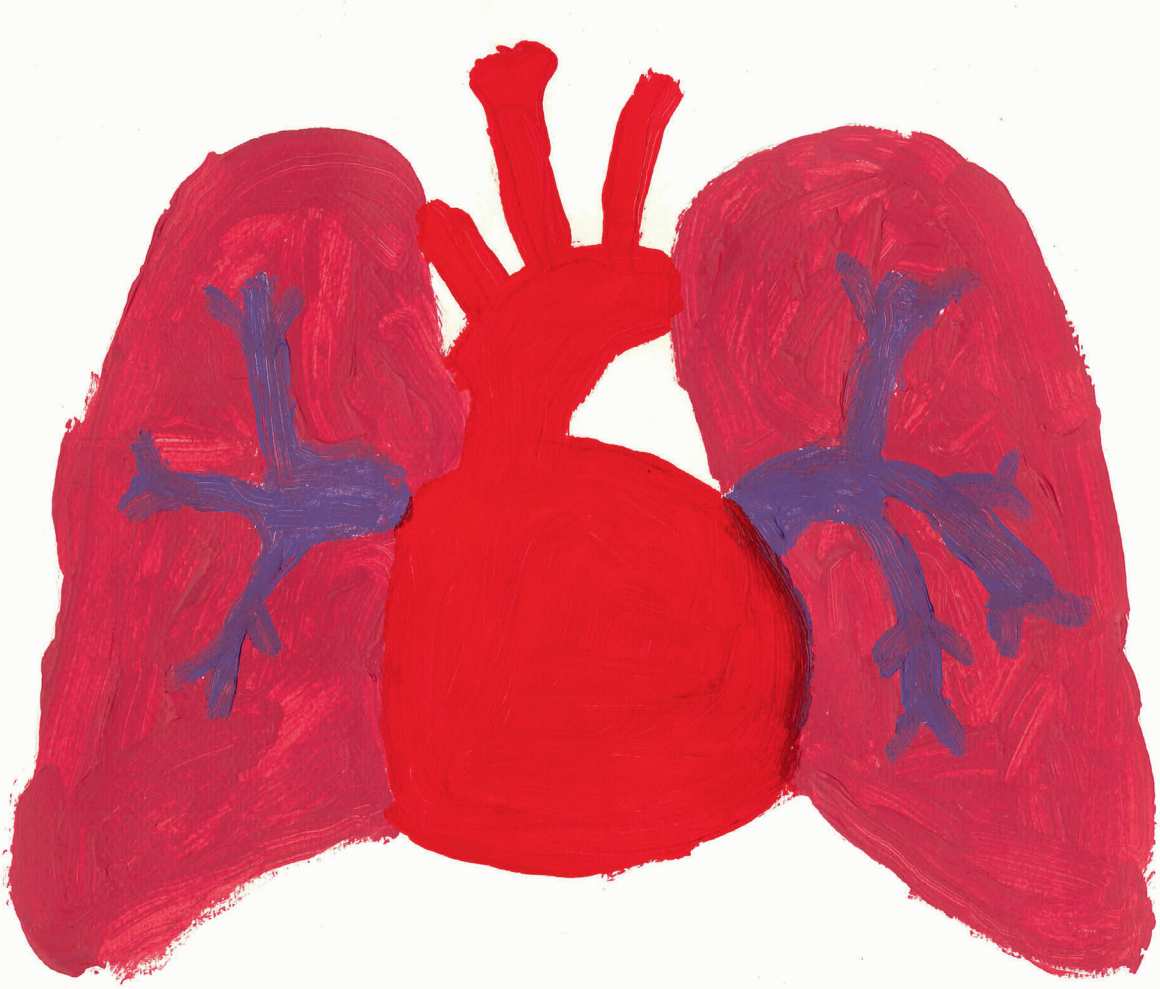

# Optimizing fluid management in critically ill patients

Ronald Jan Trof

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2012

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# Optimizing fluid management in critically ill patients

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door

Ronald Jan Trof

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*Science is organized knowledge, wisdom is organized life*

Immanuel Kant (1724 – 1804)

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The studies in this thesis were performed at the departments of Intensive Care, VU Medical Center, Amsterdam and Medisch Spectrum Twente, Enschede, The Netherlands.

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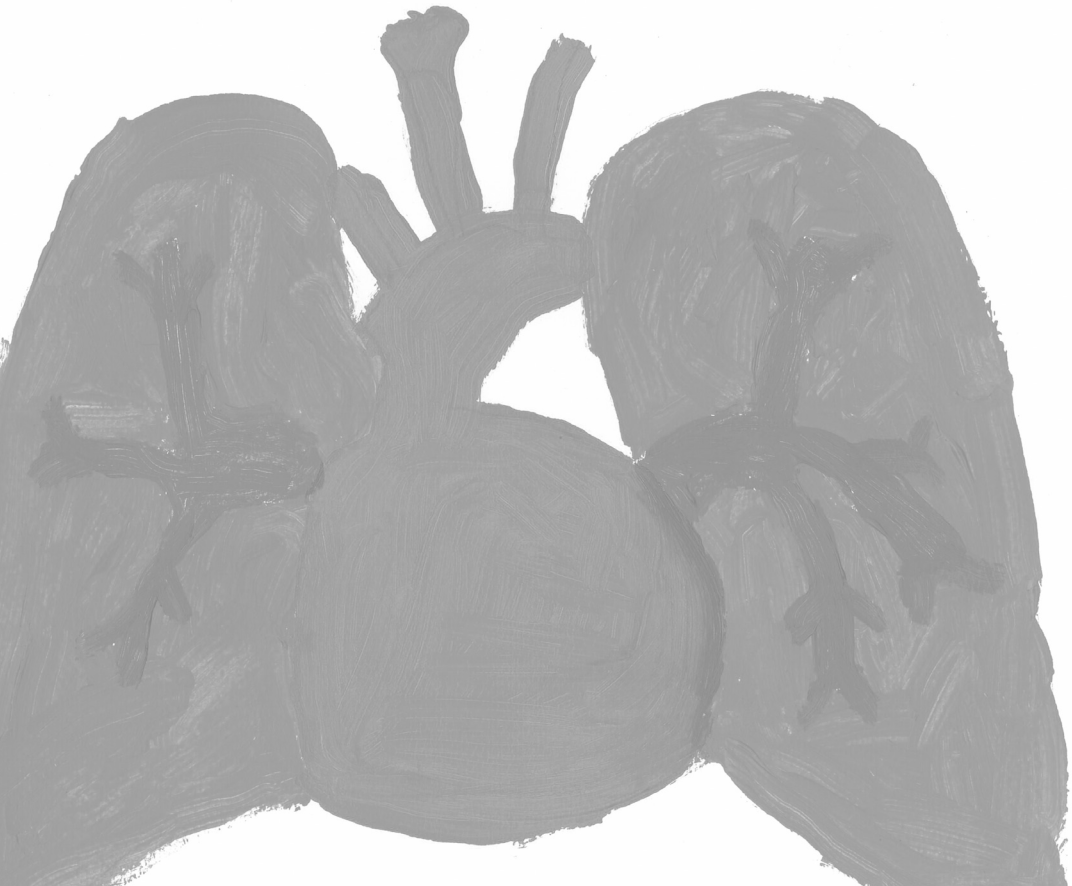
## Table of Contents

# 1

## General introduction and outline of thesis



Fluid resuscitation is a crucial intervention in the treatment of critically ill patients with circulatory shock. Fluids are primarily administered for reversal of absolute hypovolemia due to external fluid losses or due to relative hypovolemia as a consequence of an increase in venous capacitance as seen in septic shock for instance. However, there is little conclusive evidence to guide clinicians on the optimal type of resuscitation fluid; the appropriate timing, volume, and rate of fluid administration; or on the optimal way to monitor the efficacy and safety of fluid resuscitation in various clinical conditions. The main goal of fluid resuscitation is restoration or conservation, at least in part, of an effective circulating volume which is required to maintain optimal oxygen delivery, which in turn is necessary for adequate tissue oxygenation and cellular metabolism. Persistent hypovolemia may contribute to microcirculatory compromise, leading to organ dysfunction and, ultimately, multiple organ failure and should therefore be avoided or corrected, if possible[1,2]. On the other hand, abundant fluid administration accompanied with a cumulative positive fluid balance may also negatively influence outcome due to the development of pulmonary and interstitial edema which may prolong the duration of mechanical ventilation and ICU stay[3-7]. Therefore, it seems reasonable that fluid therapy should be tailored and directed on clearly defined (hemodynamic) endpoints, also called "goal directed therapy", which is associated with improved outcome. Indeed, in the last decade it has been demonstrated that goal directed fluid therapy reduces mortality in surgical as well as non-surgical patients with (impending) shock[8-14], which now has formed the basis of (international) guidelines on treating patients with circulatory shock[2,15]. Nevertheless, there is ongoing debate on a) the type of fluid to be used and b) whether hemodynamic monitoring may be beneficial to guide fluid therapy. Answering these two important questions will provide the basis of this thesis.

## PART I
## Fluids: type, dosing and timing

The Surviving Sepsis Campaign Guidelines[2] recommend fluid resuscitation with either natural or artificial colloids or crystalloids, as they conclude that evidence-based support in favor of one type of fluid is lacking. This arbitrariness is however debatable,

since on (patho)physiological grounds more crystalloids than colloids need to be infused for reaching the same hemodynamic endpoints, which may increase the risk of fluid overload and harmful pulmonary edema. In addition, an emerging body of evidence suggests that the type of resuscitation fluid may adversely affect outcome in specific clinical conditions. For instance, administration of albumin solutions is associated with increased mortality in patients with traumatic brain injury[16] and high-molecular-weight preparations of hydroxyethyl starch are associated with acute kidney injury in patients with severe sepsis[17]. Conversely, improved outcomes associated with the use of albumin for resuscitation purposes have been shown in children with severe malaria[18] and in adults with severe sepsis[19,20]. However, these reports were not sufficiently conclusive to justify strong clinical recommendations on the use of a specific type of fluid. Surveys among European ICUs on the use of preferred plasma volume expanders for critically ill patients demonstrate a more frequent use of colloids than of crystalloids in first line treatment, whereas hydroxyethyl starch is the most widely used synthetic colloid, but with large differences between countries[21-24]. Despite a demonstrated lack of survival benefit with the use of colloids[25], this did not seem to be convincing enough to adapt local habits, unless other properties may render colloids a preferable resuscitation fluid. It may be hypothesized that one of the reasons for the widespread colloid use may be the potential hemodynamic effects associated with a lower volume needed to reach certain hemodynamic end-points. This hypothesis will further be explored in this thesis.

## PART II
## Monitoring fluid therapy

The effectiveness of hemodynamic monitoring depends on both the available technology and on the ability to diagnose and effectively treat the disease processes for which it is being used. The utility of hemodynamic monitoring has evolved as it merged with information technology while our understanding of disease pathophysiology has also improved. Within this context, hemodynamic monitoring represents a functional tool that may be used to derive estimates of performance and physiological reserve that may in turn direct treatment, for instance fluid resuscitation, in order to reverse the disease process identified.

It must be emphasized that a monitoring tool itself cannot improve outcome unless 1) the data obtained from the monitoring device is sufficiently accurate to be able to influence therapeutic decision making, 2) the data obtained from the monitoring system is relevant to the patient being monitored, and 3) changes in management made as a result of the data obtained are able to improve outcomes[26]. If the data are interpreted or applied incorrectly, then fluid therapy itself may be ineffective or harmful, and the resultant change in management will not improve outcome and may even be deleterious[26]. If these three conditions are not met, monitoring is unlikely to be associated with improved outcomes, and this may count for the lack of evidence of improved outcomes in critically ill patients with the use of any monitoring device[27].

In this thesis we will focus on the pulmonary artery catheter and the transpulmonary (thermo)dilution technique and compare both techniques for guiding fluid therapy and hemodynamic management in patients with different disease etiologies.

**Pulmonary artery catheter**

The pulmonary artery catheter (PAC) has been used for decades for monitoring hemodynamics in the perioperative setting or in critically ill patients. By measurement of the pulmonary artery occlusion pressure (PAOP) via balloon occlusion of the pulmonary artery, an estimation can be made for left ventricular end-diastolic pressure as a surrogate for left ventricular preload (Figure 1). In addition, by generating a thermodilution curve via a central venous bolus of isotonic saline, right ventricular stroke volume and cardiac output (CO) can be measured. The PAC derived PAOP and CO provide bedside estimations of left ventricular performance in critically ill patients, which may help the clinician diagnose and treat circulatory shock.

*Pulmonary artery occlusion pressure.* The PAOP is most often used for assessment of (a) pulmonary edema, (b) pulmonary vasomotor tone, (c) intravascular volume status and (d) left ventricular performance. In mechanically ventilated patients however, the atmospheric pressure referenced PAOP may be confounded by airway pressures and may thereby poorly predict cardiac preload, fluid responsiveness, and pulmonary capillary filtration[28]. These technical limitations however are surmountable; by using a firm understanding of the technical determinants of PAOP during ventilation, PAOP values may be interpreted correctly at the bedside under many circumstances[29].

Nevertheless, 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[30,31].

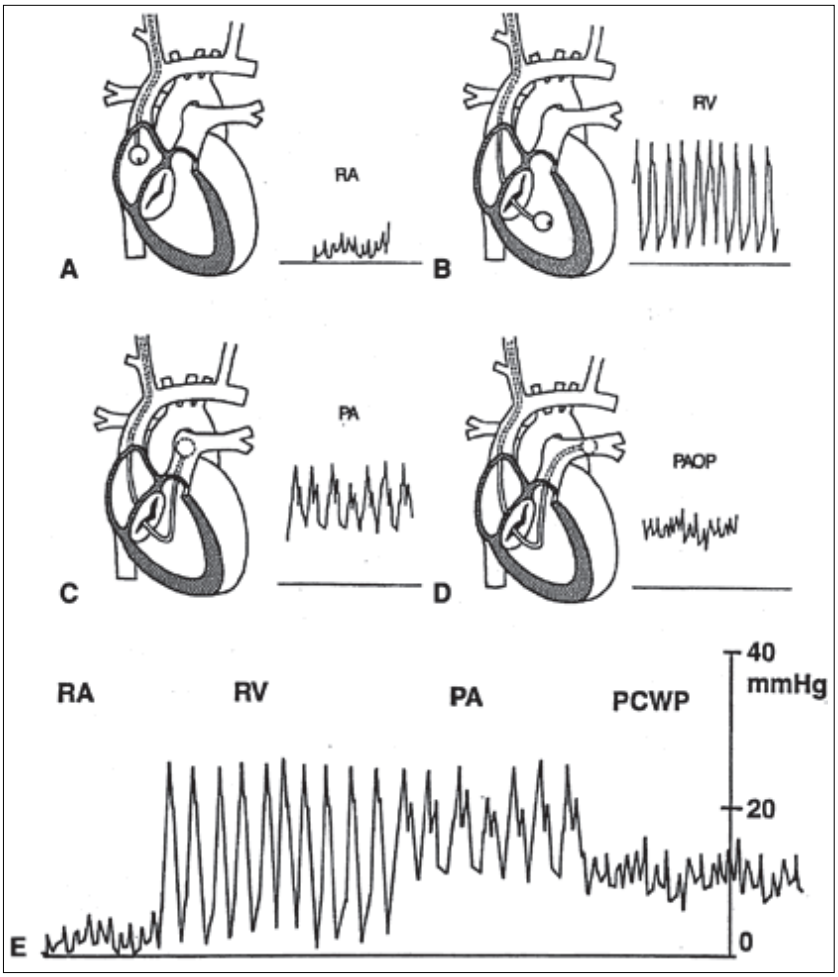



**Figure 1.** Pulmonary artery catheter tip pressure tracings and chamber location during placement. Specific chamber location and representative tracings are shown for the right atrium (**A**), right ventricle (**B**), pulmonary artery (**C**), and pulmonary capillary wedge pressure (**D**). An entire pulmonary artery catheterization pressure tracing is shown in (**E**). (Modified from Mihm FG, Rosenthal MH: Pulmonary artery catheterization. In Benito JL, ed.: Clinical Procedures in Anesthesia and Intensive Care, p 416. Philadelphia, JB Lippincott, 1994).

**Transpulmonary (thermo)dilution technique**

A relatively new, less invasive hemodynamic monitoring technique is the transpulmonary (thermo)dilution technique, which was introduced in the 1990s. This technique uses a double-indicator thermal dye dilution, with ice-cold indocyanine green allowing intravascular determination of the dye and the thermal signal after central venous injection. The mean transit time of the dye (detected in the aorta via a femoral artery catheter) multiplied by cardiac output (CO) yields the intrathoracic blood volume (ITBV), whereas the mean transit time of the thermal signal multiplied by CO yields the intrathoracic thermal volume (ITTV). The CO is derived from the transpulmonary thermodilution curve based on the Stewart-Hamilton formula[32]. Combining ITBV and ITTV, additional parameters can be computed such as the global end-diastolic volume (GEDV), reflecting cardiac preload, and extravascular lung water (EVLW), which reflects the amount of water outside the pulmonary vasculature (note: without any distinction between interstitial and alveolar water). This double-indicator thermal dye dilution technique is however very time consuming and using indocyanine green as an intravascular indicator is relatively expensive and requires specialized densitometry equipment or a fiberoptic catheter to detect the dye curve. Therefore, after validation, the thermal-dye technique has now been replaced by the current transpulmonary thermodilution (TPTD) technique allowing simultaneous measurement of CO, GEDV and EVLW using a single thermal indicator (Figure 2). Furthermore, by using an algorithm based on the analysis of the arterial pulse contour, it is possible to continuously monitor cardiac output since the contour of the arterial pressure curve is proportional to the stroke volume and pulse pressure[33]. This technique yields beat to beat variations of stroke volume and pulse pressure and thus cardiac output in response to changing preload conditions and allows the clinician to predict fluid responsiveness without actually giving fluids. It has however been demonstrated that these dynamic indices only have predictive value under certain conditions, since interpretation of these parameters is highly dependent on multiple factors, such as ventilatory settings and heart rhythm[34,35].

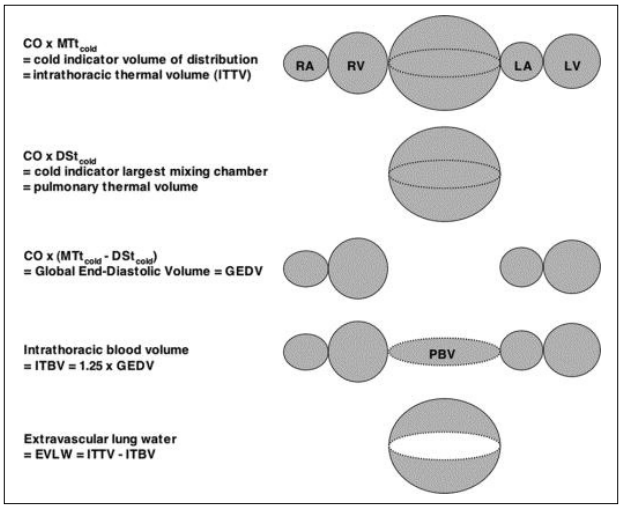



**Figure 2.** Principles of extravascular lung water (EVLW) estimation by the single-indicator dilution method. The intrathoracic blood volume (ITBV) is derived from the measurement of the global end-diastolic volume (GEDV) with the equation ITBV = 1.25 × GEDV. The difference between the volume of distribution of the thermal indicator and ITBV yields EVLW. CO, cardiac output; MTt, mean transit time; Dst, down slope time; RA, right atrium; RV, right ventricle; PBV, pulmonary blood volume; LA, left atrium; LV, left ventricle. (from: Michard F. Bedside assessment of extravascular lung water by dilution methods: Temptations and pitfalls. Crit Care Med 2007;35:1186-1192).

*Global end-diastolic volume.* Global end-diastolic volume (GEDV) represents the volumes of the right and left heart at the end of diastole and often reflects left ventricular end-diastolic volume as estimated by echocardiography in the absence of overt right ventricular dilatation[36] and has been demonstrated to reflect cardiac preload better than filling pressures[37,38]. A relatively low GEDV predicts fluid responsiveness (and a relatively high GEDV the absence thereof), but its predictive value is not perfect and the role of (right ventricular) systolic and/or diastolic dysfunction remains unclear, even though changes in stroke volume or cardiac output correlates to changes in GEDV (or intrathoracic blood volume)[38-40]. Therefore, it may be hypothesized that in patients with systolic dysfunction, due to a right- and downward shift of the cardiac function curve, pressures may better predict and monitor fluid responsiveness than volumes, which has been suggested previously[41-43].

*Extravascular lung water.* The pathologic accumulation of pulmonary edema can be quantified as extravascular lung water (EVLW). Although pulmonary edema

can be assessed by oxygenation indexes and chest radiographic techniques, EVLW has been shown to be more sensitive than these assessments[44,45]. EVLW estimated by TPTD has been shown to correlate quite closely with EVLW assessed by the thermal-dye technique[46] and gravimetric measurement[47]. It the last few years it has been demonstrated that a persistently increased EVLW is well correlated with poor outcome[48,49] while conservative fluid management has shown to reduce the duration of mechanical ventilation and length of stay in the ICU in patients with acute lung injury[5]. As has previously been suggested, the use of EVLW as an additional guidance for fluid therapy may influence outcome[50]. Restriction of fluid therapy based on upper limits of EVLW may potentially affect duration of mechanical ventilation or even outcome.

## Outline of the thesis

The first part of this thesis is focused on the controversy of crystalloids versus colloids for fluid resuscitation and aims to elucidate the possible (hemodynamic) benefits of colloids versus crystalloids weighed against potential harmful side effects. In **Chapter 2** we study whether crystalloid versus colloid fluid loading in patients with sepsis versus nonsepsis with clinical hypovolemia may differ with regard to hemodynamic effects. In **Chapter 3** we will describe the mechanisms of fluid loading on cardiac output and review the clinical data regarding the crystalloid-colloid volume ratio in determining hemodynamic effects. In **Chapter 4** we will discuss the major controversial issues of fluid resuscitation in acute lung injury/acute respiratory distress syndrome with regard to dosing, timing and choosing the type of fluid. In **Chapter 5** we will review the merits and detriments, in particular the risk of acute kidney injury, of the use of synthetic colloids, as compared to natural colloids and crystalloids in critically ill patients with sepsis.

The second part is focused on hemodynamic monitoring as guidance for fluid therapy. We will discuss whether disease etiology and (related) cardiac (dys)function may play a distinctive role in using pulmonary artery catheter derived parameters versus transpulmonary (thermo)dilution derived parameters for hemodynamic management. It may be hypothesized that hemodynamic management based on tool-

derived parameters may differ among disease etiologies and that interpretation of these parameters may be influenced by cardiac (dys)function. In **Chapter 6** we will compare cardiac filling volumes versus pressures for predicting fluid responsiveness after cardiovascular surgery, and examine whether systolic cardiac function may have a contributing role. In **Chapter 7** we will study whether cardiac dilatation, reflected by increased values of global end-diastolic volumes, affects fluid responsiveness in sepsis-induced cardiac depression. In **Chapter 8** we will review current insights concerning the measurement of extravascular lung water as an index of pulmonary edema using transpulmonary dilution techniques. Lastly, in **Chapter 9** we performed a large two center prospective, randomized controlled trial comparing volume-limited versus pressure-limited fluid therapy and hemodynamic management in septic and nonseptic shock and hypothesized that incorporation of extravascular lung water and global end-diastolic volume compared to pulmonary artery occlusion pressure in hemodynamic management algorithms may decrease the risk of fluid overloading and explored whether septic and nonseptic shock may differ in this respect.

The results of all studies are summarized and discussed in **Chapter 10**, together with a general discussion and future perspectives.

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# 2

## Greater cardiac response of colloid than saline fluid loading in septic and nonseptic critically ill patients with clinical hypovolemia

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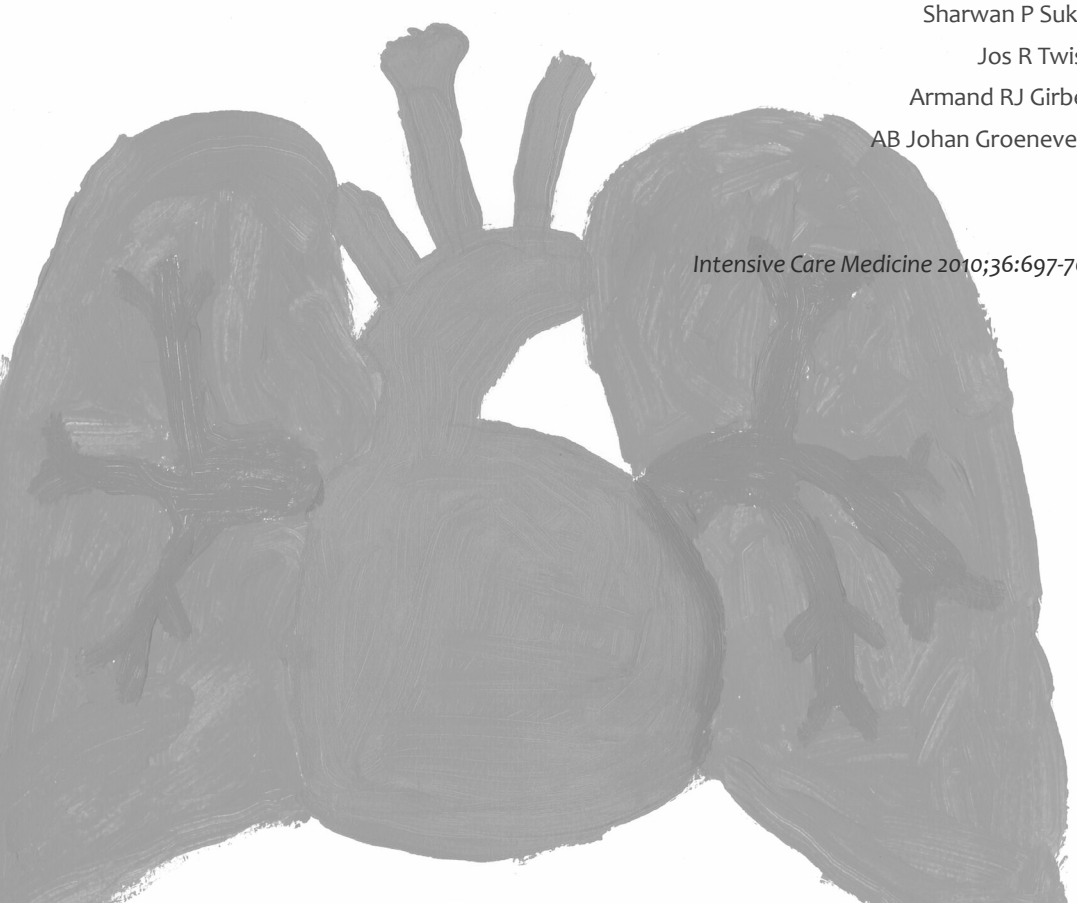

## Abstract

### Background and objective

The hemodynamics of crystalloid and colloid fluid loading may depend on underlying disease, i.e. sepsis vs. nonsepsis.

### Design and setting

A single-center, single-blinded, randomized clinical trial on 24 critically ill sepsis and 24 nonsepsis patients with clinical hypovolemia, assigned to loading with normal saline, gelatin 4%, hydroxyethyl starch 6% or albumin 5% in a 90 min (delta) central venous pressure (CVP)-guided fluid loading protocol. Transpulmonary thermal-dye dilution was done each 30 min, yielding, among others, global end-diastolic volume and cardiac indices (GEDVI, CI).

### Results

Sepsis patients had hyperdynamic hypotension in spite of myocardial depression and dilatation, and greater inotropic/vasopressor requirements than nonsepsis patients. Independent of underlying disease, CVP and GEDVI increased more after colloid than saline loading ($p < .018$), so that CI increased by about 2% after saline and 12% after colloid loading ($p = .029$). The increase in preload-recruitable stroke work was also greater with colloids and did not differ among conditions.

### Conclusions

Fluid loading with colloids results in a greater linear increase in cardiac filling, output and stroke work than saline loading, in both septic and nonseptic clinical hypovolemia, in spite of myocardial depression and presumably increased vasopermeability potentially decreasing the effects of colloid fluid loading in the former.

## Introduction

Hypovolemia is common in septic and nonseptic critical illness and fluid resuscitation is aimed at a rapid increase of cardiac output and tissue oxygenation. It is still controversial whether crystalloid or colloid (albumin) fluids should be used, since, among others, the clinical outcome may not differ according to fluid types or may be even somewhat worse for colloids (albumin)[1,2]. Other studies[3,4] suggest that resuscitation with albumin tends to benefit morbidity and survival over that with saline during sepsis.

The crystalloid-colloid controversy includes the role of colloid osmotic pressure (COP) in plasma in retaining fluids intravascularly and in the speed and extent by which colloids, maintaining COP, restore plasma volume and blood flow as opposed to crystalloids, which dilute plasma proteins, lower COP and rapidly leak into the interstitium[1,5-9]. When using crystalloids, 2 to 4 times more fluid may be required to restore and maintain intravascular fluid volume compared to colloids[1,5-8]. This is controversial, however, since, for instance, the ratio in the SAFE study comparing albumin with saline resuscitation was 1:1.3, whereas the rise in central venous and arterial blood pressures was only slightly greater with albumin[3]. A potential difference between fluid types may critically depend on underlying disease, so that, during sepsis, a decrease of cardiac function and an increase of vasopermeability may attenuate hemodynamic differences between fluids by decreasing the slope of the cardiac function curve and diminishing the contribution of plasma COP and thus the ability of colloids in retaining fluids intravascularly, respectively[1,8,10-14]. If so, a potential survival benefit of albumin over saline in sepsis[4] may not relate to its colloid osmotic properties[15]. Indeed, the colloid-colloid controversy refers to the potential of artificial colloids to replace human protein colloids[1,2,8]. For instance, starch infusions may result in better cardiac performance than infusions of albumin[11], which may have negative inotropic effects via binding of circulating calcium[16]. Finally, controversies may also stem in part from the monitored endpoints for fluid resuscitation, which, if imprecise, may mask hemodynamic differences. Absolute (rather than changes in) filling pressures of the heart may be poor indicators of cardiac preload and fluid responsiveness and global end-diastolic volume, assessed from transpulmonary thermodilution, may be superior[17-19]. In our study on cardiovascular surgery and fluid loading guided by (delta) filling pressures, colloid had more effects on plasma volume and cardiac filling and output than saline loading[9].

For the current study, the hypothesis was that fluid loading with colloids results in a greater increase in preload-recruitable cardiac output and stroke work than saline loading, more so in patients with nonseptic than in those with septic clinical hypovolemia in the intensive care unit (ICU), because of differences in cardiac and vascular function. We thus compared saline with colloids and evaluated COP and cardiac output and function, using a standard (delta) central venous pressure-guided fluid challenge protocol over 90 min[9], verified by the transpulmonary thermal-dye dilution technique[17], in septic and nonseptic clinical hypovolemia. We also hypothesized for this study that exogenous colloids perform similarly to human albumin.

## Patients and methods

This is a companion study on the same patients of a prospective study involving pulmonary (and few (t=0-90 min) raw hemodynamic) data regarding fluid loading[20].

Patients were included after random assignment (sealed envelope method to 4 different groups of n=6, both in n=24 sepsis and n=24 nonsepsis patients), to normal saline (NaCl 0.9%), or the roughly isooncotic colloid solutions Gelofusin$^{R}$ (gelatin 40 g/L, B Braun Medical, Melsungen AG, Germany, in 154/120 mmol/L NaCl), Hemohes$^{R}$ (hydroxyethyl starch (HES) 6%; MW 200,000 substitution 0.45-0.55, Braun Melsungen AG, Germany, in saline) or albumin 5% (100 mL Cealb® 20%, Sanquin, CLB, Amsterdam, The Netherlands, diluted in 300 mL of saline). The inclusion criteria were clinical hypovolemia, defined by a systolic blood pressure <110 mmHg, and by a reduced central venous pressure (CVP ≤12 mm Hg if positive end-expiratory pressure, PEEP, ≤15 cm $H_2O$, and CVP ≤16 mm Hg if PEEP >15 cm $H_2O$) in the presence of a central venous (n=45, or pulmonary artery, n=3) catheter inserted in the subclavian or internal jugular vein and in the absence of overt major bleeding. Exclusion criteria were age <18 or >78 years, pregnancy, preterminal illness with life expectancy <24 hours, recent traumatic brain injury, and known anaphylactic reactions to colloids. Sepsis was defined by two or more of the following clinical findings: body temperature >38 or <36°C; heart rate (HR) >90/min; presence of mechanical ventilation; abnormal white blood cell counts >12,000 or <4,000 x$10^9$/L and a clinically evident or microbiologically proven source of infection. The origin of sepsis was defined by clinical signs and symptoms and positive local and/or

blood cultures. Nonsepsis was defined as an injury severity score above 15 for multiple trauma, gastrointestinal hemorrhage or major, non-cardiovascular surgery, for which admission into the ICU was required.

*Measurements.* Pressures were measured after calibration and zeroing to atmospheric pressure at mid-chest level (Tramscope®, Marquette, Wisc., USA). CVP was taken at end-expiration, with patients in the supine position. For the measurement of cardiac output (CO), stroke volume (SV) and global end-diastolic volume (GEDV), the transpulmonary thermal-dye dilution technique was used[9,17,18,20]. This involves a central venous injection of a dye and thermal bolus, 15 mL of 1 mg/mL indocyanine green in an ice-cold (4°C) dextrose 5% solution and concomitant registration of the dye dilution and thermal shift in the femoral artery, using a 3F catheter equipped with a thermistor and fiberoptic (PV 2024, Pulsion Medical Systems, Munich, Germany) connected to a bedside computer (COLD Z-021, Pulsion Medical Systems, Munich, Germany). The catheter was introduced via the introducing sheath. Measurements were done in duplicate, irrespective of the ventilatory cycle, and averaged values were taken. The technique yields the transpulmonary thermodilution CO and GEDV, typically at 10% reproducibility (17). CO, SV and GEDV were indexed to body surface area ($m^2$), yielding cardiac index (CI, L/min/$m^2$), SV index (SVI, mL/$m^2$) and GEDV index (GEDVI, n 680-800 mL/$m^2$), respectively. The ratio between SVI and GEDVI/4 is the global ejection fraction (GEF, n 0.25-0.35), an index of systolic cardiac function (18). The left ventricular stroke work index (LVSWI, gm/$m^2$) was calculated from SVI x (mean arterial pressure (MAP) minus CVP) x 0.0136, where the CVP was substituted for the PCWP since in the 3 patients in whom the PCWP was measured CVP and PCWP highly correlated ($r = .97$, $p < .001$, n=15) and differed by only 3±1 mm Hg. The LVSWI to GEDVI/4 relation is denoted as preload-recruitable stroke work, another index of systolic cardiac function. Arterial and central venous blood samples were obtained for determinations of Hb/Hct, creatinine (Sysmex SE-9000, Sysmex Corporation, Kobe, Japan), $O_2$ pressures and saturations. The colloid oncotic pressure (COP) was measured by a membrane osmometer (Osmomat 050, Gonotex, Berlin, molecular cut-off at 20 kDa). Systemic vascular resistance index (SVRI), $O_2$ delivery ($DO_2$) and oxygen consumption ($VO_2$) were calculated according to standard formulae.

*Protocol.* This was started within 3 hrs after surgery or gastrointestinal hemorrhage and 12 h after meeting criteria for sepsis. At baseline, patient characteristics and clinical data were recorded, including the acute physiology and chronic health evaluation (APACHE) II score. Doses of vasoactive drugs, ventilatory settings and hemodynamics were recorded. After baseline measurements (t=0 min), fluids were given during 90 min on the basis of the response within predefined limits and changes in CVP, according to a fluid challenge protocol as described[20]. Boluses of maximum 200 mL were given per 10 min, so that the maximum fluid challenge was 1800 mL in 90 min. Concomitant treatment was unchanged. All measurements were repeated after completing the fluid challenge (t=90 min). Every 30 min until t=90 min, CVP, CO and GEDV were measured also.

*Statistical analysis.* The study had 80% power to detect a statistically significant difference between saline and colloid fluids (at $\alpha<0.05$) in fluid loading-induced increases in CI, the primary study parameter, of 10% (at standard deviation of 10% of the increase). Data are expressed as mean±standard deviation (SD), except in the figures, where mean±standard error of mean (SEM) are shown. Data were normally distributed (Kolmogorov-Smirnov test), after logarithmic transformation where appropriate. We used GEE to test for effect of underlying disease and fluid type on baseline values and, taking repeated measurements in the same patients and first order interactions into account, on changes in time with baseline values as covariates. Then, interactions allowed to assess whether effects of fluid types in time were dependent of underlying disease. Fishers exact or $X^2$ tests were used for categorical variables. A similar analysis was done to compare colloid fluids. A value of $P<0.05$ was considered statistically significant and exact values >0.001 are reported.

## Results

*Patient characteristics.* Patient characteristics are shown in Table 1, 2 A+B. Groups were comparable, except for a higher APACHE II score, creatinine, PEEP, more inotropic/vasopressor treatment and less diuresis in sepsis (Table 1). More colloid than saline fluid had been administered, irrespective of underlying disease.

**Table 1.** Patient characteristics.

| | Nonsepsis | | Sepsis | | *p* value | | |
|---|---|---|---|---|---|---|---|
| | Saline (n=6) | Colloid (n=18) | Saline (n=6) | Colloid (n=18) | U | Ty | UxTy |
| Age | 54±19 | 55±17 | 63±12 | 59±11 | .196 | .819 | .599 |
| Sex (male/female) | 4/2 | 13/5 | 5/1 | 13/5 | .563 | .805 | .563 |
| APACHE II | 9±3 | 11±4 | 14±6 | 14±5 | .002 | .402 | .498 |
| Nonsepsis | | | | | | | |
| Abdominal surgery | 4 | 11 | | | | | |
| Polytrauma | 1 | 4 | | | | | |
| Spinal surgery | 1 | 2 | | | | | |
| Miscellaneous | | 1 | | | | | |
| Sepsis | | | | | | | |
| Abdominal | | | | | | | |
| C. Albicans | | | 1 | | | | |
| P. Aeruginosa | | | | 2 | | | |
| Pneumonia | | | | | | | |
| Gram-positive | | | | 4 | | | |
| Gram-negative | | | 2 | 2 | | | |
| M. Tuberculosa | | | | 1 | | | |
| C. Albicans | | | 1 | | | | |
| A. Fumigatus | | | 1 | | | | |
| Urogenital | | | | | | | |
| E. Coli | | | | 1 | | | |
| Catheter-related sepsis | | | | | | | |
| Gram-positive | | | | 3 | | | |
| C. Albicans | | | 1 | | | | |
| Meningitis | | | | | | | |
| S. Epidermidis | | | | 1 | | | |
| N. Meningitidis | | | 1 | | | | |
| Unknown focus | | | | | | | |
| B-Hemolytic Streptococcus | | | 1 | | | | |
| Bacteremia | | | 1 | 9 | | | |
| Dopamine, µg/kg/min | 0.7±1.2 | 2.0±2.8 | 7.2±5.2 | 5.9±3.6 | <.001 | .663 | .297 |
| Norepinephrine, µg/kg/min | 0 | 0.00±0.02 | 0.03±0.06 | 0.09±0.10 | .002 | .126 | .247 |
| PEEP, cm $H_2O$ | 5.6±0.9 | 7.9±3.4 | 7.8±5.6 | 13.4±4.7 | .004 | .003 | .215 |
| Fluid input t=0-90 min , mL | 1642±387 | 1531±328 | 1783±41 | 1380±290 | .962 | .004 | .098 |
| Diuresis t=0-90 min, mL | 800±595 | 496±384 | 263±198 | 163±180 | .001 | .239 | .423 |
| Creatinine, µmol/L | 77±9 | 88±22 | 107±65 | 153±88 | .003 | .074 | .292 |
| Mortality in the ICU | 0 | 2 (11) | 2 (33) | 7 (39) | For fluid types: 1.0 (nonsepsis) 1.0 (sepsis) | | |

Mean ± SD or number (percentage) where appropriate *APACHE* acute physiology and chronic health evaluation, *PEEP* positive end-expiratory pressure. *p*: *U* underlying disease (sepsis vs. nonsepsis), *Ty* fluid type (saline versus colloids), *UxTy* interaction. Fishers exact test for mortality.

Sepsis patients had hyperdynamic hypotension, as indicated by higher HR and CI (after fluid loading) and lower MAP, in spite of myocardial depression and dilatation as indicated by higher CVP and GEDVI, and lower GEF and LVSWI (to GEDVI/4 ratio, indicative of preload-recruitable stroke work) compared to nonseptic patients, respectively (Table 3). Baseline SVRI was lower in sepsis than in nonsepsis ($p = .013$, data not shown). The albumin level was also lower ($p < .001$). Sepsis carried a higher ICU mortality than nonsepsis ($p = .017$), irrespective of fluid types.

**Table 2A.** Patient characteristics: nonsepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) |
|---|---|---|---|
| Age (yr) | 53±18 | 54±21 | 58±15 |
| Sex (male/female) | 4/2 | 5/1 | 4/2 |
| APACHE II | APACHE II | APACHE II | APACHE II |
| Nonsepsis: | | | |
| Abdominal surgery | 4 | 4 | 3 |
| Polytrauma | 1 | 1 | 2 |
| Spinal surgery | | 1 | 1 |
| Miscellaneous | 1 | | |
| Dopamine, µg/kg/min | 1.0±1.8 | 3.3±3.6 | 1.8±2.7 |
| Norepinephrine, µg/kg/min | 0.00±0.01 | 0 | 0.01±0.03 |
| PEEP, cm $H_2O$ | 8.2±4.3 | 8.2±4.3 | 8.3±4.5 |
| Fluid t=0-90 min, mL | 1617±172 | 1483±422 | 1492±380 |
| Diuresis, mL | 252±121 | 659±344 | 537±498 |
| Creatinine, µmol/L | 87±19 | 97±34 | 82±10 |
| Mortality in the ICU | 1 (17) | 1 (17) | 0 |

Mean ± SD or number (percentage) where appropriate HES hydroxyethyl starch, APACHE acute physiology and chronic health evaluation, PEEP positive end-expiratory pressure. See Table 2B for statistics.

Baseline values were comparable among fluid types, except for a slightly lower hemoglobin and a higher PEEP and thus CVP in colloid than in saline-loaded patients. Hemoglobin levels fell more in colloid than in saline loading whereas COP increased in colloid-loaded patients only, irrespective of underlying disease (Table 4). The rises in MAP, CVP, GEDVI and CI were greater with colloid than saline loading, independent of underlying disease and baseline values (Table 3). Indeed, CVP and CI increased with time (t=0, 30, 60, 90 min), dependent on fluid type ($p = .007$ or lower), irrespective of underlying disease (Figure 1).

**Table 2B.** Patient characteristics: sepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) | *p* value U | Ty | UxTy |
|---|---|---|---|---|---|---|
| Age | 57±14 | 60±12 | 60±9 | .419 | .70 | .953 |
| Sex (male/female) | 5/1 | 4/2 | 4/2 | 1.000 | .844 | .650 |
| APACHE II | 14±6 | 13±5 | 16±2 | .018 | .568 | .661 |
| Sepsis | | | | | | |
| Abdominal | | | | | | |
| C. Albicans | | 1 | | | | |
| P. Aeruginosa | | 1 | | | | |
| Pneumonia | | | | | | |
| Gram-positive | 1 | 1 | 2 | | | |
| Gram-negative | | 1 | 1 | | | |
| M. Tuberculosa | 1 | | | | | |
| C. Albicans | 1 | | | | | |
| Urogenital | | | | | | |
| E. Coli | 1 | | | | | |
| Catheter-related sepsis | | | | | | |
| Gram-positive | | 1 | 2 | | | |
| C. Albicans | | 1 | | | | |
| Meningitis | | | | | | |
| S. Epidermidis | 1 | | | | | |
| Unknown focus | | | | | | |
| B-Hemolytic Streptococcus | 1 | | | | | |
| Bacteremia | 1 | 6 | 2 | | | |
| Dopamine (µg/kg/min) | 5.9±4.2 | 6.9±1.5 | 4.8±4.5 | <.001 | .135 | .589 |
| Norepinephrine (µg/kg/min) | 0.07±0.13 | 0.07±0.06 | 0.11±0.12 | <.001 | .531 | .880 |
| PEEP (cm $H_2O$) | 10.8±4.7 | 14.2±4.3 | 14.5±4.1 | <.001 | .180 | .515 |
| Fluid input t=0-90 min (mL) | 1358±344 | 1317±240 | 1467±308 | .126 | .729 | .603 |
| Diuresis t=0-90 min (mL) | 149±101 | 96±59 | 244±288 | <.001 | .018 | .005 |
| Creatinine (µmol/L) | 174±117 | 151±62 | 134±90 | .002 | .660 | .797 |
| Mortality in the ICU | 3 (50) | 2 (33) | 2 (33) | For fluid types: .80 nonsepsis .80 sepsis | | |

Mean ± SD or number (percentage) where appropriate *HES* hydroxyethyl starch, *APACHE* acute physiology and chronic health evaluation, *PEEP* Positive End-Expiratory Pressure. *p*: *U* underlying disease (sepsis vs. nonsepsis) *Ty* fluid type (HES versus gelatin versus albumin), *UxTy* interaction. X2 test for mortality.

**Table 3.** Hemodynamics.

| | Nonsepsis | | Sepsis | | *p* value | | |
|---|---|---|---|---|---|---|---|
| | Saline (n=6) | Colloid (n=18) | Saline (n=6) | Colloid (n=18) | U | Ty | UxTy |
| HR, beats/min | | | | | | | |
| t=0 min | 72±27 | 69±19 | 93±33 | 97±22 | .004 | .964 | .721 |
| t=90 | 72±28 | 70±17 | 89±29 | 98±18 | .411 | .165 | .115 |
| MAP, mm Hg | | | | | | | |
| t=0 min | 82±12 | 82±15 | 74±10 | 75±10 | .033 | .889 | .804 |
| t=90 | 84±6 | 93±15 | 83±10 | 89±16 | .212 | .004 | .398 |
| CI, L/min/m$^2$ | | | | | | | |
| t=0 min | 3.6±1.4 | 3.8±1.7 | 4.3±1.2 | 3.7±1.1 | .450 | .621 | .342 |
| t=90 | 3.5±1.2 | 4.1±1.1 | 4.6±0.9 | 4.4±1.3 | .001 | .029 | .371 |
| CVP, mm Hg | | | | | | | |
| t=0 min | 4±4 | 6±3 | 5±2 | 8±4 | .064 | .003 | .319 |
| t=90 | 5±3 | 9±3 | 6±4 | 13±4 | .180 | <.001 | .551 |
| SVI, mL/m$^2$ | | | | | | | |
| t=0 min | 51±9 | 55±15 | 5224 | 3912 | .147 | .434 | .114 |
| t=90 | 49±9 | 60±13 | 4617 | 4512 | .330 | .059 | .009 |
| GEDVI, mL/m$^2$ | | | | | | | |
| t=0 min | 664±102 | 813±234 | 698±264 | 846±215 | .010 | .832 | .039 |
| t=90 | 653±117 | 898±276 | 1029±215 | 921±232 | .276 | .018 | .117 |
| LVSWI, gm/m$^2$ | | | | | | | |
| t=0 min | 55±14 | 5±715 | 50±25 | 35±10 | .022 | .248 | .139 |
| t=90 | 54±13 | 69±15 | 60±22 | 46±13 | .706 | .040 | .005 |
| GEF | | | | | | | |
| t=0 min | 0.31±0.05 | 0.28±0.06 | 0.21±0.06 | 0.19±0.07 | <.001 | .198 | .756 |
| t=90 | 0.31±0.06 | 0.28±0.06 | 0.22±0.05 | 0.20±0.07 | .568 | .895 | .890 |
| $DO_2$ ,mL/min/m$^2$ | | | | | | | |
| t=0 min | 533±204 | 495±173 | 623±217 | 474±145 | .979 | .110 | .184 |
| t=90 | 546±149 | 498±156 | 667±272 | 505±143 | .262 | .511 | .568 |
| $VO_2$ ,mL/min/m$^2$ | | | | | | | |
| t=0 min | 106±50 | 140±48 | 148±68 | 127±61 | .999 | .609 | .301 |
| t=90 | 124±38 | 138±64 | 163±78 | 125±66 | .901 | .902 | .192 |

Mean ± SD

*HR* heart rate, *MAP* mean arterial pressure, *CI* cardiac index, *CVP* central venous pressure, *SVI* stroke volume index, *GEDVI* global end-diastolic volume index, *LVSWI* left ventricular stroke work index, *GEF* global ejection fraction, $DO_2$ oxygen delivery, $VO_2$ oxygen consumption, *p* : *U* underlying disease (sepsis vs. nonsepsis), *Ty* fluid type (saline versus colloids), *UxTy*, interaction.

The latter shows that the increases of GEDVI (t=0, 30, 60, 90 min) were greater with colloid than saline loading in septic and nonseptic patients ($p$ = .003). Indeed, the change in GEDVI predicted the change in CI ($p$ < .001), irrespective of underlying disease or fluid types. However, the rise in SVI and LVSWI with saline loading was greater in sepsis than in nonsepsis patients, but greater in colloid than in saline-loaded patients (Figure 2). The $S_{cv}O_2$ increased, particularly in the colloid-loaded patients with nonsepsis, while lactate levels did not change. $DO_2$ increased and $VO_2$ was unchanged, independent of underlying disease and fluid type.

Baseline values did not differ among colloid fluid types. Albumin loading increased albumin levels; COP similarly increased with all colloid fluids, irrespective of underlying disease. The lactate level decreased with HES and albumin (Table 5 A+B). For the increase in CI (from 0-30-60-90 min), there was no difference among underlying diseases and fluid types and the increase in CVP and GEDVI was greatest with HES ($p$ = .012, $p$ = .029 respectively), irrespective of underlying disease (Table 6 A+B). However, preload-recruitable stroke work was comparable between colloid fluid types (Figure 3).

**Table 4.** Biochemical data.

| | Nonsepsis | | Sepsis | | *p* value | | |
|---|---|---|---|---|---|---|---|
| | Saline (n=6) | Colloid (n=18) | Saline (n=6) | Colloid (n=18) | U | Ty | UxTy |
| Hemoglobin, mmol/L | | | | | | | |
| t=0 min | 6.9±1.1 | 5.7±1.1 | 6.2±1.4 | 5.4±0.5 | .134 | .009 | .548 |
| t=90 | 6.7±0.8 | 5.0±0.8 | 5.9±1.3 | 4.7±0.5 | .205 | <.001 | .385 |
| Colloid osmotic pressure, mm Hg | | | | | | | |
| t=0 min | 15±2 | 15±3 | 15±3 | 16±2 | .693 | .444 | .800 |
| t=90 | 13±1 | 19±3 | 14±3 | 19±2 | .993 | <.001 | .737 |
| $S_{cv}O_2$ | | | | | | | |
| t=0 min | 0.80±0.04 | 0.76±0.09 | 0.78±0.04 | 0.76±0.09 | .471 | .125 | .552 |
| t=90 | 0.80±0.07 | 0.80±0.09 | 0.81±0.05 | 0.77±0.08 | .920 | .514 | .030 |
| Lactate, mmol/L | | | | | | | |
| t=0 min | 1.3±0.7 | 1.4±0.8 | 1.6±1.3 | 1.8±0.8 | .326 | .548 | .913 |
| t=90 | 1.2±0.6 | 1.4±0.8 | 1.6±1.2 | 1.7±0.7 | .638 | .897 | .424 |

Mean ± SD

$S_{cv}O_2$ central venous oxygen saturation, *p*: *U* underlying disease (sepsis vs. nonsepsis), *Ty* fluid type (saline versus colloids), *UxTy* interaction.

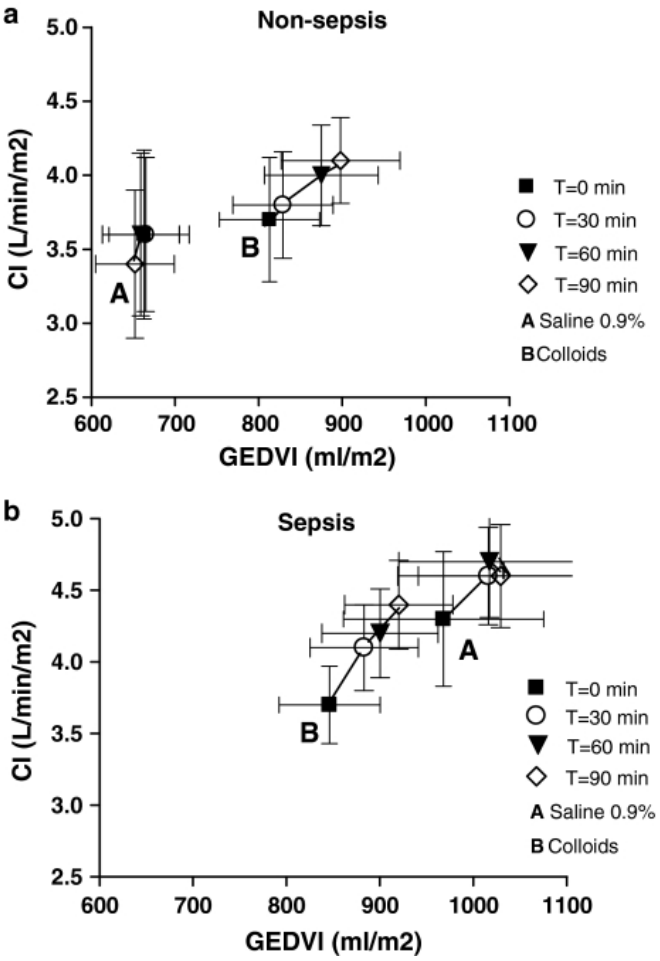


**Figure 1. a.** Mean±SEM for cardiac index (*CI*) versus global end-diastolic volume index (*GEDVI*) according to fluid type (*A* saline; *B* colloid), at four time points of fluid loading, in nonsepsis patients. **b.** Mean±SEM for cardiac index (*CI*) versus global end-diastolic volume index (*GEDVI*) according to fluid type (*A* saline; *B* colloid), at four time points of fluid loading, in sepsis patients. For GEDVI and CI: increases differed between fluid types ($p = .007$ or lower), indicating greater rises in colloid than in saline-loading, irrespective of underlying disease.

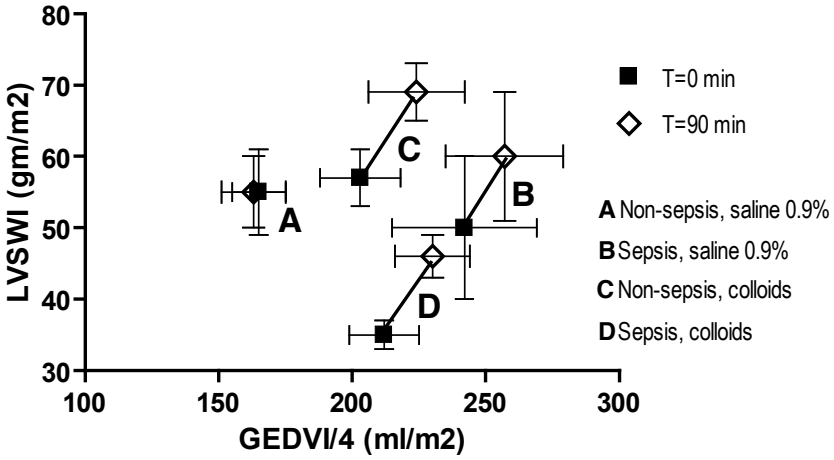


**Figure 2.** Mean ± SEM for left ventricular stroke work index (LVSWI) versus global end-diastolic volume index (GEDVI/4) as index of preload-recruitable stroke work, in nonsepsis and sepsis, according to fluid types. The figure suggests myocardial depression of sepsis (vs. nonsepsis) and increases of preload-recruitable stroke work that are greater with colloids than saline, particularly in nonseptic patients (for statistics see Table 3).

**Table 5A.** Biochemical data: nonsepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) |
|---|---|---|---|
| Hemoglobin, mmol/L | | | |
| t=0 min | 5.2±0.9 | 5.7±0.7 | 6.3±1.4 |
| t=90 | 4.6±0.8 | 5.1±0.6 | 5.4±0.7 |
| Albumin, g/L | | | |
| t=0 min | 18±4 | 19±5 | 19±4 |
| t=90 | 15±3 | 16±4 | 31±6 |
| Colloid osmotic pressure, mm Hg | | | |
| t=0 min | 14±3 | 16±3 | 16±3 |
| t=90 | 19±4 | 19±2 | 18±2 |
| $S_{cv}O_2$ | | | |
| t=0 min | 0.71±0.09 | 0.79±0.06 | 0.80±0.09 |
| t=90 | 0.76±0.11 | 0.83±0.04 | 0.82±0.08 |
| Lactate, mmol/L | | | |
| t=0 min | 1.4±0.8 | 1.5±1.1 | 1.5±0.5 |
| t=90 | 1.4±0.7 | 1.5±1.1 | 1.4±0.5 |

Mean ± SD

*HES* hydroxyethyl starch, $S_{cv}O_2$ central venous oxygen saturation. See Table 5B for statistics.

**Table 5B.** Biochemical data: sepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) | *p* value U | Ty | UxTy |
|---|---|---|---|---|---|---|
| Hemoglobin, mmol/L | | | | | | |
| t=0 min | 5.8±0.7 | 5.1±0.4 | 5.3±0.3 | .187 | .444 | .036 |
| t=90 | 5.0±0.7 | 4.5±0.2 | 4.6±0.3 | .525 | .729 | .558 |
| Albumin, g/L | | | | | | |
| t=0 min | 12±4 | 12±1 | 11±2 | <.001 | .903 | .737 |
| t=90 | 10±3 | 10±1 | 27±3 | .151 | <.001 | .236 |
| Colloid osmotic pressure, mm Hg | | | | | | |
| t=0 min | 15±2 | 17±2 | 15±2 | .483 | .171 | .724 |
| t=90 | 19±2 | 20±2 | 18±2 | .715 | .097 | .547 |
| $S_{cv}O_2$ | | | | | | |
| t=0 min | 0.76±0.12 | 0.76±0.08 | 0.77±0.07 | .934 | .441 | .442 |
| t=90 | 0.76±0.11 | 0.77±0.09 | 0.79±0.05 | .070 | .795 | .670 |
| Lactate, mmol/L | | | | | | |
| t=0 min | 1.9±1.0 | 1.5±0.5 | 2.0±0.9 | .188 | .647 | .566 |
| t=90 | 1.7±0.8 | 1.6±0.6 | 1.7±0.7 | .495 | .029 | .142 |

Mean ± SD

*HES* hydroxyethyl starch, *ScvO2* central venous oxygen saturation, *p*: *U* underlying disease (sepsis vs. nonsepsis), *Ty* fluid type (HES versus gelatin versus albumin), *UxTy* interaction.

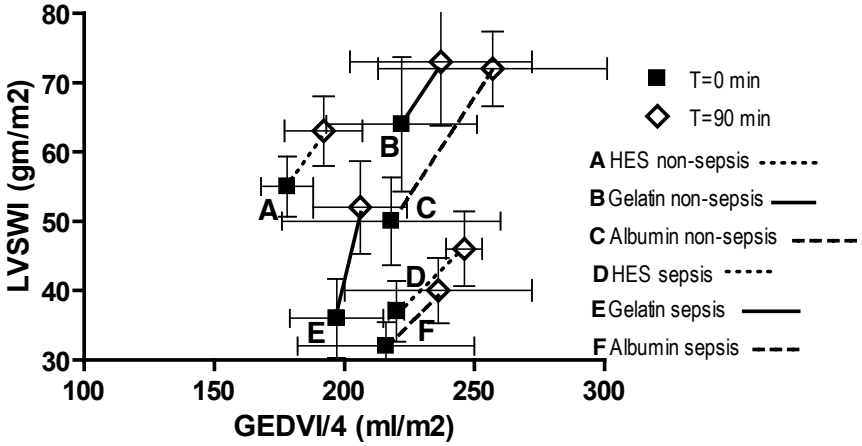


**Figure 3.** Mean ± SEM for left ventricular stroke work index (LVSWI) versus global end-diastolic volume index (GEDVI/4) as index of preload-recruitable stroke work, in nonsepsis and sepsis, according to fluid types (A+D, HES; B+E, Gelatin; C+F, Albumin). For statistics: see Table 6B. The figure suggests myocardial depression of sepsis (versus nonsepsis) and increases of preload-recruitable stroke work independent of underlying disease and fluid type.

**Table 6A.** Hemodynamics: nonsepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) |
|---|---|---|---|
| HR, beats/min | | | |
| t=0 min | 63±21 | 67±16 | 78±19 |
| t=90 | 66±18 | 70±20 | 74±16 |
| MAP, mm Hg | | | |
| t=0 min | 84±20 | 84±15 | 78±8 |
| t=90 | 96±16 | 96±12 | 87±16 |
| CI, L/min/m$^2$ | | | |
| t=0 min | 3.4±1.5 | 3.8±0.9 | 4.4±2.7 |
| t=90 | 3.5±1.0 | 4.2±0.9 | 4.6±1.5 |
| CVP, mm Hg | | | |
| t=0 min | 6±2 | 5±4 | 6±4 |
| t=90 | 10±1 | 8±4 | 9±4 |
| SVI, mL/m$^2$ | | | |
| t=0 min | 54±13 | 61±18 | 51±18 |
| t=90 | 55±12 | 63±18 | 63±9 |
| GEDVI, mL/m$^2$ | | | |
| t=0 min | 711±101 | 887±256 | 873±340 |
| t=90 | 768±149 | 947±317 | 1030±351 |
| LVSWI, gm/m$^2$ | | | |
| t=0 min | 55±11 | 64±22 | 50±13 |
| t=90 | 64±12 | 73±21 | 721±1 |
| GEF | | | |
| t=0 min | 0.30±0.06 | 0.28±0.05 | 0.25±0.08 |
| t=90 | 0.29±0.05 | 0.27±0.05 | 0.27±0.10 |
| $DO_2$ ,mL/min/m$^2$ | | | |
| t=0 min | 398±122 | 561±128 | 558±248 |
| t=90 | 390±83 | 549±176 | 596±140 |
| $VO_2$ ,mL/min/m$^2$ | | | |
| t=0 min | 126±33 | 143±47 | 159±71 |
| t=90 | 137±66 | 113±57 | 170±72 |

Mean ± SD

*HES* hydroxyethyl starch, *MAP* mean arterial pressure, *CVP* central venous pressure, *CI* cardiac index, *SVI* stroke volume index, *GEDVI* global end-diastolic volume index, *LVSWI* left ventricular stroke work index, *GEF* global ejection fraction, *DO2* oxygen delivery, *VO2* oxygen consumption. See Table 6B for statistics.

**Table 6B.** Hemodynamics: sepsis.

| | HES 6% (n=6) | Gelatin 4% (n=6) | Albumin 5% (n=6) | *p* value U | Ty | UxTy |
|---|---|---|---|---|---|---|
| HR, beats/min | | | | | | |
| t=0 min | 95±33 | 96±14 | 100±18 | <.001 | .88 | .809 |
| t=90 | 102±26 | 85±13 | 97±16 | .049 | .147 | .323 |
| MAP, mm Hg | | | | | | |
| t=0 min | 73±8 | 76±13 | 77±10 | .094 | .902 | .442 |
| t=90 | 89±13 | 94±17 | 84±18 | .708 | .216 | .759 |
| CI, L/min/m$^2$ | | | | | | |
| t=0 min | 3.7±1.2 | 4.1±1.5 | 3.3±0.6 | .810 | .698 | .584 |
| t=90 | 4.4±1.5 | 4.7±1.4 | 4.0±1.0 | .050 | .677 | .512 |
| CVP, mm Hg | | | | | | |
| t=0 min | 7±1 | 10±5 | 9±4 | .012 | .515 | .273 |
| t=90 | 12±2 | 13±6 | 13±4 | .072 | .041 | .401 |
| SVI, mL/m$^2$ | | | | | | |
| t=0 min | 41±8 | 43±19 | 35±8 | .001 | .391 | .080 |
| t=90 | 43±6 | 50±18 | 4±212 | .249 | .007 | .117 |
| GEDVI, mL/m$^2$ | | | | | | |
| t=0 min | 882±31 | 790±163 | 864±334 | .783 | .634 | .670 |
| t=90 | 987±62 | 826±163 | 945±350 | .400 | .022 | .126 |
| LVSWI, gm/m$^2$ | | | | | | |
| t=0 min | 37±11 | 36±13 | 32±8 | <.001 | .265 | .670 |
| t=90 | 46±13 | 52±15 | 40±12 | .618 | .046 | .126 |
| GEF | | | | | | |
| t=0 min | 0.18±0.04 | 0.22±0.09 | 0.17±0.06 | <.001 | .370 | .405 |
| t=90 | 0.18±0.03 | 0.25±0.09 | 0.19±0.07 | .618 | .046 | .271 |
| $DO_2$ ,mL/min/m$^2$ | | | | | | |
| t=0 min | 496±73 | 534±234 | 402±87 | .604 | .237 | .097 |
| t=90 | 502±168 | 558±116 | 456±148 | .699 | .293 | .444 |
| $VO_2$ ,mL/min/m$^2$ | | | | | | |
| t=0 min | 116±96 | 153±41 | 117±23 | .445 | .492 | .451 |
| t=90 | 114±62 | 150±92 | 113±43 | .512 | .816 | .236 |

Mean±SD

*HES* hydroxyethyl starch, *MAP* mean arterial pressure, *CVP* central venous pressure, *CI* cardiac index, *SVI* stroke volume index, *GEDVI* global end-diastolic volume index, *LVSWI* left ventricular stroke work index, *GEF* global ejection fraction, *DO2* oxygen delivery, *VO2* oxygen consumption. *p*: *U* underlying disease (sepsis vs. nonsepsis), *Ty* fluid type (HES versus gelatin versus albumin), *UxTy* interaction.

## Discussion

As expected, sepsis patients had lower baseline albumin levels, presumably following increased vasopermeability, and MAP, but higher HR and cardiac filling than nonsepsis patients. The latter may have resulted from myocardial depression, characteristic for severe sepsis, as shown by a lower GEF and down- and rightward displacement of preload-recruitable stroke work[10]. Nevertheless, the hemodynamic response to fluid loading was similar to that in nonsepsis, in disagreement with the literature[10]. The slope of preload-recruitable stroke work did not differ among fluid types, suggesting unaltered cardiac function during fluid loading, so that the difference between fluid types in cardiac output responses were primarily caused by differences in filling. However, a rise in LVSWI that, in contrast to cardiac filling and output, seemed somewhat greater in saline loading in sepsis than in nonsepsis patients, can be explained in part by a greater effect on SVI. The greater cardiac filling and output with colloid than with saline loading maintained in sepsis, argue against increased vasopermeability that may increase (rapid) equilibration of infused proteins and artificial colloids with the extravascular space and thereby limit the intravascular retention of fluids, but such effect in more severely ill septic patients with higher permeability cannot be excluded[1,7,8,12]. We neither can exclude a slowly increased extravasation of colloids in sepsis, even though nearly complete equilibration between the intra- and extravascular space is expected within 90 minutes[7]. The similar COP in sepsis and nonsepsis after colloid fluid loading agrees with the literature showing that colloid/albumin solutions are able to increase, at least transiently, a low COP/albumin in critically ill patients with sepsis and shock[6,7,12]. Our results may also help explain a potential survival benefit of albumin over saline resuscitation in sepsis[3]. In animal experiments, some authors[13,14] found that, even in sepsis and shock, colloids were effective, and even more so than crystalloids, in maintaining COP, cardiac filling and output. Otherwise, that colloids, per unit volume and time, are better able to recruit cardiac preload than rapidly extravasating crystalloid solutions is in line with our previous study in cardiovascular surgery patients with less elevated permeability[9,20]. When using crystalloids, 2 to 4 times more fluid may be required to restore and maintain intravascular fluid volume compared to colloids, but true evidence is scarce[1,5-7,9]. Our results agree with the idea, even in septic clinical hypovolemia, since

the difference in cardiac output increase multiplied by the difference in volume infused was 3 for colloids versus saline. The ratio in the SAFE study[3] comparing albumin with saline resuscitation was 1:1.3, however. This can be explained by either insufficient need for fluid resuscitation, severely increased permeability, poor monitoring and guidance of therapy, or combinations. The current data finally indicate that our clinical criteria were useful in selecting patients with, on average, a linear increase in cardiac output upon fluid loading in the steep part of the cardiac function curve.

There was no evidence for a different hemodynamic effect among colloid solutions (at roughly isooncotic concentrations), in accordance with the literature[6,19]. This may refute the clinical suggestion of a negative inotropic effect of albumin infusion[11,16], the experimental observations that albumin may have a positive inotropic effect after endotoxin injection[21], and the idea that HES may plug leaks and thereby exert a greater hemodynamic benefit than albumin infusion[11,13]. Nevertheless, we cannot exclude that the study was too small to detect small differences among colloid fluids. However, it was apparently not too small to reveal a small effect of HES as compared to gelatin and albumin, irrespective of underlying disease. Even though the rise in CVP and GEDVI was greater and the rise in SVI was smaller with HES than with gelatin or albumin, the slopes of preload-recruitable stroke work did not significantly differ, suggesting similar cardiac contractility during loading with HES as compared to that with gelatin or albumin. Although groups differed in baseline serum creatinine levels and urinary output during fluid infusion, with greater impairments in the sepsis group, the diuretic response to HES was particularly diminished in the nonsepsis group in spite of presumably similar renal function as in the other fluid groups, in line with the potential adverse effects of HES on the kidney. Impaired diuresis may have contributed to the seemingly greater cardiac preload response following HES. The somewhat greater fall in lactate with HES and albumin than with gelatin loading can be attributed to somewhat higher baseline values in the former.

The limitations of our study include the coincidental imbalance in hemoglobin and CVP between fluid types at baseline. The latter can be explained by a coincidental imbalance in PEEP and the effect of transmitted airway pressure on atmospheric pressure-referenced CVP. We did not measure mixed venous $SO_2$, which may be lower than $S_{cv}O_2$. However, changes may be similar, so that the unchanged $VO_2$ is probably true.

The increase in $DO_2$ did not differ among fluid types since a higher cardiac output was offset by greater hemodilution after colloid than saline loading. The relatively high $S_{cv}O_2$ and low lactate levels may otherwise imply adequate tissue oxygenation. Admittedly, the number of patients in this study was relatively small, but sufficient for analyses of fluid pathophysiology, the principal aim, rather than therapy, of our study. Finally, we cannot exclude that infusion of even more saline, for instance guided by GEDVI[19], would have resulted in greater rises in preload-recruitable CI and LVSWI. By comparing (and pooling) different, roughly isooncotic colloid fluids, our study carries the advantage over others, in which only one or two colloid fluid types were studied[3,4,6,7,12,13,19], of evaluating the contribution of COP independent of other fluid properties. Finally, most studies, unlike ours, did not separate effects in sepsis from those in nonsepsis[2,3,6].

In conclusion, fluid loading with colloids results in a greater linear increase in cardiac filling, output and stroke work than saline loading, in both septic and nonseptic clinical hypovolemia, in spite of myocardial depression and presumably increased vasopermeability potentially decreasing the effects of colloid fluid loading in the former.

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# 3

## Crystalloid or colloid fluids: A matter of volumes?

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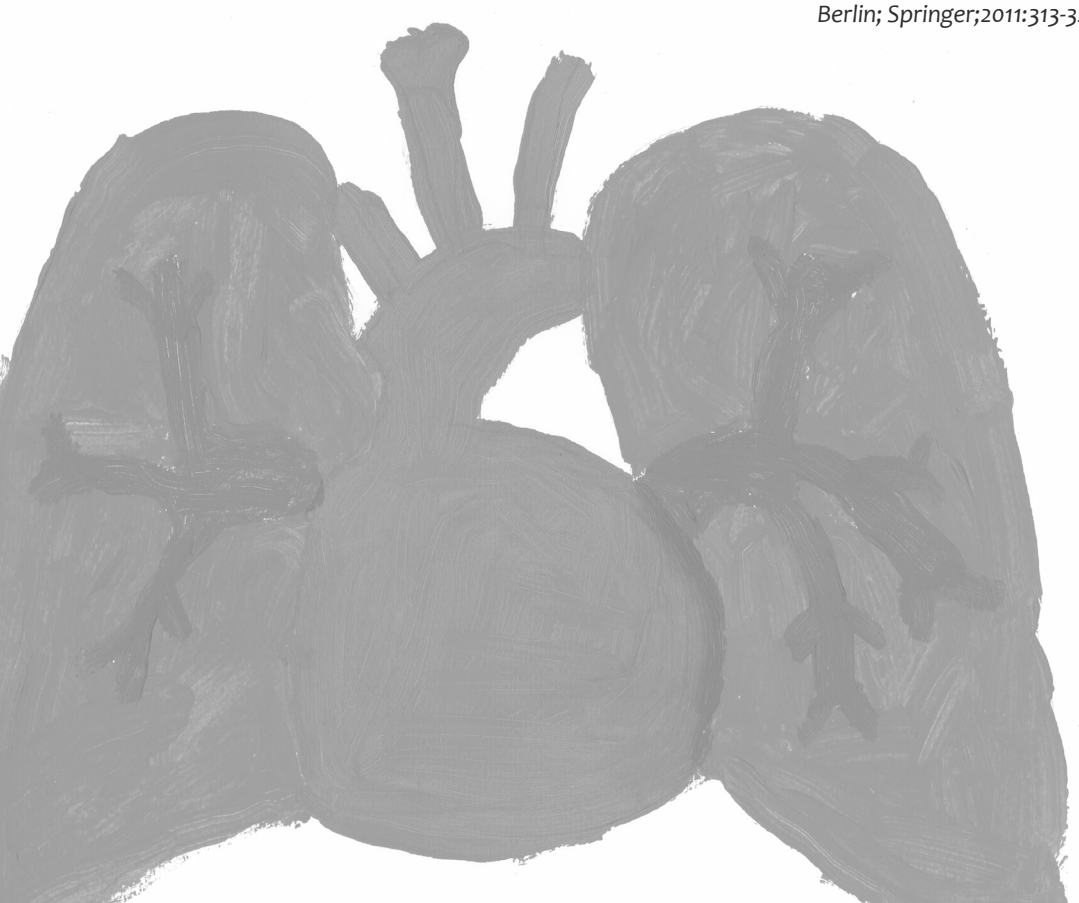

## Introduction

Fluid infusion is a key element in the treatment of critically ill patients with hypovolemia and shock. The debate on the relative merits and detriments of (isotonic) crystalloid versus (roughly isooncotic) colloid fluids is ongoing. Large clinical trials and systemic reviews suggest that the use of one fluid type over the other does not affect overall mortality, but this similarity does not exclude heterogeneity of effects on hemodynamics, adverse effects and outcome among patient populations, so that benefits may be offset by detriments in some but not in other patient populations[1-7]. In the SAFE study, for instance, albumin 4% versus saline loading may improve survival of septic patients but not of those with traumatic brain injury[1].

This narrative review of the available literature on the topic is meant to summarize current knowledge on the hemodynamic differences, if any, between the fluid types, governed by heart function and underlying condition on the one hand and infusion volume on the other, since, in contrast to standard textbook statements, review papers, guidelines and common beliefs[4,5,8], the volume of crystalloid required may not be 3 to 4 times the volume of colloid in the treatment of hypovolemia and shock[1,3,6,7]. This is an important issue in an era where fluid restriction policies to avoid harmful fluid overloading are increasingly propagated, taking the relative, dose-dependent adverse effects of fluid types into account[3,4,6].

First, we will review the mechanisms of a cardiac output increase with fluid loading. Second, we will review the clinical data regarding the crystalloid-colloid volume ratio in determining hemodynamic effects, excluding hypertonic or hyperoncotic solutions and animal studies. We will not address the issue of balanced versus unbalanced solutions either.

## How does fluid loading increase cardiac output?

The response of the heart to fluid loading is far more complex than usually assumed. It is commonly believed that fluid infusion increases cardiac output by increasing plasma volume. However, this relationship may not be straightforward when infused fluids are differently partitioned in stressed and unstressed plasma volume compartments and

thereby variably increase end-diastolic volume, as demonstrated for instance in cardiac surgery patients[9,10]. Figure 1 shows the relation between plasma volume changes calculated from hemoglobin/hematocrit changes, which may have shortcomings, and changes in global end-diastolic volume upon crystalloid or colloid loading in septic and nonseptic patients that do not differ in this respect in spite of septic myocardial depression (unpublished data from ref 11). This relatively loose relationship confirms earlier findings and suggests that the relationship between plasma volume and cardiac filling and output, apart from measurement difficulties, is not straightforward[9,11,12]. Although end-diastolic volume of the ventricles (preload) is an important determinant of cardiac output, fluid loading may also affect blood viscosity and may (thereby) lower cardiac afterload and increase contractility, both in healthy volunteers as well as in critically ill septic or nonseptic patients, so that changes in cardiac output upon fluid loading are not solely determined by changes in preload[9-11,13-15]. Finally, baseline loading and function of both ventricles and their interaction may affect the (mechanisms of the) cardiac output increase with fluid loading[16]. Indeed, fluid responsiveness, i.e. the increase in stroke volume or cardiac output upon fluid loading, is not only a matter of (type and volume) of fluid infused but also of baseline biventricular filling and (systolic and diastolic) function, that may differ among patients, conditions and stages of disease. Conversely, the imperfect and sometimes controversial value of parameters thought to help predict fluid responsiveness is partly related to the complexity of effects of fluid loading on the heart and differences herein among patients and conditions. Otherwise, the increase in cardiac output with fluid loading mostly outweighs concomitant hemodilution, so that $O_2$ delivery is increased, but a potential difference in hemodynamic effects of fluid types may not translate in a difference in tissue oxygenation, when a greater increase in cardiac output is offset by greater hemodilution (with colloids)[10,11,17-19].

## More saline than colloid needed?

One of the arguments used in favor of colloids is that their infusion increases plasma volume and cardiac preload more (rapidly) than that of crystalloids[4,12]. If colloids are capable of expanding the plasma volume to a greater extend than crystalloids, then the same volume of colloids would have greater effects on hemodynamics than crystalloids.

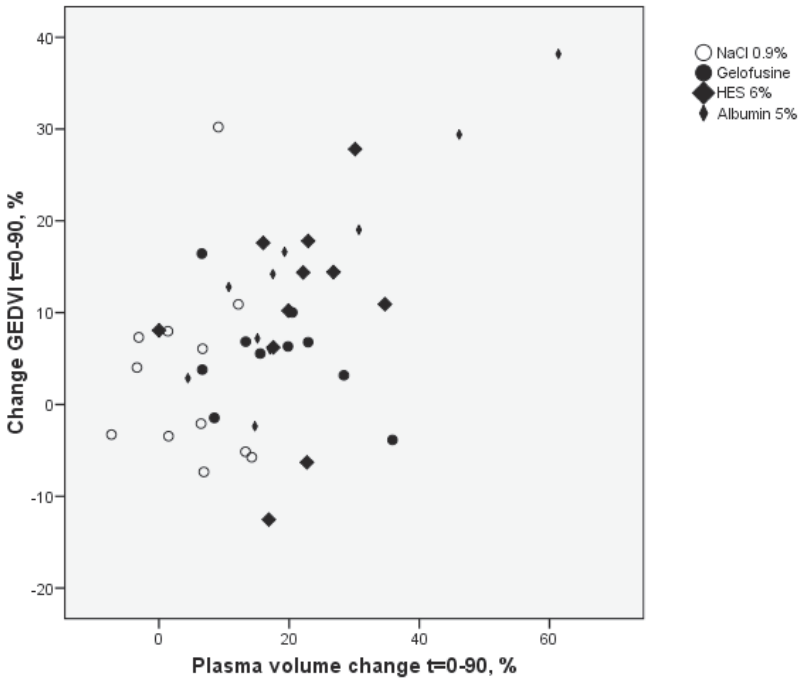


**Figure 1.** Loose correlation between the change in plasma volume and the change in global end-diastolic volume index (GEDVI) after 90 minutes of fluid loading in septic and nonseptic patients, according to fluid types (unpublished data from ref. 11): r = .51, *p* <.001.

The volume ratio of crystalloid to colloid relative to hemodynamic effectiveness depends on the rate and fate of the infused fluids and the hemodynamic monitoring tool and endpoint utilized. The hemodynamic endpoint of resuscitation varies from one study to the other between clinical judgment, arterial and central venous pressures, to pulmonary artery occlusion pressures and cardiac output and variables obtained by transpulmonary thermodilution. The variety is likely responsible, in part, for the widely varying volume ratios during resuscitation reported in the literature. In the SAFE study (comparing albumin with saline), for instance, the volume and rate of fluid administration was determined by treating clinicians according to each patients clinical status and response to treatment, without using a specific fluid loading protocol[1]. This resulted in an albumin to saline volume ratio of 1.4 to 1, but also in higher central venous pressures in the albumin group, suggesting dissimilar resuscitation. Conversely,

judging the difference in hemodynamic effects during fixed and similar volume infusions depends on the parameter that is monitored to judge that response and how well the parameter reflects (changes in) plasma volume, which is only rarely (and certainly not routinely) measured[9-12,17,18,20-23]. For instance, in a fluid non-responsive state, in the presence of severe cardiac dysfunction, the type of fluid infused would not translate into hemodynamic differences upon infusion, irrespective of plasma volume changes. We now elaborate on the theoretical and the practical differences reported in the literature on the hemodynamic effects and volume ratios of (isotonic/isooncotic) crystalloid and colloid fluids.

## Theory: fluid properties

In theory, crystalloid solutions expand the plasma volume by about 200 mL per liter infused, concomitantly with lowering, by diluting circulating proteins, of plasma colloid osmotic pressure (COP), as indeed demonstrated in patients[4,10-12,21,24-26]. Depending on the rate of infusion, the equilibration rate of crystalloid with the interstitial space is rapid (minutes) even in patients with hypovolemia or shock, thereby resulting in potentially harmful interstitial overhydration[4,17-19,26-29]. In theory, crystalloids thus need to be administered at volumes approximately 3 to 5-fold greater than those of (isooncotic) colloids, that are largely maintained in the plasma compartment because of maintenance of COP, in order to achieve comparable plasma volumes and resuscitation endpoints[4,8,10,11,24-26,30]. Conversely, the intravascular COP after colloid infusion is influenced by baseline COP, the degree of hemodilution and the COP of the infused volume and its plasma retention, determined by the molecular weight distribution. Albumin solutions are monodisperse (molecular weight of 69 kDa). Gelatins are polydisperse and in excess of 75% of the molecules are thought to be smaller than the renal threshold of 30 kDa. The large number of small molecules exerts a powerful initial COP effect making gelatins good for short-term volume expansion, but molecules with a molecular weight less than 15 kDa have a similar clearance to that of creatinine and will be filtered by the glomerulus. They are thus rapidly cleared from the intravascular space, with a half-life of 3.5-4 hours[8]. Hydroxyethyl starch solutions are very polydisperse, defined by degree of substitution (via partial hydrolysis) and by molecular weight, both of which affect

pharmacokinetics[8,30]. The greater the degree of substitution the greater the resistance to degradation, which therefore prolongs the effectiveness of hydroxyethyl starch as a plasma expander. After substitution, the starch is refined into the final product by hydrolysis to the required molecular weight. The molecular weight distribution can be described using the COP50/COP10 ratio[8,30]. This is the ratio of measured COP's across 2 different membranes, with a 50-kDa and a 10-kDa pore size, respectively, and reflects the relative proportion of molecules retained by filters with those pore sizes. Colloids with a low COP50/COP10 ratio will be lost more rapidly from the intravascular space. Small particles with a low molecular weight exert a greater COP effect and, for a given number of molecules, will have a lower viscosity than larger molecules. Thus, the concentration and molecular weight of colloid molecules and hence the COP, determine the initial degree of volume expansion, whereas both the molecular weight and surface charge characteristics determine the rate of loss through the capillary endothelial barrier and loss into the urine by glomerular filtration. Therefore, the intravascular retention and half time of colloids amount to hours, dependent on dispersion and weight of molecules. Conversely, plasma volume expansion differences with crystalloid fluid infusions may depend on time[19]. In addition, (endothelial) properties of the vessel wall and overlying luminal glycocalyx, which may change in disease states, may ultimately affect permeability (for proteins and colloids) and hydraulic conductance (to plasma water)[4]. Due to its electrostatic properties, albumin penetrates and binds to the endothelial surface glycocalyx and influences its barrier function. The resulting sealing effect may attenuate fluid extravasation independently of the COP by albumin. Similarly, large hydroxyethyl starch molecules have been claimed to 'seal pores' but the clinical significance thereof is not yet convincingly demonstrated. During conditions with increased vasopermeability as in septic shock, albumin or starch administration may help in ameliorating the permeability defect on the one hand but may increasingly filtrate into the interstitium on the other thereby attenuating the potential superiority of colloids in increasing plasma volume[17,21,22,31,32]. Finally, hypovolemia and shock are likely to lower capillary hydrostatic filtration pressure and promote resorption of interstitial fluids, so that intravascular retention of infused fluids may differ from that in normal individuals, without negating potential differences between fluid types[29,33]. We will now summarize the evidence obtained in clinical practice for the volume differences between fluid types.

## Practice

### Volunteers

A recent study in healthy volunteers demonstrated that for the same volume of administered fluids, saline was a less effective plasma volume expander than gelatin 4% and hydroxyethyl starch 6%, which did not differ in this respect up to 6 h after starting infusion[34]. After infusion, 68%, 21% and 16% of the infused volumes of saline, gelatin and starch, respectively, had escaped from the intra- to the extravascular space, as estimated from hematocrit/hemoglobin changes. This indeed concord with a 3-fold greater (and prolonged) effectiveness, for a given volume infused, of colloids than of crystalloids in plasma volume expansion[26].

### Iso- or normovolemic hemodilution

Anesthetized patients undergoing hemodilution and receiving 3 times the volume of crystalloid for each unit of blood removed, or the same volume of (icooncotic) colloid fluid for the volume of blood removed achieved similar hemodynamic endpoints[35]. In volunteers receiving equal volumes of crystalloid or colloid for a given volume of withdrawn blood, the latter had better restoration of hemodynamics, unless twice the volume of crystalloid was given[27,33].

### Perioperative states and trauma

Following spinal anesthesia, fluid requirements of colloids were higher than during crystalloid-based regimens, resulting in higher cardiac outputs in the former[36]. The increase in plasma volume, for a given fluid infusion volume, was about 5x greater with albumin 5% than with crystalloid after cardiac surgery[9,18]. Older studies already had suggested that colloid resuscitation required about twice less volume than that with crystalloids in reaching similar hemodynamic endpoints during and after (cardiovascular) surgery thereby avoiding some postoperative complications of fluid overload[21,24,25,29,37-44]. During emergency resuscitation from trauma and hemorrhage, colloid regimens were more (rapidly) effective in restoring the circulation than crystalloid regimens, at volume ratios of about 1 to 3[45,46]. More recently, Lang et al. again demonstrated that for reaching the same central venous pressure in patients after major abdominal surgery, 2-fold

higher volumes of Ringer's lactate than hydroxyethyl starch 6% were required[47]. Verheij et al. showed that 4-6% colloid fluid loading (for 90 min) according to changes in filling pressures after cardiac or major vascular surgery resulted in a 4-fold greater increase in preload-recruitable stroke work than that with saline, because of a greater plasma volume expansion following an increase in plasma COP, whereas about 15% less colloid than crystalloid was administered (volume ratio about 1.2:1; ref. 10). A recent study in postoperative patients with hypovolemia showed that the administration of different types (but similar volumes) of colloids was associated with greater increases in cardiac filling, output and $O_2$ delivery than that of Ringer's lactate[19].



**Sepsis**

Ernest et al. suggested that albumin 5 % infusion results in greater fluid extravasation in septic than in nonseptic patients, but the (5-fold) superiority over saline in expanding the plasma versus interstitial volumes, per fluid volume administered, was maintained[17]. Hence, twice the volume of saline was needed to reach the same hemodynamic endpoints as with albumin 5% loading. Nevertheless, Marx et al. suggested that severe septic shock accompanied by clinical evidence of a capillary leak syndrome was associated with shorter and less intravascular retention of intravenously administered albumin 20% than in controls[22]. The VISEP trial documented that target values of central venous pressure in severe sepsis were reached faster with hydroxyethyl starch 10% loading than that with Ringer's lactate, at an averaged volume ratio of 1:1.3, but mortality did not differ[3]. The central venous pressure and central venous $O_2$ saturation in the hydroxyethyl starch group were somewhat higher than in the Ringer's lactate group, perhaps suggesting underestimation of saline requirements or overinfusion of starch. Trof et al., however, demonstrated, in perhaps less severely ill septic patients, that 90 min fluid loading with 4-6% colloids results in greater linear increase in cardiac filling, output and left ventricular stroke work than that with saline loading both in septic and nonseptic patients, probably due to a larger plasma volume following increased COP with the former and in spite of the characteristic myocardial depression of sepsis[11]. The effectiveness of colloids was 3-fold greater than of saline, regardless of underlying condition, even though about 17% more crystalloid was infused (volume ratio 1.2:1 see electronic supplement to ref. 11), confirming older data suggesting 2 to 5-fold greater

fluid requirements with crystalloids in hypovolemic and septic shock aiming at similar hemodynamic endpoints[28,48]. In children with Dengue shock syndrome, Ringer's lactate administration resulted in higher hematocrits, lower arterial (pulse) pressures and cardiac outputs, and slower shock reversal than that of (similar volumes of) colloids[2,32]. In children with septic shock, up to 67% more saline than gelatin (volume ratio 1.7:1) was required to reach similar plasma volume and hemodynamic targets[23].

**General critical conditions**

In patients with respiratory insufficiency and hemodynamic instability from sepsis or nonsepsis, Ringer's lactate was compared to 5% albumin infusions to maintain hemodynamic 'stability'[49]. In attaining similar hemodynamics, 1.8 volume of crystalloid for 1 volume of colloid had to be infused, although the difference did not reach statistical significance[49]. As mentioned, the SAFE study[1] compared 4% albumin with saline, guided by clinical parameters, and the volume ratio was about 1:1.4.

## Conclusion

Although a mortality benefit has not been documented, the use of (isooncotic) colloids results in more (rapid) plasma volume expansion and hemodynamic optimization than resuscitation with (isotonic) crystalloids, in a variety of conditions, even when accompanied by presumed increased vasopermeability. Although recently suggested otherwise, the volume ratio for similar hemodynamic endpoints is approximately 1 colloid to 3 crystalloids. The factor is maintained when multiplying lower ratios, when applied, with the difference in hemodynamic endpoints attained. In randomized trials comparing colloids with crystalloids for fluid resuscitation and deviating from the ratio, the accurateness of hemodynamic monitoring and guiding of fluid therapy should be evaluated. Indeed, potential dissimilar resuscitation among groups may confound interpretation of relative benefits and detriments of solution types and future metaanalyses should take that disparity into account.

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# 4

# Replacing or restricting fluids: timing, dosing and choosing the type of fluid in patients with or at risk for ALI/ARDS

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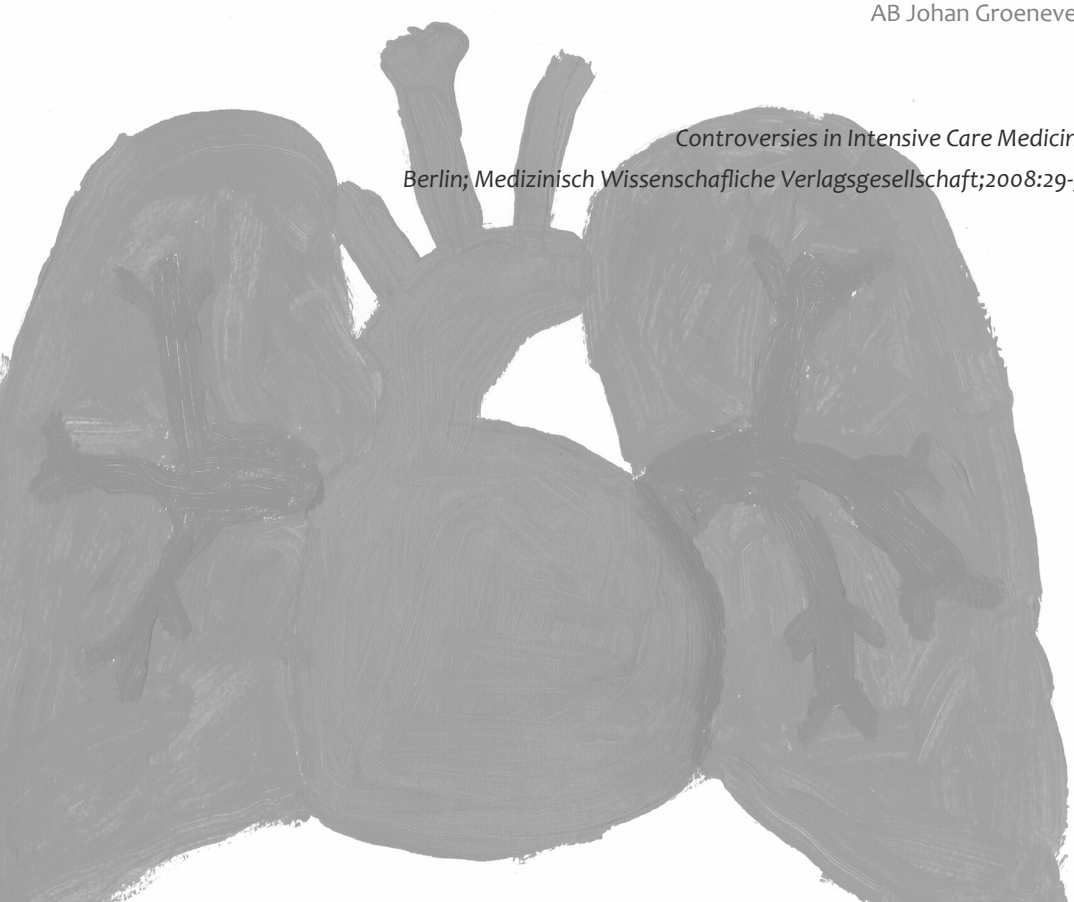

## Introduction

The ongoing debate on fluid resuscitation includes effects of timing, dosing, and choosing the type of fluid on pulmonary hydration status, particularly during (impending) acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), when pulmonary capillary permeability may be increased[1].

From physiological considerations, animal and (limited) clinical observations, it can be assumed that extravasation of fluids in vivo is governed by pericapillary hydrostatic and colloid osmotic pressures (COP), and permeability. This does not necessarily equate with edema formation, however, when increased lymph flow (up to a factor 9 in normal lungs) may offset increased fluid filtration. Also, the effect of plasma COP to attenuate filtration (or a low COP to increase filtration) is expected to increase when hydrostatic pressure increases and drives fluids out of the bloodstream[2]. Furthermore, an increased permeability and a resultant decrease in the pericapillary COP gradient may attenuate potential differences between fluid types, decreasing (crystalloids) and maintaining or even increasing plasma COP (colloids), respectively. Figure 1 illustrates these concepts, based on filtration forces rather than adaptations in lymph flow and suggests that differences in fluid types are expected to be less in modulating pulmonary edema formation in the steep part of the cardiac function curve, which is associated with a relatively low hydrostatic filtration pressure in the lungs.

Both pulmonary capillary permeability and edema can be measured at the bedside; many ALI and all ARDS patients meeting accepted criteria have a measurably increased pulmonary capillary permeability but only up to 70% have supranormal extravascular lung water (EVLW)[3-7]. Indeed, the single transpulmonary thermal dilution technique is currently the reference standard for measuring and monitoring extravascular thermal volume in the lungs as a measure of accessible lung water - EVLW - at the bedside. This technique has shown excellent correlation with the gravimetric method[8] and may have prognostic significance[6,9]. With this technique, however, pleural fluid is not measured. CT scanning gives an indirect measure of edema but is, by nature, intermittent at best, involving transportation and interruption of, for instance, renal replacement therapy instituted to attenuate fluid overloading. There is some evidence that EVLW (plus pulmonary blood volume) fairly correlates to tissue lung weights (i.e. pulmonary

blood plus extravascular fluid volumes) estimated from CT scans[10]. CT scanning carries the advantage of assessing pleural fluid also. Indeed, accumulation of pleural fluid in mechanically ventilated patients is common and physiology predicts that this may serve as an overflow system for increased intrapulmonary fluid filtration, when draining lymph flow is overwhelmed. Increased pleural pressure hampering parietal resorption in the course of mechanical ventilation may further contribute.

After elaborating these basic physiologic principles, we will now address the major controversial issues on fluid resuscitation, when clinically needed, in ALI/ARDS or in patients at high risk for these syndromes. We will focus on clinical studies.

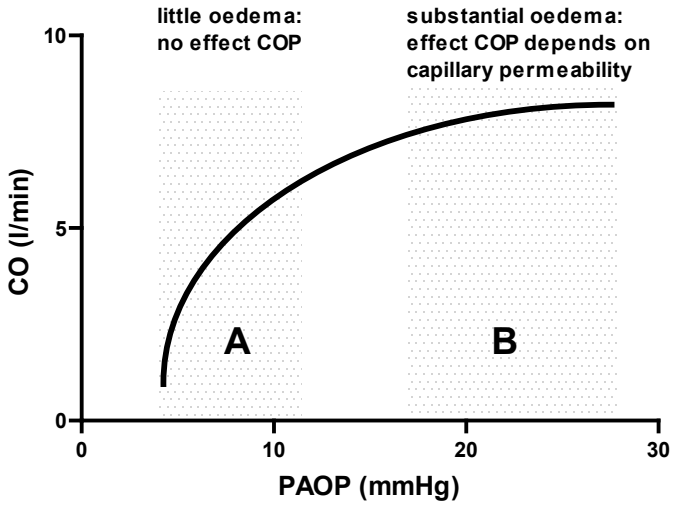


**Figure 1.** Schematic representation of the classical cardiac function curve: *CO* cardiac output versus *PAOP* pulmonary artery occlusion pressure. **A** denotes the area in which only little edema occurs regardless of the *COP* colloid oncotic pressure. **B** denotes the area in which substantial pulmonary edema may occur in which the effect of COP depends on capillary permeability.

## Controversy 1: guiding fluid resuscitation and avoiding overhydration

The goals of fluid resuscitation, when needed, in (impending) ALI/ARDS is aimed at preventing or decreasing new organ failures and ultimately survival. However, intermediate hemodynamic and metabolic endpoints aimed at reaching those goals vary among studies. In any case, overhydration, particularly with crystalloids, is a serious

threat and may, among other adverse effects, confound diagnosing and aggravate (pulmonary edema in) ALI/ARDS[11-13]. Fluid overloading is probably also a common cause of pleural fluid which in turn may compress the lungs, thereby, together with an increased permeability, aggravate edema, contributing to ventilatory dependency in ALI/ARDS. Fluid overloading leading to an abdominal compartment syndrome may further compromise pulmonary function[12].

Fluid overloading can be prevented by defining goals of fluid resuscitation and refining monitoring techniques. Indeed, predicting fluid responsiveness (i.e. a rise in stroke volume, cardiac output and thus oxygen delivery upon fluid loading) by dynamic or static preload indicators or their combination may help to decide on fluid challenges, provided that there is a clinical problem likely ameliorated by an increased oxygen delivery[1,14-21]. Obviously, instead of measuring and monitoring preload indicators as surrogate markers of fluid responsiveness, (semi-)continuous measurements of stroke volume or cardiac output could serve that purpose as well, provided that they are accurate[14-19,21-23]. Fluid loading should be continued until direct or indirect measures reach a particular point likely associated with improved and sufficient tissue oxygenation. To this end, regional as well as global parameters can be used, together with a careful clinical assessment, including near infrared spectroscopy/tissue oxymetry, microcirculatory imaging and gastrointestinal $PCO_2$ tonometry for the former, or central or mixed venous oxymetry for the latter[19,20,24,25]. Adequate, optimal, goal-directed, goal-oriented or targeted fluid therapy/resuscitation, terms used in the literature, are not unequivocally defined, but may nevertheless imply similar or related endpoints for resuscitation, albeit varying among studies[14,16-21,23,24]. In any case, continuing fluid loading when cardiac output does not further increase on the plateau of the cardiac function curve, might result in harmful fluid overloading, particularly in the lungs, deteriorating gas exchange and compliance, while fluid loading in the steep part of the cardiac function curve may not (measurably) increase edema formation, even in case of mildly increased permeability edema and ALI after major surgery (ref 1,4,11; conform Figure 1). However, when using refined monitoring tools, including EVLW measurements, in patients with or at risk for ALI/ARDS, after major surgery for instance, the amount of fluid given and the duration of mechanical ventilation were, paradoxically, greater than when fluid loading was based on traditional filling pressure measurements[22]. Yet, there is no single, universally

accepted tool to prevent fluid overloading, when fluid resuscitation is deemed to be necessary.

## Controversy 2: is 'dry' better than 'wet' in preventing/ameliorating pulmonary edema in ALI/ARDS?

Whereas completely withholding fluids or deliberately overhydrating patients for some time will certainly overwhelm physiologic (renal) compensation mechanisms and carry a fatal outcome, restrictive and liberal fluid therapy may be relatively meaningless terms if departing from different fluid regimens. Hence, the use of fixed, for instance perioperative, fluid dosages is probably also less useful than individual optimization. The key question thus is the adequacy of fluid resuscitation, as elaborated above, rather than the relative superiority of a restrictive or liberal regimen.

Nevertheless, authors have advocated perioperative restricted rather than liberal fluid therapy, in order, among others, to prevent occasionally fatal postoperative pulmonary edema, associated with too liberal fluid therapy and not preceded by any warning signs[26-29]. Indeed, the widely held belief that surgery may be associated with contraction of the extracellular fluid volume necessitating liberal fluid therapy, may be incorrect[30]. When departing from (fixed dose) liberal fluid therapy, some fluid restriction can indeed reduce some morbidity (but not mortality) of surgical patients[27-29], whereas a more liberal (as in individualized goal-directed) fluid therapy better maintained tissue oxygenation and decreased morbidity after surgery, as compared to a more restricted or standard policy in other studies[14,16-21,24,25,29,31]. However, the effect on pulmonary (permeability) edema and even gas exchange remained unclear in most of these latter studies on patients often at risk for ALI/ARDS after surgery[14,16-19,21,24,25,28,29,31,32]. The discussion on restricted versus liberal fluid therapy otherwise also applies to trauma/hemorrhagic shock, in which, when bleeding cannot be immediately controlled, small rather than large volume resuscitation may be recommended[33].

The restricted and liberal policies may affect the lungs in keeping them 'dry' or rendering them 'wet', respectively, even though some studies on liberal policies, paradoxically reported unchanged or even diminished duration of ventilation after surgery, associated with improved ventilatory function[20,27,31,32]. More complete

resuscitation may thus shorten ventilation and ICU durations of stay[14,21,23]. Nevertheless, a positive fluid balance has been associated with an increasing EVLW, prolonged mechanical ventilation/ICU stay and a worse outcome in sepsis and ALI/ARDS, and vice versa, but this does not necessarily imply cause-effect relationships[13,22,34-37]. Refining and guiding fluid resuscitation in the course of (impending) ALI/ARDS may benefit from predicting fluid responsiveness and monitoring EVLW in order to prevent edema formation and thus prolonged need for mechanical ventilation[1,4,11,13,22,23,34,38]. In patients requiring pulmonary artery catheter monitoring who had an elevated EVLW, a fluid strategy based on EVLW measurements, for instance, resulted in less fluid balance positivity and a shorter ventilation duration / ICU stay than a strategy based on the pulmonary artery occlusion pressure[38]. In patients with risk factors for ALI/ARDS, such as sepsis and major surgery, or those with established pulmonary edema or ALI/ARDS, restricting fluids after the initial phase of resuscitation may be beneficial[13,39]. In fact, the ARDS Network trial suggests that, after initial resuscitation, a regimen aimed at less positivity of 7-daily and cumulative fluid balance may improve lung function (edema ?) and reduce ventilator/ICU days but may not reduce mortality in the first 28 days, in patients with ALI/ARDS[39]. Obviously, keeping the lungs 'dry' rather than 'wet' should be weighted against potential hypoperfusion of extrapulmonary, injured or vital organs such as the kidneys[13]. This may require additional attention and monitoring, but, apparently, additional organ failure was minimal in the restricted fluid group of the ARDS network trial[39]. Taken together, timing and dosing fluid therapy in patients with or at risk for ALI/ARDS is still a controversial issue.



## Controversy 3: colloid versus crystalloid in preventing/ameliorating pulmonary edema during ALI/ARDS

It follows from physiology that the 'dry' and 'wet' issue should also include a discussion on potential merits and detriments of fluid types (crystalloids versus colloids) in ALI/ARDS or patients with an elevated risk for these syndromes[40,41]. Although, roughly, colloids may not confer a survival benefit nor prevent pulmonary edema as compared to crystalloids in mixed patients populations, albumin administration may be associated with less pulmonary complications, according to meta-analyses, even though edema

was not directly measured[40-42]. Hence, the controversy on colloid and crystalloids, when used for fluid resuscitation in ALI/ARDS is ongoing. Notwithstanding, adverse effects of gross overhydration are, obviously, independent of fluid types.

In a small series of mechanically ventilated ALI/ARDS patients with hypoproteinemia and presumably a low COP, albumin and furosemide versus furosemide alone ameliorated gas exchange and some other surrogate indices of pulmonary edema, which again was not directly measured[43]. In critically ill, hypoalbuminemic patients with a presumably low COP, albumin administration was associated with less positive fluid balance and improved pulmonary function[37]. Verheij et al. used a bedside technique for measuring pulmonary permeability for proteins that is specific for ALI/ARDS[4]. They showed in postoperative, presumably hypovolemic patients with ALI, in half of them accompanied by mild permeability edema, that the type of fluids (saline versus gelatin, albumin or starch) did not affect pulmonary edema formation in the presence of an increased cardiac output, i.e. in the steep part of the cardiac function curve (as in Figure 1). Alternatively, increased permeability may have diminished the contribution of plasma COP on edema formation, thereby diminishing differences between fluid types, or adaptation of Starling forces and increased lymph flow may have fully compensated for slightly increased fluid transport, or both.

## Controversy 4: colloid versus colloid in preventing or ameliorating pulmonary edema and lung injury in ALI/ARDS

Among the colloids, albumin and high-molecular weight starch preparations have potential anti-inflammatory and anti-permeability properties, respectively, as suggested by animal experiments. Indeed, HES as compared to gelatin used after abdominal aortic surgery was suggested to ameliorate some gas exchange and other respiratory abnormalities, used as surrogate indices of edema[44]. Verheij et al.[4] confirmed a mild attenuation of directly measured permeability in the lungs, in patients after major surgery, but the clinical consequences remained unclear. Conversely, the favorable effects of albumin suggested by others[37,43] could have been caused, in part, by a mild anti-inflammatory effect rather than by amelioration of hypoproteinemia, a low COP and pulmonary edema. However, sufficient clinical data to decide in this matter are lacking.

## Summary

Many questions regarding fluid resuscitation during ALI/ARDS remain unanswered, and this is partly related to the frequent use of surrogate indicators of pulmonary edema, including gas exchange parameters and chest radiography, which may not reflect pulmonary edema. This prompts for using direct measures of permeability and edema, with proven feasibility at the bedside[4], in evaluating fluid resuscitation in patients with or at risk for ALI/ARDS after sepsis, trauma or major surgery.



## Key points for clinical practice

1. The timing, dosing and choosing the type of fluid therapy, when clinically needed, in patients with or at risk for ALI/ARDS, is best accomplished by careful weighing potential benefits and hazards for the individual patient in the course of disease. There is no consensus on this issue.
2. Fluid resuscitation remains the treatment of choice, provided that the patient is likely to be fluid responsive, in case of hypotension and tissue hypooxygenation (accompanied by clinical signs). Adequate fluid resuscitation may ameliorate morbidity/mortality and prevent harmful fluid overloading.
3. While relative fluid restriction, after initial resuscitation, may ameliorate pulmonary edema formation and shorten ventilator days particularly when permeability is increased (in ALI/ARDS), this is likely to benefit only when hemodynamically tolerated and when tissue oxygenation and renal perfusion are unlikely to be severely diminished.
4. 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. Predicting and monitoring fluid responsiveness as well as EVLW may prevent (further) pulmonary edema formation and may guide fluid loading, when needed, during ALI/ARDS, regardless of dose and type of fluid.

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# 5

## Use of synthetic colloids in sepsis: a critical review on efficacy, safety and patient benefits

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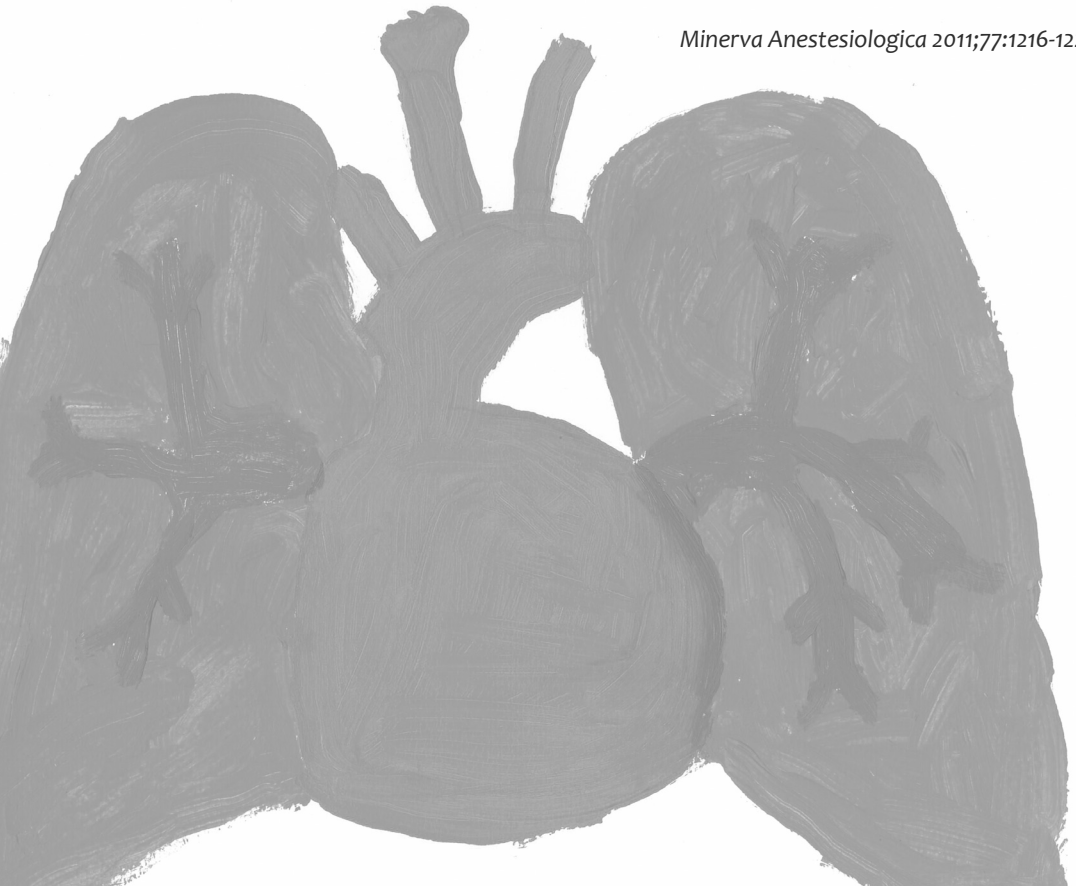

## Abstract

In this narrative review, the studies and analyses are discussed that pertain to benefits and detriments of synthetic colloids versus natural colloids or crystalloids used for fluid resuscitation in sepsis and septic shock. The relative amount of fluid infusions used to reach clinical or hemodynamic endpoints are reviewed, as well as potential toxicity of starch solutions and on the kidney. Hence, it cannot be excluded that adverse effects partly offset beneficial hemodynamic effects that are similar to that of natural colloids, so that in most analyses a mortality benefit of synthetic colloid fluid resuscitation in sepsis and septic shock cannot be demonstrated.

## Introduction

Although administration of fluids is one of the most common interventions in the management of patients with sepsis in the intensive care unit (ICU), there is limited high quality evidence for the safety/benefit ratios of the most commonly used fluid types[1]. In a recently published systematic review comparing crystalloids with colloids used for resuscitation, the authors argued that colloids are not associated with improved survival and that, as they are more expensive than crystalloids, their continued use may not be justified outside the context of clinical trials[2]. This may also be applied to children[3]. An older metaanalysis even suggested that colloids could be detrimental in sepsis, possibly because of increased extravascular leakage[4]. Formal sepsis guidelines, however, state that either colloids or crystalloids can be used for resuscitation in a volume ratio of approximately 1 to 3, but the evidence for the latter, again, is scarce[5].



In contrast, surveys among ICUs on the use of preferred plasma volume expanders for critically ill patients demonstrate more frequent use of colloids than of crystalloids in the first-line treatment, whereas hydroxyethyl starch (HES) is the most widely used colloid, with large differences between countries[6-9]. It seems that the observed variation depends on local practice rather than on (individual) patient characteristics[9]. So, current research evidence suggesting a lack of survival benefit with the use of colloids may not be convincing enough to override local habits, unless other properties may render colloids as a resuscitation fluid preferable in order to justify their continued use.

One of the reasons of continuing widespread colloid use is the possible beneficial hemodynamic effect associated with perhaps lower needs for volume infusion for a given hemodynamic endpoint. Use of colloids may thus beneficially limit the amount of fluids infused without the risk for underresuscitation[10]. Indeed, fluid overhydration is associated with increased mortality in sepsis[11,12], partly because of prolonged pulmonary edema and dependency on ventilators[6]. Conversely, potential adverse effects may offset beneficial actions so that overall patient benefits are small and hard to prove. In fact, synthetic colloids may have adverse effects and recent evidence accumulates that HES preparations in particular may have deleterious effects on renal function[13-17].

In this paper we will critically review merits and detriments of the use of synthetic colloids as gelatins and HES solutions, as compared to natural colloids and crystalloids,

in critically ill, septic patients. This includes studies solely on septic patients or studies in which >25% of patients had documented sepsis, including those with acute lung injury/ acute respiratory distress syndrome and children, in contrast to the limited number of studies used by Wiedermann in his recent metaanalysis on HES in sepsis[18]. We will not discuss animal experiments nor include papers by a German group against which doubts have recently been raised[19]. For a general overview of pharmacology, properties or safety of fluids, the reader is referred to recent literature[17,20-22]. We will focus the discussion around three questions and will not dwell upon hyperoncotic or hypertonic solutions nor upon dextrans since use of the latter is not widespread.

## 1. Are synthetic colloids more effective than crystalloids and similarly effective as natural colloids in sepsis?

It is widely believed that severe sepsis and septic shock, are characterized, among others, by myocardial depression, endothelial injury and vascular leakage, both in the lungs and systemically, that may, in theory, limit the relative hemodynamic efficacy of colloid versus crystalloid fluid resuscitation[23]. Indeed, the plasma disappearance of intravenously injected large molecules including (radiolabeled) albumin is more rapid in septic than nonseptic conditions, perhaps depending on the severity of sepsis[24-27].

In theory, crystalloid solutions expand the plasma volume by about 200 mL per liter infused, concomitantly with lowering, by diluting circulating proteins, of plasma colloid osmotic pressure (COP), as demonstrated in nonseptic subjects[27,28]. Depending on the rate of infusion, the equilibration rate of crystalloid with the interstitial space is rapid (minutes) even in patients with hypovolemia or shock, thereby resulting in potentially harmful interstitial (pulmonary) overhydration[27,29,30]. Crystalloids thus need to be administered at volumes approximately 3 to 5-fold greater than those of (isooncotic) colloids, that are largely maintained in the plasma compartment because of maintenance of COP, in order to achieve comparable plasma volumes and resuscitation endpoints[21,27,28]. Conversely, the intravascular COP after colloid infusion is influenced by baseline COP, the degree of hemodilution and the COP of the infused volume and its plasma retention, determined by the molecular weight (Mw) distribution. Colloid Mw is important because of its relationship to pharmacokinetics; small particles with a low Mw

exert a greater oncotic effect and, for a given number of molecules, will have a lower viscosity than larger molecules[31]. In contrast, they have a shorter intravascular retention before being filtered in the glomerulus or lost into the interstitium. Larger molecules are retained in the intravascular space longer but, as there are fewer of them, exert less osmotic forces across the semi-permeable membrane of the endothelium and therefore have a less volume expanding effect[31]. While albumin solutions are monodisperse (molecular weight of 69 kDa), hydroxyethyl starch (HES) solutions are polydisperse, defined by the degree of substitution (MS) (via partial hydrolysis) and by Mw, both of which affect pharmacokinetics[21]. The greater the degree of substitution the greater the resistance to degradation, which therefore prolongs efficacy of HES as a plasma expander. After substitution, the starch is refined into the final product by hydrolysis to the required Mw. The molecular weight distribution can be described using the COP50/COP10 ratio[31]. This is the ratio of measured COP's across 2 different membranes, with a 50 kDa and a 10 kDa pore size, respectively, and reflects the relative proportion of molecules retained by filters with those pore sizes. Colloids with a low COP50/COP10 ratio will be lost more rapidly from the intravascular space. Thus, the concentration and Mw of colloid molecules and hence the COP, determine the initial degree of volume expansion, whereas both the Mw and surface charge characteristics determine the rate of loss through the capillary endothelial barrier and loss into the urine by glomerular filtration. Therefore, the intravascular retention and half time of colloids amount to hours, dependent on dispersion and weight of molecules.

Gelatins are polydisperse and in excess of 75% of the molecules are thought to be smaller than the renal threshold of 30 kDa. The large number of small molecules exerts a powerful initial COP effect making gelatins good for short-term volume expansion, but molecules with a Mw less than 15 kDa have a similar clearance to that of creatinine and will be filtered by the glomerulus. They are thus rapidly cleared from the intravascular space, with a half-life of 3.5-4 hours[21]. In sepsis, the hemodynamic effects of gelatins may be similar to that of isooncotic HES preparations, but gelatins may decrease gastric tonometric $PCO_2$ and improve adequacy of mucosal blood flow more than HES[26,28,32,33].

If colloids are capable of expanding the plasma volume to a greater extend than crystalloids, then the same volume of colloids would have greater effects on hemodynamics than crystalloids. The volume ratio of crystalloids to colloids relative

to hemodynamic efficacy depends on the rate and fate of the infused fluids and the hemodynamic monitoring tool and endpoint utilized. The hemodynamic endpoint of resuscitation varies from one study to the other between clinical judgment, arterial and central venous pressures, to pulmonary artery occlusion pressures and cardiac output and variables obtained by transpulmonary thermodilution. The variety is likely responsible, in part, for the widely varying volume ratios during resuscitation as reported in the literature. For instance, the VISEP trial documented that target values of central venous pressure in severe sepsis were reached faster with HES (10%, 200/0.5) loading than that with Ringer's lactate, at an averaged volume ratio of 1:1.3, but 28 day mortality did not differ[13]. The central venous pressure and central venous $O_2$ saturation in the HES group were somewhat higher than in the Ringer's lactate group, perhaps suggesting underestimation of crystalloids requirements or more appropriate infusion of HES products. Trof et al., however, demonstrated, in perhaps less severely ill septic patients described before[26], that 90 min fluid loading with 4-6% colloids, either gelatins, HES or albumin, resulted in a greater linear increase in cardiac filling, output and left ventricular stroke work than that with saline loading both in septic and nonseptic patients, probably due to a larger plasma volume following increased COP with the former and in spite of the characteristic myocardial depression of sepsis[28]. The efficacy of isooncotic colloids, regardless of their type, was 3-fold greater than of saline, independent of underlying condition, even though about 17% more crystalloid was infused. This confirms older data suggesting a 2 to 5-fold greater fluid requirement with crystalloids in both hypovolemic and septic shock aiming at similar hemodynamic endpoints, and thus far greater interstitial volume expansion, for a given plasma volume expansion, than with colloids[29,30,34]. In children with Dengue shock syndrome, Ringer's lactate administration resulted in higher hematocrits, lower arterial (pulse) pressures and cardiac outputs, and slower shock reversal than that of (similar volumes of) synthetic colloids dextrans, gelatins or HES[35,36]. In children with septic shock, up to 67% more saline than gelatin (volume ratio 1.7:1) was required to reach similar plasma volume and other hemodynamic targets[37]. In a recent study comparing HES (6%, 130/0.4) versus normal saline during early goal directed therapy of septic patients, the volume ratio was 1:2.4 for reaching similar hemodynamic endpoints after 24 hours[38]. Resuscitation with HES improved the sublingual microcirculation more than that with saline. Indeed,

HES 130/0.4 is an effective plasma volume expander and favorably increases global hemodynamics in sepsis[39].

Therefore, based on correct interpretation of the current literature, the volume ratio for similar hemodynamic endpoints is approximately 1 (isooncotic) colloid to 2-3 crystalloid volume units, even in sepsis, in line with the guidelines[5]. The factor is maintained when multiplying lower ratios, when applicable, with the difference in hemodynamic endpoints attained. Otherwise, appropriate resuscitation (with colloids) may contribute, among others, to prevention of kidney injury and renal failure[7,14]. Taken together, the studies cited imply that in sepsis, unless the condition is perhaps very severe, increased leakage of colloids is not a major factor limiting their plasma volume expanding effects, in contrast to common beliefs and recent suggestions[17].



## 2. What are the current insights regarding renal toxicity and other adverse effects attributable to synthetic colloids in sepsis?

The most discussed adverse effects of synthetic colloids, in particular HES, is the risk of acute kidney injury (AKI)[13-17,22]. A recent systematic review examining the effects of HES on renal function compared to other fluid resuscitation therapies in different patient populations demonstrated an overall relative risk of author-defined acute renal failure (by serum creatinine, creatinine clearance or calculation/estimation of glomerular filtration rate) of 1.50, and 1.38 for requiring renal replacement therapy (RRT) as compared to crystalloid or non-HES colloid, whereby subgroup analyses suggested an increased risk in septic versus nonseptic patients[15]. However, the 183 randomized controlled trials (RCT) identified by this review evaluated the need for RRT as the primary outcome measure and not other renal outcomes. Second, in none of the studies, the newly developed and validated criteria to objectively define and stage AKI, were used. Third, despite the presence of probably sufficient data to suggest a difference between HES-treated sepsis and nonsepsis patients with respect to the risk of AKI, the studies in nonseptic patients were inadequately powered to confirm this difference. Finally, the variability of type and volume of the used HES solutions may have confounded outcome results; that type and volume matters is supported by some literature. For instance, the cumulative amount of HES administered in the largest sepsis study[13] to date was considerably higher than

in most other studies. The mean cumulative dose of HES was 70.4 mL/kg and volume expansion was performed exclusively with Ringer's lactate or HES. This volume is far above the manufacturer's recommendation of 33 mL/kg on day 1, followed by 20 mL/kg/day. Furthermore, this study used second generation (pentastarch 10%, 200/0.5) HES preparations instead of more modern generation tetrastarches (HES 130/0.4). Indeed, in 2001 already, Schortgen et al. suggested that the use of second generation HES, as compared to gelatin solutions was an independent risk factor for acute renal failure in patients with severe sepsis or septic shock[40]. Meanwhile, recent retrospective work suggests that resuscitation with (low volumes of) low Mw (130/0.4) tetrastarch HES (third generation) in critically ill patients (>25% sepsis) is not associated with increased development of AKI[41,42]. Also a large retrospective study involving >3000 patients (>25 % sepsis) demonstrated that the use of HES did not influence renal function or the need for RRT in multivariable analysis[43]. Although the median amount of HES was below the recommended maximum dose, it did not predict the subsequent need for RRT. The type of HES was not reported specifically but the use of third generation HES could have contributed to the more favorable results. Nevertheless, there is currently inadequate clinical data to prove the claim that safety differences exist between different HES products[15,22].

The mechanism of potential HES-induced AKI is not well understood. It may include reabsorption of the macromolecule into (proximal) renal tubular cells leading to osmotic nephrotic lesions 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 than hydrostatic pressure[14]. Prolonged elevation of COP, reached by a higher Mw and a more extensive MS as accomplished by first and second generation HES solutions, might explain why these old generation HES products could be more nephrotoxic, if at all, than the third generation tetrastarches. We also do not know the comparative action of colloid concentrations on the kidney, since elevation of COP by itself may inhibit glomerular filtration[14]. Moreover, gelatins may increase low Mw proteinuria even in volunteers, probably by competitively inhibiting tubular resorption rather than by tubular injury[44]. They may, at high doses, be independently associated with AKI[41]. Unbalanced crystalloid solutions as compared to balanced or bicarbonate-containing solutions may negatively affect renal perfusion and function, because of high

chloride concentrations, and the validity of infusion of these solutions as a control for colloid effects can therefore be doubted[14].

Alleged non-renal toxicities of HES finally include long-term pruritus and hepatocellular injury with jaundice, but there is no literature on these side effects in septic patients only[18,22]. Two studies from the same group argue that pentastarch or hetastarch HES does not affect coagulation as compared to albumin during sepsis, even though circulating von Willebrand factor was decreased[45,46]. Although some resuscitation fluids have been suggested to modify inflammatory responses, there is no specific information or comparison of patient-centered outcomes in sepsis. Human-derived albumin carries the theoretical risk of transmittable disease, but there is no evidence for that and natural colloids are therefore regarded as safer than synthetic colloids[22].



A survey on non-hyperoncotic colloids and crystalloids in France suggested that fluids were associated with similar incidences of overhydration and acute lung injury/acute respiratory distress syndrome, irrespective of sepsis[47]. Indeed, prospective studies in septic patients suggested that both crystalloid and (synthetic) colloid fluid loading does not aggravate pulmonary permeability-edema, provided that loading is in the steep part of the cardiac function curve[26,32,39,47-49], whereas maintaining a fixed pulmonary capillary wedge pressure resulted in pulmonary overhydration with use of crystalloids (only)[29]. There is some evidence that HES may even ameliorate increased pulmonary permeability[48]. Hyperoncotic albumin solutions may[50-52] or may not[53,54] ameliorate oxygenation and perhaps edema in sepsis-induced acute lung injury (as compared to crystalloid or isooncotic synthetic colloid), whether or not combined with furosemide.

## 3. How should we interpret pooled data on mortality[2] comparing colloids versus crystalloids for fluid resuscitation in critically ill, septic patients?

The Cochrane systematic reviews comparing colloids versus crystalloids and colloids versus colloids for fluid resuscitation in general critically ill patients demonstrated that resuscitation with colloids may not reduce the risk of death, in spite of their hemodynamic superiority[2], and that colloids may not be different in this respect[55]. This may, among others 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 more critically to the extracted and analyzed data, most studies were not powered for mortality nor was mortality defined as a primary outcome measure, as in the Wiedermann systematic review on HES in sepsis[18]. Table 1 shows an overview of the available and analyzed studies on sepsis comparing (modified) gelatin or HES solutions with crystalloids or natural colloids (human albumin), or comparing HES versus (modified) gelatin, and reporting data for mortality. Remarkably, most of the studies included small number of patients except two[13,36] and only the VISEP trial was powered for mortality as primary outcome measure[13]. This recent German multicenter study was powered at 600 sepsis patients to detect a reduction in mortality from 40% to 30% at 28 days. However, after enrollment of 600 patients, the planned interim analysis showed a greater incidence of renal failure and a trend toward higher 90-day mortality among patients who received HES than among those who received Ringer's lactate. Therefore, the study was suspended. Among the 537 patients who could be evaluated, the rate of death at 28 days did not differ between the HES group and the Ringer's lactate group. The rate of death at 90 days was increased among patients who received a higher dose of HES, as compared with those who received a lower dose (58 versus 31%). All the other studies were underpowered for mortality as primary outcome measure. And although most of these studies showed a tendency to higher mortality for synthetic colloids treated patients, displayed by higher risk ratios, it is hard to definitively conclude that synthetic colloids affect survival as compared to crystalloids or human albumin and vice versa. In septic children also, lack of evidence of an effect on mortality by either crystalloid or colloid fluids could be caused in part by the fact that none of the studies included, had mortality as the primary endpoint[3]. In contrast, the use of albumin solutions compared to crystalloids may improve mortality in sepsis[56,57], and this may lead to the speculation that adverse effects of synthetic colloids may offset potential beneficial effects and thereby attenuate a potential survival benefit.

Currently, the CHEST trial (NCT 00935168) is underway comparing HES 130/0.4 versus normal saline for fluid resuscitation in ICU patients with mortality as primary outcome measure. Also a few other RCT's are currently performed or analyzed comparing HES 130/0.4 with crystalloids such as Ringer's acetate (NCT 00962156, n=800) or normal saline (NCT 00273728, n=250; NCT 00464204, n=200) on mortality in patients with sepsis. Results of these studies may also reveal whether HES 130/0.4 is safer than older HES preparations or not, as current evidence remains inconclusive[15,22]. Also new albumin studies (versus crystalloids) are underway such as the Italian ALBIOS study (NCT00707122, n=1350). The French multicenter trial (NCT00327704, n=800) on albumin in severe sepsis and septic shock has been completed. Preliminary results indicate lack of survival benefit of albumin over saline, partly due to underpowering.



## Conclusion and recommendations

Based on the current literature, there is sufficient evidence that the use of (synthetic) colloids results in more (rapid) plasma volume expansion and hemodynamic optimization than resuscitation with crystalloids, even when accompanied by presumed increased vasopermeability in sepsis. Although suggested otherwise[17], the volume ratio for similar hemodynamic endpoints is approximately 1 colloid to 2-3 crystalloids. The factor is maintained when multiplying lower ratios, when applied, with the difference in hemodynamic endpoints attained. The risk of renal toxicity with the use of HES solutions must be qualified according to type, concentration and volume of the HES solution used. When it comes to outcome, there is no evidence that the use of synthetic colloids for resuscitation purposes negatively influences mortality in sepsis as compared to crystalloids or natural colloids. Large prospective studies comparing low Mw tetrastarches or albumin with crystalloids for fluid resuscitation in sepsis are currently being performed. The results are eagerly awaited. In the meantime, we suggest that the use of newer generations HES solutions (e.g. 130/0.4) should not be discouraged for resuscitation purposes in patients with sepsis or septic shock. The clinician should weigh benefits versus disadvantages, thereby taking the maximum recommended dose of 50 mL/kg/day into account.

**Table 1.** Overview of studies with data on mortality comparing HES or Gelatin with crystalloids or natural colloids or HES versus Gelatin for fluid resuscitation in sepsis.

| Study | Shock origin (no. of patients) type of study | Gelatin; mean $M_w$ or HES; concentration, $M_w$ / Substitution | Risk Ratio for mortality | Mortality as primary outcome | Powered for mortality | Primary outcome measure |
|---|---|---|---|---|---|---|
| Rackow et al.[29]<br>HES vs. HA vs. NS | mixed (26)<br>RCT | 10%, 670/0.75 | 0.92[a]<br>1.00[b] | No | No | COP changes, cardiorespiratory parameters |
| Dung et al.[35]<br>Gel VS NS VS RL[1] | DSS (50)<br>RCT | 35 kDa | 1.00[c] | No | No | Shock reversal |
| Asfar et al.[33]<br>HES VS Gel | Sepsis (34)<br>RCT | 35 kDa / 6%, 200/0.5 | 0.94 | No | No | Reversal of gastric mucosa acidosis |
| Molnar et al.[32]<br>HES VS Gel | Sepsis (30)<br>RCT | 30 kDa / 6%, 200/0.6 | 1.07 | No | No | Cardiorespiratory parameters |
| Veneman et al.[53]<br>HES VS HA VS NS | Sepsis / SIRS (63)<br>RCT | 10%, 200/0.5 | 1.12[a]<br>1.88b | No | No | Effects on COP |
| Upadhyay et al.[37]<br>Gel VS NS | Sepsis (60)<br>RCT | 35 kda | 1.07 | No | No | Restoration of plasma volume, cardiorespiratory parameters |
| Wills et al.[36]<br>HES vs. RL[1] | DSS (512)<br>RCT | 6%, 200/0.5 | 1.00[d] | No | No | Shock reversal, need for rescue colloid infusion |
| Palumbo t al.[39]<br>HES VS HA | Sepsis (20)<br>RCT | 6%, 130/0.4 | N.A. | No | No | Cardiorespiratory parameters |
| Brunkhorst et al.[13]<br>HES VS RL | Sepsis (537)<br>RCT | 10%, 200/0.5 | 1.21 | Yes | Yes | Mortality |
| Huang et al.[48]<br>Only HES | Septic ARDS (20)<br>OS | 10, 200/0.5 | N.A. | No | No | Cardiorespiratory parameters |
| Dolecek et al.[52]<br>HES VS HA | Sepsis (56)<br>RCT | 6%, 130/0.4 | N.A. | No | No | Pulmonary edema by measurement of EVLW |
| Van der Heijden et al.[26] / Trof et al.[28]<br>HES vs. Gel vs. HA vs. NS | Sepsis / nonsepsis (48)<br>RCT | 30 kDa / 6%, 200/0.5 | 1.00[e]<br>1.36[b]<br>1.47[f]<br>2.00[a] | No | No | Cardiorespiratory parameters, pulmonary edema |

*HES* hydroxyethyl starch, *HA* human albumin, *Gel* gelatin, *NS* normal saline, *RL* Ringer's lactate, *RCT* randomized controlled trial, *OS* observational study, *DSS* Dengue Shock Syndrome, *SIRS* systemic inflammatory response syndrome, *COP* colloid osmotic pressure, *ARDS* acute respiratory distress syndrome, *mW* molecular weight, *kDa* kilodalton, *EVLW* extravascular lung water, *N.A.* not applicable. [1]dextrans not included, [a]HES vs. HA, [b]HES vs. NS, [c]no deaths reported, [d]HES vs. RL or NS in moderately severe shock, [e]Gel vs. NS, [f]Gel vs. HA.

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# 6

# Cardiac filling volumes versus pressures for predicting fluid responsiveness after cardiovascular surgery: the role of systolic cardiac function

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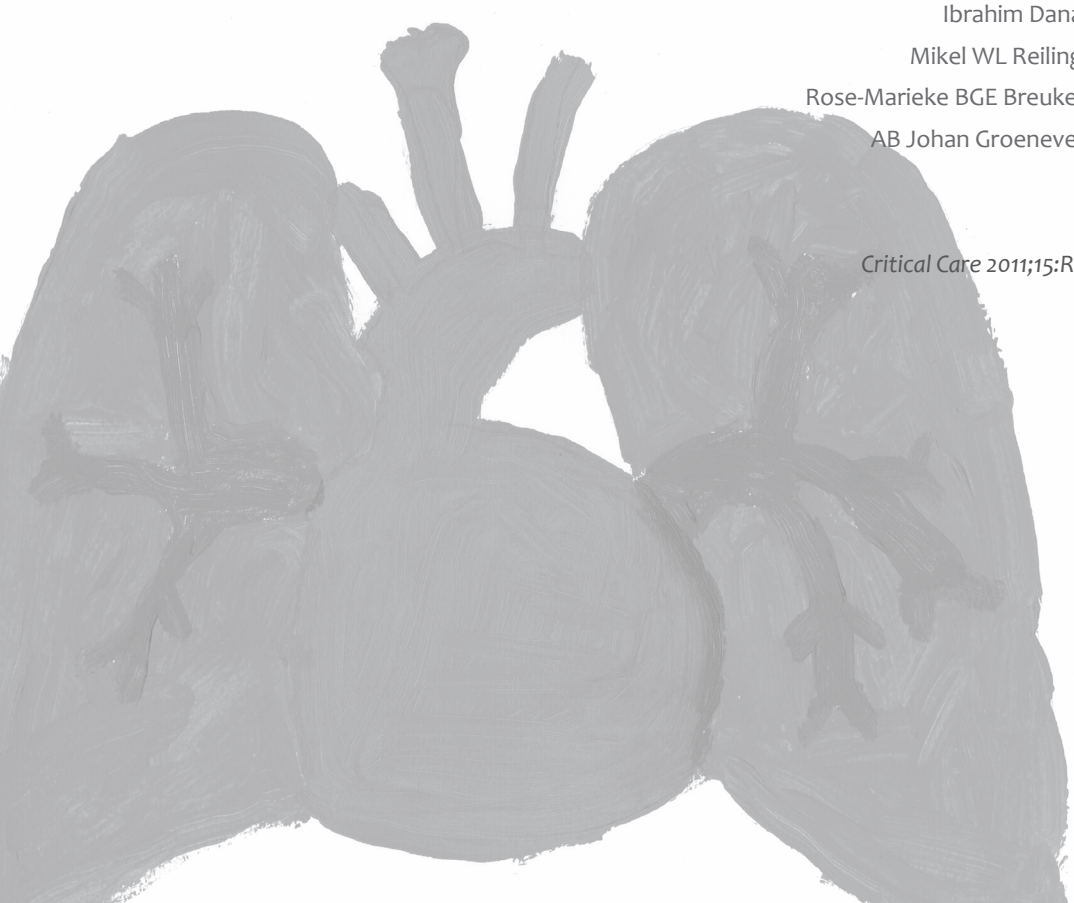

## Abstract

### Introduction

Static cardiac filling volumes have been suggested to better predict fluid responsiveness than filling pressures, but this may not apply to hearts with systolic dysfunction and dilatation. We evaluated the relative value of cardiac filling volume and pressures for predicting and monitoring fluid responsiveness, according to systolic cardiac function, estimated by global ejection fraction (GEF, normal 25-35%) from transpulmonary thermodilution.

### Methods

We studied hypovolemic, mechanically ventilated patients after coronary (n=18) or major vascular (n=14) surgery in the intensive care unit. We evaluated 96 colloid fluid loading events (200-600 mL given in 3 consecutive 30 min intervals, guided by increases in filling pressures), divided into groups of responding events (fluid responsiveness) and non-responding events, in patients with low GEF (<20%) or near-normal GEF (≥20%). Patients were monitored by transpulmonary dilution and central venous (n=9)/pulmonary artery (n=23) catheters to obtain CI, global end-diastolic volume index (GEDVI), central venous (CVP) and pulmonary artery occlusion pressure (PAOP).

### Results

Fluid responsiveness occurred in 8 (≥15% increase in CI) and 17 (≥10% increase in CI) of 36 fluid loading events when GEF was <20%, and 7 (≥15% increase in CI) and 17 (≥10% increase in CI) of 60 fluid loading events when GEF was ≥20%. Whereas a low baseline GEDVI predicted fluid responsiveness particularly when GEF ≥20% ($p$ = .002 or lower), a low PAOP was of predictive value particularly when GEF <20% ($p$ = .004 or lower). The baseline CVP was lower in responding events regardless of GEF. Changes in CVP and PAOP paralleled changes in CI particularly when GEF <20%, whereas changes in GEDVI paralleled CI regardless of GEF.

### Conclusion

Regardless of GEF, CVP may be useful for predicting fluid responsiveness in patients after coronary and major vascular surgery provided that positive end-expiratory pressure is low. When GEF is low (<20%), PAOP is more useful than GEDVI for predicting fluid responsiveness, but when GEF is near-normal (≥20%) GEDVI is more useful than PAOP. This favors predicting and monitoring fluid responsiveness by pulmonary artery catheter-derived filling pressures in surgical patients with systolic left ventricular dysfunction and by transpulmonary thermodilution-derived GEDVI when systolic left ventricular function is relatively normal.

## Introduction

The clinical benefit of various hemodynamic monitoring techniques in the critically ill is still under debate[1-5]. Static filling volumes, such as the transpulmonary dilution-derived global end-diastolic volume, have been suggested to better predict fluid responsiveness than filling pressures such as the central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) obtained from a pulmonary artery catheter[6-19]. Most studies, however, often included patients with relatively normal left ventricular systolic function, undergoing coronary artery surgery[6-13,15,16,19]. Mundigler et al. suggested that pressures were superior to transpulmonary thermodilution-derived volumes for monitoring changes in cardiac preload during fluid loading in non-surgical patients with left ventricular systolic dysfunction, measured by transesophageal echocardiography[20]. We also suggested this in patients with presumed left ventricular systolic dysfunction based on transpulmonary thermodilution-derived global ejection fraction (GEF) following valvular surgery[21]. However, others did not reach the same conclusion[14,17]. Nevertheless, according to Laplace's Law, pressures and volumes may both contribute to end-diastolic wall stress as a true measure of cardiac preload. Based on the curvilinear left ventricular pressure-volume relationship at end-diastole, volumes may increase more than pressures with fluid loading at low cardiac filling, while at higher cardiac filling, pressures may increase more than volumes[5]. At low cardiac filling, volumes may thus better predict fluid responsiveness than pressures, while in hearts with systolic dysfunction and dilatation, pressures may better predict and monitor fluid responsiveness than volumes[5,22].

We hypothesized that during fluid loading in patients with reduced systolic cardiac function as compared to those with normal function, filling pressures may be superior to filling volumes (i.e. global end-diastolic volume, GEDV) for predicting and monitoring of fluid responsiveness, and vice versa. We thus measured prospectively cardiac filling pressures and volumes in hypovolemic patients following cardiovascular and major vascular surgery, using the pulmonary artery catheter and transpulmonary thermodilution technique, prior to, during and following colloid fluid loading.

## Patients and methods

This is a sub study of a prospective, non-randomized, single-center clinical trial, investigating the volume expanding effects of various resuscitation fluids[23]. The study was approved by the Ethics Committee of the Vrije Universiteit Medical Center. Written informed consent was obtained pre-operatively. We analyzed the effect of colloid fluid loading in patients who had undergone coronary artery (n=18) or major vascular surgery (n=14). Colloid fluid loading was given with modified fluid gelatin 4%, hydroxyethyl starch (HES) 6% or albumin 5%, all of which have similar oncotic properties and hemodynamic responses[23]. We only analyzed patients who completed fluid loading and measurements up to t=90 min. Inclusion criteria, at enrollment and start of the protocol, were presumed hypovolemia, defined as a systolic blood pressure <110 mm Hg and reduced filling pressures: PAOP <13 mm Hg (in the presence of a pulmonary artery catheter) or CVP <12 mm Hg. Exclusion criteria were age >75 year, preterminal illness with a life expectancy of less than 24 hours, or know anaphylactic reactions to colloids. All perioperative care was given by attending physicians who were not involved in the study.

*Study protocol.* The protocol was started upon arrival of the patients in the intensive care unit (ICU). Demographic characteristics were recorded, including the acute physiology and chronic health evaluation (APACHE-II) score and transesophageal echocardiographic findings prior to surgery. At baseline (t=0 min), hemodynamic measurements were performed. Heart rate (HR) and mean arterial pressure (MAP) from a radial artery were recorded at t=0 and 90 min. The HR was taken from the continuously recorded electrocardiogram. The mean pulmonary artery pressure (MPAP) was measured at t=0 and 90 min. Cardiac output, GEDV, CVP and PAOP were measured every 30 min, from t=0 to 90 min. Pressures were measured with patients in the supine position after calibration, zeroing to atmospheric pressure and, for PAOP, after proper wedging, at the midchest level at end-expiration (Tramscope®, Marquette, GE, Milwaukee, Wisconsin). For the measurements of cardiac output and GEDV, the transpulmonary thermal-dye indicator dilution technique was used[1,6]. These measurements involve a central venous injection of 15 mL of ice-cold indocyanine green in 5% glucose solution and concomitant registration of the dilution curves in the femoral artery, by a 3F catheter equipped with a thermistor (PV 2024, Pulsion Medical Systems, Munich, Germany). This catheter

was inserted at the end of surgery via a 4F introducing sheath (Arrow, Reading, USA) and connected to a bedside computer (COLD Z-021, Pulsion Medical Systems, Munich, Germany. The COLD Z-021 is the precursor to the current pulse contour cardiac output (PiCCO™) technique. GEDV represents the volumes of the right and left heart at end-diastole and reflects left ventricular dimensions obtained by echocardiography in the absence of overt right ventricular distention[7,12-17]. The ratio between stroke volume and global end-diastolic volume/4 is defined as the global ejection fraction (GEF, normal values 25-35%), and is an indicator of left ventricular systolic function, provided that there is no right ventricular dysfunction[24,25]. Reproducibility of these measurements is typically within 10%[1]. After baseline measurements were taken, fluids were given over 90 min on the basis of the response within predefined limits of increases in pressures (CVP or - when available - PAOP), according to a previously described protocol[23,26,27]. Up to 200 mL of fluid were given every 10 min, provided that the increase in filling pressures with the fluid loading did not exceed critical values, and this policy has been proven safe in previous studies[23,26,27] (i.e. not evoking pulmonary edema). The maximum amount of fluid infused was 1800 mL. Concomitant vasoactive and sedative drug treatment and ventilatory settings remained unchanged during fluid loading. Indeed, all patients were received volume-controlled mechanical ventilation and positive end-expiratory pressure (PEEP). Drainage of blood was <50 mL/hour in all patients, and no patient underwent repeated surgery for bleeding within 12 hours post surgery.

*Statistical analysis.* The groups to be analyzed were divided into low GEF (<20%) and near-normal GEF (≥20%). The cutoff of 20% approximately reflects a cutoff of 40% ejection fraction of the left ventricle, the lower limit of normal, as measured by echocardiography, provided that there is no right ventricular dysfunction[24,25]. We also analyzed data according to a cutoff of 15%. Stroke volume, cardiac output and global end-diastolic volume were indexed to body surface area (BSA), giving stroke volume index (SVI, mL/m$^2$), cardiac index (CI, L/min/m$^2$) and global end-diastolic volume index (GEDVI, n 680-800 mL/m$^2$), respectively. Cardiac distensibility was determined as the surrogate for cardiac compliance and was calculated by GEDVI/(CVP+PAOP)/2 (mL/m$^2$/mm Hg), or GEDVI/CVP if PAOP was not available[28]. Fluid responsiveness was defined as an increase of CI or SVI ≥10% or ≥15%, in accordance with the literature[4,9,17], between t=0-30, t=30-60 and t=60-90 min during fluid loading. For categorical data, $X^2$ and Fisher exact tests

were used. Since continuous data were normally distributed (Kolmogorov-Smirnov test, $p > .05$), they were summarized by mean ± standard deviation (SD) and parametric tests were done. Paired and unpaired t-tests were used to compare data in time and between GEF groups. Generalized estimating equations were used to evaluate differences in baseline and changes in variables between summated responding and non-responding fluid loading events in each GEF group, to evaluate their predictive and monitoring values, respectively, taking repeated measurements in the same patients into account, with the amount and type of fluid infused entered as covariates to adjust for potential confounding. Partial correlation coefficients (r), adjusted for repeated measurements by entering patient number and for type and amount of fluids as covariates were calculated. Coefficients were compared after z transformation. Receiver operating characteristic curves (ROC) plotting sensitivity against 1-specificity were constructed to evaluate the predictors of fluid responsiveness by the areas under the curve (AUC, with 95% confidence intervals) for pooled data, in the absence of accepted methods to adjust for repeated measurements, and were compared with each other. Optimum cutoff values with associated combinations of highest sensitivity and specificity were calculated (MedCalc Software, Belgium). Exact two-sided *p* values >.001 are given and considered statistically significant when <.05. All analyses were conducted using SPSS version 15.0 (SPSS Inc, USA).

## Results

Table 1 summarizes the demographic, hemodynamic and respiratory characteristics of patients. Patients underwent coronary artery or major vascular surgery (in three cases on the distal thoracic aorta). Surgery was uneventful in all patients. The table shows the differences between patient groups with a GEF <20% and ≥20% and the changes with fluid loading. There was no difference in the amount and type of fluids infused and fluid balances between the GEF groups. GEF did not change during fluid loading. Baseline GEDVI was higher when GEF was <20% than ≥20% suggesting cardiac dilatation. Preoperative echocardiography did not document severe right ventricular dysfunction and dilatation in any patient. There was no postoperative pulmonary hypertension and MPAP was 28 mm Hg at maximum in one patient. Indeed, MPAP at t=90 min in the low

GEF group was 23±7 and 25±2 mm Hg and in the near-normal GEF group 21±4 and 22±4 mm Hg, in responders and non-responders, respectively (GEE: $p$ = .44 for response, $p$ = .99 for GEF). Similarly, the MAP at t=90 min in the low GEF group was 95±16 and 86±25 mm Hg and in the near-normal GEF group 83±7 and 85±12 mm Hg, in responders and non-responders, respectively (GEE: $p$ = .52 for response, $p$ = .98 for GEF).

*Fluid loading events.* Among the 96 fluid loading events, the proportion of responding events (increase in CI ≥10%) decreased from t=0 to 90 min ($p$ = .031). The amount infused was somewhat lower in non-responding than in responding events when GEF was low (<20%), (Table 2). Baseline CI was lower in responding events, regardless of GEF and cutoff percentage of fluid responsiveness. When GEF was low, baseline CVP and PAOP were lower for responding events (≥10% increase in CI) while baseline GEDVI did not differ from that in non-responding events, irrespective of the amount and type of fluids. When GEF was near-normal (≥20%), baseline GEDVI and CVP were lower for responding events (≥10% increase in CI), while baseline PAOP did not differ from that in non-responding events.

Similar results were obtained for a GEF cutoff of 15% (Table 3). For fluid responsiveness defined as an increase in CI ≥15%: only baseline PAOP and not CVP predicted fluid responsiveness in the low GEF group (Table 4). In contrast, GEDVI particularly predicted fluid responsiveness when GEF was near-normal. Changes in GEDVI paralleled CI responses in both GEF groups, while changes in CVP paralleled CI responses only in the low GEF group. Changes in PAOP particularly paralleled responses in CI when GEF was low.

**Table 1.** Patient characteristics.

| | **GEF <20%** (n=12) | **GEF ≥20%** (n=20) | *p* value |
|---|---|---|---|
| **Demographic variables** | | | |
| Age | 66±7 | 61±7 | .082 |
| Male / female | 9/3 | 16/4 | 1.000 |
| APACHE II | 9±4 | 9±3 | .690 |
| Coronary artery / major vascular surgery | 5/7 | 13/7 | .277 |
| CPB yes / no | 4/1 | 9/4 | .648 |
| Time of CPB, minutes | 97±72 | 78±58 | .564 |
| Echocardiography (LVEF before surgery) good (≥40%) / poor (<40%) | 3/9 | 16/4 | 1.000 |
| **Hemodynamic and respiratory variables** | | | |
| HR, b/min | | | |
| t=0 | 75±11 | 68±12 | .112 |
| t=90 | 72±12 | 72±14[1] | .101 (for increase) |
| MAP, mm Hg | | | |
| t=0 | 85±15 | 74±12 | .034 |
| t=90 | 92±19 | 84±10[2] | .608 (for increase) |
| CVP, mm Hg | | | |
| t=0 | 5±2 | 3±2 | .047 |
| t=30 | 7±3 | 5±2 | N.A. |
| t=60 | 8±3 | 6±2 | N.A. |
| t=90 | 8±2[3] | 7±2[3] | .813 (for increase) |
| mPAP, mm Hg | | | |
| t=0 | 17±6 | 15±4 | .260 |
| t=90 | 23±5 | 21±4 | .627 (for increase) |
| PAOP, mm Hg | | | |
| t=0 | 6±3 | 7±3 | .477 |
| t=30 | 9±2 | 9±2 | N.A, |
| t=60 | 11±3 | 10±3 | N.A, |
| t=90 | 12±2[3] | 11±2[3] | .037 (for increase) |
| GEDVI, mL/m$^2$ | | | |
| t=0 | 1049±247 | 830±195 | .009 |
| t=30 | 1132±360 | 840±174 | N.A. |
| t=60 | 1170±387 | 857±171 | N.A. |
| t=90 | 1220±476 | 861±189 | .089 (for increase) |
| SVI, ml/m$^2$ | | | |
| t=0 | 42±10 | 52±12 | .022 |
| t=90 | 47±9[4] | 56±14[5] | .030 (for increase) |
| CI, mL/min/m$^2$ | | | |
| t=0 | 3.1±0.7 | 3.4±0.6 | .170 |
| t=30 | 3.5±0.7 | 3.7±0.7 | N.A. |
| t=60 | 3.7±0.9 | 3.9±0.8 | N.A. |
| t=90 | 3.9±0.9[3] | 3.9±0.6[3] | .101 (for increase) |
| GEF, % | | | |
| t=0 | 16±4 | 25±5 | N.A. |
| t=90 | 19±3 | 26±4 | N.A. |

| | | | |
|---|---|---|---|
| Distensibility, mL/m²/mm Hg | | | |
| t=0 | 241±167 | 229±124 | .830 |
| t=90 | 132±64[1] | 124±60[2] | .910 (for decrease) |
| PEEP, cm $H_2O$ | | | |
| t=0 | 7.5±2.0 | 6.7±2.7 | .385 |
| Fluid infused, mL | 1466±296 | 1585±291 | .300 |
| Gelatin / HES / albumin | 2 / 3 / 7 | 5 / 8 / 7 | .436 |
| Fluid balance, mL | 1001±334 | 1034±497 | .839 |

Mean ± SD

*LVEF* left ventricular ejection fraction, *CPB* cardiopulmonary bypass, *GEF* global ejection fraction, *APACHE II* acute physiology and chronic health evaluation, *LV* left ventricular, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *MPAP* mean pulmonary artery pressure, *PAOP* pulmonary capillary occlusion pressure, *GEDVI* global end-diastolic volume index, *CI* cardiac index, *PEEP* positive end-expiratory pressure, *HES* hydroxyethyl starch. t=0 and 90 min: prior to and at completion of fluid loading; [1]$p < .05$; [2]$p = .001$; [3]$p < .001$; [4]$p = .017$; [5]$p = .007$ vs. t=0, *N.A.* not applicable.

**Table 2.** Summated fluid loading responsiveness (≥10% increase in cardiac index) when global ejection fraction is <20% or ≥20%.

| | **GEF <20%** (n=12) | | | **GEF ≥20%** (n=20) | | |
|---|---|---|---|---|---|---|
| | R (n=17 steps in 10 patients) | NR (n=19 steps in 11 patients) | *p* value | R (n=17 steps in 14 patients) | NR (n=43 steps in 20 patients) | *p* value |
| CI, L/min/m² | | | | | | |
| baseline | 3.3±0.9 | 3.6±0.8 | .095 | 3.3±0.5 | 3.8±0.8 | .028 |
| after | 3.9±0.9 | 3.6±0.8 | | 3.9±0.7 | 3.8±0.7 | |
| change | 0.6±0.2 | 0.0±0.1 | N.A. | 0.6±0.6 | 0.0±0.3 | N.A. |
| GEDVI, mL/m² | | | | | | |
| baseline | 1254±518 | 1102±246 | .506 | 812±163 | 869±179 | .011 |
| after | 1123±422 | 1111±234 | | 754±176 | 877±167 | |
| change | 130±175 | -8±73 | <.001 | 586±3 | -8±62 | .003 |
| CVP, mm Hg | | | | | | |
| baseline | 5±3 | 8±3 | .004 | 3±2 | 5±2 | .027 |
| after | 6±2 | 9±2 | | 5±2 | 6±2 | |
| change | 1±1 | 1±2 | .013 | 1±1 | 1±1 | .468 |
| PAOP, mm Hg | | | | | | |
| baseline | 8±3 | 11±3 | .003 | 8±2 | 9±3 | .150 |
| after | 10±2 | 13±4 | | 10±3 | 11±3 | |
| change | 2±1 | 1±2 | .083 | 1±1 | 1±2 | .563 |
| Fluid input per step, mL | 541±100 | 442±135 | .019 | 541±123 | 523±113 | .377 |

Mean ± SD

*GEF* global ejection fraction, *R* responding fluid loading step (≥10% increase in CI), *NR* non-responding fluid loading step, *CI* cardiac index, *GEDVI* global end diastolic volume index, *CVP* central venous pressure, *PAOP* pulmonary capillary occlusion pressure: n=13, n=10, n=11 and n=21, in R and NR at GEF <20% and ≥20%, respectively, *N.A.* not applicable. *p* values adjusted for amount and type of fluid.

**Table 3.** Summated fluid loading responsiveness, defined as ≥10% increase in cardiac index, when global ejection fraction (GEF) is ≤15% or >15%.

| | **GEF <20%** (n=4) | | | **GEF ≥20%** (n=28) | | |
|---|---|---|---|---|---|---|
| | R (n=6 steps in 4 patients) | NR (n=6 steps in 3 patients) | *p* value | R (n=28 steps in 19 patients) | NR (n=56 steps in 28 patients) | *p* value |
| CI, L/min/m² | | | | | | |
| baseline | 3.0±0.7 | 3.4±0.8 | .068 | 3.4±0.7 | 3.8±0.8 | .037 |
| after | 3.6±0.7 | 3.4±0.9 | | 4.0±0.8 | 3.8±0.7 | |
| change | 0.6±0.3 | 0.0±0.2 | N.A. | 0.6±0.5 | 0.0±0.3 | N.A. |
| GEDVI, mL/m² | | | | | | |
| baseline | 1531±458 | 1275±329 | .114 | 811±182 | 915±172 | .014 |
| after | 1746±587 | 1270±362 | | 880±187 | 904±180 | |
| change | 215±270 | -5±104 | .775 | 68±69 | -9±61 | .008 |
| CVP, mm Hg | | | | | | |
| baseline | 5±2 | 9±2 | .002 | 3±2 | 6±3 | .042 |
| after | 6±3 | 9±2 | | 5±2 | 7±3 | |
| change | 1±1 | 1±1 | .277 | 1±1 | 1±1 | .975 |
| PAOP, mm Hg | | | | | | |
| baseline | 8±3 | 12±3 | .039 | 8±2 | 9±3 | .488 |
| after | 11±2 | 14±2 | | 10±3 | 14±4 | |
| change | 2±2 | 2±2 | .639 | 1±1 | 1±2 | .137 |

Mean ± SD

*GEF* global ejection fraction, *R* responding fluid loading step (≥10% increase in CI), *NR* non-responding fluid loading step, *CI* cardiac index, *GEDVI* global end diastolic volume index, *CVP* central venous pressure, *PAOP* pulmonary capillary occlusion pressure: n=13, n=10, n=11 and n=21, in R and NR at GEF ≤15% and >15%, respectively, *N.A.* not applicable. *P* values adjusted for amount and type of fluid.

*Correlations.* For the low GEF group, baseline PAOP and CVP inversely correlated to changes in CI, irrespective of amount and type of fluids (r = -.57 and -.44, *p* = .008 and .010, respectively; Figure 1). In the near-normal GEF group, only baseline CVP inversely correlated to CI changes (r = -.35, *p* = .009) and PAOP did not (Figure 2). Baseline GEDVI inversely correlated to changes in CI in the near-normal GEF group (r = -.29, *p* = .03; Figure 3). Changes in CI were paralleled by changes in GEDVI (r = .74, *p* <.001) in the low GEF group. Changes in CI correlated to changes in both CVP and GEDVI in the near-normal GEF group (r = .36 and r = .72, *p* = .007 and <.001, respectively). Changes in PAOP correlated better to CVP in the near-normal GEF group (r = .67, *p* <.001) than in the low GEF group (r = .21, *p* = .404).

**Table 4.** Summated fluid loading responsiveness, defined as ≥15% increase in cardiac index, when global ejection fraction (GEF) is <20% or ≥20%.

| | GEF <20% (n=12) | | | GEF ≥20% (n=20) | | |
|---|---|---|---|---|---|---|
| | R (n=8 steps in 6 patients) | NR (n=28 steps in 10 patients) | *p* value | R (n=7 steps in 6 patients) | NR (n=53 steps in 20 patients) | *p* value |
| CI, L/min/m² | | | | | | |
| baseline | 3.2±0.6 | 3.5±0.9 | .009 | 3.1±0.5 | 3.8±0.7 | .024 |
| after | 3.9±0.6 | 3.7±0.9 | | 4.0±0.9 | 3.8±0.7 | |
| change | 0.7±0.2 | 0.0±0.2 | N.A. | 0.9±0.8 | 0.1±0.3 | N.A. |
| GEDVI, mL/m² | | | | | | |
| baseline | 1328±532 | 1057±227 | .027 | 644±104 | 869±169 | <.001 |
| after | 1536±633 | 1070±231 | | 730±84 | 869±178 | |
| change | 209±228 | 13±77 | <.001 | 85±88 | 0±60 | .010 |
| CVP, mm Hg | | | | | | |
| baseline | 4±3 | 7±3 | .269 | 3±1 | 5±2 | .169 |
| after | 5±2 | 8±2 | | 5±2 | 6±2 | |
| change | 1±2 | 1±1 | .020 | 2±2 | 1±1 | .575 |
| PAOP, mm Hg | | | | | | |
| baseline | 6±3 | 11±3 | <.001 | 9±2 | 9±3 | .604 |
| after | 9±2 | 12±4 | | 12±3 | 11±4 | |
| change | 3±1 | 1±1 | .004 | 2±0 | 1±1 | .022 |
| Fluid input per step, mL | 563±106 | 468±128 | .025 | 549±151 | 526±111 | .498 |

Mean ± SD

*GEF* global ejection fraction, *R* responding fluid loading step (≥10% increase in CI), *NR* non-responding fluid loading step, *CI* cardiac index, *GEDVI* global end diastolic volume index, *CVP* central venous pressure, *PAOP* pulmonary capillary occlusion pressure, *N.A.* not applicable. *p* values adjusted for amount and type of fluid.

*Predictors of fluid responsiveness in ROC curves.* In the near-normal GEF group, baseline GEDVI and CVP predicted fluid responsiveness (increase in both CI ≥10% and ≥15%), while in the low GEF group baseline PAOP and CVP had predictive value (Table 5). This table also shows the optimum cutoff values and associated sensitivities and specificities for fluid responsiveness. Table 6 shows identical results for cutoffs of SVI responses (0-90 min) rather than of CI responses.

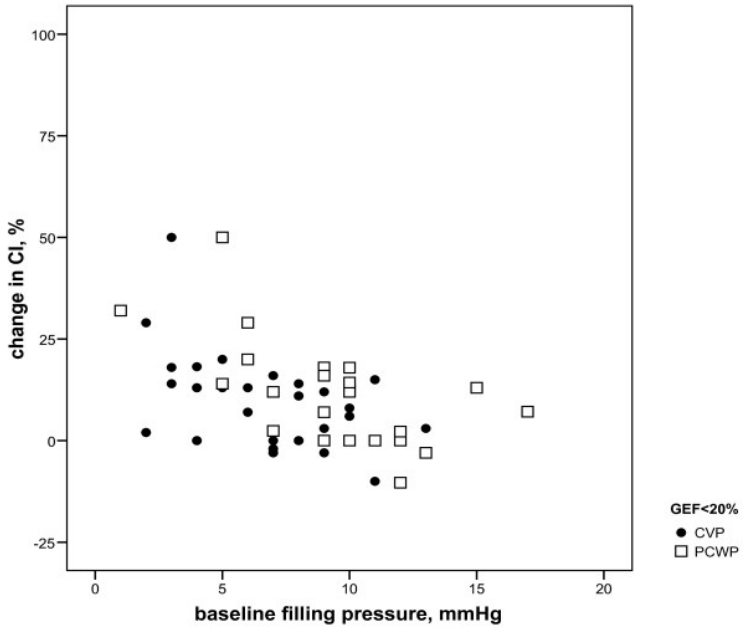


**Figure 1.** Baseline filling pressures (PAOP, CVP) versus change in cardiac index (CI) when global ejection fraction (GEF) is low (<20%): r = -.57, *p* = .008 and r = -0.44, *p* = .010, respectively.

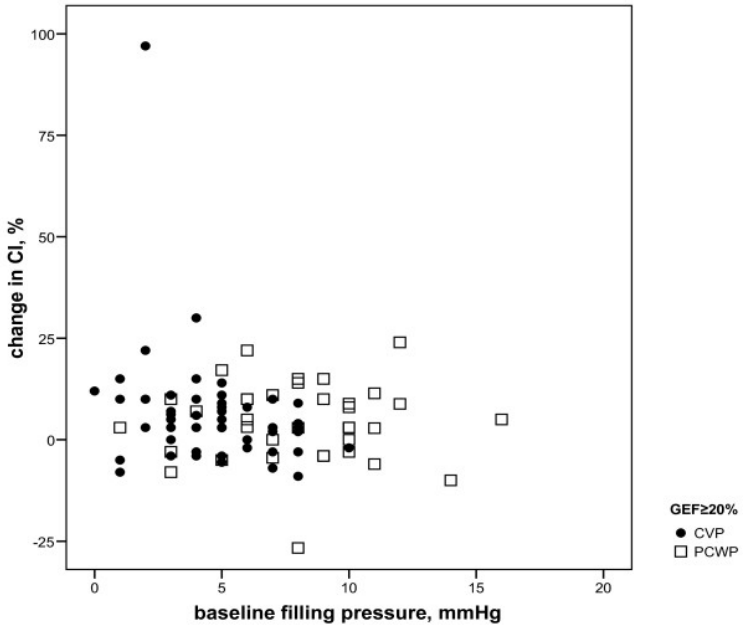


**Figure 2.** Baseline filling pressures (PAOP, CVP) versus change in cardiac index (CI) when global ejection fraction (GEF) is near-normal (≥20%): r = -.01, *p* = .951 and r = -.35, *p* = .009, respectively. For difference between r: *p* = .023.

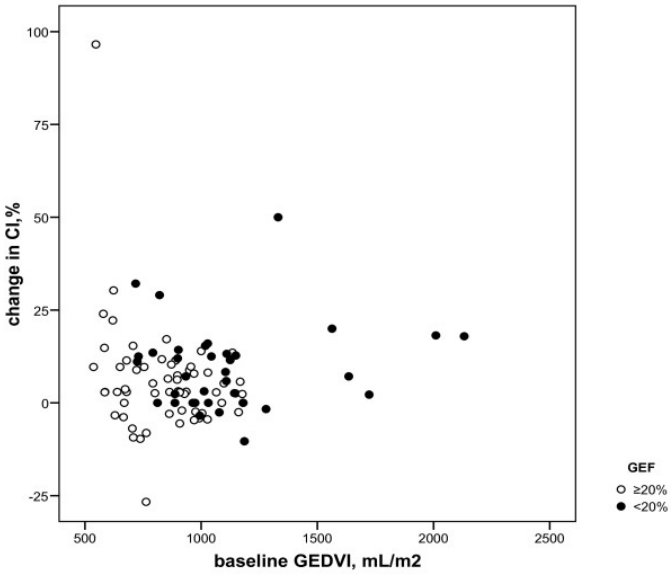


**Figure 3.** Baseline global end-diastolic volume (GEDVI) versus change in cardiac index (CI) according to global ejection fraction (GEF). In ≥20% GEF group r = -.29, *p* = .03, in <20% GEF group r = .17, *p* = .33. For difference between r: *p* = .048.



**Table 5.** Areas under the receiver operating characteristic curve (AUC's, 95% confidence intervals) for prediction of fluid responsiveness (increase in cardiac index ≥10% (**A**) or ≥15% (**B**)) by baseline values, according to global ejection fraction (GEF).

| | GEF <20% | | | GEF≥20% | | |
|---|---|---|---|---|---|---|
| | AUC | *p* value | Cutoff | AUC | *p* value | Cutoff |
| **A** | | | | | | |
| GEDVI | 0.56 (0.39-0.73) | .511 | 902 | 0.72 (0.58-0.83) | .002 | 890 |
| CVP | 0.76 (0.59-0.88) | .001 | 6 | 0.73 (0.60-0.84) | <.001 | 2 |
| PAOP | 0.79 (0.57-0.93) | .004 | 10 | 0.65 (0.46-0.81) | .129 | 9 |
| **B** | | | | | | |
| GEDVI | 0.62 (0.44-0.77) | .330 | 1279 | 0.89 (0.78-0.95) | <.001 | 623 |
| CVP | 0.77 (0.60-0.89) | .002 | 5 | 0.73 (0.60-0.84) | .013 | 4 |
| PAOP | 0.84 (0.63-0.96) | <.001 | 9 | 0.50 (0.32-0.69)* | .98 | 9 |

*GEF* global ejection fraction, *GEDVI* global end diastolic volume index (mL/m$^2$), *CVP* central venous pressure (mm Hg), *PAOP* pulmonary capillary occlusion pressure (mm Hg)

**p* = .008 vs. AUC GEDVI; for A and low GEF: PAOP sensitivity 92%, specificity 60%, positive predictive value 75%, negative predictive value 86%; for normal GEF: GEDVI sensitivity 82%, specificity 56%, positive predictive value 42%, negative predictive value 89%; for B and low GEF: PAOP sensitivity 86%, specificity 69%, positive predictive value 55%, negative predictive value 92%; for normal GEF: GEDVI sensitivity 71%, specificity 94%, positive predictive value 63%, negative predictive value 93%.

**Table 6.** Areas under the receiver operating characteristic curve (AUC's, 95% confidence intervals) for prediction of fluid responsiveness (increase in SVI ≥10% from t=0-90 min (**A**) or ≥15% (**B**)) by baseline values at t=0, according to global ejection fraction (GEF).

| | GEF <20% | | GEF≥20% | |
|---|---|---|---|---|
| | AUC | *p* value | AUC | *p* value |
| **A** | | | | |
| GEDVI | 0.53 (0.17-0.89) | .865 | 0.88 (0.72-1.03) | .005 |
| CVP | 0.89 (0.70-1.08) | .034 | 0.67 (0.42-0.92) | .203 |
| PAOP | 1.00 (1.00-1.00) | .020 | 0.72 (0.45-0.99) | .175 |
| **B** | | | | |
| GEDVI | 0.49 (0.14-0.83) | .935 | 0.74 (0.52-0.96) | .099 |
| CVP | 0.80 (0.54-1.06) | .088 | 0.74 (0.53-0.96) | .091 |
| PAOP | 1.00 (1.00-1.00) | .020 | 0.75 (0.48-1.03) | .157 |

*GEF* global ejection fraction, *GEDVI* global end diastolic volume index (mL/m$^2$), *CVP* central venous pressure (mm Hg), *PAOP* pulmonary artery occlusion pressure (mm Hg).

## Discussion

Our study suggests that in patients after coronary and major vascular surgery the predictive value of cardiac filling pressures and volumes for fluid responsiveness depends on GEF, as calculated by transpulmonary dilution-derived parameters.

In patients with low GEF indicating systolic cardiac dysfunction, PAOP has a greater predictive value than GEDVI for fluid responsiveness, whereas in patients with near-normal GEF, GEDVI is superior to PAOP. This suggests the increasing value of filling pressures over volumes for predicting fluid responsiveness in patients with left ventricular systolic dysfunction. Indeed, the suggestion that a low GEF reflects systolic dysfunction of the left ventricle is supported by the fact that changes in PAOP did not correlate with changes in CVP, as reported by others[29-31]. Furthermore, our data suggest that PAOP relates to systolic and not to diastolic function since distensibility did not differ between the low and near-normal GEF groups, both prior to and after fluid loading. There was no sign of pulmonary hypertension or difference in MPAP according to fluid responses, thus diminishing the likelihood for right ventricular dysfunction confounding GEDVI as a reflection of left ventricular end-diastolic volume. Hence, the low GEF was likely caused by postoperative left ventricular dysfunction, as the preoperative echocardiographic left ventricular function did not differ among GEF groups. Hence, the greater predictive

value of PAOP than of CVP, according to GEF, can be explained by greater effect of left than of right ventricular loading on fluid responsiveness, although we did not directly assess postoperative biventricular function, for instance by echocardiography. Conversely, the predictive value of CVP for fluid responsiveness regardless of GEF may indicate the importance of venous return for augmenting cardiac output, rather than right ventricular dysfunction following increased afterload limiting a rise in cardiac output with fluids when CVP is relatively high as suggested recently[32]. Finally, the similar course of MAP according to fluid responses disfavors alterations in systemic vascular tone confounding the effect of preload augmentation and its assessment during fluid loading.

The frequency of fluid responsiveness generally agrees with the literature, utilizing various loading protocols, and also involving variable amounts of fluid, in cardiac surgery patients[9,10,12,14-17,19,20]. That both CVP and PAOP were of predictive and monitoring value in our study can be attributed in part to the fact that a relatively low PEEP was applied, so that atmospheric pressure-referenced filling pressures may have approached transmural values. That fluid responsiveness was not uniformly observed in spite of clinical signs of hypovolemia can be attributed to the relatively poor predictive value of the latter, as commonly described[33]. Our study does not address the effect of mathematical coupling of GEDVI to CI, when volumes are derived from the same transpulmonary dilution curve as cardiac output. The often observed superiority of cardiac volumes over filling pressures in predicting and monitoring cardiac output responses, i.e. fluid responsiveness, may indeed be overestimated by the phenomenon, as recently described by our group also[1,6-8,10-16,18,19,27]. In hearts with systolic dysfunction and dilatation, a right- and downward shift on the Frank-Starling curve and along the curvilinear pressure-volume relationship at end-diastole, preload recruitability may be more dependent on and thus predicted and monitored by pressures than by volumes[5,22]. Indeed, GEDVI was higher in patients with a low versus a near-normal GEF, suggesting cardiac dilatation. Cardiac distensibility did not differ among GEF groups, favoring a similar position of the diastolic pressure-volume relation and diastolic function. Our data, obtained in surgical patients, thus confirms the Mundigler et al. data in non-surgical patients with reduced left ventricular systolic function due to dilated and ischemic cardiomyopathy[20]. The authors showed that in patients with left ventricular systolic dysfunction, the value of transpulmonary thermodilution-

derived total end-diastolic volume is particularly insensitive for monitoring the effects of fluid administration on cardiac preload when compared to filling pressures. On the other hand, in patients with normal left ventricular systolic function, volumes and pressures were of equal value[20].

Reuter et al. and Preisman et al.[14,17] did not observe different monitoring values of filling volumes or pressures according to left ventricular ejection fraction and this can be attributed, in part, to the small number of patients in their studies and their (varying) definitions of left ventricular systolic dysfunction (ejection fraction <35% in the former and <40% in the latter). Nevertheless, the trend was for the increasing value of pressure monitoring in patients with low versus those with normal GEF in the study by Reuter et al.[14]. The current data also agree with our previous study in a cohort of valvular and coronary artery surgery patients[21], showing the superior value of the pulmonary artery catheter-derived pressures over transpulmonary dilution-derived volumes for assessing fluid responsiveness in the former with a low GEF and presumed left ventricular systolic dysfunction. The current study thus suggests that systolic cardiac function and the degree of cardiac dilatation, rather than underlying disease (type of surgery), determines the relative value of pressures and volumes for predicting and monitoring fluid responsiveness, as suggested previously[5].

Our study has some limitations. Since our analyses adjusted for amount and type of fluids, it is unlikely that small differences in the amounts of fluids (mean 100 mL when GEF <20%, for instance) rather than differences in cardiac preloading, were responsible for different increases in CI (of 0.6 L/min/m$^2$ when GEF <20%) in responding versus non-responding fluid loading events. The fluid loading protocol guided by changes in filling pressures was used to prevent deleterious fluid overloading rather than to guide treatment on the basis of fluid responsiveness, as recently advocated to ensure safety[23,26,27]. By virtue of its design, the study did not address the potential clinical benefits of one hemodynamic monitoring technique over the other. Although our results were obtained by thermal-dye dilution, the current standard is single transpulmonary thermodilution (PiCCO™ technique)[10,34], because double and single dilution methods yield similar values for GEDVI. Hence, our results should also be applied to single transpulmonary thermodilution. Although dynamic indices (e.g. pulse pressure or stroke volume variation) are better predictors of fluid responsiveness (provided that

they are interpreted properly)[32,33], we did not include these indices, since the aim was to study the value of static cardiac preload indicators. That static filling pressures were of predictive value for fluid responsiveness in our study can be explained by the low PEEP used in our patients, and this may not apply when higher PEEP is needed. Finally, predictors and monitors of fluid responsiveness were independent of the definition of the latter, even though most commonly CI responses >10% are used[33].

## Conclusions

Our study suggests that, after coronary artery and major vascular surgery, prediction and monitoring of fluid responsiveness by pressures or transpulmonary thermodilution-derived volumes depends on systolic cardiac function and the degree of cardiac dilatation. Whereas CVP may be useful for predicting fluid responsiveness in patients after coronary and major vascular surgery regardless of GEF, GEDVI is less and PAOP is more useful for predicting fluid responsiveness when GEF is low than when it is near-normal, respectively, provided that positive end-expiratory pressure is low. In practice, our data may imply use of the pulmonary artery catheter and derived filling pressures in hemodynamic monitoring of patients with impaired left ventricular systolic function and dilatation, and use of transpulmonary thermodilution and derived filling volumes in cases of relatively normal left ventricular systolic function. This may help in refining fluid therapy and preventing harmful fluid overloading.

## Key Messages

- In patients after coronary artery or major vascular surgery, the relative predictive value of filling pressures and volumes for fluid responsiveness depends on left ventricular systolic function as measured by GEF
- Whereas, CVP may be useful for predicting fluid responsiveness regardless of GEF, in patients with low GEF, PAOP has a greater predictive value than GEDVI for fluid responsiveness
- In patients with near-normal GEF, GEDVI is superior to PAOP for predicting fluid responsiveness

- This study argues in favor of using pulmonary artery catheter-derived filling pressures in hemodynamic monitoring of patients with impaired left ventricular systolic function and of using transpulmonary thermodilution-derived volumes in relatively normal left ventricular systolic function

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# 7

# Global end-diastolic volume increases to maintain fluid responsiveness in sepsis-induced systolic dysfunction

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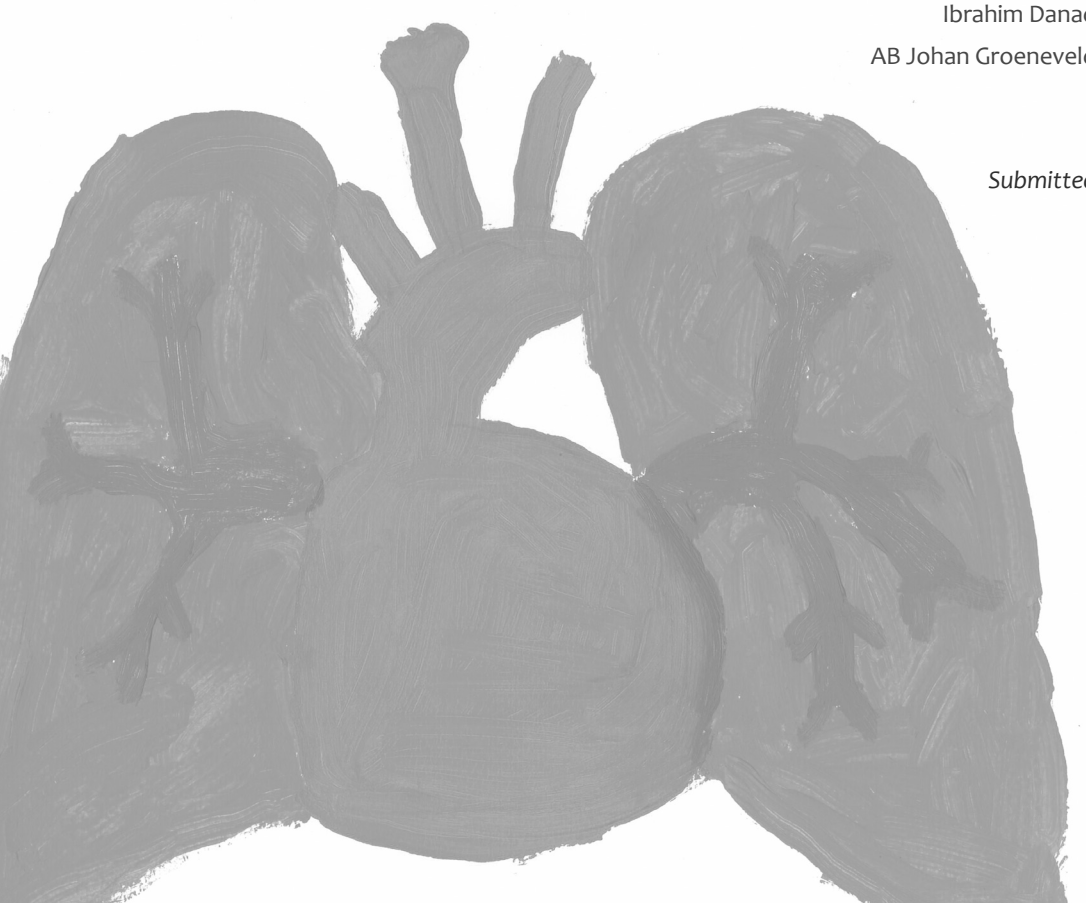
*Submitted*



## Abstract

### Background

Sepsis-induced cardiac dysfunction may limit fluid responsiveness and the mechanism thereof remains unclear. Since cardiac function may affect the relative value of cardiac filling pressures, such as the recommended central venous pressure (CVP), versus filling volumes in guiding fluid loading, we studied these parameters as determinants of fluid responsiveness, according to cardiac function.

### Methods

A delta CVP-guided, 90 min colloid fluid loading protocol was performed in 16 mechanically ventilated patients with sepsis-induced hypotension and three 30 min consecutive fluid loading steps of about 450 mL per patient were evaluated. Global end-diastolic volume index (GEDVI), cardiac index (CI) and global ejection fraction (GEF) were assessed from transpulmonary dilution. Baseline and changes in CVP and GEDVI were compared among responding (CI increase ≥10% and ≥15%) and non-responding fluid loading steps, in patient with low (<20%, n=9) and near-normal (≥20%) GEF (n=7) at baseline.

### Results

A low GEF was in line with other indices of impaired cardiac (left ventricular) function, prior to and after fluid loading. Of 48 fluid loading steps, 9 (of 27) were responding when GEF <20% and 6 (of 21) when GEF ≥20. Prior to fluid loading, CVP did not differ between responding and non-responding steps and levels attained were higher in the former, regardless of GEF ($p$ = .004). Prior to fluid loading, GEDVI (and CI) was higher in responding (1007±306 mL/m$^2$) than non-responding steps (870±236 mL/m$^2$) when GEF was low ($p$ = .002), but did not differ when GEF was near-normal. Increases in GEDVI were associated with increases in CI and fluid responsiveness, regardless of GEF ($p$ <.001).

### Conclusions

As estimated from transpulmonary dilution, about half of patients with sepsis-induced hypotension have systolic cardiac dysfunction. During dysfunction, cardiac dilation with a relatively high baseline GEDVI maintains fluid responsiveness by further dilatation (increase in GEDVI rather than of CVP) as in patients without dysfunction. Absence of fluid responsiveness during systolic cardiac dysfunction may be caused by diastolic dysfunction and/or right ventricular dysfunction.

## Introduction

Patients with severe sepsis or septic shock commonly develop cardiac dysfunction, even in the absence of cardiac ischemia[1-3]. These abnormalities may include depression of left and/or right ventricular systolic function and/or diastolic dysfunction and may be accompanied by ventricular dilatation, as estimated from echocardiography or radionuclide cineangiography[4,5]. This cardiac dysfunction is usually reversible and returns to normal in 7 to 10 days in survivors[6-8]. Systolic dysfunction-induced ventricular dilatation is suggested to be an adaptive mechanism to maintain a high cardiac output which is associated with survival[4,9], while other investigators denied such a dilatory response arguing in favor of impaired relaxation and diastolic (often upon systolic) dysfunction contributing to non-survival[8,10-16].

Fluid loading is often the initial treatment of sepsis-induced hypotension and the response may be diminished in sepsis-induced cardiac depression associated with severe disease and non-survival[5,13,14]. On the other hand, fluid overloading when the heart is non-responsive and the central venous pressure (CVP) is inadvertently elevated is potentially harmful and also associated with mortality, emphasizing the value of appropriate hemodynamic monitoring[17]. By optimizing preload and assessing fluid responsiveness, deleterious hypoperfusion and fluid overloading may be prevented. Traditionally, filling pressure, like CVP, have been used to guide fluid loading in sepsis-induced hypotension[17-20], even though its predictive value for fluid responsiveness during mechanical ventilation and altered cardiac function is doubtful[21-23]. Alternatively, the transpulmonary dilution technique estimates the global end-diastolic volume index (GEDV), and pulmonary blood volume index (PBVI) as a superior and global measures of cardiac preload[11,23,24]. The GEDVI represents the volumes of the right and left heart at the end of diastole and often reflects left ventricular end-diastolic volume estimated by echocardiography provided that right ventricular dilatation is absent[25].

A relatively low GEDVI may predict fluid responsiveness (and a relatively high GEDVI absence thereof), but the role of systolic and/or diastolic dysfunction with respect to interpretation of absolute values remains unclear, even though changes in stroke volume or cardiac output correlate to changes in GEDVI[21,23,26]. Indeed, the relative value of GEDVI and filling pressures in determining fluid responsiveness depends on systolic cardiac function, at least in non-septic patients[27]. Conversely, echocardiographic end-

diastolic left ventricular dimensions poorly predicted fluid responsiveness but changes were superior to filling pressures in monitoring changes in cardiac output upon fluid loading in some studies on sepsis[9,23]. In contrast, fluid responsiveness was found to be associated with biventricular dilatation by nuclear angiography and non-responsiveness appeared attributable to right ventricular systolic dysfunction following mild pulmonary hypertension in other studies on sepsis[6,9].

In view of the above controversies on mechanisms and predictive values, we evaluated and compared filling volumes to pressures in determining the cardiac response to fluid loading according to systolic cardiac function in sepsis-induced hypotension, in the hypothesis that, even in dysfunctional hearts, cardiac dilatation is required to increase cardiac output upon fluid loading.

## Patients and methods

This was a sub-study of a prospective, non-randomized, single-center clinical trial, investigating the cardiorespiratory effects of various resuscitation fluids in presumed hypovolemia during sepsis and non-sepsis, in mechanically ventilated patients in the intensive care unit (ICU)[24,28]. We analyzed, retrospectively, 16 patients with sepsis monitored by both CVP and the transpulmonary dilution technique. These patients were divided in two groups according to a low GEF (<20%) and near-normal GEF (≥20%). The cutoff of 20% approximately reflects a cutoff of 40% ejection fraction of the left ventricle as measured by echocardiography, provided that there is no right ventricular dysfunction[29-31]. The original study was approved by the Ethics Committee of the Vrije Universiteit Medical Center and written informed consent was obtained. We analyzed the effect of colloid fluid loading in patients with sepsis-induced hypotension. Colloid fluid loading was given with modified fluid gelatin 4%, hydroxyethyl starch (HES) 6% or albumin 5%, all of which have similar oncotic properties and hemodynamic responses[24,28]. We only analyzed patients who completed fluid loading and measurements up to t=90 min. Inclusion criteria, at enrollment and start of the protocol, were presumed hypovolemia, defined as a systolic blood pressure <110 mmHg and a relatively low CVP taking positive end-expiratory pressure (PEEP) into account (Table 1). Exclusion criteria were age >75 year, preterminal illness with a life expectancy of less than 24 hours, or

known anaphylactic reactions to colloids. Sepsis was defined according to international guidelines[32]. The origin of sepsis was defined by clinical signs and symptoms, imaging techniques and positive local and/or blood cultures[32]. All patients were on controlled mechanical ventilation and positive end-expiratory pressure (PEEP).

*Study protocol.* The protocol was started in the ICU when patients met the inclusion criteria. Demographic characteristics were recorded, including the acute physiology and chronic health evaluation (APACHE-II). After baseline measurements were taken, fluids were given over 90 min on the basis of the response within predefined limits of increases in CVP, according to a previously described protocol[16,28] (Table 1). Up to 200 mL of fluid were given every 10 min, provided that the increase in CVP upon fluid loading did not exceed critical values, and this policy has been proven safe in previous studies[24,28] (i.e. not evoking pulmonary edema). The maximum amount of fluid infused was 1800 mL. Fluid responsiveness was defined as an increase of CI ≥10 and 15%, in accordance with the literature[22,23], between t=0-30, t=30-60 and t=60-90 min upon fluid loading. Concomitant vasoactive and sedative drug treatment and ventilatory settings remained unchanged during fluid loading.

*Measurements.* Heart rate (HR) and mean arterial pressure (MAP) were recorded at t=0 and 90 min. MAP and CVP were measured in the supine position after calibration, zeroing to atmospheric pressure at the midchest level at end-expiration (Tramscope$^{R}$, Marquette GE, Milwaukee, Wisconsin). Cardiac output, GEDVI, PBVI and CVP were measured every 30 min, from t=0 to 90 min. Relevant measurements were indexed to body surface area (BSA), giving stroke volume index (SVI, mL/m$^2$), cardiac index (CI, L/min/m$^2$), GEDVI (n 680-800 mL/m$^2$) and PBVI (n 150-250 mL/m$^2$), respectively. For these measurements, the transpulmonary thermal-dye indicator dilution technique was used[11]. These measurements involve averages obtained from 2-3 central venous injections of 15 mL of ice-cold indocyanine green in 5% glucose solution and concomitant registration of the dilution curves in the femoral artery, by a 3F catheter equipped with a thermistor (PV 2024, Pulsion Medical Systems, Munich, Germany). This catheter was inserted via a 4F introducing sheath (Arrow, Reading, USA) and connected to a bedside computer (COLD Z-021, Pulsion Medical Systems, Munich, Germany. The COLD Z-021 is the precursor to the current transpulmonary thermodilution pulse contour cardiac output (PiCCO™) technique and yields the same cardiac parameters. Reproducibility of measurements

is typically within 10%[11]. GEDVI represents the volumes of the right and left heart at end-diastole and reflects left ventricular dimensions obtained by echocardiography in the absence of overt right ventricular distention[25]. The ratio between stroke volume index (cardiac index/HR) and GEDVI/4 is defined as the global ejection fraction (GEF, normal values 25-35%), and is an indicator of left ventricular systolic function, provided that there is no right ventricular dysfunction[29-31]. Left ventricular stroke work index (LVSWI, gm/m$^2$) was calculated from SVI x (MAP-CVP) x 0.0136 and cardiac function index (CFI, n 18.0-26.0 1/min) from CI/(GEDVI/4)[30,31]. Preload-recruitable stroke work was defined by LVSWI/GEDVI[24]. CFI, LVSWI and LVSWI/GEDVI were used to assess cardiac (e.g. left ventricular) systolic function. The lung injury score was calculated from radiographic densities, oxygenation ratio $P_aO_2/F_iO_2$, PEEP and dynamic compliance and ranges between 0-4. Mortality refers to death in the ICU.

*Statistical analysis.* For categorical data, Fisher exact tests were used. Since continuous data were normally distributed (Kolmogorov-Smirnov test, $p$ >.05), they were summarized by mean±standard deviation (SD) and parametric tests were done. Paired and unpaired t-tests were used to compare data in time and between GEF groups, respectively generalized estimating equations (GEE) were used to evaluate differences in baseline and changes in variables between summated responding and non-responding fluid loading steps in each GEF group, to evaluate their determining values, respectively, taking repeated measurements in the same patients and type and volume of fluid administered (as covariates) into account. Exact two-sided $p$ values >.001 are given and considered statistically significant when <.05. All analyses were conducted using SPSS version 15.0 (SPSS Chicago, Ill, USA).

**Table 1.** Fluid challenge protocol.

| | | |
|---|---|---|
| CVP at start: | ≤ 8 if PEEP ≤15 | 200 mL/10 min |
| | ≤ 12 if PEEP >15 | 200 mL/10 min |
| | ≤ 10 if PEEP ≤15 | 100 mL/10 min |
| | ≤ 14 if PEEP >15 | 100 mL/10 min |
| | ≤ 12 if PEEP ≤15 | 50 mL/10 min |
| | ≤ 16 if PEEP >15 | 50 mL/10 min |
| CVP during infusion: | increase >5 | stop |
| CVP after 10 min waiting: | increase ≤2 | continue |
| | 2< increase ≤5 | wait 10 min |
| | increase >5 | stop |
| CVP after 10 min waiting: | increase >2 | stop |
| | increase ≤2 | repeat |

*CVP* central venous pressure (mm Hg), *PEEP* positive end-expiratory pressure (cm $H_2O$).

## Results

Table 2 summarizes the characteristics of patients. The hemodynamic variables differ according to GEF and changes upon fluid loading. There was no difference in the amount and type of fluids infused between the GEF groups. GEF did not change during fluid loading. In the low GEF group, other function indices also pointed to systolic cardiac dysfunction, prior to and after fluid loading, even though the CI attained with fluid loading did not differ among the groups. The number of fluid loading responses did not differ according to GEF, but the increase in CI decreased with increasing fluid loading steps only when GEF was low ($p$ =.04). The increases with fluids in CVP, GEDVI, MAP, LVSWI and CI did not differ among GEF groups, even though SVI, PBVI and LVSWI/GEDVI increased in the low GEF group only.

*Fluid loading steps in GEF groups.* Responses were independent of the type of colloid fluid, regardless of GEF and cutoff for fluid responsiveness. CI prior to each fluid loading step was higher in responding than non-responding steps in the low GEF group, but lower in the near-normal GEF group (Table 3). CVP did not differ between responding and non-responding steps in both GEF groups but attained higher values after fluid loading in non-responding than in responding steps, regardless of GEF.

**Table 2.** Patient characteristics.

| | | GEF <20% (n=9) | GEF ≥20% (n=7) | *p* value |
|---|---|---|---|---|
| Age | | 62±9 | 57±9 | .32 |
| Male/female | | 7/2 | 4/3 | .60 |
| APACHE II | | 16±4 | 12±5 | .08 |
| Cardiac premorbidity | | 4 | 1 | .31 |
| Sepsis origin | | | | .38 |
| | Pulmonary | 4 | 3 | |
| | Abdominal | 2 | 0 | |
| | CNS | 0 | 1 | |
| | Urogenital | 1 | 0 | |
| | Unknown | 2 | 3 | |
| Bloodstream infection | | | | .41 |
| | Gram - | 2 | | |
| | Gram + | 2 | | |
| | Fungi | | 2 | |
| PEEP, cm $H_2O$ | | 14±6 | 12±3 | .17 |
| Tidal volume, mL/kg | | 8.0±0.8 | 9.0±1.6 | .08 |
| $P_aO_2/F_IO_2$ | | 209±54 | 193±62 | .60 |
| Lung injury score | | 2.2±0.8 | 2.5±0.8 | .60 |
| ICU mortality | | 4 | 2 | .37 |
| **Hemodynamics** | | | | |
| HR, min | | | | |
| t=0 | | 106±18 | 90±25 | .15 |
| t=90 | | 103±16 | 95±22 | .42 |
| MAP, mm Hg | | | | |
| t=0 | | 73±12 | 74±9 | .84 |
| t=90 | | 88±19[1] | 89±13[1] | .87 |
| CVP, mm Hg | | | | |
| t=0 | | 9±5 | 8±3 | .61 |
| t=90 | | 12±5[2] | 12±3[2] | .83 |
| CI, L/min/$m^2$ | | | | |
| t=0 | | 3.3±0.6 | 4.3±1.5 | .06 |
| t=90 | | 3.9±1.0[2] | 5.0±1.4[3] | .09 |
| SVI, ml/$m^2$ | | | | |
| t=0 | | 31±6 | 49±12 | .002 |
| t=90 | | 38±9[1] | 53±11 | .01 |
| LVSWI, gm/$m^2$ | | | | |
| t=0 | | 27±5 | 43±8 | <.001 |
| t=90 | | 39±11[1] | 55±11[1] | .01 |

| | | | |
|---|---|---|---|
| GEDVI, mL/m$^2$ | | | |
| t=0 | 891±257 | 787±140 | .35 |
| t=90 | 963±273[1] | 866±170[1] | .43 |
| GEF, % | | | |
| t=0 | 15±2 | 25±5 | N.A. |
| t=90 | 16±4 | 25±7 | .005 |
| CFI, 1/min | | | |
| t=0 | 15.2±2.9 | 22.1±6.2 | .01 |
| t=90 | 16.8±4.0 | 23.4±5.5 | .01 |
| LVSWI/GEDVI, gm/mL | | | |
| t=0 | 0.13±0.04 | 0.22±0.04 | <.001 |
| t=90 | 0.17±0.07[3] | 0.26±0.07 | .02 |
| Dopamine, µg/kg/min | 5.6±3.4 | 4.9±4.3 | .92 |
| Norepinephrine, µg/kg/min | 0.09±0.11 | 0.06±0.12 | .25 |
| Fluid, mL | 1456±296 | 1271±269 | .22 |
| Gelatin / HES / albumin | 3 / 2 / 4 | 2 / 3 / 2 | .66 |

Mean±SD or number of patients, where appropriate.
*GEF* global ejection fraction, *APACHE II* acute physiology and chronic health evaluation, *CNS* central nervous system, *PEEP* positive end-expiratory pressure, *ICU* intensive care unit, $P_aO_2/F_IO_2$ arterial partial pressure of $O_2$ over inspiratory $O_2$ fraction, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *CI* cardiac index, *SVI* stroke volume index, *LVSWI* left ventricular stroke volume index, *GEDVI* global end-diastolic volume, *CFI* cardiac function index, *HES* hydroxyethyl starch. [1]*p* = .02 , [2]*p* = .002, [3]p = .009, vs. t=0, *N.A.* not applicable.



When GEF was low, GEDVI was higher prior to responding than non-responding fluid loading steps, while GEDVI in the near-normal GEF group did not differ prior to fluid loading steps. GEDVI and PBVI increased in responding fluid loading steps regardless of GEF. Hence, baseline CVP and GEDVI were poor predictors of fluid responsiveness in both GEF groups. When fluid responsiveness was defined as an increase in CI ≥15%, changes in CO were also directly associated with changes in GEDVI, but not in PBVI. Otherwise there were only 4 out of 9 responding steps remaining when defining fluid responsiveness by 15 vs. 10% CI increases, in patients with low GEF needing relatively large amounts of fluid. Baseline GEDVI was not lower in responders than non-responders.

**Table 3.** Summated fluid loading steps, with responsiveness defined as ≥10% and ≥15% increase in cardiac index (CI), when systolic cardiac function is reduced or near-normal at 20% cutoff of global ejection fraction (GEF).

| | **GEF <20%** (n=9) | | | **GEF ≥20%** (n=7) | | |
|---|---|---|---|---|---|---|
| **Increase CI ≥10%** | R (n=9 steps in 6 patients) | NR (n=18 steps in 9 patients) | *p* value | R (n=6 steps in 5 patients) | NR (n=15 steps in 7 patients) | *p* value |
| CI, L/min/m² | | | | | | |
| baseline | 3.7±0.7 | 3.5±0.7 | .04 | 3.6±1.2 | 5.0±1.5 | .008 |
| after | 4.4±0.8 | 3.4±0.6 | | 4.3±1.4 | 5.0±1.5 | |
| change | 0.7±0.3 | 0.0±0.3 | N.A. | 0.7±0.3 | 0.0±0.2 | N.A. |
| GEDVI, mL/m² | | | | | | |
| baseline | 1007±306 | 870±236 | .002 | 801±186 | 834±163 | .83 |
| after | 1102±313 | 858±208 | | 872±199 | 843±167 | |
| change | 96±59 | -12±54 | <.001 | 70±85 | 8±38 | <.001 |
| CVP, mm Hg | | | | | | |
| baseline | 9±6 | 11±5 | .41 | 10±3 | 10±3 | .68 |
| after | 10±6 | 12±4 | | 10±2 | 11±3 | |
| change | 1±1 | 1±2 | <.001 | 1±2 | 2±1 | .004 |
| PBVI, mL/m² | | | | | | |
| baseline | 215±95 | 203±64 | .25 | 212±51 | 225±50 | .86 |
| after | 250±54 | 204±52 | | 224±40 | 227±50 | |
| change | 34±63 | 16±9 | <.001 | 11±52 | 2±53 | <.001 |
| Fluid input per step, mL | 522±120 | 467±161 | .07 | 450±176 | 467±145 | .75 |
| Gelatin / HES / Albumin | 3 / 1 / 5 | 6 / 5 / 7 | .65 | 5 / 6 / 4 | 1 / 3 / 2 | .24 |
| **Increase CI ≥15%** | R (n=9 steps in 6 patients) | NR (n=23 steps in 9 patients) | *p* value | R (n=5 steps in 4 patients) | NR (n=16 steps in 7 patients) | *p* value |
| CI, L/min/m² | | | | | | |
| baseline | 3.6±1.0 | 3.6±0.7 | .50 | 3.6±1.3 | 4.9±1.5 | .001 |
| after | 4.4±1.1 | 3.7±0.7 | | 4.4±1.5 | 5.0±1.5 | |
| change | 0.90.3 | 0.0±0.3 | N.A. | 0.8±0.3 | 0±0.0 | N.A. |
| GEDVI, mL/m² | | | | | | |
| baseline | 802±214 | 935±271 | .26 | 814±205 | 829±160 | .83 |
| after | 935±254 | 940±277 | | 886±219 | 841±162 | |
| change | 133±42 | 5±63 | <.001 | 73±96 | 12±39 | <.001 |
| CVP, mm Hg | | | | | | |
| baseline | 10±4 | 11±5 | .59 | 9±3 | 10±3 | .61 |
| after | 11±4 | 12±5 | | 10±3 | 11±3 | |
| change | 1±1 | 1±1 | .76 | 1±2 | 1±1 | .05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PBVI, mL/m² | | | | | | |
| baseline | 159±105 | 216±67 | .17 | 213±57 | 224±48 | .68 |
| after | 218±26 | 220±60 | | 215±38 | 230±50 | |
| change | 59±87 | 4±63 | .56 | 1±51 | 6±53 | <.001 |
| Fluid input per step, mL | 600± | 465±153 | < .001 | 460±195 | 462±140 | .84 |
| Gelatin / HES / Albumin | 1 / 1 / 2 | 8 / 5 / 10 | .67 | 1 / 3 / 1 | 5 / 6 / 5 | 1.0 |

Mean±SD or number of patients where appropriate
CI cardiac index, GEF global ejection fraction, R responding fluid loading step, NR non-responding fluid loading step, CVP central venous pressure, GEDVI global end-diastolic volume index, PBVI pulmonary blood volume index, HES hydroxyethylstarch, N.A. not applicable.

*Correlations.* Changes in PBVI did not correlate to changes in GEDVI and only the latter related to changes in CI, regardless of GEF (r=0.56, *p* <.001; Figure 1). Changes between 0-90 min in SVI correlated to changes in GEDVI in the low GEF group only (r=0.70, *p* =.03, n=9).

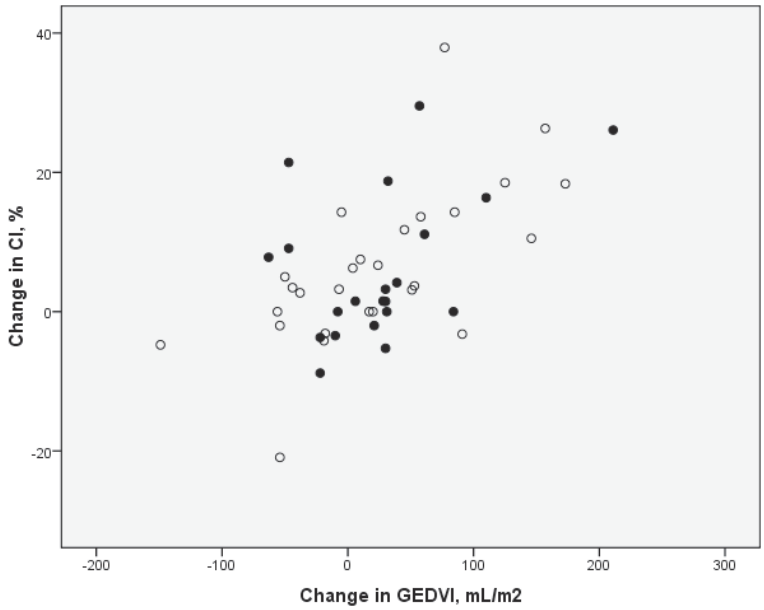



**Figure 1.** Similar changes in cardiac index (CI, %) versus changes in global end-diastolic volume index (GEDVI, mL/m²) upon fluid loading steps in patients with low global ejection fraction (open circles, r = .65 *p* < .001) and those with near-normal global ejection fraction (closed circles, r = .42 *p* = .05) during severe sepsis or septic shock.

## Discussion

Our study suggests that systolic cardiac dysfunction evidenced by a low GEF[29,30] is common in patients with severe sepsis or septic shock. This dysfunction occurring in 56% of our patients, independent of cardiac premorbidity, agrees with the literature[1-3,31]. Although this phenomenon might impair fluid responsiveness[9,18,24], our study suggests that fluid responsiveness can be maintained when the heart dilates, even during myocardial depression. In contrast, the optimum GEDVI in patients after cardiovascular surgery[34-36] ranges from 680-800 mL/m$^2$, and these values may therefore not apply in sepsis. Maintaining fluid responsiveness at higher GEDVI conforms to the idea that dilatation during sepsis-induced systolic dysfunction is as an adaptive response associated with survival by maintaining a relatively high CI[1-3,6,7,9,37]. Indeed, GEDVI was higher prior to responding than to non-responding steps according to CI ≥10% increases when GEF was low (7 of 9 (77%) responding steps had a baseline GEDVI >850 mL/m$^2$). Also, it was not lower in responding than non-responding steps according to CI ≥15% increases, in contrast to the observations that a low baseline GEDVI, albeit dependent on GEF[25], is more often associated with fluid responsiveness than a relatively high GEDVI[21,26]. This confirms that the predictive value for fluid responsiveness of baseline GEDVI or end-diastolic dimensions, rather than changes, is imperfect by its dependency of systolic function, also in sepsis[21,26,27,38,39]. That the GEDVI prior to responding fluid loading steps was not lower compared to non-responding steps when GEF ≥20%, can be attributed to a difference in systolic function[26], since CI was lower in the latter. Finally, baseline GEDVI may depend on age and gender[40].

In contrast, we observed that patients with both systolic dysfunction and inability to dilate, were not fluid responsive. The inability to dilate upon systolic dysfunction could comply with the impaired relaxation and diastolic dysfunction found on echocardiography either as an isolated phenomenon or concomitant with systolic dysfunction in 20-60% of patients with severe sepsis or septic shock[10-16,25]. The phenomenon appeared was associated with non-survival and was often transient and reversible in survivors. An additional hypothesis may be the presence of right ventricular dysfunction, in view of the increase in CVP. It cannot be excluded that the presence of predominant right ventricular dysfunction and dilatation limiting left ventricular filling though pericardial

constraint may contribute to the lack of fluid responsiveness. Indeed, right ventricular dysfunction caused by moderate pulmonary hypertension (which was not monitored in this study) has been described to limit fluid responsiveness before[6,39]. Out data show that CVP increases upon fluid loading were slightly greater in non-responding than in responding steps which may also point to right ventricular dysfunction and dilatation in some of our patients with low GEF. However, in our study, the increase in CVP was also greater in non-responding than in responding fluid loading steps when GEF was near-normal, which may argue against predominant right ventricular dysfunction in non-responding fluid loading steps of low GEF patients. Since we did not perform operator-dependent, bedside echocardiography simultaneously, to differentiate between right or left ventricular dilatation, we cannot definitively decide on diastolic and/or right ventricular dysfunction in non-responding steps when GEF is low.

Patients with near-normal systolic function were also fluid-responsive by dilatation when operating in the steep part of the cardiac function curve. The dilatation associated with fluid responsiveness, as measured by an increase in GEDVI, is thus independent of systolic cardiac function. Our study partially agrees with data obtained by others suggesting that changes in filling pressures are less helpful in this respect than changes in GEDVI[21-23,26]. Apparently, the phenomenon that impaired systolic function renders filling pressures more important than volumes in the predictive and monitoring value of fluid responsiveness, while the opposite is true when systolic function is relatively normal, after cardiovascular surgery[33], may not apply to sepsis-induced cardiac dysfunction. Otherwise, a higher PEEP level applied in this series than in the previous one[27], may have contributed to the poor predictive value of CVP at low GEF.

Our study has some limitations. The number of patients is relatively small but the study was undertaken to improve interpretation of transpulmonary dilution data with fluid loading in severe sepsis and septic shock rather than to prove benefits thereof. The correlation between changes in GEDVI and CI, regardless of GEF, can be overestimated by mathematical coupling when both are derived from the same thermodilution curve, as argued before[41]. Since both PBVI and GEDVI are also derived, among others, from the same thermodilution curve, mathematical coupling with CI would affect both variables. That PBVI differed from GEDVI in responding to fluid loading and a rise in CI ≥15% and, in contrast to GEDVI, did not correlate to CI changes may, however, disfavor mathematical coupling.

In conclusion, our study suggests that in patients with sepsis-induced hypotension and systolic cardiac dysfunction, occurring in about half of patients, fluid responsiveness is maintained by global cardiac dilatation, as measured by transpulmonary dilution-derived GEDVI, rather than by an increase in CVP. Absence of fluid responsiveness in systolic cardiac dysfunction may be explained by diastolic dysfunction and/or concomitant right ventricular dysfunction. 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 targeted levels of preload (GEDVI 680-800 mL/$m^2$) may not be applied in this condition.

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# 8

## Transpulmonary dilution-derived extravascular lung water as a measure of lung edema

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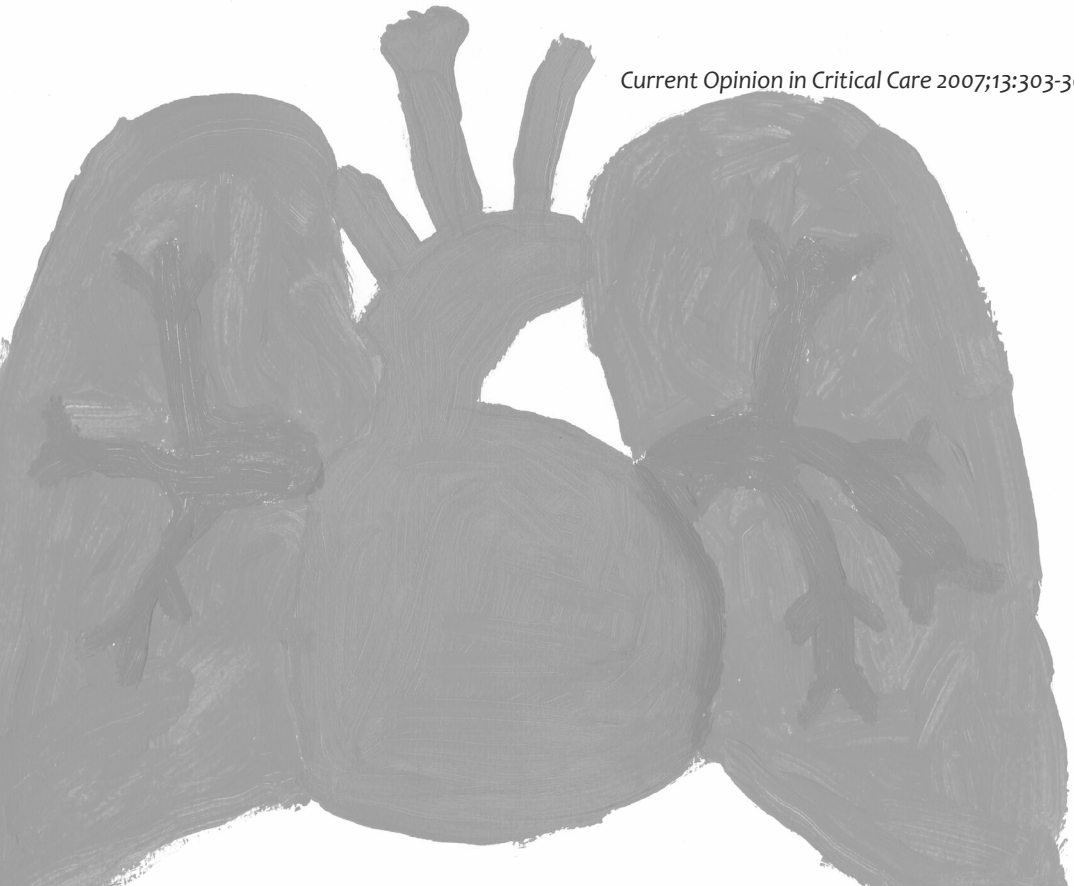

## Abstract

### Purpose of review

This review highlights current insights concerning the (measurement of) extravascular lung water as an index of pulmonary edema, by transpulmonary dilution techniques. The focus is on the applicability of the technique at the bedside in monitoring critically ill patients.

### Recent findings

Several (animal) studies have been performed to validate the technique by postmortem gravimetry in different conditions. Moreover, recent clinical data emphasize the utility of the thermodilution-derived extravascular lung water, its contribution to the clinical manifestations of acute lung injury/acute respiratory distress syndrome, its response to treatment aimed at edema prevention or resolution, and as a prognostic parameter.

### Summary

The thermodilution-derived extravascular lung water is a useful adjunct to assess lung vascular injury, cardiogenic edema and overhydration and to guide treatment in critically ill patients. The effects on morbidity and mortality of this approach need to be studied further.

## Introduction

Impaired gas exchange, reduced pulmonary compliance and pulmonary opacities on chest radiography are, either alone or together, poor indicators of the amount and course of pulmonary edema, of various causes, while positive fluid balances and pulmonary edema are associated with worse outcomes in critically ill patients[1-4]. Therefore, investigators have searched for methods to directly quantify pulmonary edema. The bedside method to directly assess the amount of extravascular lung water (EVLW) as a measure of pulmonary edema in critically ill patients, which has been applied most often, is the assessment of extravascular thermal volume with the help of transpulmonary thermal-dye indicator dilution, formerly involving a dye and a cold solution, central venous bolus infection and detection in the aorta via a femoral artery catheter of the respective dilution curves[2]. The differences in dilution curves between the intravascular dye and the cold, of which some dissipates into the pulmonary structures, dependent on their hydration status, and thus the difference in mean transit times multiplied by cardiac output, yield an extravascular thermal distribution volume as a rough indicator of EVLW – pulmonary edema. Using the Edwards densitometer technique, Mihm et al.[5] and others already noted that the EVLW overestimated gravimetric EVLW at a postmortem examination – the gold standard in dogs and human organ donors, regardless of the cause of edema, that is hydrostatic forces or increased permeability. Nevertheless, the correlation, over a wide range of volumes, between the two was high[5].

The technique was revived in the 1980s and 1990s by a German company, utilizing a similar approach with a fiberoptic and thermistor-equipped 4F femoral artery catheter and thermal-dye dilution, to assess the EVLW with the help of the so-called COLD machine[6-26]. The technique was later on further simplified into a single thermodilution measurement (PiCCO, Pulsion Medical Systems, Munich, FRG)[12,19,27-36]. The mean transit time of the thermal signal multiplied by cardiac output yields the intrathoracic thermal volume. The intrathoracic blood volume (ITBV) is derived from multiplication of the global end diastolic volume (GEDV), determined from cardiac output and down-slope time of the thermodilution curve, by a factor of 1.25, at least in humans[27]. Subtracting ITBV from intrathoracic thermal volume gives the extravascular thermal volume –

EVLW (upper limit of normal about 7–10 mL/kg body weight; Table 1)[9]. The correlation in studies between ITBV and GEDV is high, even though coefficients of the regression equation relating ITBV to GEDV vary among species and, perhaps, conditions[12,27,36,37]. The correlation is relatively high between EVLWs measured by single or double indicator dilution techniques[12,19,27].

**Table 1.** Principles and calculations involved in thermodilution-derived extravascular lung water (EVLW).

| |
|---|
| Intrathoracic thermal volume (ITTV, mL) = cardiac output (CO) x mean transit time of the thermal indicator |
| Pulmonary thermal volume (PTV, mL) = CO x exponential downslope time of the thermodilution curve |
| Global end-diastolic volume (GEDV, mL) = ITTV – PTV |
| Intrathoracic blood volume (ITBV, normal 850-1000 mL/m$^2$) = 1.25x GEDV (-28.4) |
| Extravascular lung water (EVLW, normal EVLW 3-7 mL/kg body weight) = ITTV – ITBV |

Another parameter evolving is the permeability index – the ratio of EVLW to ITBV or pulmonary blood volume[15,22-25,33,34]. Pulmonary blood volume is determined from the difference between pulmonary thermal volume (intrathoracic thermal volume minus GEDV) and EVLW. Indeed, congestive heart failure leading to a rise in pulmonary blood volume and edema is expected to increase the ratio less than an increase in permeability in the course of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Hence, the ratio is critically dependent upon a steady state between blood volumes and EVLW, so that changes in cardiac size upon treatment or fluid loading can confound the ratio independently of permeability changes. Moreover, an increase in EVLW to blood volume ratios can be evoked by low colloid osmotic pressures' increasing the propensity for pulmonary edema formation, even in the absence of increased protein permeability[22]. The correlation in septic ALI/ARDS between protein permeability in the lungs and EVLW to blood volume ratios is imperfect. Figure 1 shows the relationship between pulmonary leak index (PLI, as measured from 68Ga transferrin uptake in the lungs as a measure of protein permeability) and the ratio between EVLW and ITBV, which is normally 0.2–0.3, in patients with pneumonia or extrapulmonary sepsis ($r_s$ = 0.46, $p$ = .032). A similar direct relation was observed for PLI compared with EVLW/

pulmonary blood volume[24]. Hence, the clinical value of the ratio in differentiating cardiogenic from permeability edema associated with ALI/ARDS and in guiding therapy remains unclear. Similarly, the EVLW may not help in differentiating between ALI/ARDS and overhydration[38]. The amount of alveolar edema is not only dependent on hydrostatic and colloid osmotic forces, permeability and lymph flow, but also on active, ß-receptor-mediated alveolar water resorption, and the EVLW measurements may be able to track the development and resorption of lung edema in animal and clinical studies[35].

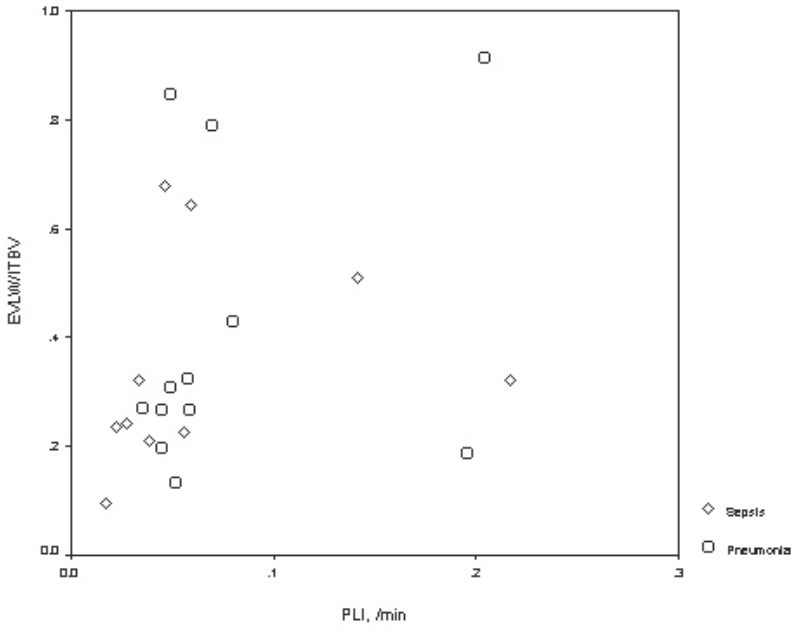


**Figure 1.** Relationship between pulmonary leak index and extravascular lung water/intrathoracic blood volume.

## Animal studies

The gold standard for EVLW measured by (single thermo) dilution is postmortem gravimetry in animal models of lung edema and high correlations have been observed, even though some systematic (positive) bias may be present[5,8,21,29,30,36,39-41]. Kirov et al.[30] induced pulmonary edema with either oleic acid or lipopolysaccharide in awake and spontaneously breathing sheep and EVLW measured by single transpulmonary thermodilution correlated closely with postmortem gravimetric EVLW measurements. Despite similar relative increases, the absolute values of EVLW were overestimated by single transpulmonary thermodilution, with greater overestimation at more severe lung injury[30]. This was accounted for in part by physical factors and the varying relationship between ITBV and GEDV in experimental and clinical settings. These findings have been confirmed in other studies[21,36,39]. In toxic pulmonary edema, mimicking ALI/ARDS in humans, EVLW has also been shown to highly correlate with gravimetric measurements.

## Clinical studies

Pulmonary thermal volume was shown to highly correlate with estimated lung weight on computer tomography scans in ARDS patients[20]. There was a weaker correlation between EVLW and computer tomography-derived lung weight. Other studies addressed clinically relevant correlates and determinants of EVLW. Bindels et al.[10] analyzed pulmonary capillary wedge pressure and EVLW in patients with acute cardiogenic pulmonary edema requiring mechanical ventilation. There was no correlation between the two variables, while EVLW decreased when cardiac function increased with treatment. This was confirmed by Boussat et al.[14] in septic patients, who observed a direct relation between EVLW and ITBV, rather than with pressures. EVLW and ITBV may vary independently even though mathematically coupled[22,24,29,33]. After cardiac surgery, however, a rise in (thermal-dye) EVLW may better relate to Starling forces than to increased permeability, cardiac output or ITBV[22]. Other clinically relevant counterparts of EVLW measurements include a negative correlation between oxygenation, compliance and EVLW, which is reported in several studies[7,31,33,34,42].

In other studies on ALI/ARDS[15,20,22,23,31,39], however, EVLW only poorly related to oxygenation, suggesting that edema itself only partially contributes to gas exchange abnormalities. Authors showed increased EVLW in ALI/ARDS, and more so when ARDS was severe, which was associated, paradoxically, with survival in one study but not in others[16,33,34,42]. The fact that increased EVLW can be demonstrated in only about 70% of patients with ALI/ARDS according to the consensus criteria can be taken as evidence of the contribution of consolidation or atelectasis to the syndrome, rather than as a failure of the technique to measure edema in poorly perfused or atelectatic areas (see below)[22-24,31,33]. EVLW may indicate that portion of the lung that is not immediately accessible to the tidal volume and may fall during recruitment of collapsed alveoli, although this is controversial[7,8,11,17,20,31].

A study[16] utilizing the double dilution technique demonstrated the prognostically adverse effect of a high EVLW, regardless of the type and severity of underlying disease, in 373 critically ill patients, having sepsis, ARDS or other conditions. The authors showed an increased EVLW in nonsurvivors compared with survivors (15.6 compared with 12.2 mL/kg, respectively): the mortality was 65% in patients with EVLW of more than 15 mL/kg compared with 33% in patients with EVLW of less than 10 mL/kg. Also, patients with ARDS had higher EVLW (14.9 mL/kg) compared with other patients (11.9 mL/kg). Mortality varied by diagnosis and was 67, 45 and 27% in septic, ARDS and all other patients, respectively, and the relation of the EVLW with mortality tended to be maintained in the subgroups. Martin et al.[33] studied EVLW in severely septic patients, with and without ARDS, with the help of the PiCCO. EVLW was higher in nonsurvivors (n = 12) compared with survivors (n = 17): 14.0 compared with 8.0 mL/kg, respectively. Furthermore, 57% of the patients without ARDS had an increased EVLW, possibly as a consequence of overhydration, while, conversely, four of 15 ARDS patients had normal EVLW. The median EVLW in the ARDS group compared with the non-ARDS group was 12.0 and 7.7 mL/kg, respectively. In both ARDS/non-ARDS subgroups, chest radiographs and lung injury scores did not differ when EVLW was low or high. Finally, Kuzkov et al.[34] recently demonstrated the clinical and prognostic significance of single thermodilution-derived EVLW in septic patients.

Preliminary clinical data show that EVLW monitoring may guide treatment[24-26,35]. The (old) thermal-dye EVLW measurement has been compared with pulmonary artery

catheter-based pressure monitoring for the treatment of patients with ALI[43]. Indeed, (fluid) therapy based on this EVLW rather than on a pulmonary wedge pressure after pulmonary artery catheterization was associated, in critically ill patients with ALI and pulmonary edema, with an increase in ventilator-free days and decreased morbidity[43]. No new diagnostic therapeutic studies, however, utilize the (relatively new) single thermodilution technique, aimed at preventing or ameliorating an increase in EVLW and subsequent morbidity and mortality, thereby confirming and extending the Mitchell et al.[43] study. Pressure support ventilation proved more effective when EVLW was low than when it was high[7].

## Confounding factors

Despite its potential, there are some drawbacks of the dilution EVLW method, inherent to the technique. Obviously, the thermodilution assessment is hampered by systemic and accidental errors. Even though reproducibility is within 10%[9], EVLW may be underestimated in underperfused areas, such as after pulmonary resection, embolism and pulmonary arterial occlusion, but less so after tracheal instillation of fluid[21,28,32,36]. Obstructing pulmonary arteries in a pig model, mimicking pulmonary arterial embolization, lowered thermal-dye EVLW[13]. As alluded to above, some types of pulmonary edema, in animal studies[18,39-41], are less well reflected by EVLW measurements than others, partly associated with redistribution of intrapulmonary blood flow. Cardiac output may also be too high for thermal equilibration with the extravascular distribution volume, and positive end-expiratory pressure (PEEP) may increase the distribution of the thermal indicator and increase EVLW, although this is controversial and opposite observations have been made, dependent on models, techniques and effects of PEEP on cardiac output and ventilator-associated lung injury[6,8,17,31,40,41]. Boldt et al.[44] observed that altering cardiac output after cardiac surgery in humans did not affect the (old) thermal-dye EVLW (densitometer technique). The effect of atelectasis, and thus of tidal volumes, on EVLW assessment is still not completely understood[8,17,19,22,23,31,36].

## Conclusion

The thermodilution technique for assessing extravascular thermal volume in the thorax as a bedside measure of EVLW is a promising technique to evaluate the severity and course of both permeability and cardiogenic/hydrostatic pulmonary edema, and may serve as a guide to treatment. Hence, the method can be easily integrated with the hemodynamic assessments to achieve an optimal balance between intra and extravascular hydration in patients with (impending) shock, hypotension or oliguria. The time constant for changes in EVLW upon changes in pulmonary capillary wedge pressure, the value in decision making, morbidity and mortality of the critically ill patient remain some of the unresolved issues. Potential areas of clinical evaluation of the EVLW measurements include drug treatment for ARDS and resorption of pulmonary edema[25,35], strategies to prevent or limit ventilator-associated lung injury, monitoring fluid resuscitation[26] and manipulating fluid balances[38].

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# 9

# Volume-limited versus pressure-limited hemodynamic management in septic and nonseptic shock

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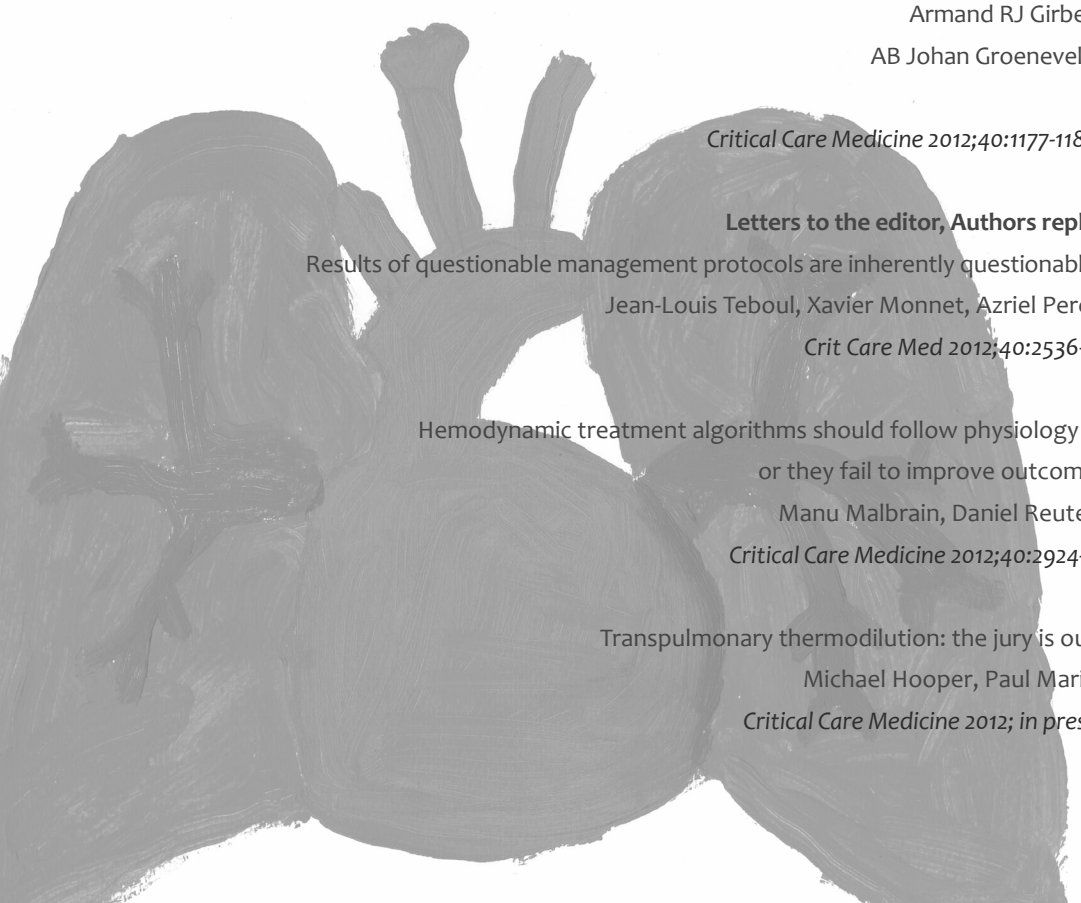
**Letters to the editor, Authors reply**

Results of questionable management protocols are inherently questionable
Jean-Louis Teboul, Xavier Monnet, Azriel Perel
*Crit Care Med 2012;40:2536-7*

Hemodynamic treatment algorithms should follow physiology – or they fail to improve outcome
Manu Malbrain, Daniel Reuter
*Critical Care Medicine 2012;40:2924-5*

Transpulmonary thermodilution: the jury is out
Michael Hooper, Paul Marik
*Critical Care Medicine 2012; in press*



## Abstract

### Objectives
To evaluate the effect of hemodynamic management guided by upper limits of cardiac filling volumes or pressures on durations of mechanical ventilation and lengths of stay in critically ill patients with shock.

### Design
Prospective, randomized, clinical trial.

### Setting
Mixed intensive care unit of a large teaching hospital and mixed intensive care unit of a tertiary care, academic medical center.
Patients: A total 120 septic (n=72) and nonseptic (n=48) shock patients, randomized (after stratification) to transpulmonary thermodilution (n=60) or pulmonary artery catheter (n=60) between February 2007 and July 2009.

### Interventions
Hemodynamic management was guided by algorithms including upper limits for fluid resuscitation of extravascular lung water (<10 mL/kg) and global end-diastolic volume index (<850 mL/m$^2$) in the transpulmonary thermodilution group and pulmonary artery occlusion pressure (<18–20 mm Hg) in the pulmonary artery catheter group for 72 hrs after enrollment.

### Measurements and main results
Primary outcomes were ventilator-free days and lengths of stay in the intensive care unit and the hospital. Secondary outcomes included organ failures and mortality. Cardiac comorbidity was more frequent in nonseptic than in septic shock. Ventilator-free days, lengths of stay, organ failures, and 28-day mortality (overall 33.3%) were similar between monitoring groups. Transpulmonary thermodilution (versus pulmonary artery catheter) monitoring was associated with more days on mechanical ventilation and longer intensive care unit and hospital lengths of stay in nonseptic ($p$=.001) but not in septic shock. In both conditions, fewer patients met the upper limit of volume than of pressure criteria at baseline and transpulmonary thermodilution (versus pulmonary artery catheter) monitoring was associated with a more positive fluid balance at 24 hrs.

### Conclusions
Hemodynamic management guided by transpulmonary thermodilution versus pulmonary artery catheter in shock did not affect ventilator-free days, lengths of stay, organ failures, and mortality of critically ill patients. Use of the a transpulmonary thermodilution algorithm resulted in more days on mechanical ventilation and intensive care unit length of stay compared with the pulmonary artery catheter algorithm in nonseptic shock but not in septic shock. This may relate to cardiac comorbidity and a more positive fluid balance with use of transpulmonary thermodilution in nonseptic shock.

## Introduction

In critically ill patients, fluid resuscitation is the first step in the treatment of hypovolemia and shock. Both under- and overtreatment may be detrimental because of inadequate tissue oxygenation or development of pulmonary edema, which may prolong mechanical ventilation, respectively[1-10].

Traditionally, the pulmonary artery catheter (PAC) has been used to guide hemodynamic management. In mechanically ventilated patients, however, atmospheric pressure-referenced filling pressures such as the pulmonary artery occlusion pressure (PAOP) may be confounded by airway pressures and may thereby poorly predict cardiac preload, fluid responsiveness, and pulmonary capillary filtration[1-3,6,9,11-13]. New, less invasive techniques such as transpulmonary thermodilution (TPTD) may provide better indicators of cardiac preload and fluid responsiveness such as the global end-diastolic volume[3,11,14]. The TPTD-derived extravascular lung water (EVLW) accurately reflects interstitial, alveolar, and clinically manifest lung edema if >10 mL/kg[15-18].

While we enter an era of less liberal fluid therapy[4,19], fluid overloading with increased EVLW (above the normal 7 mL/kg) was already suggested in the past to prolong mechanical ventilation and to be preventable by monitoring of EVLW (versus PAOP)[1]. Hence, the combined use of global end-diastolic volume and EVLW may allow fine-tuning of hemodynamic management, because fluid loading in the steep (as opposed to the flat) part of the cardiac function curve may prevent rapid formation of pulmonary edema[17]. However, nonrandomized studies suggest that the use of volume monitoring by TPTD (up to EVLW of 10 mL/kg) is associated with higher fluid requirements, more complete resuscitation, and less need of vasopressors as compared with pressure-based monitoring, although the effects on ventilator-free days (VFDs) remain undetermined[3,14]. Finally, hemodynamic management and its outcome may differ among shock etiologies[6,8-10,19,20]. In septic shock, volume-based prediction of cardiac output responses to fluid loading may be superior to pressure-based prediction, whereas the reverse may be true in nonseptic shock in patients with relatively poor cardiac function after cardiovascular surgery, for instance[11,21,22].

Therefore, we hypothesized that the risk of fluid overloading is less when fluid administration is restricted by upper limits of volumes by TPTD than of pressures by PAC and translates into more VFDs while safeguarding adequate resuscitation. We conducted a prospective, randomized, two-center trial comparing volume-guided hemodynamic management by TPTD- versus PAC-guided management in critically ill patients and explored whether septic and nonseptic shock differ in this respect.

## Material and methods

*Study Design.* This prospective, randomized, nonblinded clinical trial was conducted in intensive care units (ICUs) of a university hospital and a large teaching hospital in The Netherlands from February 2007 to July 2009. Patients meeting inclusion criteria were randomly assigned to receive either a TPTD or PAC catheter when inclusion criteria for advanced hemodynamic monitoring were met (see subsequently). The medical ethics committee at each study center had approved the protocol.

*Eligibility.* Patients were eligible when they were on mechanical ventilation with an expected stay in the ICU >48 hrs together with the presence of shock, indicating a clinical reason for invasive hemodynamic monitoring as determined by the attending physicians. Shock was defined by acute circulatory failure characterized by persistent arterial hypotension defined as a mean arterial pressure <65 mm Hg (or <80 mm Hg with previous hypertension) despite assumingly adequate volume resuscitation and/or the need for vasopressors to maintain a mean arterial pressure ≥65 mm Hg (or ≥80 mm Hg in case of known hypertension)[7]. We consecutively included patients in two major groups, septic and nonseptic shock until the predefined number of 120 was reached. Septic shock was defined by shock plus two or more of the following for systemic inflammatory response syndrome criteria: abnormal body temperature (>38°C, <36°C), tachycardia (>90 beats/min), mechanical ventilation, and abnormal white blood cell counts (≤4 or ≥12 x $10^9$/L or >10% immature bands) plus a clinically evident and/or microbiologically proven focus on infection[7]. The nonseptic shock group consisted of patients in shock after 1) (surgery for) major trauma (Injury Severity Score >25, without documented traumatic brain injury); 2) elective and emergency major abdominal surgery (including esophageal resection, gastric resection, liver

surgery, pancreatic surgery, colorectal surgery); 3) cardiac surgery (coronary bypass surgery, aortic root and/or valvular surgery); 4) major vascular surgery (thoracic aorta, abdominal aorta, and iliac/mesenteric reconstructions); and 5) a group with miscellaneous conditions (e.g., cardiogenic, obstructive, or unclassified shock).

*Randomization.* Randomization was done by the sealed envelope method after meeting eligibility criteria. The randomization was stratified per center for sepsis versus nonsepsis (no blocks were used). Written informed consent (by proxy) was obtained before randomization or, for reasons of urgency, delayed and obtained within 24 hrs after enrollment. In case of rejected consent by proxy, the allocation code was reused in new envelopes. Patients were included as soon as possible after randomization.

*Exclusion Criteria.* Exclusion criteria were age <18 or >80 yrs, pregnancy, preterminal illness with life expectancy <24 hrs, therapeutic hypothermia after cardiac arrest, traumatic brain injury, absence of mechanical ventilation, known (unrepaired) cardiac or vascular aneurysms, bifemoral vascular surgery, known pulmonary hypertension (defined as mean pulmonary artery pressure >50 mm Hg), or absence of informed consent.

*Outcomes.* Primary outcome measures were VFDs from enrollment to extubation until day 28 survival[23], days on mechanical ventilation, and lengths of stay in the ICU and in the hospital, including ICU- and hospital-free days. Secondary outcome measures were Sequential Organ Failure Assessment scores during the first 72 hrs after enrollment; 72-hr, 28-day, and hospital mortality (up to 100 days after enrollment); and protocol adherence for fluid administration, defined by the percentage of fluid challenges within the predefined upper limits and complications associated with catheter insertion or use. The latter was defined by technical failures such as pneumothorax, bleeding, suspected femoral artery obstruction and poor wedging, or defective central venous oxygen saturation or cardiac output measurements. We finally evaluated daily fluid intake and balances, lung injury score, hemodynamic measurements, and vasopressor requirements during the first 72 hrs after enrollment to determine adequacy of hemodynamic resuscitation.

*Study Protocol.* The ICU staff (doctors and nurses) underwent training in the conduct of the protocol. The assigned catheter was inserted as soon as possible after inclusion.

Fluid resuscitation and hemodynamic management was guided by either TPTD or PAC-derived parameters according to a predefined algorithm (Figure 1 and 2) for up to 72 hrs after enrollment, after which PACs are routinely removed in our ICUs. Fluid challenges were performed by colloids (gelatin 4% or hydroxyethyl starch solutions 6%, 130/0.4) at a dose of 250–500 mL per 30 minutes[7] when indicated clinically and according to the TPTD or PAC parameters defining upper limits of safe infusion (see subsequently). Clinical indications for a fluid challenge were, among others, mean arterial pressure <65 mm Hg (or <80 mm Hg in case of known hypertension), tachycardia >110 beats/min suggestive for hypovolemia, mixed venous oxygen saturation ($SvO_2$) <65% or central venous oxygen saturation ($ScvO_2$) <70%, oliguria <0.5 mL/kg/hr (suspected prerenal cause), peripheral perfusion deficits such as cold extremities and skin discolorations, and hyperlactatemia (>2.0 mmol/L). Fluid challenges were withheld when the safety limits by TPTD or PAC monitoring had been reached (see subsequently) and when there was <10% rise in cardiac output. End points of resuscitation, reflecting adequacy of fluid and hemodynamic management, were mean arterial pressure ≥65 mm Hg (or ≥80 mm Hg in case of known hypertension), $ScvO_2$ ≥70% or $SvO_2$ ≥65%, lactate clearance, diuresis ≥0.5 mL/kg/hr (unless development of intrinsic renal failure), and restoration of peripheral perfusion deficits.

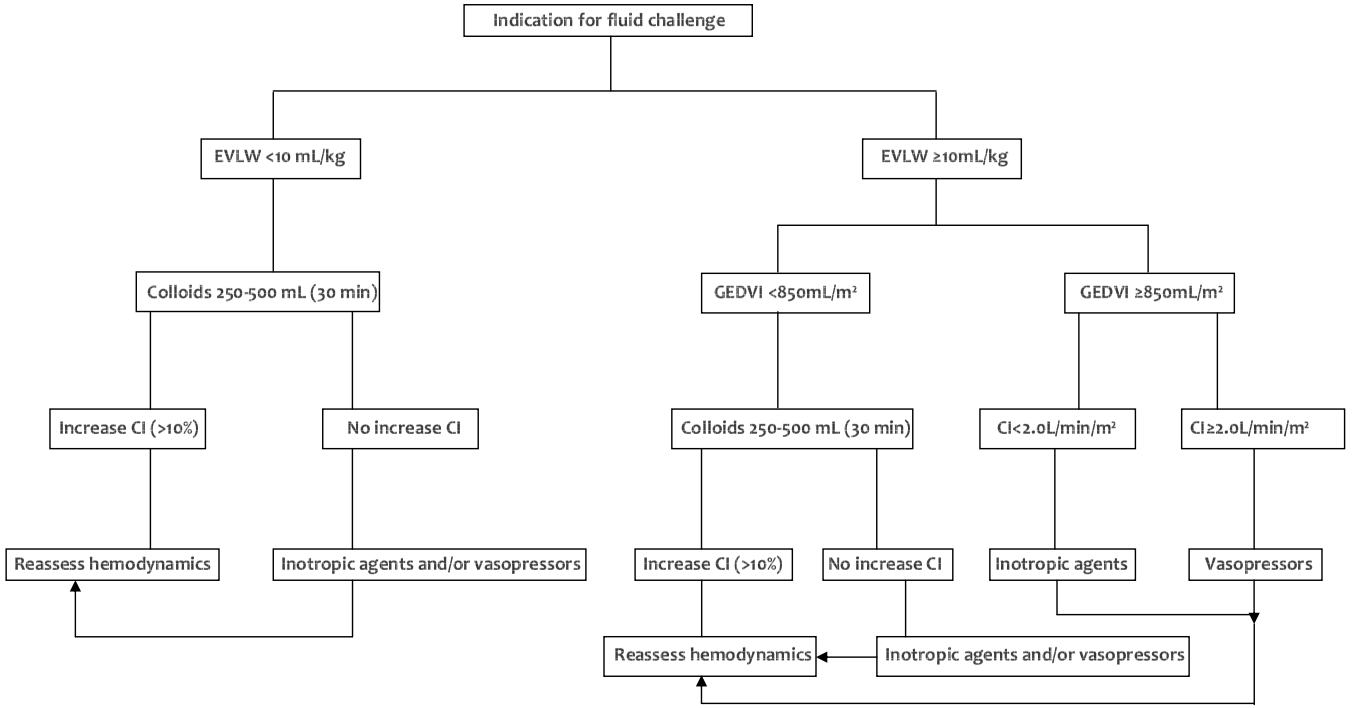



**Figure 1.** Algorithm for hemodynamic management according to *TPTD* transpulmonary thermodilution derived data. *EVLW* extravascular lung water index, *GEDVI* global end-diastolic volume index, *CI* cardiac index, *PEEP* positive end-expiratory pressure.

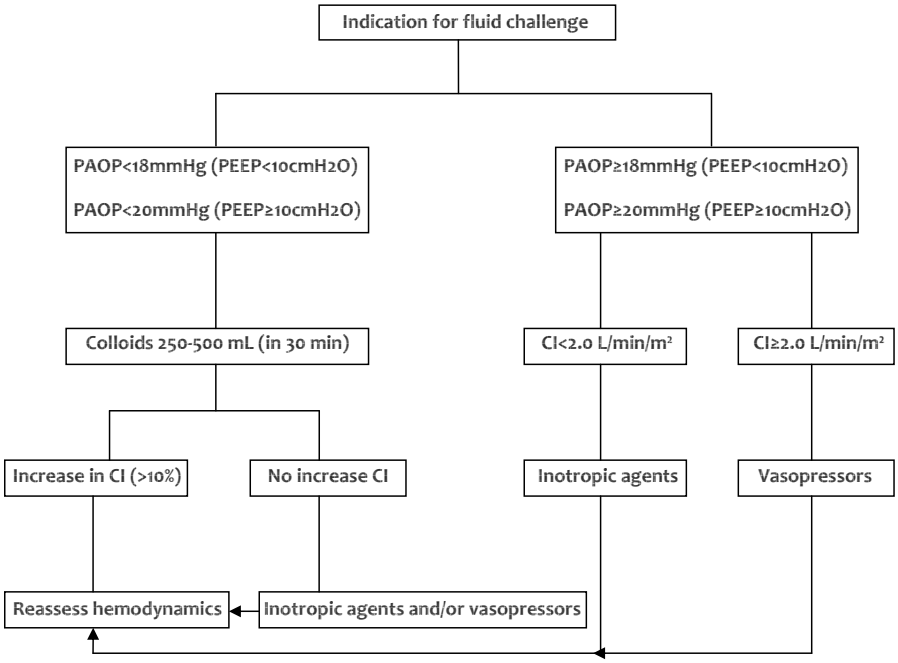



**Figure 2.** Algorithm for hemodynamic management according to *PAC* pulmonary artery catheter derived data. *CI* cardiac index, *PAOP* pulmonary artery occlusion pressure, *PEEP* positive end-expiratory pressure.

*TPTD Protocol.* The TPTD catheter (PiCCO; Pulsion Medical Systems AG, Munich, Germany) was inserted in the femoral artery and measurements were performed through an injection of a 20-mL ice-cold (4°C) saline bolus through a central venous catheter (different sizes were used: 16 cm for right subclavian or internal jugular vein, 20 cm for left subclavian or internal jugular vein). Measurements were obtained in triplicate and averaged. Fluid resuscitation and hemodynamic management was done according to a predefined algorithm (Figure 1). Upper limits of EVLW and global end-diastolic volume index (GEDVI) were 10 mL/kg predicted body weight and 850 mL/m$^2$, respectively[1,11,14-18]. Variables were obtained both before and following a fluid challenge and when clinically indicated on other grounds, but at least every 4 hrs.

*PAC Protocol.* Fluid resuscitation and hemodynamic management in this group were guided by clinical parameters and by baseline values and responses to fluid loading within upper safety limits of PAOP of 18 mm Hg at positive end-expiratory pressure <10 cm $H_2O$ and 20 mm Hg at positive end-expiratory pressure ≥10 cm $H_2O$ (Figure 2).

These PAOP limits may relate to the development of hydrostatic pulmonary edema[12]. Filling pressures and cardiac output were measured when clinically indicated, but at least every 4 hrs, and before and after fluid challenges, after calibration, zeroing to atmospheric level, proper wedging (for PAOP), and at the end of expiration (indicated by the ventilation curve) with patients in supine position (Marquette, Milwaukee, WI). Thermodilution cardiac output measurements were done in triplicate, irrespective of the ventilatory cycle, and averaged after central venous bolus injections of 10 mL normal saline.

*Therapeutic Protocol.* Fluid losses were supplemented by infusion of normal or half-normal saline. After 72 hrs, vasopressors and inotropic drugs were administered and dosed on clinical grounds in case of, but not limited to, persistent and fluid-refractory hypotension, suspected impairment of tissue $O_2$ delivery, lactic acidosis, and oliguria. Norepinephrine was the vasopressor drug of first choice in our ICUs, which was continuously infused and dosed on the basis of hemodynamic responses. Dobutamine was the inotropic drug of choice followed by enoximone. All patients were pressure-controlled ventilated (Servo-i; Maquette or Evita 4; Dräger, Lübeck, Germany), aiming at tidal volumes <8 mL/kg predicted body weight and positive end-expiratory pressure was dosed (≤20 cm $H_2O$) to maintain arterial $PO_2$ >65 mm Hg at an inspiratory $O_2$ fraction of at least 40%. Pressure-controlled ventilation was changed into pressure-support ventilation when clinically justified. Weaning was attempted through clinical protocols. Sedatives, analgesics, and antibiotics were prescribed by attending physicians according to strict clinical guidelines. Systemic corticosteroids were initialized in case of persistent vasopressor-dependent septic shock, defined as a norepinephrine dose ≥1 mg/hr. After the initial 72-hr period of the protocol, when the PACs were removed, patients in both groups were treated at the discretion of the attending physicians.

*Data Collection.* Hemodynamic measurements were done and arterial and central venous (in TPTD group) or mixed venous (in PAC group) blood samples were taken every 4 hrs, at baseline, and up to 72 hrs after enrollment. Partial gas pressures, $O_2$ saturations, and lactate levels were determined (ABL Radiometer, Copenhagen, Denmark, and i-STAT 1, Abbott, Abbott Park, IL). Cardiac output was indexed to body surface area, calculated from gender, weight, and height, and yielding cardiac index (CI) like the GEDVI, whereas the EVLW was indexed to predicted body weight.

The amount and type of fluid infusion, drainage, and diuresis to calculate 24-hr fluid balances were recorded together with doses and types of inotropic/vasopressor drugs. Daily measured clinical and laboratory variables allowed calculation of Sequential Organ Failure Assessment. Daily chest x-rays were made and scored by independent radiologists for quadrants of alveolar consolidations to calculate, together with the level of positive end-expiratory pressure, the arterial $PO_2$/inspiratory $O_2$ fraction, and total respiratory dynamic (tot.respir.dyn.) compliance, the lung injury score. To this end, relevant variables were taken from the ventilators. The $compliance_{tot.respir.dyn.}$ was calculated from tidal volume/($P_{insp}$ - positive end-expiratory pressure), where $P_{insp}$ is end-inspiratory airway pressure (cm $H_2O$). The acute respiratory distress syndrome was defined using the consensus conference criteria[24]. Patients were followed until death or hospital discharge up to 100 days after enrollment.

*Statistical Analysis.* A prestudy power analysis by t-test showed that at least 50 evaluable patients would be needed per monitoring group to demonstrate a difference of mean 2 VFDs (9 versus 7 days), assuming a SD of 50% (at $\alpha = 0.05$ and $\beta = 0.80$). Analysis was done on an intention-to-treat basis in the absence of premature study discontinuations and, as anticipated, stratification was taken into account. After logarithmic conversion of nonnormally distributed data (Kolmogorov-Smirnov test $p < .05$) to normalize distributions where appropriate, generalized estimating equations were done to evaluate the contribution of monitoring (TPTD versus PAC) and underlying condition (septic versus nonseptic shock) and their first-order interaction on differences in categorical and continuous variables. The interaction yields the effect of monitoring dependent on underlying condition. For evaluation of changes in time, repeated measures in the same patients were taken into account after entering baseline variables as covariates. Multiple Cox proportional hazard regression modeling with backward elimination on the basis of statistical significance was done to evaluate determinants (hazard ratios) of duration of mechanical ventilation and hospital stays. Kaplan-Meier curves were made to evaluate, in septic and nonseptic shock, the likelihood of mechanical ventilation in the ICU (until day 28). The log-rank test was used. Fisher's exact test was used to compare categorical data. Two-sided *p* values < .05 were considered statistically significant. Values are summarized as median (interquartile range = 75th–25th percentile) or as box and whisker plots in figures. All analyses were conducted using SPSS version 16.0 (SPSS, Chicago, IL).

## Results

In the study period, 192 patients with septic and nonseptic shock were screened (Figure 3). Finally, 120 patients were randomized; 60 patients received a TPTD and 60 a PAC catheter (Table 1). The study was started within 24 hrs of ICU admission in 63% of TPTD- and 67% of PAC-assigned patients. There were no premature study discontinuations. TPTD and PAC groups were comparable at baseline (Table 1), except for an interaction for Acute Physiology and Chronic Health Evaluation II scores between monitoring groups and underlying condition.

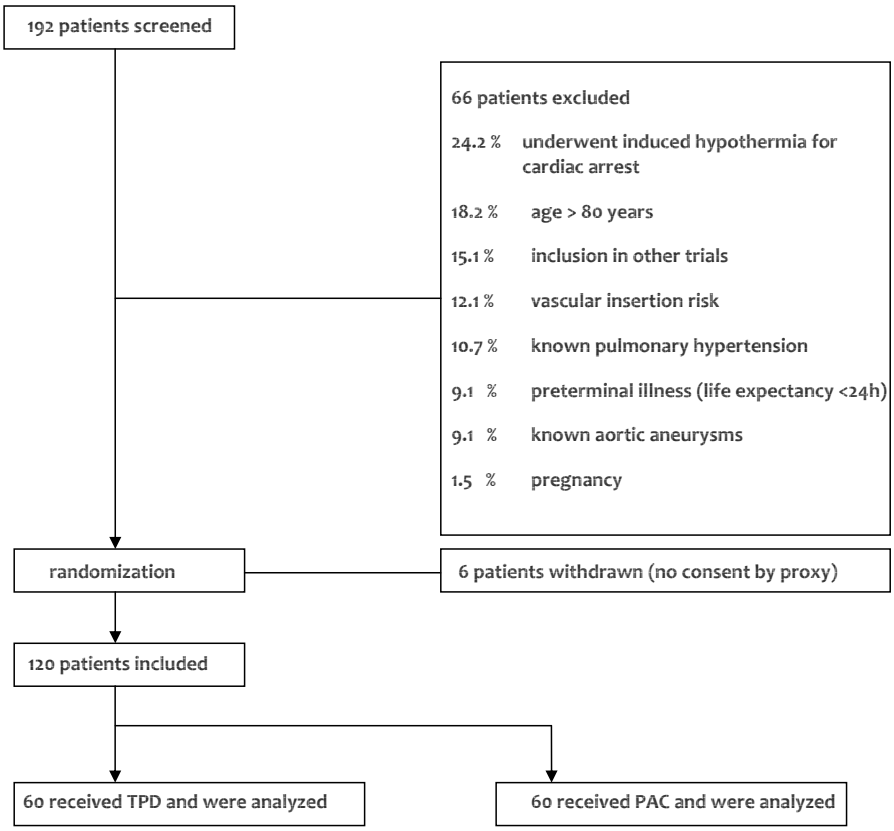



**Figure 3.** Consort diagram. *TPTD* transpulmonary thermodilution, *PAC* pulmonary artery catheter.

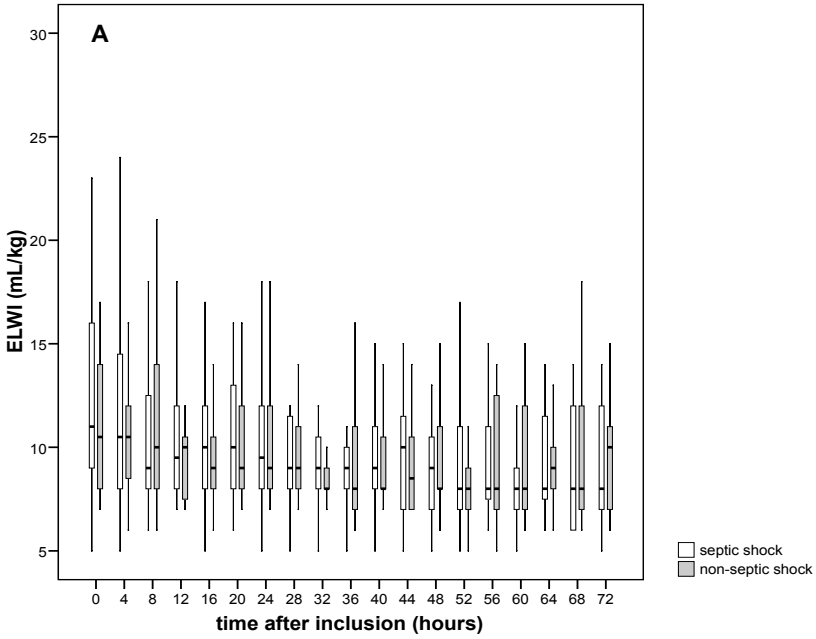
**Table 1.** Patient and baseline characteristics for monitoring by pulmonary artery catheter (PAC) or transpulmonary thermodilution (TPTD), according to shock etiology.

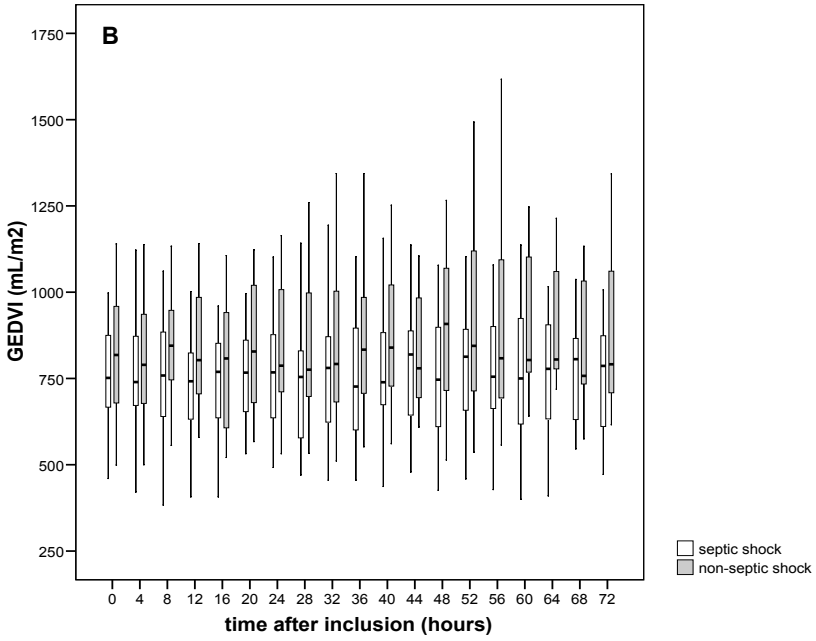
| | sepsis | | nonsepsis | | *p* value | | |
|---|---|---|---|---|---|---|---|
| | PAC (n=34) | TPTD (n=38) | PAC (n=26) | TPTD (n=22) | M | U | U*M |
| Age, year | 67 (15) | 67 (19) | 69 (15) | 69 (13) | .83 | .55 | .79 |
| Male/female sex, n (%) | 18(53)/16(47) | 20(53)/18(47) | 19(73)/7(27) | 15(68)/7(32) | .75 | .05 | .78 |
| APACHE II | 26 (15) | 27 (13) | 29 (12) | 24 (11) | .39 | .21 | .02 |
| SOFA | 9 (5) | 10 (6) | 10 (4) | 10 (4) | .72 | .87 | .75 |
| Inclusion <24 h admission, n (%) | 24 (71) | 25 (74) | 14 (54) | 12 (55) | .82 | .05 | .87 |
| Comorbidity, n (%) | | | | | | | |
| Cardiovascular | 7 (21) | 11 (29) | 16 (62) | 16 (73) | .25 | <.001 | .94 |
| Respiratory | 2 (6) | 3 (8) | 2 (8) | 0 | .65 | .50 | N.A. |
| Renal | 1 (3) | 4 (11) | 3 (12) | 2 (9) | .47 | .39 | .28 |
| Neurological | 4 (12) | 3 (8) | 1 (1) | 1 (1) | .87 | .28 | .71 |
| **Diagnostic group** | | | | | | | |
| Sepsis, n (%) | | | | | .56 | N.A. | .95 |
| Respiratory | 11 (32) | 13 (34) | - | - | | | |
| Abdominal | 12 (35) | 17 (45) | - | - | | | |
| Other | 11 (32) | 8 (21) | | | | | |
| Nonsepsis, n (%) | | | | | | | |
| Nonsurgical | - | - | 10 (38) | 7 (32) | | | |
| Cardiac surgery | - | - | 7 (27) | 6 (27) | | | |
| Vascular surgery | - | - | 4 (15) | 4 (18) | | | |
| Trauma | - | - | 1 (1) | 1 (1) | | | |
| Other surgery | - | - | 4 (15) | 4 (18) | | | |
| Associated microorganisms in sepsis, n (%) | | | | | .72 | N.A. | N.A. |
| Gram positive | 8 (24) | 6 (16) | - | - | | | |
| Gram negative | 10 (29) | 14 (37) | - | - | | | |
| Other | 1 (3) | 12 (31) | - | - | | | |
| Bacteremia, n (%) | 13 (39) | 12 (31) | | | .33 | N.A. | N.A. |
| **Hemodynamics** | | | | | | | |
| Heart rate, b/min | 112 (27) | 105 (27) | 89(29) | 93(31) | .72 | <.001 | .96 |
| MAP, mm Hg | 77 (15) | 77 (15) | 78 (19) | 78 (29) | .29 | .32 | .53 |
| Cardiac index, mL/min/m$^2$ | 3.7 (1.7) | 3.2 (1.7) | 2.8 (1.5) | 2.8 (1.2) | .26 | <.001 | .27 |
| CVP, mm Hg | 13 (7) | 12 (5) | 10 (7) | 10 (7) | .23 | .38 | .47 |
| MPAP, mm Hg | 29 (11) | - | 26 (8) | - | N.A. | .16 | N.A. |
| PAOP, mm Hg | 18 (1) | - | 12 (8) | - | N.A. | .02 | N.A. |
| GEDVI, mL/m$^2$ | - | 752 (217) | - | 818 (295) | N.A. | .33 | N.A. |
| $S_{(c)v}O_2$ | 0.74 (0.21) | 0.75 (0.17) | 0.69 (0.13) | 0.74 (0.17) | .01 | .38 | .63 |
| Lactate, mmol/L | 3.3 (4.2) | 3.7 (4.2) | 2.1 (1.9) | 2.4 (4.2) | .67 | .08 | .68 |
| Norepinephrine, µg/kg/min | 0.50 (0.55) | 0.48 (0.63) | 0.29 (0.21) | 0.24 (0.34) | .57 | .007 | .91 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Respiration** | | | | | | | |
| $P_aO_2/F_IO_2$ | 178 (91) | 170 (123) | 189 (98) | 188 (110) | .32 | .85 | .72 |
| Tidal volume, mL/kg PBW | 7.8 (1.9) | 7.4 (1.9) | 7.3 (2.5) | 7.4 (1.2) | .10 | .23 | .69 |
| $P_{insp}$, $cmH_2O$ | 33 (11) | 31 (10) | 29 (9) | 28 (9) | .23 | .009 | .36 |
| PEEP, $cmH_2O$ | 13 (6) | 12 (6) | 10 (7) | 12 (6) | .19 | .16 | .28 |
| Compliance, mL/cm $H_2O$ | 28 (10) | 27 (12) | 32 (15) | 30 (11) | .27 | .13 | .55 |
| Radiographic score | 1 (2) | 2 (2) | 0 (0) | 0 (1) | .27 | .001 | .97 |
| Lung injury score | 2.4 (1.0) | 2.5 (1.0) | 1.9 (1.0) | 2.2 (1.0) | .19 | .06 | .69 |
| ARDS at inclusion, n (%) | 11 (32) | 11 (29) | 2 (8) | 2 (9) | .96 | .007 | .77 |
| EVLW, mL/kg PBW | - | 11.0 (7.0) | - | 11.0 (6.0) | N.A. | .12 | N.A. |

Median (interquartile range) or number (percentage), where appropriate *PAC* pulmonary artery catheter, *TPTD* transpulmonary thermodilution, *APACHE II* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment score, *MAP* mean arterial pressure, *CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure, *GEDVI* global end-diastolic volume index, $S_{(c)v}O_2$ central or mixed venous $O_2$ saturation, $P_aO_2$ partial pressure of $O_2$ in arterial blood, $F_IO_2$ inspiratory $O_2$ fraction, *PBW* predicted body weight, $P_{insp}$, end-inspiratory pressure, *PEEP* positive end-expiratory pressure, *ARDS* acute respiratory distress syndrome, *EVLW* extravascular lung water, *M* monitoring, *U* underlying condition, *U*M* interaction, *N.A.* not applicable.

*Septic versus nonseptic shock.* There were more males and cardiovascular comorbidities among nonseptic than septic shock patients (Table 1). At baseline, septic shock patients had more often acute respiratory distress syndrome and had higher radiographic scores and ventilatory pressures than nonseptic shock patients. At baseline, patients with septic shock had higher heart rate, CI, and PAOP, whereas central venous pressure and GEDVI did not differ from those in nonseptic shock patients. Patients with septic shock had less improvement in Sequential Organ Failure Assessment scores, shorter length of stay in the hospital, higher inhospital mortality, and greater fluid and vasopressor requirements than nonseptic shock patients (Table 2 and 3). The course of hemodynamic variables guiding treatment was similar between septic and nonseptic shock except for the GEDVI, which was higher in the latter (Figure 4). The fall in lactate was greater in septic shock.


A
ELWI (mL/kg)
30
25
20
15
10
5
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
time after inclusion (hours)
septic shock
non-septic shock


B
GEDVI (mL/m2)
1750
1500
1250
1000
750
500
250
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
time after inclusion (hours)
septic shock
non-septic shock

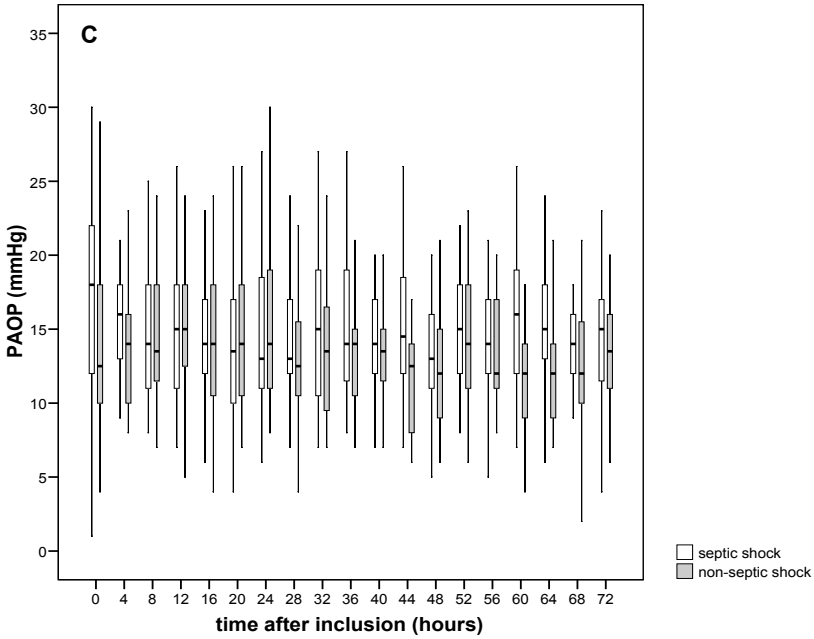



**Figure 4.** Course of guiding variables (**A**. *EVLW* extravascular lung water; **B**. *GEDVI* global end-diastolic volume index, **C**. *PAOP* pulmonary artery occlusion pressure, ) in the septic shock (closed symbols) and nonseptic shock (open symbols); box and whisker plots. The mean daily EVLW and GEDVI decreased in the TPTD group ($p$ = .027 or lower), while PAOP decreased in the PAC group ($p$ = .034). Only for GEDVI: $P$=0.05 between septic and nonseptic shock groups.

*Primary Outcome.* The number of VFDs did not differ between monitoring groups (Table 2; Figures 5,6,7). Although overall not differing between monitoring groups, the duration of mechanical ventilation (including patients who died within 28 days) and length of stay in the ICU were longer in TPTD than in PAC-monitored nonseptic shock but not in septic shock patients ($p$ = .001 for interaction). The number of ventilation days directly related to the EVLW and lung injury score at 72 hrs ($p \leq .05$) regardless of underlying condition. When lung injury score at 72 hrs was entered as a covariate, the number of ventilation days and days in the ICU was similar among groups ($p$ = .30 for monitoring, $p$ = .69 for underlying condition, and $p$ = .29 for interaction of monitoring with underlying condition). The hospital length of stay was also prolonged in nonseptic shock patients in the TPTD group. For the prediction of time on the ventilator until day 28, in Cox regression analysis, there was no contribution of both monitoring group,

underlying condition, and their interaction. Nevertheless, there was a tendency toward greater ventilator dependency until day 28 in the nonseptic shock patients randomized to TPTD than to PAC ($p$ = .06) (Figures 8 and 9), which reached statistical significance ($p$ = .01) when considering the entire mechanical ventilation period (up to day 100).

**Table 2.** Primary and secondary outcomes.

| | sepsis | | nonsepsis | | *p* value | | |
|---|---|---|---|---|---|---|---|
| | PAC (n=34) | TPTD (n=38) | PAC (n=26) | TPTD (n=22) | M | U | U*M |
| **Primary** | | | | | | | |
| VFDs | 0 (16) | 0 (16) | 6 (22) | 0 (19) | .44 | .34 | .71 |
| VFDs=0 | 18 (53) | 23 (61) | 11 (42) | 12 (55) | .29 | .37 | .81 |
| VFDs=0 and MV>day 28 | 5 (15) | 7 (18) | 4 (15) | 7 (32) | .69 | .05 | .58 |
| Ventilation days† | 13 (14) | 10 (15) | 8 (15) | 21 (34) | .38 | .15 | .001 |
| LOS ICU, days | 15 (15) | 11 (17) | 9 (13) | 22 (34) | .39 | .07 | .001 |
| ICU free days# | 0 (13) | 0 (14) | 9 (20) | 0 (15) | .29 | .27 | .35 |
| LOS hospital, days | 25 (25) | 27 (42) | 29 (25) | 34 (55) | .60 | .01 | .04 |
| Hospital free days# | 0 (0) | 0 (0) | 0 (0) | 0 (1) | .71 | .18 | .82 |
| **Secondary** | | | | | | | |
| Correct / total fluid challenges, n (%) | 152 / 175(85) | 209 / 242 (84) | 87 / 94 (92) | 84 / 104 (75) | .002 | .59 | .06 |
| Protocol non-adherence, n (%) | 10 (30) | 12 (32) | 6 (23) | 11 (50) | .11 | .58 | .18 |
| Catheter dysfunction, n (%) | 4 (12) | 3 (8) | 4 (15) | 2 (9) | .39 | .70 | .90 |
| SOFA,$ | | | | | | | |
| at baseline | 9 (5) | 10 (6) | 10 (4) | 10 (4) | .49 | .02 | .89 |
| at 24 h | 10 (6) | 9 (6) | 9 (4) | 10 (5) | | | |
| at 48 h | 9 (6) | 10 (7) | 9 (7) | 10 (8) | | | |
| at 72 h | 9 (6) | 10 (8) | 8 (6) | 8 (7) | | | |
| Mortality until 72 h, n (%) | 4 (12) | 10 (26) | 3 (12) | 0 | .51 | .05 | .13 |
| Mortality until day 28, n (%) | 13 (38) | 16 (42) | 6 (23) | 5 (23) | .87 | .05 | .83 |
| Mortality in ICU, n (%) | 13 (38) | 17 (45) | 6 (23) | 5 (23) | .77 | .04 | .73 |
| Mortality in hospital, n (%) | 15 (44) | 21 (55) | 8 (31) | 5 (23) | .97 | .01 | .29 |

Median (interquartile range) or number (percentage), where appropriate *PAC* pulmonary artery catheter, *TPTD* transpulmonary thermodilution, *VFDs* ventilator free days, *MV* mechanical ventilation, *LOS* length of stay, *ICU* intensive care unit, *SOFA* sequential organ failure assessment score, *M* monitoring, *U* underlying condition, *U*M* interaction. †including all patients; # ICU-free days / Hospital-free days = 0 if patient dies before day 28, = (28-x) if patient is successfully discharged from the ICU / hospital, where x is the number of days spent in the ICU / hospital, = 0 if the patient stays in the ICU / hospital for 28 days or more; $ for change vs. baseline.

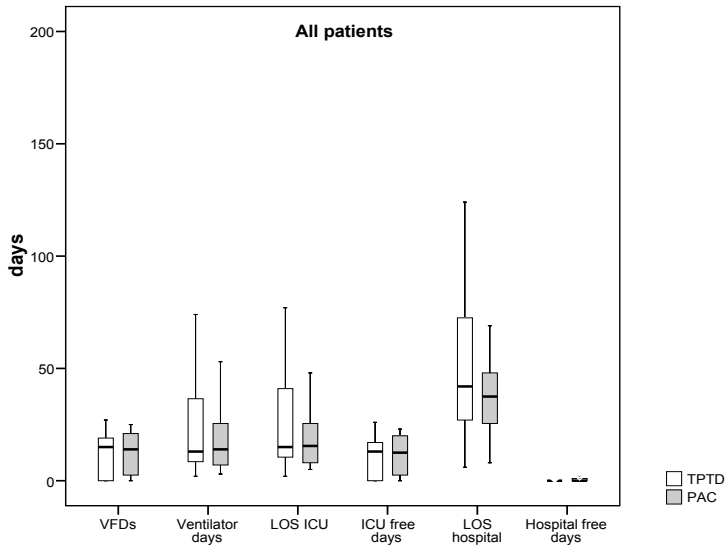



**Figure 5.** A plot of primary outcome measures in all patients for *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter. *VFDs* ventilator-free days, *LOS* length of stay, *ICU* intensive care unit.

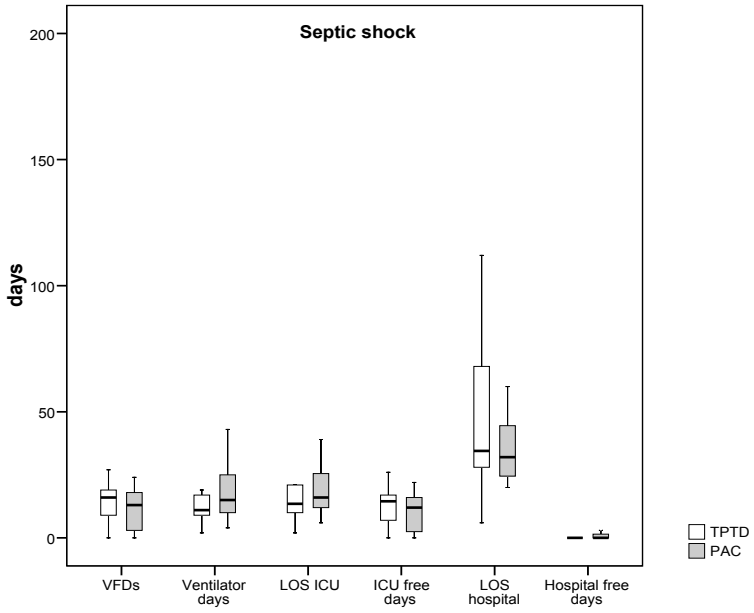



**Figure 6.** A plot of primary outcome measures in patients with septic shock for *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter. *VFDs* ventilator-free days, *LOS* length of stay, *ICU* intensive care unit.

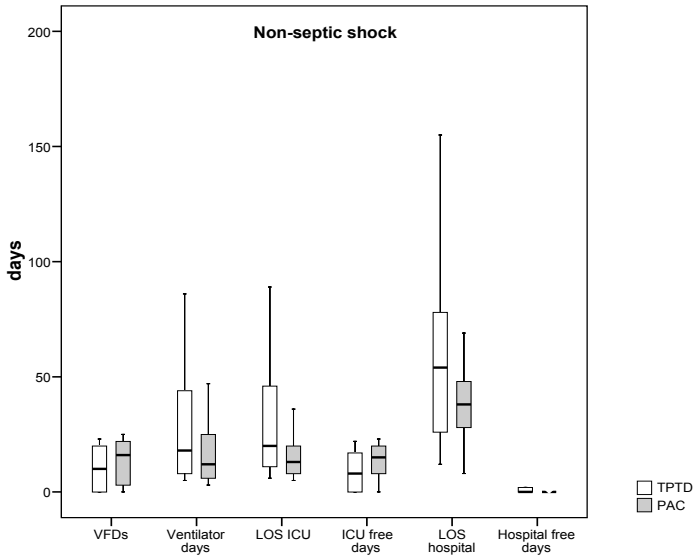
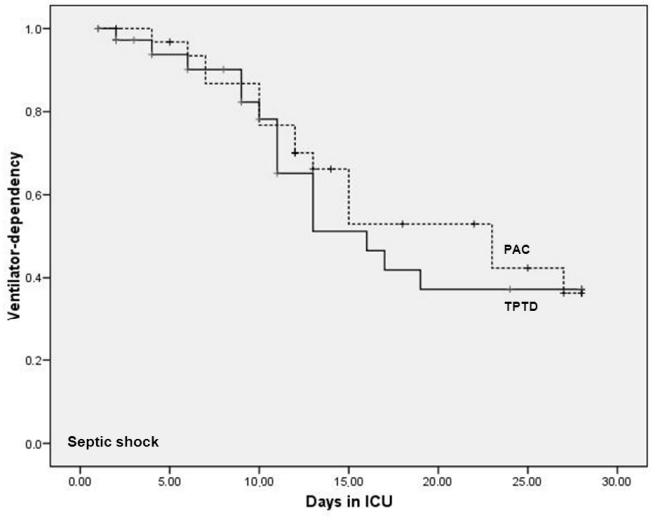
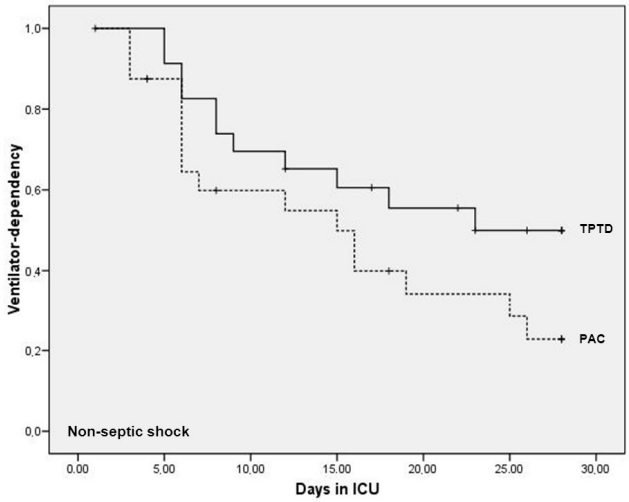



**Figure 7.** A plot of primary outcome measures in patients with nonseptic shock patients, for *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter. *VFDs* ventilator-free days, *LOS* length of stay, *ICU* intensive care unit.




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| PAC | 34 | 31 | 26 | 15 | 11 | 8 | 5 |
| TPTD | 38 | 26 | 20 | 11 | 8 | 7 | 7 |

**Figure 8.** Likelihood of ventilator-dependency in septic shock (log-rank test $p$ = .68), in *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter groups, until day 28 in the ICU. Crosses are censored data.



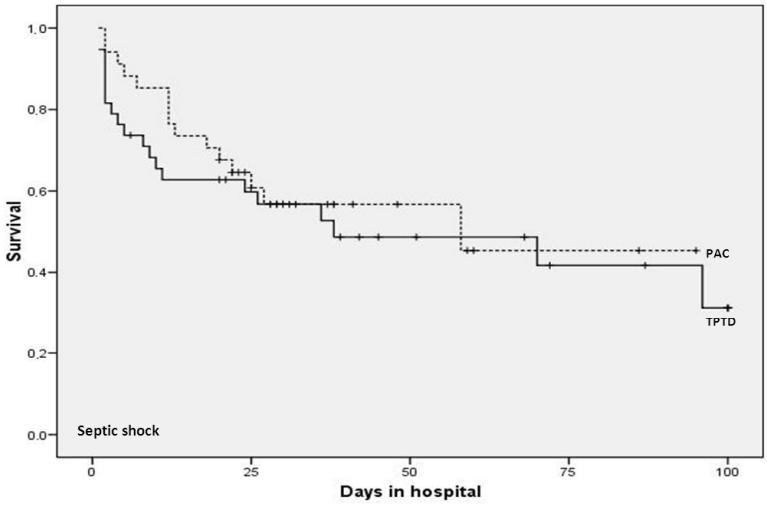

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| PAC | 26 | 20 | 12 | 11 | 6 | 6 | 4 |
| TPTD | 22 | 22 | 16 | 14 | 10 | 9 | 7 |

**Figure 9.** Likelihood of ventilator-dependency in nonseptic shock (log-rank test $p$ = .06), in *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter groups, until day 28 in the ICU. Crosses are censored data.

*Secondary Outcomes.* There was no difference in mortality between monitoring groups. Overall, 21 patients (35%) died in the TPTD group before day 28 and 19 (32%) in the PAC group ($p$ = .85). This 3% difference had 95% confidence intervals between 0.4% and 11%. Age, Acute Physiology and Chronic Health Evaluation II score, and underlying condition predicted both survival duration to day 28 in either the ICU or in the hospital ($p$ = .01 or lower), whereas monitoring groups (and first-order interactions) did not contribute (Figures 10 and 11, represent Kaplan-Meier curves for likelihood of survival as a function of days inhospital for the study groups). Protocol adherence was higher in the PAC group as compared with the TPTD group independent of underlying condition (Table 2). In the subgroup of patients with full protocol adherence, VFDs did not depend on monitoring group, underlying condition, and interaction. The number of catheter-related complications and Sequential Organ Failure Assessment scores did not differ among monitoring groups. In the TPTD group, the femoral artery catheter was removed in two patients because of fear for vascular occlusion, although without further adverse consequences. In one patient, the thermistor was defective and in

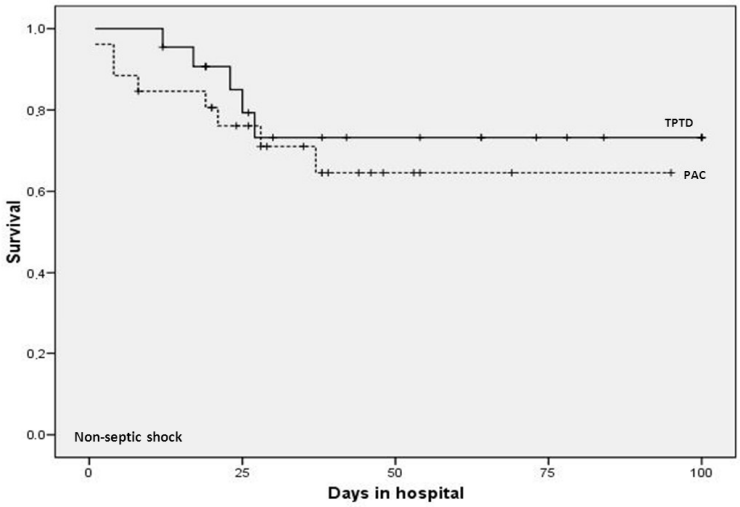
another one, central venous blood sampling was not feasible after 48 hrs. In the PAC group, no catheter-related complications occurred. In six patients, the PAOP could not be measured and in another patient, mixed venous blood sampling was not possible after 48 hrs.

*Efficacy of Resuscitation.* Baseline hemodynamics were similar among monitoring groups, but baseline $ScvO_2$ in the TPTD group was higher than the $SvO_2$ in the PAC group (Table 3). The CI and $ScvO_2$ increased more with time in the TPTD than the CI and $SvO_2$ in the PAC group. The decrease in norepinephrine requirements tended to favor the TPTD group ($p = .06$). Forty-six percent of patients in the PAC group already had reached the upper limit (PAOP ≥18 mm Hg) of fluid administration at baseline compared with 25% of patients in the TPTD group (GEDVI ≥850 mL/m$^2$ plus EVLW ≥10 mL/kg predicted body weight, $p = .047$). Fluid volume infusions per day inversely related in time to the mean daily GEDVI in the TPTD group ($p = .004$) and the mean daily PAOP in the PAC group ($p = .003$). Fluid infusions and balances were greater at 24 hrs and less so at 48 and 72 hrs ($p < .001$ for time), so that at 24 hrs, the TPTD group had a more positive balance than the PAC group ($p = .044$) independent of underlying condition.




| No. at risk | | | | | |
|---|---|---|---|---|---|
| PAC | 34 | 17 | 5 | 2 | 0 |
| PiCCO | 38 | 20 | 8 | 5 | 3 |

**Figure 10.** Likelihood of survival in septic shock (log-rank test $p$ = .59) in *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter groups, as a function of (up to 100) hospital days. Vertical lines are censored data.




| No. at risk | | | | | |
|---|---|---|---|---|---|
| PAC | 26 | 17 | 4 | 1 | 0 |
| PiCCO | 22 | 16 | 9 | 5 | 3 |

**Figure 11.** Likelihood of survival in nonseptic shock (log-rank test $p$ = .50) in *TPTD* transpulmonary thermodilution and *PAC* pulmonary artery catheter groups, as a function of (up to 100) hospital days. Vertical lines are censored data.

**Table 3.** Cardiorespiratory parameters.

| | sepsis | | nonsepsis | | *p* value (for change) | | |
|---|---|---|---|---|---|---|---|
| | PAC (n=34) | TPTD (n=38) | PAC (n=26) | TPTD (n=22) | M | U | U*M |
| CVP, mm Hg | | | | | | | |
| at baseline | 13 (7) | 12 (5) | 10 (7) | 10 (7) | .65 | .22 | .13 |
| at 24 h | 10 (5) | 10 (5) | 10 (6) | 10 (7) | | | |
| at 48 h | 10 (5) | 12 (6) | 10 (6) | 11 (4) | | | |
| at 72 h | 10 (8) | 8 (6) | 10 (6) | 11 (4) | | | |
| MAP, mm Hg | | | | | | | |
| at baseline | 77 (15) | 77 (15) | 78 (19) | 78 (29) | .31 | .97 | .17 |
| at 24 h | 80 (18) | 75 (12) | 80 (15) | 81 (19) | | | |
| at 48 h | 79 (16) | 77 (15) | 81 (18) | 83 (16) | | | |
| at 72 h | 83 (14) | 88 (19) | 76 (25) | 88 (27) | | | |
| CI, L/min/m$^2$ | | | | | | | |
| at baseline | 3.7 (1.7) | 3.2 (1.7) | 2.8 (1.5) | 2.8 (1.2) | .21 | .008 | .87 |
| at 24 h | 3.2 (1.5) | 3.6 (1.3) | 3.4 (1.5) | 3.6 (1.2) | | | |
| at 48 h | 3.1 (1.5) | 3.5 (1.2) | 3.6 (1.8) | 3.0 (1.1) | | | |
| at 72 h | 3.2 (1.1) | 3.7 (1.9) | 2.6 (2.0) | 3.2 (0.9) | | | |
| $S_{(c)v}O_2$ | | | | | | | |
| at baseline | 0.74 (0.21) | 0.75 (0.17) | 0.69 (0.13) | 0.74 (0.17) | .15 | .02 | .13 |
| at 24 h | 0.72 (0.09) | 0.80 (0.08) | 0.72 (0.13) | 0.78 (0.16) | | | |
| at 48 h | 0.74 (0.21) | 0.77 (0.13) | 0.76 (0.12) | 0.77 (0.08) | | | |
| at 72 h | 0.69 (0.12) | 0.79 (0.09) | 0.71 (0.16) | 0.76 (0.11) | | | |
| Lactate, mmol/L | | | | | | | |
| at baseline | 3.3 (4.2) | 3.7 (4.2) | 2.1 (1.9 ) | 2.4 (4.2) | .003 | .52 | .27 |
| at 24 h | 2.3 (2.0) | 2.1 (2.2) | 1.5 (1.5) | 1.7 (1.9) | | | |
| at 48 h | 2.2 (1.2) | 1.6 (1.7) | 1.3 (1.5) | 1.2 (0.8) | | | |
| at 72 h | 1.7 (1.4) | 1.5 (1.0) | 1.1 (1.2) | 1.2 (0.8) | | | |
| Fluids in, mL | | | | | | | |
| at 24 h | 5793 (2293) | 5608 (3240) | 4495 (2040) | 4852 (2105) | .002 | .31 | .98 |
| at 48 h | 4531 (2538) | 4598 (2022) | 3931 (1671) | 4187 (1929) | | | |
| at 72 h | 4130 (1804) | 3741 (1961) | 3258 (1318) | 3577 (1440) | | | |
| Fluid balance, mL | | | | | | | |
| at 24 h | 3159 (2993) | 4506 (3880) | 2699 (2238) | 3221 (2355) | .005 | .31 | .46 |
| at 48 h | 2229 (2226) | 2655 (2268) | 2450 (2016) | 2023 (2468) | | | |
| at 72 h | 1979 (1435) | 1641 (2490) | 827 (2747) | 1526 (2974) | | | |
| Norepinephrine, µg/kg/min | | | | | | | |
| at baseline | 0.50 (0.55) | 0.48 (0.63) | 0.29 (0.21) | 0.24 (0.34) | .15 | .06 | .13 |
| at 24 h | 0.21 (0.39) | 0.34 (0.62) | 0.19 (0.24) | 0.17 (0.47) | | | |
| at 48 h | 0.11 (0.26) | 0.15 (0.42) | 0.13 (0.22) | 0.09 (0.28) | | | |
| at 72 h | 0.10 (0.23) | 0.08 (0.25) | 0.01 (0.10) | 0 (0.11) | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $P_aO_2/F_IO_2$, | | | | | | | |
| at baseline | 178 (91) | 170 (123) | 189 (98) | 1188 (110) | .81 | .77 | .29 |
| at 24 h | 218 (97) | 245 (125) | 210 (58) | 212 (83) | | | |
| at 48 h | 240(90) | 225 (93) | 237 (104) | 204 (66) | | | |
| at 72 h | 213 (90) | 239 (102) | 272 (95) | 209 (67) | | | |
| PEEP, cm $H_2O$ | | | | | | | |
| at baseline | 13 (6) | 12 (6) | 10 (7) | 12 (6) | .72 | .40 | .48 |
| at 24 h | 12 (5) | 12 (4) | 12 (7) | 12 (5) | | | |
| at 48 h | 10 (6) | 12 (6) | 10 (7) | 12 (5) | | | |
| at 72 h | 10 (6) | 10 (6) | 8 (6) | 11 (6) | | | |
| Lung injury score | | | | | | | |
| at baseline | 2.4 (1.0) | 2.5 (1.0) | 1.9 (1.0) | 2.2 (1.0) | .15 | .60 | .42 |
| at 24 h | 2.0 (1.0) | 2.0 (1.0) | 1.7 (1.0) | 2.0 (1.0) | | | |
| at 48 h | 1.9 (1.0) | 2.0 (1.0) | 1.5 (1.0) | 2.0 (1.0) | | | |
| at 72 h | 1.7 (1.0) | 1.7 (1.0) | 1.0 (1.0) | 1.7 (1.0) | | | |

Median (interquartile range) *PAC* Pulmonary Artery Catheter, *TPTD* Transpulmonary Thermodilution, *CVP* central venous pressure, *MAP* mean arterial pressure, *CI* cardiac index, $S_{(c)v}O_2$ central or mixed venous $O_2$ saturation, $P_aO_2$ partial pressure in arterial blood of $O_2$, $F_IO_2$ inspiratory $O_2$ fraction, *PEEP* positive end-expiratory pressure, *U* underlying condition, *M* monitoring arm, *U*M* interaction.

## Discussion

As far as we know, this is the first prospective randomized clinical trial of TPTD versus PAC using predefined algorithms recommending upper limits for fluid loading and guiding hemodynamic management of critically ill patients with shock of various etiologies.

The main finding of our study is that the major primary end point, VFDs, did not differ among monitoring techniques. Also, the total number of ventilation days (including all patients) and length of stay in the ICU and hospital did not differ between TPTD and PAC. Approximately 50% of patients had 0 VFDs because of early death before day 28. Although our patients had higher mortality rates than in other reports[5], disease severities were also higher. It might be suggested that, in retrospect, this study was underpowered for detecting a difference in VFDs as a result of relatively high 28-day mortality and resultant low VFDs and high range. In any case, monitoring groups of the study did not differ with respect to 28-day and hospital mortality, which is in line with the absence of a demonstrated survival benefit of many hemodynamic monitoring tools[25]. The current study was not powered to demonstrate such effect,

although it was large enough to show an expected higher mortality in septic than in nonseptic shock patients.

The trial was conceived with the idea that volume monitoring may limit potentially harmful pulmonary fluid overloading that may occur with pressure-guided management. In this hypothesis, we thus favored goal-directed and thus individualized therapy over fixed restricted fluid regimens, as argued before[6,8-10,13,14]. However, by defining upper limits for fluid administration of both volumes and pressures, the ultimate fluid infusions and balances (after 24 hrs) were roughly similar between the monitoring groups. Nevertheless, pulmonary fluid overloading could likely be prevented by using either EVLW/GEDVI or PAOP, because the EVLW/PAOP, which were elevated at baseline, decreased in time despite fluid loading. This conforms to our earlier observations that fluid loading in the steep part of the cardiac function curve does not aggravate or induce pulmonary edema both in septic and nonseptic patients[17]. However, patients with nonseptic shock had more days on the ventilator and longer length of stay when they were monitored by TPTD, whereas this was not the case in septic shock. We cannot exclude that fluid restriction (with an upper limit of EVLW ≥7 rather than the 10 mL/kg predicted body weight in the current study) might have resulted in less prolonged ventilation in these patients, as suggested before[1]. The difference in study results according to etiology may be attributable, in part, to greater cardiovascular comorbidity in the nonseptic shock patients, suggesting that the upper limits of GEDVI and EVLW for fluid administration may have been too high and interfered with weaning of the ventilator through intermittent hydrostatic pulmonary edema[26]. Indeed, the GEDVI was higher in nonseptic than septic shock patients, at similar CI, suggesting diminished cardiac performance in the former. Filling volumes may be superior to pressures for assessing cardiac preload and predicting fluid responsiveness in patients with sepsis and relatively normal cardiac function, whereas pressures may be superior in postsurgical patients with relatively poor systolic cardiac function[11,21,22]. This may have contributed to the different effect of monitoring techniques between underlying conditions. Nevertheless, the course of EVLW did not differ between septic and nonseptic shock patients, but the frequency of acute respiratory distress syndrome was much higher in septic shock so that hydrostatic pulmonary edema may have been more frequent in patients with nonseptic shock.

Finally, incorporation EVLW or lung injury score at 72 hrs abrogated the association between monitoring by TPTD and prolonged mechanical ventilation in nonseptic shock patients, suggesting that monitoring by TPTD resulted in a too high EVLW in nonseptic patients to promote weaning. Thus, our study confirms that septic shock patients have different cardiorespiratory physiology than nonseptic shock patients and that combining these conditions for the evaluation of protocols for hemodynamic management may conceal differences. This justifies our stratified randomization and analysis. That our results are not in line with the shortened duration of mechanical ventilation during volume-guided treatment of cardiac surgery patients[14] can be explained by a difference in inclusion criteria requiring the presence of shock and thus greater severity of illness and fluid requirements accompanied by longer stays and higher mortality of our nonseptic patients. Furthermore, we used higher cutoff values for GEDVI (850 versus 800 mL/m$^2$).

EVLW/GEDVI monitoring by TPTD was associated with a greater increase in CI and $ScvO_2$ in time with a tendency for a more rapid decrease in vasopressor requirements. This was probably related to a greater 24-hr fluid balance with TPTD than with PAC in agreement with the literature[3,14]. The greater 24-hr fluid balance in turn might be explained by the fact that upper limits for fluid administration were less often met in the TPTD than in the PAC group. Indeed, fluid infusion inversely related to PAOP in the PAC and GEDVI in the TPTD group, so that these preload indices were indeed used to help dosing fluids. Otherwise, the opposing course of GEDVI and PAOP and CI over days may imply an increase in cardiac function in many patients, possibly because of transient myocardial stunning in cardiovascular surgery and amelioration of myocardial depression in septic shock patients, thereby contributing to less vasopressor requirements over days. In our study, the course of lactate and organ failure did, however, not differ between the monitoring groups, so that the increase in CI and $ScvO_2$/$SvO_2$ suggesting increased tissue oxygenation, claimed to be associated with improved survival in previous studies on septic shock[6-8,10,17] and in nonseptic surgical patients[8,13,14] probably did not benefit organ oxygenation or function. Our results agree with data obtained in a nonrandomized study after cardiac surgery[14] and with observations involving a mixed population[3], suggesting that volume monitoring may result in greater fluid and less vasopressor requirements than standard monitoring.

Our study has advantages compared with other studies by its prospective, two-center, and randomized nature. A limitation of this study is its relatively small size. The baseline characteristics were largely similar among monitoring groups, except for a lower $SvO_2$ in the PAC compared with the $ScvO_2$ in the TPTD group, which is in line with the well-known differences among the sampling sites[27,28]. Also, using dynamic indices of preload responsiveness generated by the PiCCO technique such as stroke volume variation or pulse pressure variation may be valuable for guiding fluid therapy, but these indices are strongly dependent on heart rhythm, full ventilatory support, and settings and their use was therefore not considered for the current study. With monitoring by TPTD, more protocol nonadherence for fluid loading occurred, particularly in nonseptic shock, but this did not affect the results, because the number of patients with nonadherence was not increased and results did not change after eliminating those with nonadherence. We finally cannot exclude that the relatively high upper limits for indicators of cardiac preload and pulmonary edema we used may need refinement in the future, particularly for nonseptic shock.

## Conclusions

This prospective, two-center, randomized clinical trial suggests that fluid resuscitation and hemodynamic management guided by TPTD versus PAC monitoring, using algorithms with predefined upper limits for fluid loading, results in similar VFDs and mortality in patients with septic or nonseptic shock while safeguarding resuscitation.

## Acknowledgements

The authors thank Erna Alberts, Ingrid van den Hul, Ronald Driessen, Jan Peppink, and the entire ICU staff of the two participating centers for their extensive support.

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## Letters to the editor

### Results of questionable management protocols are inherently questionable

Sir,

We read with interest the paper[1] by Trof et al. published in a recent issue of this journal, which concluded that hemodynamic management in nonseptic shock guided by the PiCCO resulted in more days on mechanical ventilation and ICU length of stay compared with a pulmonary artery catheter (PAC) algorithm, and that this difference may be attributed to a more positive fluid balance with use of transpulmonary thermodilution. The authors merit praise for conducting a randomized outcome study, which is a challenging task. However, the interpretation of the results of this study is not simple and should be done with caution. The authors often state that they have compared two hemodynamic monitoring devices, the PiCCO and the PAC, while in effect, this study compared two very different management protocols (volume *vs.* pressure guided), which employed some questionable end-points. Because of this major limitation, it may well be that opposite results could have been obtained if different endpoints were chosen. For example, the algorithm chosen for patients managed with the PiCCO uses extravascular lung water (EVLW) as the first-line variable for deciding whether to infuse fluid in septic and non-septic shock, which is quite unusual. Moreover, the authors considered that fluid loading was mandatory if EVLW was <10 ml/kg whether preload responsiveness was a present or not. Regrettably, preload responsiveness was not assessed in this study, the reason given by the authors being that pulse pressure variation and/or stroke volume variation could not be used for assessing preload responsiveness in this patient population. The authors should be reminded however, that alternatives to these variability indices have been developed[2] and can easily be used with the PiCCO system. What we find to be an even more significant flaw in the aforementioned algorithm is that patients with high lung water (EVLW ≥10 ml/kg) received fluid loading when the global diastolic volume index (GEDVI) was below 850 mL/m$^2$. No clear reason was given for choosing such

a threshold value, which, at best, is the highest GEDVI value that can be considered "normal". It seems therefore, that this protocol has led to the administration of fluids in patients who would not have received them in "real world" conditions. This is further supported by the fact that, at baseline, 46% of patients of the pulmonary artery catheter group had already reached the upper limit of fluid resuscitation (PAOP ≥18 mmHg) compared with only 25% of the patients of the PiCCO group who have reached the respective limits (GEDVI ≥850 ml/m$^2$ plus EVLW ≥10 ml/kg). This finding strongly suggests that the results of this study and the differences found in outcome were a result of the arbitrary (and questionable) end-points chosen for each protocol and not the monitoring technology that was used. What can be learned from this study is simply that fluid administration in patients with high lung water in order to achieve higher-than-normal preload values is associated with worse outcome.

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## Authors reply

We appreciate the comments on our paper[1] by Teboul, Monnet and Perel, participating in the advisory board of the manufacturer of the PiCCO device, yielding variables which we compared to those derived from a pulmonary artery catheter (PAC), in guiding

treatment of critically ill patients with septic or non-septic shock. First, the authors suggest that the hemodynamic management protocols that we compared employed questionable end-points which may explain the somewhat longer need for mechanical ventilation in non-septic (in contrast to septic) patients treated as guided by PiCCO (transpulmonary thermodilution) rather than by PAC (pressure and right-sided thermodilution) based algorithms, and they suggest that opposite results had been obtained if different end-points had been chosen. We must emphasize that we did not conduct a fluid resuscitation study. The purpose of our study was to find out whether the risk of fluid overloading can be diminished if upper limits of EVLW and GEDVI are taken into account to limit fluid loading, when otherwise indicated, compared to a strategy limited by pulmonary arterial occlusion pressure (PAOP) obtained via a PAC, while safeguarding adequate resuscitation. The latter was certainly the case for the PiCCO group (greater increase in cardiac index and venous oxygenation and more rapid tapering of vasoconstrictors suggestive of shock reversal than with PAC). To this end, we defined upper limits of each of these parameters, which, again, were not taken as targets but as limits. We only gave fluids in these shock patients, when clinically indicated on the basis of the criteria mentioned in the paper (including but not limited to hypotension, low venous oxygenation, hyperlactatemia, oliguria) and did not apply any described predictors of fluid responsiveness in a formal manner, since patients in shock can be expected to be in need of fluid and to be, as volunteers, often fluid responsive, at least initially. Moreover, many indicators of fluid responsiveness remain highly controversial in clinical practice, the use of these indicators have not been proven to individualize (and restrict) fluid management resulting in better outcomes and less ventilator requirements (issues of safety and efficacy), and some of them even have relative contraindications, such as passive leg raising that may be less practical in patients with femoral artery catheters for renal replacement therapy, etc[2]. Evaluating their patient-centered benefit would require a different study. In any case, patients in our study were ventilated with tidal volumes mostly below 8 ml/kg, often in a pressure support modus, and at least 10% in the PiCCO group had atrial fibrillation or other rhythm disturbances precluding meaningful interpretation of dynamic indices derived from (ventilator-induced) variations in arterial blood pressure[2]. Moreover, fluid administration with the PiCCO algorithm was not greater, even on the first day, than

in the PAC group, although fluid balance was, unexpectedly, somewhat higher. The EVLW declined similarly in both septic and non-septic patients in the PiCCO group in the course of shock treatment, and cardiac index indeed increased upon fluids (in the first day of PiCCO monitoring), confirming our previous observations[3] that, regardless of initial EVLW, patients increasing their cardiac index with fluid administration mostly do not increase their EVLW. In non-septic patients, the number reaching upper limits of PAOP and EVLW/GEDVI in the two arms of the study, respectively, was 35 and 27% (not different), respectively, suggesting equal chances for limiting fluids. Hence, the suggestion that these patients had received fluids in an unrealistic manner is questionable, as well as the suggestion that this may have increased their EVLW, which is simply not true. Our study thus reflects the real life practice of fluid resuscitation. This is not to say that if we would have chosen a lower EVLW limit, as explained in the discussion, a more rapid resolution of pulmonary edema, at the expensive of more (rather than less, as in the current study) vasopressor treatment, would have resulted in more rapid (rather than retarded) liberation from mechanical ventilation in non-septic shock patients. We therefore intend to repeat the study at a lower EVLW upper limit. Otherwise the EVLW of 10 ml/kg was chosen since this limit has been shown to be associated with development of clinically manifest pulmonary edema and has been used before[4]. The less different effect of PiCCO vs. PAC monitoring in septic shock patients again can be explained, among others, by their greater propensity for non-cardiogenic pulmonary edema that is less rapidly cleared as cardiogenic edema. The latter presumably predominated over non-cardiogenic edema in our non-septic patients with cardiac premorbidity, and possibly recurred in the course of weaning when the latter were not 'dry' enough, explaining the difference in duration of ventilation between the monitoring groups. Conversely, the relatively high upper limit of GEDVI we have chosen, based upon our own observations as well as other studies, does not yet completely exclude (particularly in septic shock) an increase in CI with fluid loading when needed in the treatment of shock[5-8]. Again, it may well turn out in a future study that a lower upper limit would result in a more restricted fluid regimen, of which the safety and efficacy for critically ill patients with shock remains to be proven. In any case, our study suggests that the evaluated PiCCO algorithm is safe and non-inferior to PAC-guided management (with similar mortality as a secondary

endpoint), although in need of refinement to enhance (rather than delay) resolving of cardiogenic edema and liberation from mechanical ventilation in non-septic shock patients.

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## Hemodynamic treatment algorithms should follow physiology – or they fail to improve outcome

Dear Sir,

Trof et al. are to be congratulated for having performed this trial on the use of extravascular lung water index (EVLWI) in critically ill patients. Contradictory to earlier work, they could not find any significant differences in outcome between patients, in which hemodynamic management was guided by an algorithm based on transpulmonary thermodilution (TPTD) leading to a more positive fluid balance, compared to those guided by PAOP[1,2].

In the TPTD group, an EVLWI < 10ml/kg was used as primary criterion to initiate a fluid challenge. Although the suggested threshold of EVLWI is reasonable for the detection of pulmonary edema and acute lung injury[3], it does not indicate, if a patient is fluid responsive or not. It is simply not understandable, why this parameter, serving as an indicator for exceeding vascular capacity in the lungs should serve as an entrance decision for fluid loading. In other words, an EVLWI < 10 ml/kg cannot initiate, only an EVLWI> 10 ml/kg can lead to an abdiction of fluid loading. This is a fundamental, conceptional flaw of this investigation, since unnecessary fluid boluses seem to increase morbidity and mortality[3-5]. Further, when stepping down the TPTD algorithm for patients with an already elevated EVLWI, the decision for fluid loading (in spite of this elevated EVLWI!) was determined by GEDVI. The authors predetermined a GEDVI < 850ml/m² as a sign for fluid responsiveness. This second major criterion for fluid loading needs to be discussed thoroughly. First, predetermined and arbitrarily defined ranges of static parameters of preload, i.e. CVP, PAOP or GEDVI will always be insufficient to determine fluid responsiveness in a heterogeneous patient population – which is by nature the group of critically ill patients[5,6]. The reason is simple – because of interindividual heterogeneity of "optimal" preload values, which are already seen in hemodynamically compensated patients: "Normal" GEDVI values are dependent not only on patient anthropomorphy but also age and gender[7]. A recent data analysis in critically ill patients underlined this heterogeneity[8]. Second, if, despite the knowledge of the insufficiency of generalized target values for a static preload parameter, for practical reasons a target zone is chosen for patients already showing

signs of developing pulmonary edema (EVLWI>10 ml/kg), then this target zone should surely be based on the lower margin of published clinical findings. But the here chosen target of <= 850 ml/m² is far above a) the recommended target values given by the manufacturers of TPTD devices (lower margin 640 ml/m²), b) the median GEDVI values of cardiocirculatory healthy patients at discharge from the ICU (693ml/m2), and c) the median values in septic (788 ml/m²) and surgical ICU patients (694 ml/m²)[7,8]. Thus, not to determine fluid responsiveness, but instead to use GEDVI with a clearly too high target in patients already on the edge of pulmonary edema is simply not comprehensible. The result: additional fluid boluses (TPTD: 242; PAC: 175) resulting in a higher fluid balance. Further, looking at the baseline characteristics, both groups had higher values of PAOP and GEDVI as normally seen. The sepsis group had even higher PAOP compared to the non-sepsis group (18 vs. 12 mmHg), and S(c)vO2 was normal indicating that these patients were not in need of extra fluids. The authors claim that 152/175 (PAC) and 209/242 (TPTD) fluid challenges in the septic group were identified post factum as correct, since those resulted in an increase in cardiac index of >10%. But a 10% variation is in the range of the precision of thermodilution measurements[9]. So this claimed 10% increase may have been even no increase at all. With the accepted threshold of 15%, the number of correct fluid challenges would have been much less.

In summary, a fundamental mistake in this study was the misuse of EVLWI. EVLWI can be used as a safety guide during fluid therapy[10], as a prognostic factor for ALI[3], or to guide treatment decisions in the presence of the therapeutic conflict "low preload, wet lungs", but certainly not as a primary trigger for fluid loading. No single parameter can change outcome. This can only be achieved by a good treatment strategy using the right parameters. The present study is an excellent counterexample for this.

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## Authors reply

We appreciate the comments on our paper[1] by Malbrain and Reuter, participating in the medical advisory board of the manufacturer of the transpulmonary thermodilution device (PiCCO™, Pulsion Medical Systems, Munich, Germany). We have received similar comments from a similar direction before, to which we recently replied, in this journal[2].

First the authors comment that using a threshold for 15% (instead of 10%) increase in cardiac index (CI) for defining fluid responsiveness would have decreased the number of correct fluid challenges suggesting the administration of an unnecessary amount of fluids. A 15% cutoff however can be considered as arbitrary, and largely determined by statistical (measurement error) rather than clinical considerations[3]. A 10% threshold is more commonly used than a 15% threshold[4,5], and it is completely unclear what the appropriate level to benefit patients is.

Second, the authors erroneously assume (as others have done before[2], that we used the extravascular lung water (EVLW) and the global end-diastolic volume index (GEDVI) parameters as indicators of fluid responsiveness and targets for fluid administration, which was not done, as explained previously[2]. The authors should read the algorithms that go with this study clearly and appropriately defining fluid responsiveness by CI increases. The relatively higher pulmonary artery occlusion pressure (PAOP) in sepsis than in non-sepsis can be explained by a higher PEEP level, among others. The relatively high upper limit of GEDVI we have chosen, based upon our own observations as well as other studies (by the authors of the letter), does not yet completely exclude (particularly in septic shock) an increase in CI with fluid loading when needed in the treatment of shock[6-9]. Moreover, the extravascular lung water (EVLW) declined similarly in both septic and non-septic patients in the PiCCO group in the course of shock treatment, and CI indeed increased upon fluids (in the first day of PiCCO monitoring), confirming our previous observations[10] that, regardless of initial EVLW, patients increasing their CI with fluid administration mostly do not increase their EVLW. Again, if we would have chosen a lower EVLW limit for safe fluid administration in case it is needed and the patient is predicted to be fluid responsive, as explained in the discussion, a more rapid resolution of pulmonary edema, at the expensive of more (rather than less, as in the current study) vasopressor treatment, would have resulted in more rapid (rather than retarded) liberation from mechanical ventilation in non-septic shock patients. Again, the EVLW was thus used and should be used as an upper safety limit for fluid loading when indicated, as correctly suggested by the authors of the letter, a statement with which we fully agree.



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## Transpulmonary thermodilution: The jury is out

To the Editor,

We read "Volume-limited versus pressure-limited hemodynamic management in septic and nonseptic shock" by Trof et al. with great interest. Early resuscitation of patients with shock is widely discussed and differing opinions have led to a large variation in practice patterns among clinicians. Recent data suggesting that overzealous fluid resuscitation may lead to poor outcomes has intensified the debate of this topic[1-3]. Trof et al. provide additional data on which to refine our strategies.

The study provides us with a comparison between a tool which has been largely abandoned (the PA catheter) and a tool which has not been widely adopted (Transpulmonary thermodilution or TPTD) within a heterogeneous group of critically ill patients.

The heterogeneous population is particularly troublesome as this was not only a comparison of specific medical devices, but also of the algorithms dictating care. As the authors suggest in their discussion, the use of these algorithms (particularly the TPTD algorithm) may not be appropriate for patients with any type of shock. The study was not powered to show improvement in patients with septic shock and the algorithm was not designed to care fro patients with other types of shock.

The more commonly used goals for early resuscitation (CVP, MAP, UOP) were included in both arms of the trial, but a control arm with an algorithm based on these routine measurements was not included. Thus the trial does not clarify whether or not PA catheter or TPTD based algorithms are superior to a noninvasive approach.

A third criticism of the trial is the management of patients following resolution of shock. Details regarding volume management after resolution of shock are scarce and may substantially alter the outcomes. A conservative fluid management strategy is recommended in most patients after resolution of shock and it is not clear that this strategy was maintained in either arm of this study.

In summary, we feel that the study by Trof et al. does not provide support for widespread use of TPTD in patients with shock. However, it certainly does not support abandonment of the tool. We anticipate further studies with refined algorithms in more homogenous populations of shock patients will help define the role of advanced hemodynamic monitoring in patients with shock.

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## Authors reply

We appreciate the comments on our manuscript[1] by Hooper and Marik. In their commentary they discuss, based on the results of our study, whether the use of the transpulmonary thermodilution technique (TPTD) in patients with shock may be beneficial or not.

First, we agree with the authors that overzealous fluid resuscitation may lead to poor outcomes. That is why we conducted a study yielding algorithms defining upper limits of fluid loading, in which we compared upper limits of pressures (pulmonary artery occlusion pressure, PAOP) by the pulmonary artery catheter (PAC) versus volumes (extravascular lung water, EVLW / global end-diastolic volume, GEDVI) by the TPTD technique. We hypothesized that incorporation of extravascular lung water in the TPTD algorithm (versus the PAC algorithm) would limit or prevent fluid overloading, translating into an increase in ventilator-free days. A cut off of 10 ml/kg for EVLW was chosen because exceeding this limit has been shown to be associated with development of clinically manifest pulmonary edema and has been used before[2]. Since hemodynamic management and outcome may differ among shock etiologies[3-6], we stratified patients into septic and non-septic shock. The authors however suggest that the heterogeneous population is particularly troublesome as this study was not

only a comparison of specific medical devices, but also of the algorithms dictating care. In retrospect, we have to admit that different algorithms for septic versus nonseptic shock patients would have been better, since our results demonstrated differences between these groups, to the detriment of the TPTD monitored nonseptic shock patients. However by using the same algorithm for both groups, our study revealed and confirmed the differences in cardiorespiratory (patho)physiology between septic and nonseptic shock, which seems to be an important observation. Future studies using the TPTD technique should take this observation into account; indeed, we intend to repeat the study at lower EVLW upper limits in patients with nonseptic shock.

Second, the authors suggest that incorporating a control arm in the original study protocol may have clarified whether or not "device-based algorithms" are superior to a non-invasive approach. We agree that this conception is quite interesting since other, less invasive, parameters such as lactate clearance may have additional benefit for resuscitation purposes[7]. However, the goal of our study was to compare upper limits of pressures (PAOP) by PAC versus volumes (EVLW/GEDVI) by TPTD, hypothesizing that a volume-based algorithm would be superior to a pressure-based algorithm in preventing fluid overloading.

Third, the authors question whether a conservative fluid management strategy was applied after resolution of shock in either arm of the study. Since our study protocol was only directive during the first 72 hours after inclusion we did not focus on a conservative fluid management approach after shock resolution. Fluid management after 72 hours occurred at the discretion of the attending physician. However, fluid balances in all groups of patients were increasingly less positive (table 3 supplemental digital content) during three consecutive days, suggesting a well considered fluid management strategy. Nevertheless, as recently stated in our reply to Teboul et al.[8], it may well turn out in a future study that a lower upper limit of EVLW would result in a more restricted fluid regimen, of which the safety and efficacy for critically ill patients with shock remains to be proven. In any case, our study suggests that the evaluated TPTD algorithm is safe and non-inferior to PAC-guided management (with similar mortality as a secondary endpoint), although in need of refinement to enhance (rather than delay) resolving of cardiogenic edema and liberation from mechanical ventilation in non-septic shock patients.

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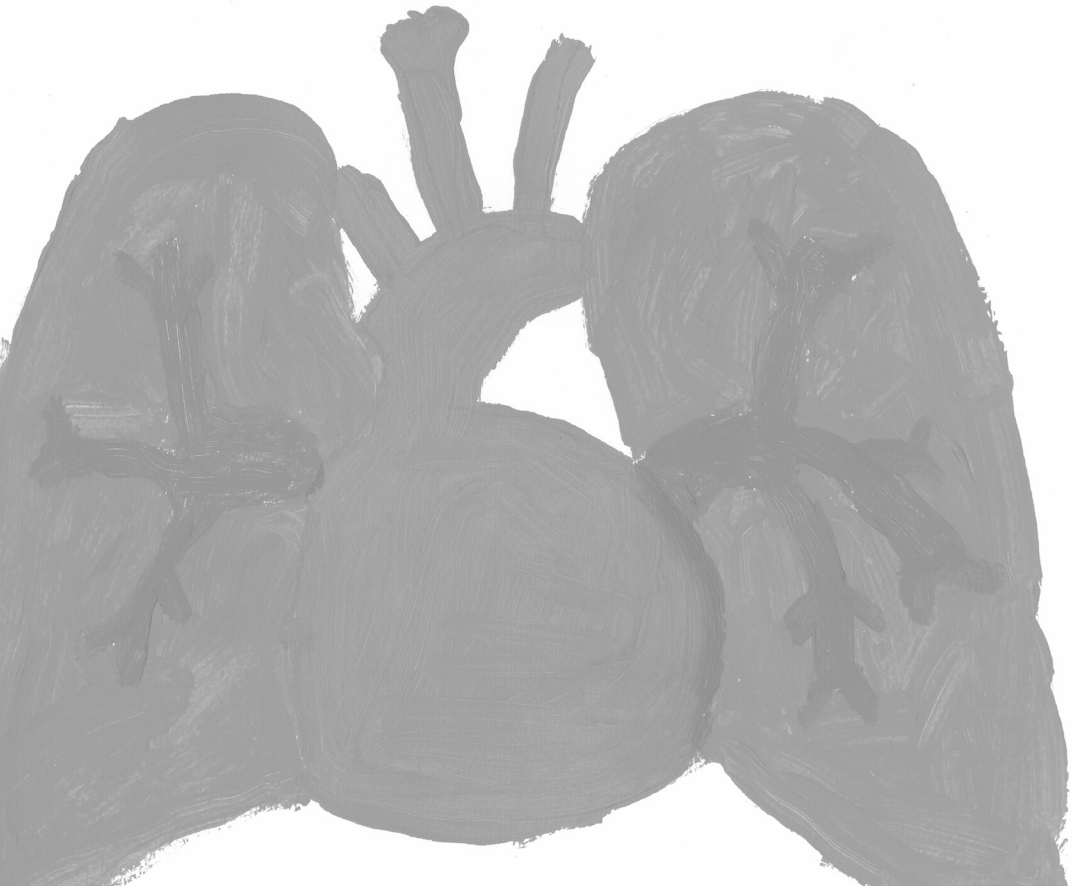
# 10

## 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.

**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.

## 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].

**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

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.

## 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.

**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 $S_{Vo2}$ and their interaction), and third, correct application of the values obtained[51].

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.

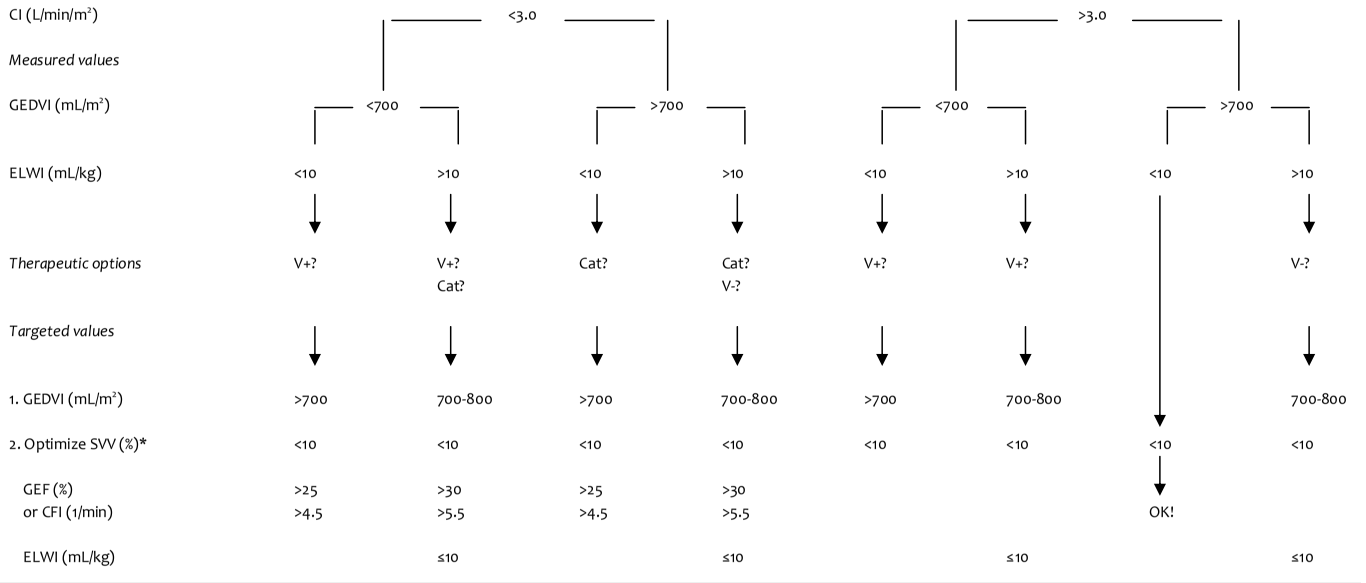
In this thesis we focused on the value of the PAC derived filling pressures versus transpulmonary dilution derived filling volumes because of potential diagnostic and therapeutic implications, in patients with different disease etiologies. Our data confirm the concept that disease etiology is relevant, 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.

**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 loading, *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.



**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



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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**PART I**

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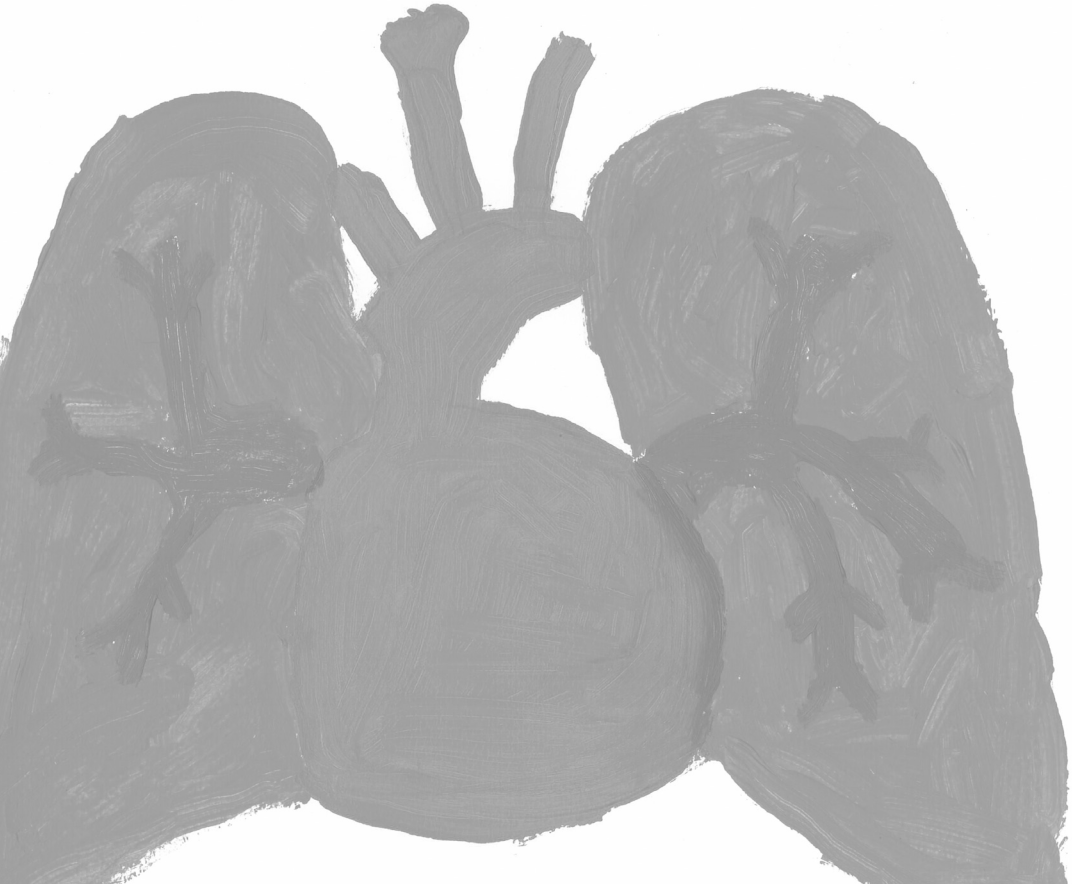
# 11

## Nederlandse samenvatting



## Samenvatting voor niet-ingewijden

### Inleiding

Het doel van deze samenvatting is om niet-ingewijden in kennis te stellen van de inhoud van dit proefschrift. De titel van het proefschrift is "optimizing fluid management in critically ill patients", ofwel vrij vertaald "Het optimaliseren van vloeistof therapie bij ernstig zieke patiënten".

Ernstig zieke patiënten worden doorgaans op de Intensive Care (IC) opgenomen omdat er sprake is van een bedreiging van een of meerdere vitale functies zoals de bloedsomloop, ademhaling en/of bewustzijn, ten gevolge van een onderliggende ziekte, zoals een ernstige infectie (sepsis), of na een ingrijpende operatie zoals na hartchirurgie. De meeste patiënten die opgenomen worden op de Intensive Care hebben veelal te maken met een bedreiging van het in standhouden van de bloedsomloop, dit meestal ten gevolge van een absoluut of relatief vochttekort (hypovolemie). Dit uit zich meestal in een verlaagde bloeddruk waarbij de afgifte van zuurstof aan de weefsels en cellen tekort kan schieten, dit wordt circulatoire shock genoemd. Indien er binnen afzienbare tijd geen herstel optreedt dan zal de kans op progressief orgaanfalen en daarmee de sterftekans aanzienlijk toenemen. Het herstellen en het behouden van een effectief circulerend volume is dan ook één van de belangrijkste initiële doelen in de Intensive Care geneeskunde.

Het toedienen van artificiële vloeistoffen vormt de hoeksteen van de behandeling van circulatoire shock. Het doel van het toedienen van vloeistoffen is dat door een toegenomen voorbelasting van het hart (preload) en hartminuutvolume (cardiac output) de bloeddruk zal stijgen waardoor getracht wordt de doorbloeding (perfusie) van de organen en daarmee het zuurstoftransport te waarborgen. Indien namelijk te weinig vloeistof wordt gegeven bestaat er een risico op een aanhoudend perfusietekort van de organen, leidende tot orgaandysfunctie en uiteindelijk orgaanfalen. Echter, indien teveel vloeistof wordt toegediend neemt het risico op overvulling toe met als gevolg het ontstaan van vocht in de longen (longoedeem) en in andere organen; hierdoor kan de toestand van de patiënt verslechteren waardoor de beademingsduur en de kans op gerelateerde complicaties kan toenemen. Om te voorkomen dat een perfusietekort persisteert of juist overvulling kan ontstaan, zou het bewaken (monitoren) van vloeistoftherapie uitkomst kunnen bieden.

In dit proefschrift staan twee aspecten van het "optimaliseren van vloeistoftherapie" centraal. Ten eerste het soort vloeistof en ten tweede de wijze waarop de effectiviteit van vloeistoftherapie bewaakt zou kunnen worden (hemodynamisch monitoren).

In het eerste gedeelte van het proefschrift wordt nader ingegaan op het soort vloeistof waarbij zogenaamde colloïdale vloeistoffen en kristalloïde vloeistoffen met elkaar vergeleken worden met betrekking tot enerzijds de effecten op het hartminuutvolume (hemodynamische effecten) en anderzijds eventueel nadelige bijwerkingen.

In het tweede gedeelte van het proefschrift zal nader worden ingegaan op het monitoren van vloeistoftherapie, waarbij twee monitoringtechnieken centraal staan en met elkaar vergeleken worden; enerzijds de arteria pulmonalis katheter (PAC) en anderzijds de transpulmonale (thermo)dilutie techniek (TPTD). Beide technieken zullen bestudeerd worden met betrekking tot de behandeling van hypovolemie bij patiënten met verschillende ziektebeelden (sepsis en non-sepsis). In een aantal studies zal tevens onderzocht worden of de (ziekte gerelateerde) hartfunctie van invloed is op de toepasbaarheid van vullingsdrukken versus vullingsvolumina.

## DEEL I
## Vloeistoffen

Er zijn verschillende soorten artificiële vloeistoffen beschikbaar om het bloedplasmavolume te doen toenemen. Deze soorten kunnen grofweg worden ingedeeld in kristalloïde en colloïdale vloeistoffen. De meest gebruikte kristalloïde vloeistoffen zijn isotoon zout (NaCl 0,9%) en Ringer's Lactaat. Een nadeel van kristalloïde vloeistoffen is dat het volume expanderend effect (toename van het bloedplasmavolume) van betrekkelijk korte duur is door snelle diffusie vanuit de bloedbaan via de celmembraan naar de weefsels. Slechts 20-25% van de toegediende hoeveelheid kristalloïde vloeistoffen blijft behouden voor (tijdelijke) volume expansie. Colloïdale vloeistoffen bevatten grote moleculen die minder snel door semipermeabele membranen kunnen diffunderen dan kristalloïden. Een theoretisch voordeel is dan ook dat colloïdale vloeistoffen langer in de bloedbaan blijven waardoor het volume

expanderend effect mogelijk langer aanhoudt. Colloïdale vloeistoffen zijn in te delen in natuurlijke colloïden (humaan albumine) en synthetische colloïden (hydroxyethyl zetmeel, gelatine).

In **hoofdstuk 2** hebben we onderzocht of het toedienen van colloïdale vloeistoffen tot een grotere toename van hartminuutvolume leidt in vergelijking met kristalloïde vloeistoffen. In zowel septische als niet-septische patiënten met klinische tekenen van hypovolemie werd gedurende 90 minuten, volgens randomisatie, colloïdale of kristalloïde vloeistoffen toegediend op geleide van een vooraf vastgesteld vloeistof toedieningsprotocol. Na toediening van vloeistof werden elke 30 minuten hemodynamische parameters gemeten.

Uit onze observatie bleek dat onafhankelijk van onderliggende ziekte het hartminuutvolume een grotere stijging liet zien na toediening van een zelfde hoeveelheid colloïdale vloeistoffen vergeleken met kristalloïde vloeistoffen (12% versus 2%). De verklaring hiervoor is een grotere toename van cardiale preload na toediening van colloïdale vloeistoffen met als gevolg een sterkere toename van cardiaal slagvolume. De groter toename van cardiale preload kan verklaard worden door een sterkere toename van de colloïd osmotische druk[1] na colloïdale vloeistoftoediening, in tegenstelling tot kristalloïde vloeistoffen, waardoor waarschijnlijk een grotere toename van het plasmavolume en dus cardiale preload. Dat na toediening van colloïdale vloeistoffen de toename van de colloïd osmotische druk, cardiale preload en het hartminuutvolume even groot was onder septische als niet-septische omstandigheden - althans binnen het gemeten tijdstraject van 90 minuten - is verassend aangezien de veronderstelde toename van vaatwandlekkage (permeabiliteit) tijdens sepsis aanleiding geeft tot snellere equilibratie van geïnfundeerde vloeistoffen met het compartiment buiten de vaatwand (extravasculaire compartiment). Klaarblijkelijk is de toename van permeabiliteit hiervoor onvoldoende hoewel een tragere equilibratie niet uitgesloten is. Onze resultaten laten zien dat vergeleken met colloïdale vloeistoffen, 2-3 maal de hoeveelheid kristalloïde vloeistoffen toegediend moeten worden voor het bereiken van een zelfde toename van hartminuutvolume.



1 colloïd osmotische druk = het drukverschil dat tussen twee eiwitoplossingen (binnen- en buiten het bloedvat) van verschillende concentraties ontstaat ten gevolge van osmose.

In **hoofdstuk 3** hebben we uitgezocht wat er in de bestaande literatuur bekend is over het volume verschil (volumeratio) tussen colloïdale en kristalloïde vloeistoffen. In hoofdstuk 2 is aangetoond dat vergeleken met colloïdale vloeistoffen er 2 tot 3 keer meer kristalloïde vloeistoffen toegediend moeten worden om hetzelfde hemodynamische eindpunt te bereiken, echter hierover bestaat controverse, waarbij gesuggereerd wordt dat deze volumeratio hooguit 1:1.5 is.

Wij beoordeelden alle studies waarbij colloïdale vloeistoffen vergeleken zijn met kristalloïde vloeistoffen. Het resultaat hiervan was dat de volumeratio inderdaad 1:2-3 is, echter vooropgesteld dat dezelfde hemodynamische effecten zijn bereikt. Het verschil tussen onze observatie (1:2-3) en andere studies (1:1.5) lijkt derhalve gebaseerd te zijn op de variatie in hemodynamische eindpunten van de onderzochte studies.

In **hoofdstuk 4** zijn we ingegaan op de controverse die bestaat met betrekking tot vloeistof therapie bij patiënten met acute longbeschadiging (ALI)/ acuut respiratoir distress syndroom (ARDS). ALI/ARDS kant ontstaan bij patiënten met sepsis, na ernstig trauma of grote chirurgie. Deze ziektebeelden worden gekenmerkt door ontsteking (inflammatie) en een toegenomen lekkage/doorlaatbaarheid (permeabiliteit) van de longvaten. Deze toegenomen permeabiliteit kan leiden tot longoedeem. Het longoedeem belemmert de gaswisseling in de long waardoor zuurstoftekort en stapeling van koolzuur kan ontstaan. Toediening van vloeistof kan het longoedeem doen verergeren door lekkage vanuit de bloedvaten (extravasatie) naar het longweefsel met als gevolg dat de patiënt zijn conditie kan verslechteren. De mate van extravasatie wordt bepaald door de hydrostatische druk in de longhaarvaten (capillairen), de colloïd osmotische druk en de mate van permeabiliteit van de longcapillairen. Indien de druk in de capillairen de druk buiten de capillairen overschrijdt neemt de filtratiedruk toe waardoor toename van longoedeem kan ontstaan. Echter toediening van vloeistof bij ALI/ARDS leidt niet tot toename van oedeem indien de filtratiedruk lager is dan de druk in het longweefsel (interstitiële druk). Indien vloeistoftoediening plaats vindt tijdens hypovolemie waardoor het hartminuutvolume significant zal toenemen (vloeistofresponsiviteit), zal door een relatief lage filtratiedruk geen toename van longoedeem ontstaan, ongeacht het soort vloeistof (kristalloïden of colloïden) en ondanks een toegenomen permeabiliteit.

Indien het hartminuutvolume echter niet meer toeneemt na toediening van vloeistof neemt het risico op de vorming van longoedeem belangrijk toe. Toediening van vloeistof tijdens ALI/ARDS is geïndiceerd zolang er sprake is van orgaan hypoperfusie waarbij verondersteld wordt dat toediening van vloeistof de mate van hypoperfusie zal verminderen, echter vooropgesteld dat de patiënt vloeistofresponsief is en de pulmonale filtratiedruk de interstitiële druk in de long niet zal overschrijden tijdens vloeistoftoediening. Indien er geen sprake meer is van hypoperfusie dan zou vloeistof beperking kunnen bijdragen aan het terugdringen van longoedeem waardoor de beademingsduur verkort zou kunnen worden.

In **hoofdstuk 5** hebben we gekeken naar de veiligheid van synthetische colloïden, in het bijzonder hydroxyethyl zetmeel oplossingen (HES) bij patiënten met sepsis. We hebben ons enerzijds gefocust op data inzake de relatie tussen het gebruik van colloïden en sterfte (mortaliteit), en anderzijds op het risico op HES geïnduceerd nierfalen.

Onze resultaten lieten zien dat op basis van de beschikbare literatuur niet kan worden gesteld dat het gebruik van colloïden (versus kristalloïden) de mortaliteit negatief of positief beïnvloedt. Echter de meeste studies die zijn onderzocht waren niet gepowered op sterfte noch was mortaliteit gedefinieerd als primaire uitkomstmaat.

Het gebruik van HES oplossingen lijkt geassocieerd te zijn met een toegenomen risico op hete ontstaan van acuut nierfalen. De oorzaak hiervan is niet geheel opgehelderd, mogelijk dat grote moleculen in HES oplossingen de niertubuli doen verstoppen waardoor nierfalen kan ontstaan. Dit verklaart wellicht waarom vooral oudere generatie HES oplossingen geassocieerd zijn met acuut nierfalen; oudere generaties HES oplossingen bevatten grotere moleculen dan de huidige HES oplossingen. Het gebruik van groot moleculaire HES oplossingen dient dan ook ontmoedigd te worden. Huidige generatie HES oplossingen lijken vooralsnog niet geassocieerd te zijn met een toegenomen risico op acuut nierfalen, ook niet bij patiënten met sepsis, hoewel er wel een dosisafhankelijk effect lijkt te bestaan.

**Conclusie**

Gesteld kan worden dat toediening van colloïdale vloeistoffen (versus kristalloïden) leidt tot een grotere expansie van het plasmavolume en dientengevolge tot snellere hemodynamische optimalisatie in zowel septische als niet-septische condities. In tegenstelling tot oudere generaties HES oplossingen lijkt het gebruik van de huidige generatie HES oplossingen vooralsnog niet geassocieerd te zijn met een toegenomen risico op acuut nierfalen, vooropgesteld dat de maximaal aanbevolen dosering niet wordt overschreden.

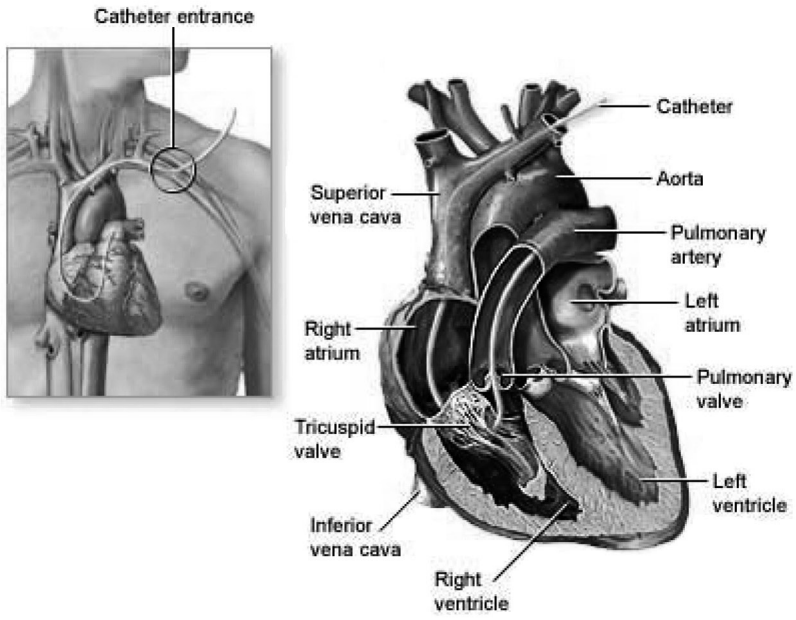
## DEEL II
## Hemodynamische monitoring van vloeistoftherapie

Het is aannemelijk dat toediening van vloeistof ten behoeve van het optimaliseren van de bloedsomloop tijdens ernstige ziekte maatwerk is. Enerzijds, toediening van te weinig vloeistof kan leiden tot een insufficiënt hartminuutvolume leidende tot een verminderd aanbod van zuurstof aan de organen (hypoperfusie). Anderzijds, toediening van teveel vloeistof kan juist leiden tot overvulling (oedeem), bijvoorbeeld in de longen, met als gevolg verdere verslechtering van orgaanfunctie, toename van beademingsduur en Intensive Care opname.

Het bewaken van vloeistof therapie gebeurt door middel van hemodynamische monitoring. In dit proefschrift zijn twee hemodynamische monitoringstechnieken nader onderzocht, te weten de arteria pulmonalis katheter (PAC) en de transpulmonale (thermo)dilutie techniek (TPTD).

De PAC techniek bestaat reeds enkele decennia en maakt gebruik van een katheter die wordt ingebracht in een grote ader (meestal in de hals of onder het sleutelbeen) en via de rechter harthelft wordt opgevoerd tot in de longslagader (figuur 1). Met deze techniek kan de druk worden bepaald in de bovenste holle ader (centraal veneuze druk, CVD), rechter hartboezem, rechter hartkamer en in de longslagader. Deze drukken worden de zogenaamde vullingdrukken genoemd. Daarnaast kan door het inspuiten van (koude) vloeistof een schatting worden gemaakt van het hartminuutvolume van de rechter harthelft. Door middel van het opblazen van een ballonnetje aan het uiteinde van de katheter stopt de flow distaal van de katheter waardoor de zogenaamde occlusie druk (PAOP) in de longslagader kan worden gemeten. Deze

occlusie druk is een surrogaat voor preload van de linker harthelft, terwijl de CVD een surrogaat is voor preload van de rechter harthelft. Een lage CVD en PAOP suggereren de mogelijkheid van preload toename en dus toename van hartminuutvolume na vloeistoftoediening, terwijl een hoge CVD en PAOP vloeistofresponsiviteit wellicht uitsluit. Deze drukken worden echter beïnvloed door de drukken die ontstaan tijdens mechanische beademing waardoor interpretatie kan worden bemoeilijkt.

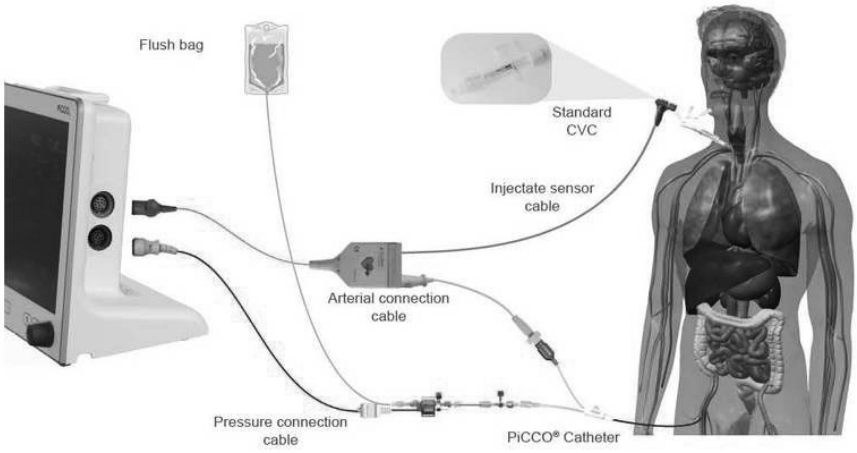



**Figuur 1.** Arteria Pulmonalis Katheter. De katheter wordt ingebracht via een centrale grote ader (catheter entrance) en via de bovenste holle ader (superior vena cava) door de rechter boezem (right atrium) door de tricuspidalis hartklep (tricuspid valve), via de rechter hartkamer (right ventricle) door de pulmonalis hartklep (pulmonary valve) in de longslagader opgevoerd (pulmonary artery).

De TPTD techniek is in de jaren 90 van de vorige eeuw ontwikkeld. Deze techniek vereist de aanwezigheid van een centraal veneuze katheter en een speciale katheter in de liesslagader. Door toediening van een zogenaamde indicator wordt door middel van subtractie (vullings)volumina berekend. Omdat geen gebruik gemaakt wordt van een katheter die door het hart opgevoerd dient te worden, wordt deze techniek als minder invasief beschouwd. Initieel werd gebruik gemaakt van een

dubbele indicator: een kleurstof indicator (indocyanine groen) en thermale indicator (koude vloeistof). Inmiddels is de dubbele indicator techniek vervangen door gebruik van alleen een thermale indicator. De thermale indicator wordt toegediend via de centraal veneuze katheter. Na toediening detecteert de katheter in de liesslagader de temperatuursverandering in de tijd (figuur 2). Een computer berekent onder andere het hartminuutvolume, het (virtuele) volume van de hartkamers als maat voor cardiale preload (globaal einddiastolisch volume, GEDV) en de mate van longoedeem (extravasculair longwater, EVLW). Door het monitoren van het EVLW kan in theorie vloeistof overbelasting worden voorkomen, een extra voordeel van deze techniek. Een ander voordeel van deze techniek is dat de gegenereerde parameters niet beïnvloed worden door mechanische beademing.

In dit gedeelte van dit proefschrift hebben we bovengenoemde monitoringstechnieken met elkaar vergeleken en onderzocht of de klinische toepasbaarheid beïnvloed wordt door onderliggende ziekte (sepsis of non-sepsis) en/of (gerelateerde) hartfunctie.




**Figuur 2.** Transpulmonale thermodilutie techniek (PiCCO™). Benodigd zijn een katheter in een centrale grote ader (standard CVC) en een katheter in de liesslagader (PiCCO® Catheter) die tevens fungeert als invasieve bloeddruk meter (pressure connection cable). Via een injectie met koude vloeistof in de centrale grote ader wordt in de katheter in de liesslagader gedetecteerd hoelang het duurt voordat de koude bolus hier arriveert. Een computer die aangesloten is op beide katheters (injectate sensor cable, arterial connection cable) berekent vervolgens het hartminuutvolume, het globaal einddiastolisch volume (GEDV) en het extravasculair longwater (EVLW).

In **hoofdstuk 6** hebben we verondersteld dat bij patiënten met een verminderde hartfunctie (systolische dysfunctie) na hart- en vaatchirurgie, vullingsdrukken (CVD en PAOP) superieur zijn aan vullingsvolumina (GEDV) voor het voorspellen van vloeistofresponsiviteit.

Hiertoe hebben we 32 patiënten onderzocht (18 na hartchirurgie, 14 na vaatchirurgie) op de Intensive Care. Deze patiënten hadden allemaal klinisch tekenen van hypovolemie. Colloïdale vloeistof werd gegeven gedurende 3 achtereenvolgende intervallen van 30 minuten op geleide van een vooraf vastgesteld algoritme gebaseerd op verandering van centraal veneuze druk. Patiënten werden onderverdeeld in twee groepen; verminderde systolische hartfunctie en normale systolisch hartfunctie. In totaal werden 32 maal 3 = 96 vloeistofstappen geëvalueerd, waarbij onderscheid werd gemaakt tussen responders (toename van hartminuutvolume na toedienen van vloeistof) en non-responders.

Uit de resultaten bleek dat de CVD voorspellende waarde had in beide groepen. Echter PAOP bleek superieur aan GEDV inzake het voorspellen van vloeistofresponsiviteit bij patiënten met systolische dysfunctie, terwijl bij patiënten met een normale systolisch functie dit juist andersom was.

Het lijkt erop dat in patiënten met systolisch dysfunctie, preload toename meer afhankelijk is van drukken dan van volumes. Derhalve kan worden gesuggereerd dat bij patiënten na hart- of vaatchirurgie met een verminderde systolische hartfunctie, het gebruik van vullingsdrukken gegenereerd door de arteria pulmonalis katheter wellicht de voorkeur heeft boven het gebruik van volume parameters zoals de TPTD techniek.

In **hoofdstuk 7** hebben we ons gericht op patiënten met ernstige sepsis / septische shock[2]. Een deel van de patiënten met ernstige sepsis / septische shock ontwikkelt cardiale dysfunctie zich uitend in systolisch falen en dientengevolge verwijding (dilatatie) van de hartkamers. Gesuggereerd wordt dat deze dilatatie een adaptief mechanisme is ten behoeve van het in stand houden een hoog hartminuutvolume, hetgeen geassocieerd is met overleving. Door toepassing van de TPTD techniek kan deze cardiale dilatatie worden gereflecteerd door een verhoogd GEDV.



2 Septische shock is de ernstigste manifestatie van sepsis. Hierbij is er meestal sprake van aanhoudend lage bloeddrukken ondanks het toedienen van adequate hoeveelheden vloeistoffen waarbij het functioneren van organen ernstig bedreigd is.

Wij onderzochten of een verhoogd GEDV als uiting van cardiale dilatatie ten gevolge van systolisch dysfunctie inderdaad geassocieerd is met het in stand houden van vloeistofresponsiviteit. Hiertoe bestudeerden we 16 patiënten met ernstige sepsis/ septisch shock op de Intensive Care. Colloïdale vloeistof werd gegeven gedurende 3 achtereenvolgende intervallen van 30 minuten op geleide van een vooraf vastgesteld algoritme gebaseerd op verandering van centraal veneuze druk. Patiënten werden onderverdeeld in twee groepen; verminderde systolische hartfunctie ( 9 patiënten) en normale systolisch hartfunctie (7 patiënten). In totaal werden 16 maal 3 = 48 vloeistofstappen geëvalueerd, waarbij onderscheid werd gemaakt tussen responders (toename van hartminuutvolume na toediening van vloeistof) en non-responders.

Uit de resultaten bleek dat in de groep van patiënten met een verminderde systolisch functie basaal GEDV hoger was in de responders dan in de non-responders. Echter in de groep patiënten met een normale systolische functie was er geen verschil in basaal GEDV tussen responders en non-responders. Onze bevinding bevestigt de resultaten van ander onderzoek dat de voorspellende waarde van basaal GEDV voor vloeistofresponsiviteit imperfect is omdat deze waarde afhangt van systolisch functie.

Geconcludeerd kan worden dat bij patiënten met een sepsis geïnduceerde systolische dysfunctie en dilatatie een hoog GEDV vloeistofresponsiviteit niet uitsluit, en GEDV dus nog verder kan toenemen. Dit is belangrijk gegeven omdat in de literatuur lagere normaalwaarden of streefwaarden worden gesuggereerd.

In **hoofdstuk 8** hebben we het principe en de toepasbaarheid van door de TPTD techniek verkregen extravasculaire longwater nader beschreven. Er is aangetoond dat EVLW metingen zeer goed correleren met de goudstandaard via post mortem gravimetry in proefdieren. Klinische studies bij patiënten toont aan dat aanhoudend verhoogd EVLW sterk gecorreleerd is met sterfte. Het is derhalve aannemelijk dat EVLW-geleide (vloeistof) therapie van invloed zou kunnen zijn op beademingsduur en wellicht opnameduur op de IC.

In **hoofdstuk 9** hebben we onderzocht of het risico op vloeistof overbelasting minder groot is wanneer vloeistof management wordt bepaald aan de hand van GEDV en EVLW metingen in vergelijking met PAOP metingen met de PAC. 120 patiënten opgenomen op de Intensive Care werden gerandomiseerd en geïncludeerd waarvan 60 patiënten werden voorzien van een PAC en 60 patiënten van de TPTD techniek. Patiënten werden gestratificeerd naar onderliggende ziekte: septische shock versus non-septische shock. Gedurende een periode van 72 uur werd op basis van vooraf gedefinieerde algoritmes vloeistof toegediend. Vloeistoftoediening was toegestaan zolang bovenste limieten van PAOP, GEDV of EVLW niet waren bereikt. Primaire uitkomstmaat was beademingsvrije dagen, secondaire uitkomstmaten waren orgaanfalen en sterfte.

Uit de studie kwam naar voren dat zowel primaire als secundaire uitkomstmaten in beide groepen (PAC versus TPTD) vergelijkbaar was, maar dat TPTD monitoring geassocieerd was met langere beademingsduur en een langer verblijf op de Intensive Care een ziekenhuis in de niet-septische shock groep, doch niet in de septische shock groep. De verklaring hiervoor zou kunnen zijn dat in de non-septische groep er meer patiënten zaten met bijkomende hartziekten. Toepassing van een maximale limiet van 10 ml/kg EVLW zou in deze groep wellicht te hoog kunnen zijn waardoor er een grotere kans bestaat op het ontstaan van longoedeem, met als gevolg een langere beademingsduur. Onze resultaten lijken te bevestigen dat patiënten met septische shock een anders reageren met betrekking tot cardiorespiratoire fysiologie dan patiënten met niet-septische shock.

**Conclusie**

We mogen stellen dat de interpretatie van parameters verkregen door hemodynamische monitoring met de PAC of TPTD techniek gerelateerd dient te worden aan onderliggende ziekte en (gerelateerde) hartfunctie. De PAC faciliteert het inzichtelijk maken van de cardiale dynamiek tijdens vloeistoftherapie, met name bij patiënten met een verminderde systolische functie. De TPTD techniek daarentegen kan door de mogelijkheid van het relatief betrouwbaar schatten van de mate van het extravasculaire longwater behulpzaam zijn tijdens vloeistoftherapie bij patiënten die een verhoogd risico hebben op (toename van) longoedeem, zoals patiënten met ARDS, om schadelijke overvulling te voorkomen.

# 12

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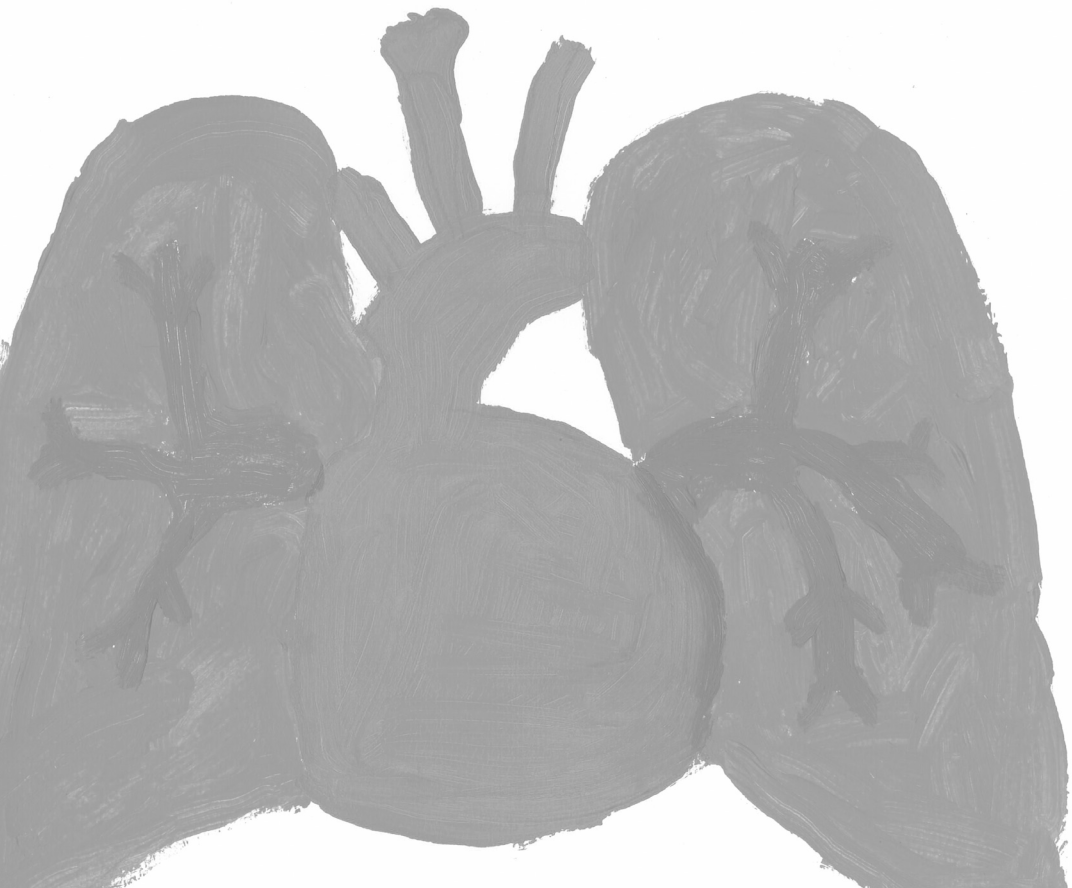
**Acknowledgments**

**Curriculum Vitae**



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## Curriculum Vitae

Ronald Jan Trof werd geboren op 21 april 1973 in Veendam, als laatste uit een gezin van 2 kinderen. Na het eindexamen VWO in 1991 aan het Wessel Gansfort College te Groningen was hij voornemens Geneeskunde te gaan studeren. Helaas moest door uitloting een andere richting worden gekozen, waarop hij Rechten ging studeren aan de Rijksuniversiteit Groningen (RUG). Doch de drang naar de medische wetenschap bleef bestaan en gelukkig kon een jaar later alsnog worden begonnen met de studie Geneeskunde, eveneens aan de RUG. Tijdens zijn studietijd was Trof zeer actief op de studenten volleybalvereniging GSVV Donitas alwaar hij enkele seizoenen op het hoogste niveau acteerde en twee jaar lang deel uit maakte van het bestuur. Na het behalen van de doctoraalbul werd gestart met de coschappen, onder andere in het Scheperziekenhuis te Emmen en het Universitair Medisch Centrum Groningen (UMCG). In 1998 werd het artsexamen afgelegd (cum laude) waarna hij begon als arts-assistent Interne Geneeskunde en Cardiologie in het Scheperziekenhuis. Al snel werd duidelijk dat hij een carrière verkoos als internist zodat hij in 2000 de overstap naar het Medisch Spectrum Twente in Enschede maakte met als doel de opleiding tot internist te gaan volgen. In 2001 werd gestart met de opleiding onder leiding van dr. Bonno Hylkema, die hem enthousiasmeerde voor de Intensive Care Geneeskunde. Via een korte terugkeer naar het UMCG begon Trof in december 2004 zijn fellowship Intensive Care Geneeskunde op de afdeling IC Volwassenen van het VUMC in Amsterdam, onder supervisie van prof.dr. Armand Girbes. Trof behaalde zijn registratie als internist-intensivist in december 2006 waarna hij qualitate qua zijn promotietraject startte bij prof.dr. Johan Groeneveld. In mei 2008 besloot Trof terug te keren naar het Medisch Spectrum Twente om Bonno Hylkema op te volgen als intensivist. Trof is getrouwd met Cathelijne Ziedses des Plantes, eveneens medisch specialist (radioloog). Zij hebben samen drie kinderen: Maryleine (2006), Quinten (2008) en Constantijn (2011).

Ronald Jan Trof was born on the 21th of April 1973 in Veendam, The Netherlands. After graduating from the Wessel Gansfort College in Groningen in 1991, he studied Dutch law at the University of Groningen for one year. In 1992 he commenced his study medicine also at the University of Groningen. He obtained his Master of Science

in medicine in 1996. Trof performed his interns at Scheper Hospital, Emmen and at University Medical Center Groningen. After obtaining his degree as Medical Doctor (cum laude) in 1998 he became a non-resident in the department of Internal Medicine at Scheper Hospital, Emmen. In 2000 he moved to Enschede where he started his residency in Internal Medicine at Medisch Spectrum Twente (dr. Bonno Hylkema). In December 2004 he started his fellowship Intensive Care at the VU Medical Center, Amsterdam, under the supervision of Prof. dr. Armand Girbes. In December 2006 he finished his fellowship and became consultant intensivist at VU Medical Center where he started his PhD on "optimizing fluid management in critically ill patients" under the supervision of Prof. dr. Johan Groenveld. In 2008 Trof moved back to Enschede to become consultant intensivist in the department of Intensive Care at Medisch Spectrum Twente where he is still working. In 2012 he married Cathelijne Ziedses des Plantes. Together they have three children: Maryleine (2006), Quinten (2008) and Constantijn (2011).

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