately 1 colloid to 2-3 crystalloids, provided that similar hemodynamic endpoints had been reached. We suggested that this factor is maintained when multiplying lower ratios with the difference in hemodynamic endpoints attained, which is an important observation since the hemodynamic endpoints of the reviewed studies were not defined similarly. Endpoints of resuscitation varied between studies; from clinical judgment, arterial and central venous pressures, to pulmonary artery occlusion pressures and cardiac output as well as variables obtained by transpulmonary thermodilution. This variety in study endpoints is likely to be responsible, in part, for the widely varying volume ratios during fluid resuscitation.

Chapter 4

In chapter 4 we discussed the timing, dosing and choice of the type of fluid in patients with, or at risk for, acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Since extravasation of fluids is assumed to be determined by pericapillary hydrostatic pressure, colloid oncotic pressure (COP), and vascular permeability, the restraint of fluid loading in ALI/ARDS is based on the assumption that fluid therapy may worsen pulmonary edema, leading to increased respiratory deterioration. However, fluid loading does not necessarily lead to edema formation if increased lymph flow may offset increased fluid filtration. Additionally, the effect of plasma COP to attenuate filtration, or a low COP to increase filtration, is expected to increase when the hydrostatic pressure increases and drives fluids out of the bloodstream.

If hydrostatic pressure does not exceed pulmonary interstitial pressures, then fluid loading related increase in pulmonary edema will probably not occur. In the steep part of the cardiac function curve, the type (and dose) of fluid used for resuscitation, i.e. colloid or crystalloid, probably does not have a major impact on fluid accumulation in the lungs, regardless of permeability. Therefore, fluid resuscitation remains the treatment of choice, provided that the patient is likely to be fluid responsive, as is the case in hypotension and impaired tissue oxygenation, accompanied by clinical signs of hypoperfusion. After initial resuscitation, fluid restriction may ameliorate pulmonary edema formation and shorten ventilator days, particularly when permeability is increased, as is seen in ALI/ARDS. However, this is only likely to be of benefit if hemodynamically tolerated and when tissue oxygenation and renal perfusion are not severely compromised.

Chapter 5

We critically reviewed the safety of synthetic colloids in patients with sepsis. We focused on synthetic colloid associated mortality and risk of acute kidney injury. When comparing colloids versus crystalloids for fluid resuscitation in critically ill patients it has been suggested in systematic reviews that resuscitation with colloids may not reduce the risk of death, in spite of their hemodynamic superiority. This observation may however partially relate to poorly defined clinical or hemodynamic endpoints and monitoring targeted to values proven to be associated with survival, as well as their insufficient application in clinical practice, so that potential benefits may not outweigh adverse effects. Moreover, looking critically at the extracted and analyzed data, most studies were not powered for mortality nor was mortality defined as a primary outcome measure. To date, there is no strong evidence that the use of synthetic colloids for resuscitation purposes negatively influences mortality in sepsis as compared to crystalloids. The risk of renal toxicity with the use of HES solutions must be qualified according to type, concentration and volume of the HES solution.

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General discussion

Despite current guidelines and expert opinions[1-6], there is still no widespread consensus on the preferred type of fluid to be used for resuscitation purposes in general. Since this part of the thesis was mainly focused on the use of synthetic colloids, in particular HES solutions, versus crystalloids, we will discuss the latest insights regarding pros and cons of HES.

Hydroxyethyl starches: PRO

Currently, there is sufficient evidence that in a variety of conditions the use of colloids results in more (rapid) plasma volume expansion and hemodynamic optimization than resuscitation with crystalloids, and based on the available data the volume ratio is approximately 1 colloid to 2 crystalloids, provided that similar hemodynamic endpoints will be achieved (this thesis). As a result, administering less volume of colloidal fluids compared to crystalloids for reaching the same hemodynamic endpoint(s) may prevent deleterious overhydration and perhaps prolongation of mechanical ventilation and ICU stay. This insight may be beneficial for patients at risk for pulmonary edema, in particular patients with ALI/ARDS. Indeed, it has been suggested that HES solutions may protect or ameliorate ischemia-reperfusion, sepsis induced lung injury and pulmonary capillary leakage[7-15]. Biophysiologically, medium molecular weight HES may plug leaks in injured endothelium and reduce interstitial edema[16,17]. Biochemically, HES may decrease sepsis or ischemia-reperfusion induced inflammatory responses and neutrophil recruitment, and thus attenuates endothelial dysfunction and reduces pulmonary capillary permeability while crystalloid solutions cause more hemodilution, which in turn causes endothelial and red blood cell edema, decreases the surface area for tissue oxygen exchange, and worsens tissue and pulmonary edema[18]. In patients with ALI/ARDS, the use of HES significantly improved hemodynamics without worsening pulmonary edema, and it even attenuated pulmonary vascular permeability[19]. It may be suggested that modulation of the oncotic pressure by administration of colloids may influence development of pulmonary edema. However, the importance of oncotic pressure in the limitation of flux is only conceivable if the barrier is intact. In case of endothelial lesions, interstitial fluid composition will contain

more proteins than plasma, theoretically limiting the contribution of increasing the plasma entotic pressure[20]. In a small series of mechanically ventilated patients with ALI/ARDS with hypoproteinemia and presumably a low COP, albumin and furosemide versus furosemide alone ameliorated gas exchange and other surrogate indices of pulmonary edema[21]. In hypoalbuminemic critically ill patients with a presumably low COP, albumin administration was associated with less positive fluid balances and improved pulmonary function[22]. This effect may also be true for HES solutions. However, at present convincing evidence that albumin or HES treatment is justified for limitation of pulmonary edema or respiratory morbidity in patients with ALI/ARDS is lacking.

Hydroxyethyl starches: CON

With regard to harmful side effects, the comparative safety of (synthetic) colloids has recently been extensively reviewed[3,23]. Potentially detrimental effects are focused on the HES solutions and consist mainly of renal toxicity and impaired coagulation.

Acute Kidney Injury

The mechanism of potential HES-induced acute kidney injury (AKI) is poorly understood. It may include reabsorption of the macromolecule into (proximal) renal tubular cells leading to osmotic nephrotic lesions[24] or renal plugging due to hyperviscosity of the filtrate, and is associated with a decrease of glomerular filtration pressure by a more rapid increase in intracapillary oncotic pressure than hydrostatic pressure[25]. The prolonged elevation of COP, reached by a higher molecular weight (Mw) and a more extensive molar substitution (MS) as accomplished by first and second generation HES solutions, might explain why these old generation HES products could be more nephrotoxic, than the third generation tetrastarches. Indeed, older generations of HES (Mw ≥200 kDa) have been shown to be an independent risk factor for acute kidney injury (AKI) in patients with severe sepsis or septic shock[26] and their use should therefore be discouraged, while recent work suggest that resuscitation with third generation tetrastarches is not associated with increased development of AKI[27-30] or may even preserve renal function and attenuate tubular damage[31]. The underlying disease may play a distinctive role; the risk of AKI may be greater during severe sepsis[32] than in trauma or in an elective surgical setting[3,32].

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Coagulopathy

The risk of potential adverse effects of HES solvents on coagulation is still under debate. The mechanism of impaired coagulation is only partially explained by the observation that the hydroxyethylated glucose polymer may reduce von Willebrand factor and interferes with fibrinogen polymerization and platelet function[33,34]. It has been suggested that the degree of coagulopathy depends on the pharmacokinetic properties of the HES molecules, such as molecular weight or the degree of substitution of carbon atoms with hydroxyl moieties[34]. To date, there is only circumstantial evidence that low molecular weight HES is associated with hypocoagulation[35]. Data from randomized controlled trials have so far not revealed any coagulation differences attributable to HES solvent or source material[23]. Nevertheless, it seems reasonable that administration of HES products should be discouraged in patients with massive bleeding.

Recent studies

Very recently, two large multicenter studies (the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial[36] and the CRYSTMAS study[37]) comparing HES 130/0.4 versus crystalloids (Ringer's acetate and 0.9% NaCl respectively) in patients with severe sepsis/septic shock have been published. The 6S trial group randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.4 or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization. Fluid administration occurred when ICU clinicians judged that volume expansion was needed, in other words, there was no predefined fluid loading protocol. The results of this study demonstrated an increased risk of death at day 90 with the use of HES 130/0.4 compared to Ringer's acetate in patients with severe sepsis/septic shock. In addition, patients receiving HES were more likely to require renal-replacement therapy (RRT), as compared with those receiving Ringer's acetate. The authors suggest that long-term toxic effects of HES deposition in tissues / organs may be responsible for the increased mortality; a high fraction of HES is taken up and deposited in tissues, where it can not be metabolized and acts as a foreign body, inducing potential toxicity. However, their explanation may be refuted

since only one patient (of 87) in the HES group was still dependent on RRT after 90 days, which may thus suggest potential reversibility of HES induced AKI. Furthermore, it cannot be excluded that other (confounding) factors may have influenced the increased mortality in the HES group. For instance, the amount of blood transfusions was significant higher in the HES group; already in the past is has been demonstrated that red blood cell transfusions are independently associated with increased morbidity and mortality in ICU patients[38]. Moreover, the results of this study are contradicted by the results of the other large, multicenter trial, the CHRYSTMAS study. This French-German study compared the hemodynamic efficacy and safety of HES 130/0.4 versus NaCl 0.9% for hemodynamic stabilization in patients with severe sepsis. The maximum allowed dose for both treatment groups was 50 mL/k/day on the first day and 25 mL/kg/day from the second to the fourth day. Primary endpoint was the amount of study drug (mL) required to achieve initial hemodynamic stability. Hemodynamic stability was defined as a mean arterial pressure ≥65 mm Hg and at least two of the following three parameters maintained for four hours: central venous pressure 8-12 mm Hg, urine output >2 mL/kg, and central venous oxygen saturation ≥70%. Safety objective was to assess the occurrence of kidney dysfunction, coagulation disorders, and pruritis. The results of this study demonstrated that significantly less HES (mean 1379 mL) compared to NaCl (mean 1709 mL) was required to reach hemodynamic stability. Furthermore, HES had no negative effects on kidney function, coagulation, or pruritis. It may be suggested that the presence of a predefined fluid loading protocol in the CHRYSTMAS study may have explained, at least in part, the differences in outcome compared to the 6S trial. Fluid administration based on predefined hemodynamic goals may limit the possible deleterious effects of synthetic colloids on renal function; in the 6S trial, the median cumulative volume of HES was 3000 mL compared to the mean 1379 mL in the CRYSTMAS study, while resuscitation in both studies was assumed to be adequate. This suggestion may be confirmed by a German study[32] showing that fluid resuscitation by HES 130/0.4 in patients with severe sepsis was associated with a greater incidence of acute kidney injury. In this study a median of 46 mL/kg of HES 130/0.4 was administered, which corresponds with approximately 3000 mL. The indication for colloid administration was left to the discretion of the attending physician and also here, no predefined resuscitation protocols were used. It can be

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hypothesized that the administration of lower, or more precisely, effective volumes of HES would have reduced the incidence of acute kidney injury. In summary, the results of these very recent studies may well suggest that HES induced kidney injury is not only particularly dose-dependent but also potentially reversible.

Future perspectives

In future randomized trials comparing (synthetic) colloids with crystalloids for fluid resuscitation that deviate from the ratio, the accuracy of hemodynamic monitoring and guiding fluid therapy should be evaluated since potential dissimilar resuscitation between groups may confound interpretation of relative benefits and detriments of solution types. The use of predefined resuscitation algorithms - to minimize inter-physician variability - based on cardiac output responses upon fluid loading may answer the question whether indeed two times less colloids (compared to crystalloids) are needed to reach similar resuscitation endpoints, and if so, whether potential harmful side effects of synthetic colloids will be minimized. Furthermore, whether randomization implies administration of only colloids versus only crystalloids is debatable, particularly when the study period is longer than 24 hours; in daily practice patients usually do not receive exclusively colloids or exclusively crystalloids for resuscitation purposes[30,39]. Therefore, future studies should preferably be performed on a "real life" basis, combining the administration of both colloids and crystalloids. Currently, some other large prospective trials comparing new generation tetrastarches or albumin with crystalloids for fluid resuscitation in the critically ill are ongoing. In the Australian-New Zealand Crystalloid Versus Hydroxyethyl Starch Trial (CHEST), all-cause mortality at 90 days will be compared after infusion of low molecular weight HES or saline (www.clinicaltrials.gov NCT00935168). Once treatment has been assigned, the participant will continue to receive either starch or saline only for all fluid resuscitation requirements in intensive care. The treating clinical team will decide the amount and frequency of the fluid given for resuscitation. A French multicenter trial is currently recruiting and comparing all types of colloids, including albumin versus all types of crystalloids on efficacy and safety by 28-day mortality and need for renal replacement therapy (NCT00318942). The amount and speed of fluid loading will

be at the physicians' discretion and the amount of starch should not exceed 30 mL/kg/24 hours. Throughout the whole ICU stay, patients will receive only crystalloids or only colloids for fluid resuscitation, according to randomization. However, in both studies, a predefined fluid loading protocol is lacking, and patients will receive either crystalloids or colloids during resuscitation. So, also here, the question concerning the colloid-crystalloid controversy will probably not be answered.

Final conclusion

To date there is still no widespread consensus on the preferred type of fluid to be used for resuscitation purposes in critically ill patients, although the use of older generations of HES solutions (medium or high molecular weight) should be discouraged, at least in patients with sepsis (grade 1B). That in a variety of conditions the use of (synthetic) colloids results in more (rapid) plasma volume expansion and hemodynamic optimization than resuscitation with crystalloids may argue in favor for the use of colloids, thereby taking the maximum recommended dose of synthetic colloids into account. The discussion of low molecular weight HES solutions on mortality and on the potential detrimental effects on kidney function is currently very topical, but has not been settled yet. A most recently updated systematic review and meta-analysis on 6% HES 130/0.4 versus other resuscitation fluids demonstrated no difference in the relative risk of death in acutely ill patients[40], while the European Society of Intensive Care Medicine (ESICM) task force[41] on colloid volume therapy in critically ill patients recommend not to use newer generations of HES solutions (130/0.4) in patients with severe sepsis or those at risk for acute kidney injury, unless applied in the context of clinical trials (level of evidence grade 2C). Grade 2C evidence however, constitutes a weak recommendation based on low or very low quality evidence[42,43], and is therefore not very persuasive. New trials comparing low molecular weight HES versus crystalloids for fluid resuscitation in critically ill patients are urgently required to address the safety and efficacy of such a fundamental intervention in intensive care medicine, provided that they are adequately performed based on predefined hemodynamic goals.

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PART II
Monitoring fluid therapy

Chapter 6

In chapter 6 we hypothesized that during fluid loading, in patients after cardiovascular surgery with reduced systolic cardiac function (reflected by global ejection fraction, GEF) as compared to those with normal function, filling pressures may be superior to filling volumes for predicting and monitoring fluid responsiveness, and vice versa. Indeed, we found that pulmonary artery occlusion pressure (PAOP) is more useful than global end-diastolic volume (GEDV) for predicting fluid responsiveness in patients with impaired systolic function (and subsequent cardiac dilatation), while GEDV is more useful in patients with normal systolic function. This finding can be explained by the assumption that in hearts with systolic dysfunction and dilatation, a right- and downward shift on the cardiac function curve and a left- and upward shift along the curvilinear pressure-volume curve at end-diastole (when there is a concomitant decrease in ventricular compliance), preload recruitability may be more dependent on and thus better predicted and monitored by pressures than by volumes. These data argue in favor of using PAC derived filling pressures for guiding fluid therapy in patients with reduced systolic cardiac function after cardiovascular surgery.

Chapter 7

In this chapter we evaluated and compared filling volumes to pressures, in determining the cardiac response upon fluid loading according to systolic cardiac function (reflected by GEF) in patients with sepsis induced hypotension and hypothesized that sepsis-induced cardiac dilatation is pivotal to maintain fluid responsiveness, even in the dysfunctional heart. Our main finding was that fluid responsiveness is maintained by cardiac dilatation, as measured by increased values of GEDVI. In contrast, patients with both systolic dysfunction and inability to dilate were not fluid responsive, possibly due to systolic right ventricular or diastolic dysfunction, in view of their increase in CVP. Patients with near-normal systolic function are fluid non-responsive when operating in the plateau phase of the cardiac function curve or, again, are responsive through cardiac dilatation when operating in the steep part of the cardiac

function curve. The dilatation associated with fluid responsiveness, as measured by an increase in GEDV is thus independent of systolic cardiac function. Our study suggests that transpulmonary (thermo)dilution-derived GEDVI is more helpful than CVP, in monitoring fluid responsiveness and non-responsiveness and their mechanisms in sepsis induced hypotension, but normal or target levels of preload (GEDVI 680-800 mL/m^2) may not apply in this condition.

Chapter 8

In chapter 8 we reviewed current insights concerning the measurement of extra vascular lung water (EVLW) as an index of pulmonary edema and suggested that this parameter is a useful adjunct to assess lung injury, cardiogenic edema and overhydration, and to guide treatment in critically ill patients since fluid resuscitation, if not carefully monitored, may induce harmful fluid overloading and subsequent pulmonary edema. The ability to measure the amount of pulmonary edema at the bedside, using the transpulmonary (thermo)dilution technique may allow the clinician to hopefully prevent pulmonary overhydration by detecting changes in EVLW upon fluid loading. The gold standard for EVLW measurement by (thermo)dilution is postmortem gravimetry in animal models of lung edema and high correlations have been observed even in toxic pulmonary edema, which mimics ALI/ARDS in humans. Preliminary data show that EVLW monitoring may guide treatment. Despite its potential there are some drawbacks which are inherent to the technique. EVLW may be underestimated in underperfused lung areas. Some types of pulmonary edema are less well reflected in EVLW measurements than others, which is partly associated with redistribution of intrapulmonary blood flow. Furthermore, cardiac output may also be too high for thermal equilibration with the extravascular distribution volume, and positive end-expiratory pressure may increase the distribution of the thermal indicator and increase EVLW. Potential areas of clinical evaluation of the EVLW measurements include treatment for ARDS and resorption of pulmonary edema, strategies to prevent or limit ventilator-associated lung injury, monitoring fluid resuscitation and manipulating fluid balances.

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Chapter 9

In chapter 9, we conducted a two-center prospective, randomized controlled trial in order to assess superiority of EVLW-guided versus PAOP-guided fluid therapy for limiting fluid overloading. We hypothesized that the risk of fluid overloading will be less when fluid administration is restricted by upper limits of EVLW and GEDV than using upper limits of PAOP, which could be translated into more ventilator free days while safeguarding adequate resuscitation. Furthermore, we explored whether disease etiology, i.e. septic and nonseptic shock may differ in this respect. We randomized a total number of 120 patients; 60 patients received a transpulmonary thermodilution technique (TPTD) catheter and 60 patients a pulmonary artery catheter (PAC). Randomization was stratified per center for sepsis versus nonsepsis. Fluid therapy together with the need for vasopressor and/or inotropic agents was aimed at well-known endpoints of resuscitation (MAP>65 mm Hg, $S_{cv}O_2$>70% or S_vO2>65%, lactate clearance, diuresis >0.5 mL/kg/hr). Fluid therapy was discouraged when upper limits of EVLW (10 mL/kg PBW) and GEDV (850 mL/m^2) were reached in the TPTD group and PAOP (18-20 mm Hg) in the PAC group. The main finding of this study was that the primary endpoint, ventilator-free days, did not differ between monitoring with the TPTD versus PAC. However, the use of the TPTD algorithm compared to the PAC algorithm resulted in more days on the ventilator and increased length of ICU stay in patients with nonseptic shock (in contrast to septic shock patients), which may relate to cardiac comorbidity and a more positive fluid balance with the use of the TPTD in the nonseptic shock group. This may suggest that the upper limits of GEDV and EVLW for fluid administration may have been too high, and thus interfered with ventilator weaning through intermittent hydrostatic pulmonary edema. It may be hypothesized that fluid restriction (with an upper limit of 7 mL/kg rather than 10 mL/kg) might have resulted in less prolonged ventilation in these patients.

General discussion

That fluid resuscitation guided by hemodynamic monitoring may be helpful and may influence outcome was recently suggested in a cohort of over 3000 children with severe sepsis in a resource-limited setting (casu quo without monitoring). Administration of fixed volume of fluid boluses significantly increased 48-hour mortality compared to no bolus-fluid resuscitation[44]. This finding suggests that fluid resuscitation should be assessed on individual needs, aimed on the prevention or restoration of (impending) tissue hypo-oxygenation. The use of a hemodynamic monitoring tool may help the clinician to guide this patient-tailored fluid therapy. The pulmonary artery catheter (PAC) has been used for decades for monitoring hemodynamics in the perioperative setting or in critically ill patients. However, the use of the PAC in general has rapidly decreased over the last decade, mainly due to negative results of prospective, randomized trials that failed to show any associated clinical benefit while its use was associated with more complications, in particular cardiac arrhythmias[45-47]. Newer, less invasive techniques as the transpulmonary thermodilution may decrease the risk of adverse events and the use of volumetric parameters have been suggested to reflect cardiac preload better than filling pressures[48,49]. In addition, the TPTD technique has demonstrated to be able to display the amount of pulmonary edema, which may improve the efficacy and safety of fluid therapy.

Pulmonary artery catheter

Over the last decade, a more than 50% reduction in the use of the pulmonary artery catheter has been observed[50], particularly due to an alleged lack of evidence for any clinical benefit associated with this technique. The apparent lack of benefit of the PAC may relate in part to adverse effects of insertion, improper use, poor interpretation of hemodynamic data, and inadequate treatment decisions based on the collected variables. Importantly, the use of a PAC has to comply with three conditions. First, correct measurement (zeroing, calibration, elimination of artifacts and proper reading of the values), second, correct interpretation (pressures, cardiac output and S_{Vo_2} and their interaction), and third, correct application of the values obtained[51].

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In the Fluid and Catheter Treatment trial (FACTT)[47], a pivotal study that may be partly responsible for the declining use of the PAC, patients were only included 36 hours after admission, at a time when further invasive monitoring probably would not be useful. It is of interest to note that this study used PAC-derived filling pressures not to guide resuscitation but to limit it, to consider the issue whether limited resuscitation to avoid increasing pulmonary edema in ARDS can improve outcome. This study suggested that the use of this protocol together with routine monitoring of the circulation with the PAC in ARDS, once it is stabilized, cannot be justified. That this tool may be of use in other critically ill patients has recently been demonstrated in a systematic review and meta-analysis of the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Half of the reviewed studies concerned PAC monitoring with hemodynamic objectives of oxygen delivery, cardiac index, and S_vO_2[52] Overall, preemptive hemodynamic intervention significantly reduced mortality and surgical complications. In addition, subgroup analysis showed a significant reduction in mortality in studies using PACs. Of course, probably not the PAC itself, but rather the use of predefined treatment algorithms aimed at hemodynamic endpoints may have improved outcome. It may be postulated that, if used and interpreted correctly and coupled with a treatment algorithm, the PAC may improve outcome compared to standard care.

In this thesis we focused on the value of the PAC derived filling pressures versus transpulmonary dilution derived filling volumes because of potential diagnostic and therapeutic implications, in patients with different disease etiologies. Our data confirm the concept that disease etiology is relevant, suggesting that septic patients do have different cardiorespiratory (patho)physiology compared to nonseptic / postoperative (cardiac) surgery patients and that combining these conditions for the evaluation of protocols for hemodynamic management may conceal differences. Pressure-guided monitoring using PAC may help to better understand cardiac dynamics in patients with compromised cardiac function, as seen in patients with non-compliant stiff hearts as a result of myocardial stunning due to (controlled) ischemia-reperfusion after cardiac surgery[53-55], as was also suggested previously[56,57]. The dynamics of PAOP measurements upon fluid loading may reflect diminished left ventricular reserve; an increase from 8 up to 20 mm Hg for instance may warn the clinician for the development of hydrostatic

pulmonary edema if fluid loading will continue. In this way, fluid therapy can be guided by closely monitoring the changes in filling pressures upon fluid loading in order to prevent exceeding critical values, even if fluid responsiveness is present.

Transpulmonary thermodilution technique

Global end-diastolic volume. Volumetric parameters such as GEDV have been proposed as a superior surrogate for cardiac preload than filling pressures[48,49], since in mechanically ventilated patients atmospheric pressure-referenced filling pressures may be confounded by airway pressures, and may thereby poorly predict cardiac preload[58,59]. As a consequence, the use of GEDV has also been proposed in various treatment algorithms. Their use has pointed towards improved outcome in cardiac surgery patients[49], which has led to the inclusion of this parameter into current guidelines for postoperative cardiac surgery patients[60]. In these guidelines, target values of 640-800 mL/m^2 are recommended for GEDV[60], which is approximately in line with the proposed algorithm of the PiCCO® technology manufacturer (700-800 mL/m^2, Figure 1). However, there are important concerns to these proposed target values, as these values are primarily based on initial measurements in healthy individuals and on expert opinion, ignoring cardiac function, age, gender, and severity of illness. Indeed, it was demonstrated that GEDV, whether indexed or non-indexed, is dependent on age and gender, at least in spontaneous breathing patients without a hemodynamic compromised condition[61]. Furthermore, these measured mean values show wide confidence intervals due to a large variance between individuals (Table 1). Since GEDV also includes the volume of the aorta from the aortic valve to the tip of the thermistor on the arterial catheter, a possible explanation for the age related increase in GEDV, may be an increased aortic diameter at older age together with elongation of the aorta. Furthermore, as we demonstrated in chapter 7, high values of GEDV may represent (bi)ventricular dilatation and as a consequence, target values may depend on cardiac systolic function.

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Figure 1. PiCCO technology: decision model.
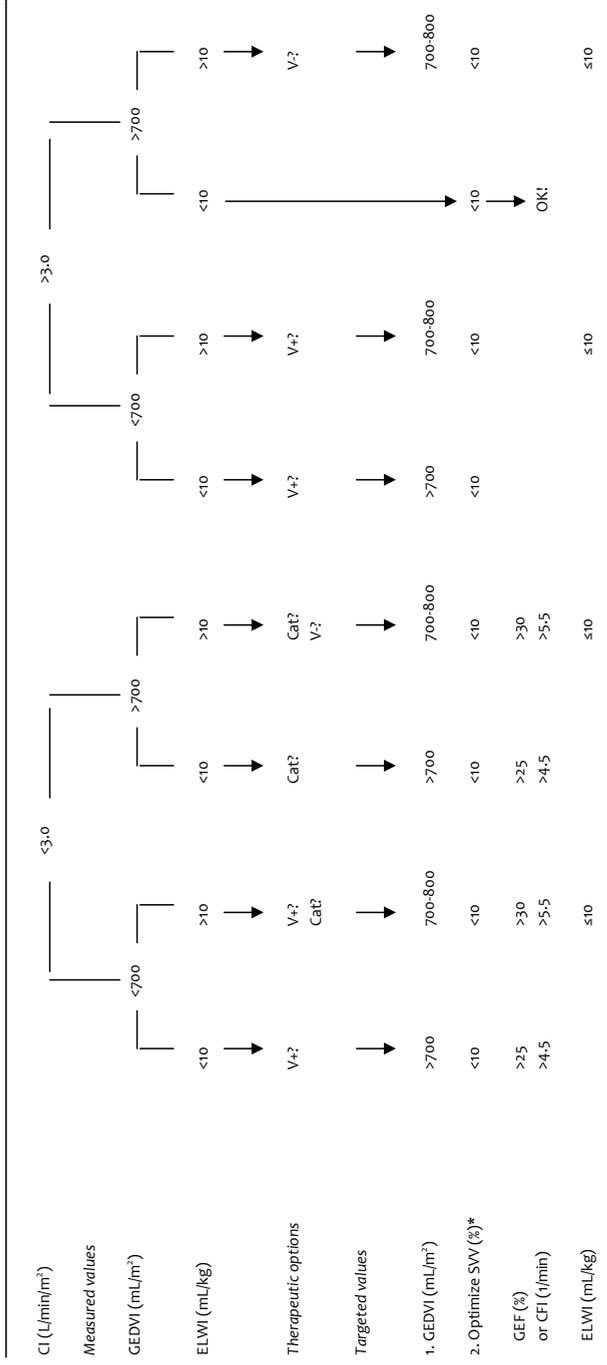
CI cardiac index, GEDVI global end-diastolic volume index, ELWI extravascular lung water index, SVV stroke volume variation, GEF global ejection fraction, CFI cardiac function index, V- volume reduction, Cat catecholamine / cardiovascular agents. *SVV is only applicable in fully ventilated patients without cardiac arrhythmia (adapted from: www.pulsion.com, PiCCO technology: decision model).

Table 1. GEDVI means with 95% confidence intervals for males and females according to age groups.

	GEDVI (mL/m²)			
Age (years)	male	95% CI	Female	95% CI
≤ 40	633	(456-880)	559	(402-779)
41-50	667	(485-916)	592	(432-812)
51-60	736	(536-1011)	654	(478-897)
61-70	802	(585-1101)	713	(520-977)
≥ 70	812	(590-1117)	720	(520-997)

CI Confidence interval, *GEDVI* global end-diastolic volume index.

Recently, this concept has also been suggested by others[62] and thus we propose that "normal" or "target" GEDV should be corrected to systolic cardiac function in critically ill patients. When used as an indicator for preload and preload optimization during fluid resuscitation, target values may differ considerably in this way (Table 2). This concept suggests important implications for the resuscitation algorithms being used. Recently, a meta-analysis demonstrated that the published data for GEDV are very heterogeneous, particularly in critically ill patients, and often exceeds the proposed normal values, in which septic patients had a significantly higher GEDV than postoperative patients[63]. When GEDVI (indexed for body surface area) is targeted at 640-800 mL/m² in order to define preload optimization, undertreatment may occur in older patients, with or without diminished cardiac function, or in patients with septic shock who may have cardiac dilatation and thus higher GEDV values, which is pivotal to maintain fluid responsiveness. In other words, a GEDV >800 mL/m² may be adequate for one patient, and a GEDV <800 mL/m² may be misleading and results in a non-optimal cardiac preload. Targeting GEDV as a parameter for preload optimization should therefore be assessed individually, taking age, gender, cardiac function, disease etiology and severity of illness into account.

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Table 2. GEF corrected volumetric target values.

GEF	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%
GEDVI-target (normal)	1175	1050	950	850	775	700	625	575	525	475
GEDVI-target (critically ill)	1450	1300	1050	1025	925	825	750	675	600	550

GEF global ejection fraction, *GEDVI* global end diastolic volume index. (Modified from reference 60).

Extravascular lung water. A recent meta-analysis demonstrated that EVLW appears to be a good predictor of mortality in critically ill patients[64]. In one report, the increase in mortality was best predicted when EVLW exceeded >10 mL/kg PBW (predicted body weight) during the first 24 hours after admission to the ICU[65], while in another study a value of a 3-day average EVLW >16 mL/kg even predicted mortality with 100% specificity and 86% sensitivity[66]. However, it must be emphasized that sequential EVLW data need to be interpreted carefully as both under and overestimation of EVLW values may occur as a result of the technique itself. For instance, extravascular lung water will not be measured in nonperfused lung areas (as seen in ARDS or when using PEEP) since the thermal indicator cannot equilibrate within the extravascular space[67]. Since PEEP levels and pulmonary perfusion usually alter during the disease process, the change in EVLW must be correlated to the changes in PEEP and pulmonary perfusion, which may impede the interpretation of sequential EVLW measurements for clinical decision making. Moreover, an increase in EVLW is difficult to predict since the amount of EVLW does not reflect (an increased) pulmonary filtration pressure. For EVLW, normal values of 3-7 mL/kg have been proposed. However, reviewing the available data on EVLW in critically ill patients revealed that in septic patients, all the mean values for EVLW exceeded the upper limit of 7 mL/kg and in nonseptic patients 50% of values[63]. Thus, even in nonseptic patients without long-term intensive care treatment and supposedly without clinically relevant pulmonary edema, half of the EVLW values exceeded the proposed normal value. This may lead to the suggestion that an upper limit of 7 mL/kg is too conservative, and may perhaps induce impaired organ perfusion when fluid administration is withheld. On the other hand, an EVLW of 10 mL/kg is associated with the development of clinically manifest pulmonary edema[49]. Therefore, it may be hypothesized that a restrictive fluid policy when the EVLW is increased (>10 mL/kg) may affect outcome in terms of ventilator free days or even in mortality. In chapter 9 we examined in both septic shock and nonseptic shock patients whether the risk of fluid overloading can be diminished if upper limits of EVLW (10 mL/kg) and GEDVI (850 mL/m^2) are taken into account to limit fluid loading, compared to a strategy limited by pulmonary arterial occlusion pressure (PAOP) obtained via a PAC, while safeguarding adequate resuscitation. EVLW values declined similarly in both septic and nonseptic patients over the course of shock treatment, and the cardiac index indeed increased

upon fluid administration, even when initial values of EVLW exceeded 10 mL/kg. This may seem surprising, but in line with our previous observations, we demonstrated that, regardless of initial EVLW, in fluid responsive hearts fluid administration mostly does not increase EVLW[68]. We speculate that the increase in interstitial pulmonary edema during fluid loading is predicted by a plateau of cardiac function and pulmonary vascular filling, rather than by pulmonary vascular permeability, and that pulmonary edema is not affected when fluid loading occurs in the steep part of the cardiac function curve[68,69]. In nonseptic shock patients however, the upper limit of 10 mL/kg of EVLW may have been too high, as these patients had more days on the ventilator and ICU stay compared to those treated with the PAC algorithm. This may be attributable, in part, to greater cardiovascular comorbidity in the nonseptic shock patients, suggesting that the upper limits of EVLW for fluid administration may have been too high and interfered with ventilator weaning via intermittent hydrostatic pulmonary edema. Indeed, the course of EVLW did not differ between septic and nonseptic shock patients, but the frequency of ARDS was much higher in septic shock, so that hydrostatic pulmonary edema may have been more frequent in patients with nonseptic shock. We cannot exclude that fluid restriction (with an upper limit of EVLW ≥7 rather than the 10 mL/kg) might have resulted in less prolonged ventilation in these patients. As suggested before, in patients with sepsis, values of up to 10-12 mL/kg may be tolerable, although more data is needed in this regard[63], while in nonseptic patients, lower values should probably be proposed. Our results suggest that septic shock patients may have different cardiorespiratory physiology than nonseptic shock patients, and that stratification for disease etiology in the evaluation of hemodynamic management protocols may reveal important differences.

Future perspectives

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It may be presumed that developing tool-derived treatment protocols that are applicable across a heterogeneous population of critically ill patients with complex co-morbidities is a difficult task. Designing global protocols to guide therapy for every patient may virtually be a mission impossible. Nevertheless, the use of treatment algorithms aimed at (hemodynamic) resuscitation endpoints, allow us to

administer the amounts of fluids and inotropic agents more precisely. By evaluating – or even predicting - fluid responsiveness, fluid overloading may be prevented, which may affect length of stay in the ICU or even outcome. To address this issue randomized trials should be performed, comparing PAC or TPTD guided hemodynamic management based on predefined algorithms for fluid and inotropic/vasopressor therapy, including the evaluation of fluid responsiveness in order to optimize hemodynamics versus treatment based on CVP and/or $S_{cv}O_2$ measurements alone, as the current Surviving Sepsis Campaign guidelines recommend[5]. Currently the THEMIS trial (NCT01263977) is investigating whether duration of septic shock can be reduced through algorithm driven volume therapy, based on TPTD-derived parameters (GEDV and EVLW) compared to volume management based on the Surviving Sepsis Campaign guidelines[5]. Furthermore, it should be studied whether benefits of one monitoring technique over the other may depend on disease etiology; i.e. sepsis versus nonsepsis and/or the influence of impaired cardiac function. There are currently no studies being performed on this issue.

Final conclusion

In the second part of this thesis we have focused on the differences between PAC-derived pressure parameters and TPTD-derived volume parameters with regard to their value in fluid therapy and hemodynamic management of critically ill patients, taking underlying disease and cardiac function into account. The PAC provides clinicians numerous important hemodynamic variables that may be helpful to accurately evaluate the hemodynamic status. It must be stressed however, that the data generated by the PAC must be interpreted carefully, since numerous inaccuracies in measurements and interpretation have been reported. If measured and interpreted appropriately, the PAC helps the clinician to better understand cardiac dynamics in complex circulatory conditions and in patients with impaired (left ventricular systolic) cardiac function and may therefore be more useful in monitoring fluid therapy than volume guided monitoring. In contrast, in patients with sepsis or in patients at great risk of (increasing) pulmonary edema, as for instance seen in patients with ALI/ARDS, hemodynamic monitoring using TPTD and measurements of EVLW may be preferable

in order to prevent harmful overhydration and, as a consequence, prolongation of mechanical ventilation and ICU stay. Nevertheless, it must be emphasized that hemodynamic monitoring is unlikely to be associated with improved outcome, if the data obtained from the monitoring device is insufficiently accurate to be able to influence therapeutic decision making, if the data obtained are irrelevant to the patient being monitored, or if changes in management made as a result of the data obtained are unable to improve outcome.

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References

PART I

1. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2011 16;(3):CD000567. Review.

2. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2011 16;(3):CD001319. Review.

3. Hartog CS, Kohl M, Reinhart K. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed. Anesth Analg 2011;112:635-645. Review.

4. American Thoracic Society. Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement. Am J Respir Crit Care Med 2004;170:1247-1259.

5. Dellinger RP, Levy MM, Carlet JM, et al. International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.

6. Toomtong P, Suksompong S. Intravenous fluids for abdominal aortic surgery. Cochrane Database Syst Rev 2010 20;(1):CD000991.

7. Chiang CH, Wu CP, Perng WC, et al: Dexamethasone and pentastarch produce additive attenuation of ischaemia/reperfusion lung injury. Clin Sci 2000; 99:413-419.

8. Hoffmann J, Vollmar B, Laschke MW, et al. Hydroxyethyl starch (130 kD), but not crystalloid volume support, improves microcirculation during normotensive endotoxemia. Anesthesiology 2002;97:460-470.

9. Tian J, Lin X, Guan R, et al. The effects of hydroxyethyl starch on lung capillary permeability in endotoxic rats and possible mechanisms. Anesth Analg 2004;98:768-774.

10. Lv R, Zhou W, Chu C, et al. Mechanism of the effect of hydroxyethyl starch on reducing pulmonary capillary permeability in a rat model of sepsis. Ann Clin Lab Sci 2005;35:174-183.

11. Di Filippo A, Ciapetti M, Prencipe D, et al. Experimentally-induced acute lung injury: The protective effect of hydroxyethyl starch. Ann Clin Lab Sci 2006;36:345-352.

12. Feng X, Ren B, Xie W, et al. Influence of hydroxyethyl starch 130/0.4 in pulmonary neutrophil recruitment and acute lung injury during polymicrobial sepsis in rats. Acta Anaesthesiol Scand 2006;50:1081-1088.

13. Marx G, Pedder S, Smith L, et al. Attenuation of capillary leakage by hydroxyethyl starch (130/0.42) in a porcine model of septic shock. Crit Care Med 2006;34:3005-3010.

14. Feng X, Liu J, Yu M, et al. Hydroxyethyl starch, but not modified fluid gelatin, affects inflammatory response in a rat model of polymicrobial sepsis with capillary leakage. Anesth Analg 2007;104:624-630.

15. Dieterich HJ, Weissmuller T, Rosenberger P, et al. Effect of hydroxyethyl starch on vascular leak syndrome and neutrophil accumulation during hypoxia. Crit Care Med 2006;34:1775-1782.

16. Zikria BA, King TC, Stanford J, et al. A biophysical approach to capillary permeability. Surgery 1989;105:624-631.

17. Vincent JL. Plugging the leaks? New insights into synthetic colloids. Crit Care Med 1991;19:316-318.

18. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983;11:839-850.

19. Huang CC, Kao KC, Hsu KH, et al. Effects of hydroxyethyl starch resuscitation on extravascular lung water and pulmonary permeability in sepsis-related acute respiratory distress syndrome. Crit Care Med 2009;37:1948-1955.

20. Roch A, Guervilly C, Papazian L. Fluid management in acute lung injury and ARDS. Ann Intensive Care 2011;30:16.

21. Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005;33:1161-1687.

22. Dubois M-J, Orellana-Jimenez C, Mélot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled pilot study. Crit Care Med 2006;34:2536-2540.

23. Groeneveld AB, Navickis RJ, Wilkes MM. Update on the comparative safety of colloids: a systematic review of clinical studies. Ann Surg. 2011 253:470-483. Review.

24. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis 2008;51:491-503.

25. Roche AM, James MFM. Colloids and crystalloids: does it matter to the kidney? Curr Opin Crit Care 2009;15:520-524.

26. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet 2001;357:911-916.

27. Schabinski F, Oishi J, Tuche F, et al. Effects of a predominantly hydroxyethyl starch (HES)-based and a predominantly non HES-based fluid therapy on renal function in surgical ICU patients. Intensive Care Med 2009;35:1539-1547.

28. Boussekey N, Darmon R, Langlois J, et al. Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury. Crit Care 2010;14:R40.

29. James MF, Michell WL, Joubert IA, et al. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a

10

randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011;107:693-702.

30. Muller L, Jaber S, Molinari N, et al. Fluid management and risk factors for renal dysfunction in patients with severe sepsis and/or septic shock. Crit Care 2012;16:R34.

31. Simon TP, Schuerholz T, Hüter L, et al. Impairment of renal function using hyperoncotic colloids in a two hit model of shock: a prospective randomized study. Crit Care 2012;16:R16.

32. Bayer O, Reinhart K, Sakr Y, et al. Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. Crit Care Med 2011;39:1335-1342.

33. Kozek-Langenecker SA. Influence of fluid therapy on the haemostatic system of intensive care patients. Best Pract Res Clin Anaesthesiol 2009;23:225-236. Review.

34. de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001;29:1261-1267. Review.

35. Hartog CS, Reuter D, Loesche W, et al. Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. Intensive Care Med 2011;37:1725-1737.

36. Perner A, Haase N, Guttormsen AB, et al. for the 6S Trial Group and the Scandinavian Critical Care Trials Group. Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis. N Engl J Med 2012;367:124-34.

37. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Crit Care 2012;16:R94.

38. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008;36:2667-74.

39. Finfer S, Liu B, Taylor C, et al. The SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 2010;14:R185.

40. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: an updated systematic review and meta-analysis. Anesth Analg 2012;114:159-169.

41. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 2012;38:368-383.

42. Atkins D, Best D, Briss PA, et al. for the GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490-1494.

43. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. Chest 2006;129:174-181.

PART II

44. Maitland K, Kiguli S, Opoka RO, et al. FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-2495.

45. Vincent JL. So we use less pulmonary artery catheters--but why? Crit Care Med 2011;39:1820-1822.

46. Pinsky MR, Vincent JL. Let us use the pulmonary artery catheter correctly and only when we need it. Crit Care Med 2005;33:1119-22.

47. Wheeler AP, Bernard GR, Thompson BT, et al. for the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006;354:2213-2224.

48. Michard F, Alaya S, Zarka V, et al. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. Chest 2003;124:1900-1908.

49. Goepfert MS, Reuter DA, Akyol D, et al. Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 2007;33:96-103.

50. Koo KK, Sun JC, Zhou Q, et al. Pulmonary artery catheters: evolving rates and reasons for use. Crit Care Med 2011;39:1613-1618.

51. Vincent JL, Pinsky MR, Sprung CL, et al. The pulmonary artery catheter: in medio virtus. Crit Care Med 2008;36:3093-3096.

52. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg 2011;112:1392-1402. Review.

53. Bolli R, Hartley CJ, Rabinovitz RS. Clinical relevance of myocardial "stunning". Cardiovasc Drugs Ther 1991;5:877-890. Review.

54. Kusuoka H, Porterfield JK, Weisman HF, et al. Pathophysiology and pathogenesis of stunned myocardium. Depressed Ca2+ activation of contraction as a consequence of reperfusion-induced cellular calcium overload in ferret hearts. J Clin Invest 1987;79:950-961.

55. Kloner RA, Przyklenk K, Kay GL. Clinical evidence for stunned myocardium after coronary artery bypass surgery. J Card Surg 1994;9(Suppl):397-402.

56. Breukers RM, Trof RJ, de Wilde RB, et al. Relative value of pressures and

volumes in assessing fluid responsiveness after valvular and coronary artery surgery. Eur J Cardiothorac Surg 2009;35:62-68.

57. Breukers RM, Trof RJ, Groeneveld AB: Cardiac filling volumes and pressure in assessing preload responsiveness during fluid challenges. In Yearbook of Intensive Care and Emergency Medicine. Edited by: Vincent J-L. Springer, Berlin, Germany; 2009:265–275.

58. Pinsky MR. Clinical significance of pulmonary artery occlusion pressure. Intensive Care Med 2003;29:175-178.

59. Pinsky MR. Pulmonary artery occlusion pressure. Intensive Care Med 2003;29:19-22.

60. Carl M, Alms A, Braun J, et al. S3 guidelines for intensive care in cardiac surgery patients: hemodynamic monitoring and cardiocirculary system. Ger Med Sci 2010;8:Doc12.

61. Wolf S, Riess A, Landscheidt JF, Lumenta CB, et al. Global end-diastolic volume acquired by transpulmonary thermodilution depends on age and gender in awake and spontaneously breathing patients. Crit Care. 2009;13(6):R202.

10

62. Malbrain ML, De Potter TJ, Dits H, et al. Global and right ventricular end-diastolic volumes correlate better with preload after correction for ejection fraction. Acta Anaesthesiol Scand 2010;54:622-631.

63. Eichhorn V, Goepfert MS, Eulenburg C, et al. Comparison of values in critically ill patients for global end-diastolic volume and extravascular lung water measured by transcardiopulmonary thermodilution: A metaanalysis of the literature. Med Intensiva 2012 Jan 25. [Epub ahead of print].

64. Zhang Z, Lu B, Ni H. Prognostic value of extravascular lung water index in critically ill patients: A systematic review of the literature. J Crit Care 2012;27:e1-8.

65. Sakka SG, Klein M, Reinhart K, et al. Prognostic value of extravascular lung water in critically ill patients. Chest 2002;122:1715-1720.

66. Phillips CR, Chesnutt MS, Smith SM. Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival. Crit Care Med 2008;36:69-73.

67. Michard F. Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls. Crit Care Med 2007;35:1186-1192. Review.

68. Aman J, Johan Groeneveld AB, van Nieuw Amerongen GP. Predictors of pulmonary edema formation during fluid loading in the critically ill with presumed hypovolemia. Crit Care Med 2012;40:793-799.

69. van der Heijden M, Verheij J, van Nieuw Amerongen GP, et al. Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. Crit Care Med 2009;37:1275-1281.

61. Eichhorn V, Goepfert MS, Eulenburg C, et al. Comparison of values in critically ill patients for global end-diastolic volume and extravascular lung water measured by transcardiopulmonary thermodilution: A metaanalysis of the literature. Med Intensiva 2012 Jan 25. [Epub ahead of print].

62. Zhang Z, Lu B, Ni H. Prognostic value of extravascular lung water index in critically ill patients: A systematic review of the literature. J Crit Care 2012;27:e1-8.

63. Sakka SG, Klein M, Reinhart K, et al. Prognostic value of extravascular lung water in critically ill patients. Chest 2002;122:1715-1720.

64. Phillips CR, Chesnutt MS, Smith SM. Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival. Crit Care Med 2008;36:69-73.

65. Michard F. Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls. Crit Care Med 2007;35:1186-1192. Review.

66. Aman J, Johan Groeneveld AB, van Nieuw Amerongen GP. Predictors of pulmonary edema formation during fluid loading in the critically ill with presumed hypovolemia. Crit Care Med 2012;40:793-799.

67. van der Heijden M, Verheij J, van Nieuw Amerongen GP, et al. Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. Crit Care Med 2009;37:1275-1281.