ADVANCED HEMODYNAMIC MONITORING IN CHILDREN

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Advanced hemodynamic monitoring in children

DOCTORAL THESIS

To obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. S.C.J.J. Kortmann,
according to the decision of the Council of Deans
to be defended in public on Thursday November 28, 2013
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by

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Table of Contents

List of abbreviations

Δ	delta
Ω	omega
95%CI	95% confidence interval
ACV	active circulation volume
ALI	acute lung injury
APCCO	arterial pressure based continuous cardiac output measurement
APV	arterial pressure variation
ARDS	adult respiratory distress syndrome
BP	blood pressure
Bpm	beats per minute
BSA	body surface area
CaO_2	arterial oxygen content
CvO_2	venous oxygen content
CBV	central blood volume
CI	cardiac index
CO	cardiac output
CO_2	carbon dioxide
CO_{TPTD}	cardiac output measured with TPTD
CO_{UFP}	cardiac output measured with UFP
CPB	cardiopulmonary bypass
CSA	cross sectional area
CVP	central venous pressure
DO_2	oxygen delivery
DSt	down slope time
EV	electrical velocimetry
EVLW	extravascular lung water
EVLWI	extravascular lung water index
$EVLWI_G$	extravascular lung water index gravimetry
$EVLWI_{TPDD}$	extravascular lung water index measured with TPDD
$EVLWI_{TPTD}$	extravascular lung water index measured with TPTD
FAP	finger arterial pressure
FiO_2	inspired oxygen fraction
FR	fluid responsiveness
GEDV	global end diastolic volume
GEDVI	global end diastolic volume index
Hb	hemoglobin concentration
HR	heart rate
IAP	intra-arterial pressure

ICG	indocyanine green
ITBV	intra thoracic blood volume
ITBVI	intra thoracic blood volume index
ITTV	intra thoracic thermal volume
LOA	limits of agreement
MAP	mean arterial pressure
mmHg	millimeters of mercury
MODS	multiple organ dysfunction syndrome
MTt	mean transit time
NIBD	non-invasive blood pressure
OER	oxygen extraction ratio
PAC	pulmonary artery catheter
PaO_2	arterial partial pressure of oxygen
PATD	pulmonary artery thermodilution
PEEP	positive end expiratory pressure
PBV	pulmonary blood volume
PCCO	pulse contour cardiac output
PDD	pulse dye densitometry
PICU	pediatric intensive care unit
PLR	passive leg raising
PPV	pulse pressure variation
PTV	pulmonary thermal volume
PvO_2	venous oxygen pressure
SAP	systolic arterial pressure
SaO_2	arterial oxygen saturation
$ScvO_2$	central venous oxygen saturation
$S\bar{v}O_2$	mixed venous oxygen saturation
SD	standard deviation
SPV	systolic pressure variation
SV	stroke volume
SVI	stroke volume index
SVV	stroke volume variation
SVR	systemic vascular resistance
TED	transesophageal Doppler ultrasound
TEDV	total end-diastolic volume
TPD	transpulmonary dilution
TPDD	transpulmonary double indicator dilution
TPLD	transpulmonary lithium dilution
TPTD	transpulmonary thermodilution using ice-cold saline
TPUD	transpulmonary ultrasound dilution

TTE	transthoracic echocardiography
UDCO	ultrasound dilution cardiac output
UFP	ultrasound transit time flow probe
VO_2	oxygen consumption
VCO_2	carbon dioxide production

Introduction

1

General introduction and outline of this thesis

General introduction

Motivation

Pediatric patients admitted to a pediatric intensive care unit (PICU) often need hemodynamic monitoring, especially if at risk for hemodynamic instability.[1] The primary aim of hemodynamic monitoring is threefold. The first aim is to detect early deterioration thereby activating a therapy "trigger", the second is to choose the most suitable therapy aimed at preserving adequate organ perfusion and oxygen supply. The third aim is to guide hemodynamic therapy towards a specific end-point, the so called goal directed approach. For hemodynamic assessment, doctors generally rely on variables obtained by physical examination and routine monitoring including capillary refill time, skin characteristics, core-peripheral temperature differences and consciousness in combination with heart rate, blood pressure and urine output. However, an apparently sufficient blood pressure does not always reflect adequate systemic blood flow. Capillary refill time and skin temperature will deviate from normal values depending on ambient temperature.[2] Heart rate and blood pressure can be influenced by factors like fever, anxiety and side effects of medication. They are indirect clinical markers of systemic blood flow and have shown to be unreliable for estimating (changes in) hemodynamic status.[3, 4]

Why is it so difficult to estimate the hemodynamic status in children? One of the explanations is that children use their compensating mechanisms masking circulatory failure. Especially young children are able to maintain a relatively normal blood pressure for a long time, despite a significant fall in cardiac output. They do so by increasing vascular resistance to extreme levels, initially in non-vital organs like the skin. By the time pediatric patients become hypotensive, organ failure may already have occurred and the resuscitation will be more difficult to stabilize the patient.
Therefore, reliable hemodynamic parameters are needed to reflect blood flow and fluid status. Cardiac output measurements, predictors of oxygen dysbalance and fluid responsiveness and indicators of fluid overload may contribute to fulfill this need. These advanced hemodynamic monitoring parameters may help to identify patients in an earlier phase of hemodynamic compromise, may guide and evaluate therapy and may prevent irreversible organ failure.

Physiologic background

The aim of systemic blood flow is to meet the metabolic demands of the tissues and ensure adequate tissue oxygenation. Hemodynamics involve complex physiologic processes and interactions.[5] For the interpretation of variables monitored, it is essential to understand the principles of the circulation and to take into account the physiological differences between adults and children.

Monitoring adequate tissue oxygenation represents the balance between systemic oxygen delivery and consumption. In critical illness both the oxygen delivery and demand are often deranged.[6] At present, no real-time monitoring tool for use at the bedside is available for tracking oxygen transport. Calculations can be made to estimate the oxygen delivery and consumption.
The delivery of oxygen to the tissues (DO_2) is determined by the product of arterial oxygen content (CaO_2) and cardiac output (CO):

$$DO_2 = CaO_2 \times CO$$

The assessment of total body oxygen consumption (VO_2) can be calculated according to the product of CO and the difference in arterial-venous oxygen content:

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

When the oxygen delivery and oxygen consumption are known, the oxygen extraction ratio (OER) can be calculated:

$$OER = \frac{VO_2}{DO_2}$$

The formulas may be simplified for practical use by ignoring the amount of oxygen dissolved in the blood. Determinants in these calculations are mixed venous oxygen saturation (SvO_2), arterial oxygen saturation (SaO_2), CO and hemoglobin concentration (Hb). Of these, advanced hemodynamic monitoring uses (changes in) SvO_2 and CO to determine the hemodynamic status.

Advanced hemodynamic monitoring

Cardiac output measurement is feasible in children and provides essential extra information on cardiac performance and fluid responsiveness.[7-13] However, despite the well-known limitations of physical examination and standard hemodynamic measurements, cardiac output is rarely measured in children.[1]

Since the introduction of the pulmonary artery catheter into clinical practice in the 1970s, an impressive number of medical devices has been developed.[14-16] Clinicians may feel somewhat confused by the multiple possibilities. Nevertheless, the perfect device still doesn't exist, being inexpensive, non-invasive, easy to use, accurate, precise, reproducible, continuous, applicable for all ages and without complications. The current advanced hemodynamic monitoring systems measure at least one or a combination

of some of the following variables: cardiac output, continuous arterial blood pressure, variations in pressure and/or volumes or blood velocities, cardiac filling pressures and/or volumes, extravascular lung water and mixed (central) venous oxygen saturation.[8, 9, 12, 17, 18] In children the applicability of the available devices is limited, depending on the technical aspects and size of probes and catheters.[10, 19] Beside these clinical limitations, only few validation studies in pediatric patients have been published. One of the clinical gold standards used in children are cardiac output monitoring devices using the transpulmonary dilution technique.[20, 21] Although validated in children, it is still unknown how reliable these hemodynamic estimations are in critically ill pediatric patients under various circumstances, while this is the target group for advanced hemodynamic monitoring.[22, 23]

Scientific background

Based on the evidence demonstrated in studies in adult patients, advanced hemodynamic monitoring can be used to improve outcome. Cardiac output and various other parameters, can be helpful diagnosing and monitoring circulatory failure and evaluating the response to the initiated treatment.[18] As previously mentioned, the available monitoring devices are still not generally used on pediatric intensive care units, partly explained by the unfamiliarity of the clinicians with the devices, unsuitability of probes and catheters for infants and small children, lack of pediatric scientific evidence and lack of target values for children. However, in the last decade mounting evidence from feasibility- and validation-studies show the applicability of several monitoring devices in children.[24-30] Still there is a need for more clinical pediatric studies supporting the evidence of improving outcome using advanced hemodynamic monitoring. Unfortunately, the results of studies in adults cannot be extrapolated to pediatric patients. For that, their physiologic responses, compensating mechanisms and body proportions are sufficiently different.

The goal of the present thesis is to demonstrate the feasibility of advanced hemodynamic monitoring in children. Cardiac output measurement, using the transpulmonary thermodilution technique, is validated in two pediatric animal models as surrogates for critically ill children. Extravascular lung water measurement, a relatively new marker in clinical practice used for the assessment of fluid overload, is validated against two gold standards. Finally, a clinical study in children is included, defining pediatric normal reference values of extravascular lung water.

Outline of this thesis

This thesis is divided into four parts.

Part I consists of two reviews. In **chapter 2** the basic physiological background and principles of hemodynamic monitoring in children are summarized. **Chapter 3** provides an overview of the various available monitoring systems, reviewing the technology and their limitations and clinical applications focusing on infants and children. The devices are listed in order of degree of invasiveness.

Part II focuses on the use of the transpulmonary thermodilution technique measuring cardiac output. In **chapter 4** the transpulmonary thermodilution technique is validated in a pediatric animal model in the presence of a left-to-right shunt. **Chapter 5** is an editorial comment discussing the interpretation of the thermodilution curves in the presence of a shunt circulation. In **chapter 6** the cardiac output measurements using the transpulmonary thermodilution method, are validated in a pediatric animal model during induction of lung injury.

Part III describes the measurement of extravascular lung water using the transpulmonary thermodilution technique. In **chapter 7** the results of extravascular lung water measured with the transpulmonary thermodilution technique are compared with the two gold standards gravimetry and transpulmonary double indicator dilution. In **chapter 8** we present near normal values of extravascular lung in a heterogeneous pediatric patient population.

Part IV consists of **chapter 9** and **chapter 10** in which the most important findings are summarized and discussed in English and Dutch (for laymen), respectively. Conclusions are presented together with suggestions for future research.

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Part I

Hemodynamic monitoring in children

Advanced hemodynamic monitoring in critically ill children

2

Pediatrics 2011; 128(3): 560-71

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Abstract

Circulatory shock is an important cause of pediatric morbidity and mortality and requires early recognition and prompt institution of adequate treatment protocols. Unfortunately, the hemodynamic status of the critically ill child is poorly reflected by physical examination, heart rate, blood pressure, or laboratory blood tests. Advanced hemodynamic monitoring consists, among others, of measuring cardiac output, predicting fluid responsiveness, calculating systemic oxygen delivery in relation to oxygen demand, and quantifying (pulmonary) edema. Here we discuss here the potential value of these hemodynamic monitoring technologies in relation to pediatric physiology.

Introduction

Circulatory shock is an important cause of pediatric morbidity and mortality.[1] Therefore, early recognition of inadequate tissue perfusion and oxygenation followed by prompt treatment are most important.[1, 2] In pediatric circulatory shock, cardiac output (CO) and blood pressure can be low, normal, or high.[3] Physical examination, although essential in the overall assessment, poorly reflects CO, preload status, or the need for fluid or other hemodynamic interventions.[4, 5] Moreover, blood pressure and heart rate often do not reflect blood flow.[6, 7] Therefore, more reliable pediatric hemodynamic parameters are most wanted.

Oxygen delivery to the tissues (DO_2) must always outweigh oxygen use (VO_2). Therefore, the balance between DO_2 and VO_2 is of vital importance in critically ill patients. The main goal of any hemodynamic intervention is to improve DO_2 while maintaining an adequate perfusion pressure. However, it could be useful to reduce the oxygen need by, for example, reducing fever, administering adequate sedation and analgesia, or starting mechanical ventilation. Because it is still impossible to quantify the need for oxygen by the various tissues or estimate the most adequate level of perfusion pressure, surrogate measures are being used. In doing so as an example, a goal directed approach based on optimizing venous oxygen saturation (SVO_2) might improve outcome in septic adult patients.[8]

Advanced hemodynamic monitoring in children seems mandatory to detect inadequate tissue perfusion and oxygenation at an early stage, long before it becomes detrimental. In contrast, the latest guidelines for treating sepsis in children advise to measure CO only at the end of the algorithm, after fluid and vasoactive therapy have already been instituted.[9] Initial aggressive fluid therapy for pediatric septic shock can be advantageous, but the resuscitation should be guided to prevent subsequent overzealous fluid therapy.[10, 11] Therefore, advanced hemodynamic monitoring in critically ill children might attribute to a lower mortality rate and a shorter intensive care length of stay.

We describe here the potential clinical value of 4 advanced hemodynamic monitoring technologies in children. CO measurement and venous oximetry provide important insight into the circulatory status and the balance between DO_2 and VO_2. However, fluid responsiveness and the determination of lung water are useful for guiding fluid therapy. In this review we provide clinicians treating severely ill children physiologic knowledge of advanced hemodynamic monitoring. The transitional and neonatal hemodynamic physiology has its own unique features, which are beyond the scope of this review.

Basic hemodynamic physiology

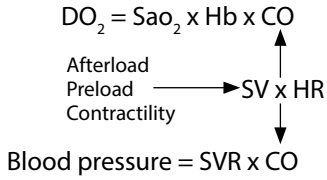
DO_2 consists predominantly of the product of CO, arterial oxygen saturation (SaO_2), and hemoglobin level (Fig 1; Table 1). Under normal conditions, SaO_2 is close to 100%. Because the body as a whole, under normal conditions, extracts 25% of oxygen from the arterial blood, the oxygen saturation of mixed venous blood (SvO_2) is ≈75%. VO_2 can be measured by using calorimetry or estimated indirectly by measuring SvO_2, hemoglobin level, and CO (Table 1). Under normal conditions, DO2 is much higher than VO_2, which reflects a wide margin of safety in the supply-to-demand ratio for oxygen. Assuming stable hemoglobin and SaO2 levels, the CO is the major determinant of DO_2 most of the time. However, one should bear in mind that DO_2 and VO_2 reflect oxygen supply and demand of the whole body, whereas important differences between organs might exist, depending on the circumstances.

CO is the product of heart rate and cardiac stroke volume (SV). SV depends on preload, afterload and contractility (Fig 1). The relation between SV and preload is reflected by the Frank- Starling curve (Fig 2A). Blood pressure is the resultant of SV and systemic vascular resistance (Table 1 and Figure 1). As a result, a low blood pressure can be caused by a low CO, a low systemic vascular resistance, or both. The net driving force of fluid from the intravascular space to the interstitium (or vice versa) is guided by Starling's law (Table 1) and reflects the balance between hydrostatic and oncotic pressures in relation to the capillary membrane permeability. Also, the amount of lymphatic drainage is important, because younger children seem to have a higher capacity to eliminate interstitial fluid. [12] Therefore, the formation of edema can be caused by several mechanisms.

In most cases of circulatory shock, either blood pressure and/or CO (thus, DO_2) are too low, which results in an insufficient perfusion pressure with organ damage and/or an unbalance in the oxygen supply-to-demand ratio, which leads to anaerobic metabolism. The most frequent causes are hypovolemia, overzealous vasodilation, and cardiac dysfunction. The latter consists of 2 components: (1) diminished systolic function with a decrease in ejection fraction, an increase in ventricular dimensions, and, subsequently, a decrease in SV; and (2) diastolic dysfunction that also results in a decrease in SV.[13]

Figure 1

Basic hemodynamic relations.



Hb indicates hemoglobin level; HR, heart rate; SVR, systemic vascular resistance.

Table 1

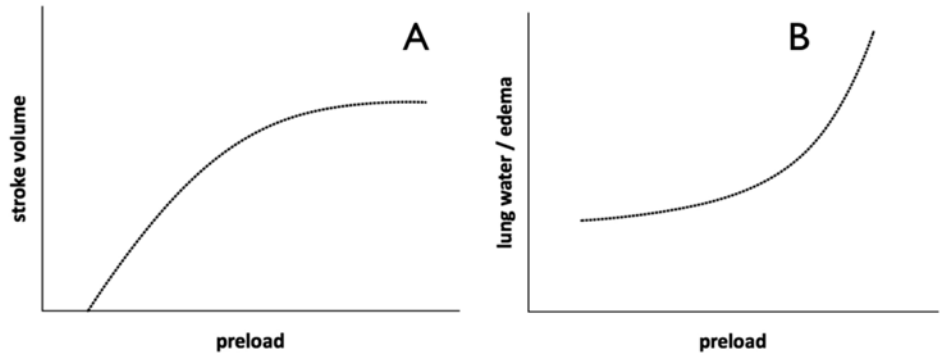
Several Hemodynamic Calculations

Parameter	Formula
SVR	80 x (MAP - CVP) / CO
CaO_2	Hb x 1.31 x SaO_2 + 0.0031 x PaO_2
CvO_2	Hb x 1.31 x SvO_2 + 0.0031 x PvO_2
DO_2	CO x CaO_2
VO_2	CO x (CaO_2 - CvO_2)
OER	(SaO_2 - SvO_2) / SaO_2
Ω	SaO_2 / (SaO_2 - SvO_2)
Jv	Kf x ([*Pc – Pi*] – σ[π*c* – π*i*])
PPV (%)	(PP_{max} – PP_{min}) / [PP_{max} + PP_{min}/2] x 100

*Units of measure: systemic vascular resistance (SVR), dyn·s·cm^{-5}; CO, L/min; VO_2 and DO_2, mL O_2/min; hemoglobin (Hb), g/L; arterial oxygen content (CaO_2) and mixed venous oxygen content (CvO_2), mL O_2/L; arterial oxygen saturation (SaO_2) and mixed venous oxygen saturation (SvO_2), fraction of 1.0; pulse-pressure variation (PPV), %; Mean arterial pressure (MAP) and central venous pressure (CVP), mmHg; venous oxygen partial pressure (PvO_2) and arterial oxygen partial pressure (PaO_2), mmHg; Ω, oxygen excess factor; Jv, the net fluid movement between compartments; Kf, proportionality constant/filtration coefficient; Pc, capillary hydrostatic pressure; Pi, interstitial hydrostatic pressure; σ, reflection coefficient; π*c*, capillary oncotic pressure; π*i*, interstitial oncotic pressure; PP_{max} and PP_{min}, maximum and minimum pulse pressure, respectively.*

Figure 2

Cardiac function curves. A, Relation between preload and SV: the Frank-Starling curve. B, Relation between preload and extravascular lung water or edema.



Several therapeutic measures might increase DO_2. CO can be increased by titrating volume therapy with inotropic medication (by increasing cardiac contractility) and with vasodilating agents (by decreasing afterload). Vasoconstrictive agents such as norepinephrine can be used to increase blood pressure when vascular resistance is too low. Fluid restriction and/or diuretics are prescribed to decrease the amount of (pulmonary) edema. The optimal intervention clearly depends on the circulatory state. Although each of these interventions can be lifesaving, inappropriate use might be deleterious. Fluid therapy aims to increase CO through a rise in preload. However, a fluid challenge will increase preload and SV only when the heart functions on the steep part of the Frank-Starling curve. This situation is called "fluid responsiveness." When fluid is administered on the more horizontal part of the curve, (pulmonary) edema might develop (Fig 2B). Also, using high amounts of vasoconstrictive agents in a low-CO state caused by decreased myocardial contractility might raise blood pressure at the expense of a detrimental further reduction in DO_2.

Apart from increasing DO_2 it might also be beneficial to decrease VO_2. Specifically in young children, hyperthermia, increased work of breathing, pain, and anxiousness my increase VO_2 to levels that cannot be met by DO_2. Therefore, mechanical ventilation, analgesia, sedation and lowering an increased body temperature are easily applicable interventions with a potential beneficial effect.

During human development hemodynamic physiology changes, especially in the first years of life. Most important is that oxygen and metabolic demands are higher, show less variation, and lack a hypermetabolic response in critical illness compared with older children or adults.[14] CO, SV, and ejection fraction (indexed to body proportions) seem to decrease with age, and heart rate is higher and blood pressure is lower in young

children.[15] The lower blood pressure in conjunction with a relatively higher CO implies that young children have a lower systemic vascular resistance.[16] Oxygen saturation of arterial and venous blood seems equal at all ages.
The CO of young children is not as strongly dependent on heart rate as was previously thought.[17] Many studies in healthy children, in children undergoing cardiac surgery, or in critically ill children have revealed that changes in CO are largely caused by changes in SV.[6, 7, 16, 18-20] Therefore, heart function in young children complies with general hemodynamic physiology (Fig 1). However, cardiac function in young children might be characterized by a higher basal contractile state, a greater sensitivity to afterload, and higher oxygen demand at higher heart rate or higher preload state.[16, 21]

CO monitoring

CO monitoring allows for the important discrimination between a low CO syndrome and a hyperdynamic state, characterized by high CO and low vascular resistance. In case of low CO, fluid therapy and/or inotropic drugs should be instituted. In case of high CO with concomitant low blood pressure, vasopressors might be instituted. Fluid therapy can be guided, ideally, by CO monitoring, because fluids should be stopped when CO does not increase (anymore).[22] Also, when administering vasopressors, CO monitoring can warn against a decrease in CO. In doing so, overzealous fluid administration and unnecessary or even deleterious vasopressor therapy can be avoided. Because hemodynamic profiles might differ between critically ill children, determination of CO might guide the clinician in the choice of intervention.[3, 23]
In adults, the pulmonary artery catheter is regarded as the clinical gold standard for measuring CO. However, because of technical problems and size restraints, the pulmonary artery catheter is not practical (and is sometimes impossible) to use in (young) children. In the last decade less invasive alternative methods have become available for measuring CO in both adults and children. These CO methods are based on multiple techniques including Doppler signals, dilution measurements, and bioimpedance methods. In general, dilution techniques deliver a reliable CO measurement for children from 3.5 kg and above, but all require insertion of central venous and arterial catheters. Less invasive methods are often less reliable. At present the transpulmonary thermodilution method is considered to be the clinical gold standard for children.[24] The transpulmonary thermodilution technology also offers the measurement of global end-diastolic volume, reflecting preload, and extravascular lung water (EVLW), which reflects pulmonary edema.[25-27] For in-depth technical information, see ref.[28] In general, the bedside CO techniques cannot be used in patients with intracardiac and extracardiac shunts. However, the transpulmonary thermodilution technology and the modified CO_2 Fick methods might be feasible in this situation.[29, 30]

Nonetheless, in adults there is no evidence that the use of a pulmonary artery catheter improves morbidity and/or mortality rates.[31] However, fluid therapy guided by CO measurement using esophageal Doppler might improve outcome after major adult surgery but not in critically ill patients.[32] Also, CO-guided volume loading in septic adults might prevent the increase in lung water.[22] Likewise, the evidence that CO monitoring improves outcome in critically ill children is also missing. CO monitoring does provide the clinician with important hemodynamic information and provides a physiologic value that can be used to determine and guide therapy.[7, 18, 23] Clinical studies of CO-guided hemodynamic therapy in children, therefore, are warranted.

Venous oximetry

According to the Fick principle, total body VO_2 equals CO multiplied by the difference between arterial and venous oxygen content (Table 1). When VO_2, SaO_2 and hemoglobin levels are relatively constant, a change in CO will cause a change in SvO_2. However, this relationship is not linear (Table 1); therefore, SvO_2, although related to CO, is not the same as CO.[33] The most important part of the SvO_2–CO curve lies between an SvO_2 value of 60% and 80%.[33] In this steepest part of the curve, a change in SvO_2 might indicate a significant change in CO. A low SvO_2 with a normal SaO_2 is almost always a sign of low CO in septic adults.[34] In case of a low SaO_2 caused by severe pulmonary dysfunction or in the presence of intracardiac and extracardiac shunts, SvO_2 will be lower also. To relate SvO_2 to SaO_2, the oxygen extraction ratio (OER) is calculated (Table 1). A normal OER is ≈0.25. Others prefer to calculate the oxygen excess factor (Ω) (Table 1), which is the inverse of the OER and has a normal value of ≈4.[35] A high OER indicates a disturbed balance between DO_2 and VO_2, which could be caused by an increased VO_2 and/or by a decreased DO_2 (see basic hemodynamic physiology).

Physiologically, the true SvO_2 is closely reflected by the "mixed" SvO_2 in the main pulmonary artery. SvO_2 reflects saturation of the mixed venous blood from the upper body, lower body, and the coronary sinus, which requires the use of a pulmonary artery catheter. Because this catheter is rarely used in children, $ScvO_2$ measurement with a central venous catheter in the superior caval vein is taken instead. $ScvO_2$ measurement in the inferior caval vein might provide different results.[36, 37] The $ScvO_2$ reflects merely the saturation of venous blood from the upper part of the body (including the brain). Under normal conditions, the saturation in the inferior caval vein is higher than that in the superior caval vein because of the higher VO_2 by the brain compared with that of the abdominal organs (especially the kidneys).[36] However, during circulatory shock, perfusion of the mesenteric organs decreases more than perfusion of the brain, which might cause saturation of the inferior caval vein to decrease. Also, mixing of desaturated blood from the coronary sinus might cause an additional decrease in SvO_2. As a result,

with sepsis or after liver transplantation the $ScvO_2$ can be ≈8% higher than SvO2.[38] Both $ScvO_2$ and SvO_2 could be equally reliable in determining changes in SvO_2 in adults and children.[38, 39] However, these values are not interchangeable in all patients with septic shock, because $ScvO_2$ and SvO_2 do not always change in the same direction[40]; this can be explained by variable changes in myocardial, cerebral, or splanchnic VO_2 under different conditions.

Although blood sampling is the most practiced way to determine $ScvO_2$, special venous catheters for continuous $ScvO_2$ monitoring are available even for (small) children. They replace the need for intermittent sampling and allow for tracking fast changes in $ScvO_2$. [41] Although continuous $ScvO_2$ monitoring has been validated in children, there have been no studies investigating the relation between $ScvO_2$ and CO or clinical condition in pediatric patients.[41, 42]

The $ScvO_2$ can be used in 2 ways: (1) relating the absolute $ScvO_2$ value to the OER (eg, a low $ScvO_2$ value [<70%] accompanied by a high OER [>0.25] could indicate relatively low CO); and (2) changes in $ScvO_2$ might guide hemodynamic therapy, although it is difficult in hyperdynamic conditions.[38] In adult patients with sepsis, restoring $ScvO_2$ to >70% might improve outcome.[8] This might also be true for children with septic shock.[43] Unfortunately, studies in septic adults have shown that many patients already have a $ScvO_2$ value of >70% at the start of therapy, although they might still need hemodynamic improvement.[44] Also, optimizing SvO_2 in adult ICU patients did not improve outcome.[45]

A complicating factor in interpreting the $ScvO_2$ value is the mitochondrial dysfunction that can occur during sepsis. The result is that although oxygen supply to the tissues is adequate, the tissues are not able to metabolize oxygen to energy-rich phosphates. Although SaO_2 and $ScvO_2$ might seem normal or even high, there is still a misbalance between VO_2 and DO_2. Indeed, adult patients with a high $ScvO_2$ level even seem to have a higher mortality rate compared with adults with a normal $ScvO_2$.[46]

At present, the additional value of $ScvO_2$ measurement in pediatric clinical practice is not clear. Nevertheless, $ScvO_2$ monitoring is already incorporated in the surviving sepsis campaign algorithm for both adults and children.[9] If $ScvO_2$ is used, it should preferably be combined with CO measurement or markers of insufficient oxygen perfusion such as lactate levels. On the one hand lactate has been shown to reflect inadequate organ perfusion reliably even when systemic oxygenation seems sufficient for metabolic demand, but on the other hand, it lacks the fast changes of $ScvO_2$ that might guide treatment.[47] However, a treatment algorithm based on lactate levels has been shown to be beneficial in adults.[48]

Cardiac shunts

A low $ScvO_2$ in children with cardiac shunts can be caused by low systemic blood flow (Qs) but also by a low pulmonary blood flow (Qp). In these clinical situations, the OER needs to be interpreted together with other hemodynamic parameters.[35] Pediatric studies during congenital cardiac surgery have revealed that low $ScvO_2$ predicts the occurrence of major adverse events.[20] $ScvO_2$ values of <40% were associated with a lower outcome score in neonates after Norwood stage 1 surgery.[20, 49] The peri-operative use of $ScvO_2$ monitoring is recommended for these patients.[50]
Intermittent or continuous monitoring of $ScvO_2$ in children is recommended when CO monitoring is difficult, impossible (cardiac shunts), or not yet available. When using $ScvO_2$ in cases of shunt, it is advised to calculate the OER and to be cautious with "normal" $ScvO_2$ values, because they still might not reflect a normal hemodynamic state.

Fluid responsiveness

The effect of fluid therapy can be determined by measuring CO before and after a fluid bolus. When CO (or, more precisely, SV) increases by >10% to 15%, the patient is considered fluid responsive. Results from adult and pediatric studies have shown that only up to half of the fluid challenges increase SV.[51-53] To avoid unnecessary fluid overload, there is a great interest in predicting fluid responsiveness. Both static and dynamic parameters are used for this purpose. Examples of static parameters are central venous pressure (CVP), heart rate, and global end-diastolic volume index (GEDVI). Dynamic values are the result of a physiologic heart-lung interactive process or a special maneuver. Examples are arterial pressure variations as a result of mechanical ventilation and changes in cardiac SV as a result of a passive leg-raising test.
CVP is often used to guide fluid therapy in both adults and children and is considered to reflect cardiac preload. However, CO is, for an important part, determined by the venous return to the heart. Venous return itself is determined by CVP, resistance to venous return, systemic vascular compliance, venous capacitance, stressed and unstressed blood volume, and mean systemic filling pressure.[54] Except for CVP, the other variables are difficult or even impossible to measure. Furthermore, the value of CVP is influenced by the diastolic compliance of the right ventricle, intra-abdominal pressure, positive end expiratory pressure, and forced expiration. Indeed, CVP does not predict fluid responsiveness and only poorly reflects preload in adults, children, and pediatric animal models.[7, 18, 19, 25, 51, 55, 56]
The other static measure is GEDVI, which is measured by using the transpulmonary thermodilution technique incorporated in the PiCCO device (Pulsion, Munich, Germany). GEDVI is a virtual blood volume measurement that includes the end-diastolic volumes

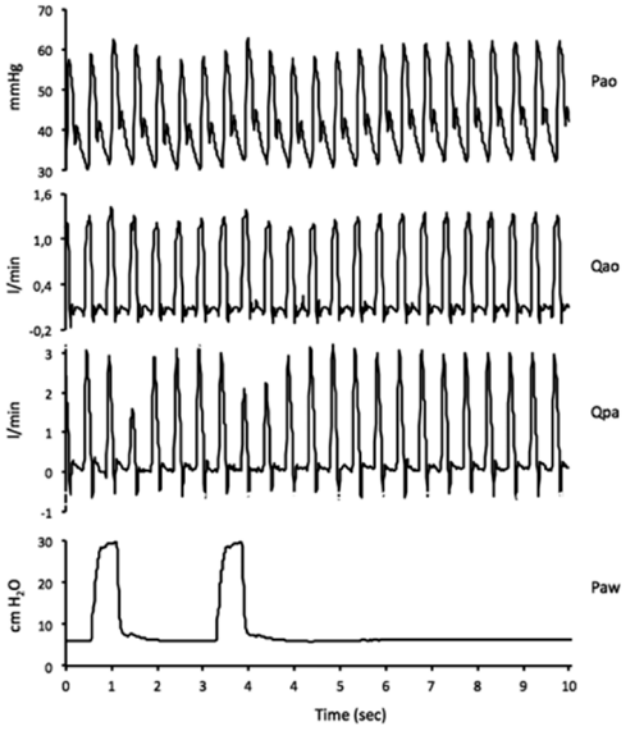
of left and right atria and ventricles, but it also includes the volume of central veins and aorta between the point of injection and the point of detection of the indicator. Therefore, GEDVI does not reflect an anatomic volume, which impedes validation.[57] However, GEDVI has been shown to be related to preload in adult patients and animals. [58, 59] A treatment algorithm based on GEDVI might reduce catecholamine use and ICU stay in adults after cardiac surgery.[60] Also, GEDVI seems to reflect preload in children. [7, 25] Results of clinical studies in children showing the value of GEDVI in predicting fluid responsiveness are not available, and it is unknown what cutoff values for GEDVI should be used, because GEDVI is lower in younger children compared with older children or adults.[18, 26, 27, 57, 61]

Dynamic parameters are the result of a temporary change in SV as a consequence of a change in the right and/or left ventricular preload or afterload induced by various mechanisms. The magnitude of the effect depends on the position of the heart on the starling curve. Two phenomena have been studied: arterial pressure variations and the passive leg-raising test.

Arterial pressure variations are mainly studied in relation to mechanical positive-pressure ventilation. During the breathing cycle the left ventricular filling varies, thus influencing SV, and as a result, fluctuations in the arterial pressure curve occur. Figure 3 shows this phenomenon in a newborn lamb. The explanation is as follows: during inspiration lung expansion causes an increase in both pleural and pericardial pressure. Subsequently, several phenomena develop simultaneously: (1) transmural pressure over the left ventricular wall decreases, thereby diminishing afterload and resulting in an immediate increase in left ventricular SV; and (2) at the same time, lung inflation squeezes blood from the pulmonary venous side to the left atrium, which enhances left ventricular SV. These 2 effects lead to an increase in arterial pressure that is called the "Δ up" (Fig 4). (3) The increased alveolar pressure causes an increase in pulmonary vascular resistance and thereby increases right ventricle afterload, and as a result, right ventricular SV decreases; (4) the increase in pericardial pressure decreases systemic venous return, thereby also decreasing right ventricular SV; and (5) the reduced right ventricular SV leads, after a few heart beats, to a decrease in left ventricular preload and thus left ventricular SV (Fig 5). Effects 3 through 5 lead to a decrease in arterial pressure that is called the "Δ down" (Fig 4).

Figure 3

Arterial pressure variations in a lamb of 9.2 kg during mechanical ventilation and apnea. During inspiration and expiration, the flow in the pulmonary artery and the descending aorta fluctuates alternatingly. These fluctuations resolve when ventilation is paused.



Pao indicates arterial pressure in the aorta; Qao, flow in the descending aorta; Qpa, flow in the main pulmonary artery; Paw, airway pressure

Figure 4

Arterial pressure variations as a result of mechanical ventilation. A indicates pressure level at expiratory hold; 1, Δ up (difference between maximal systolic pressure and pressure level at expiratory hold): 2, Δ down (difference between pressure level at expiratory hold and lowest systolic pressure); 3, difference between maximal and minimal systolic pressure, which is used for calculating systolic pressure variation; a and b, pulse-pressure difference (systolic pressure minus diastolic pressure), which is used to calculate pulse-pressure variation.

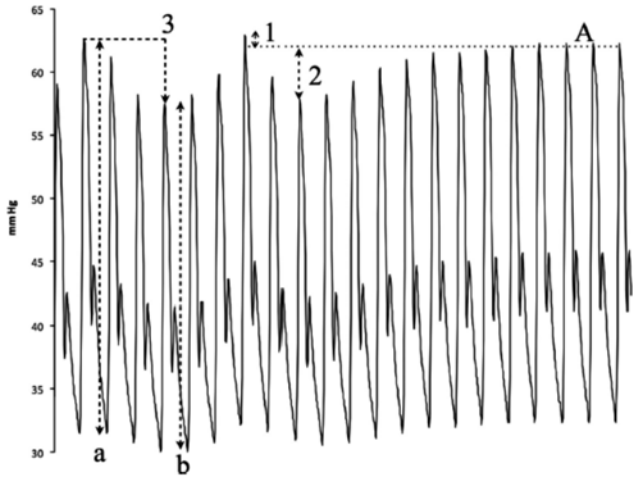
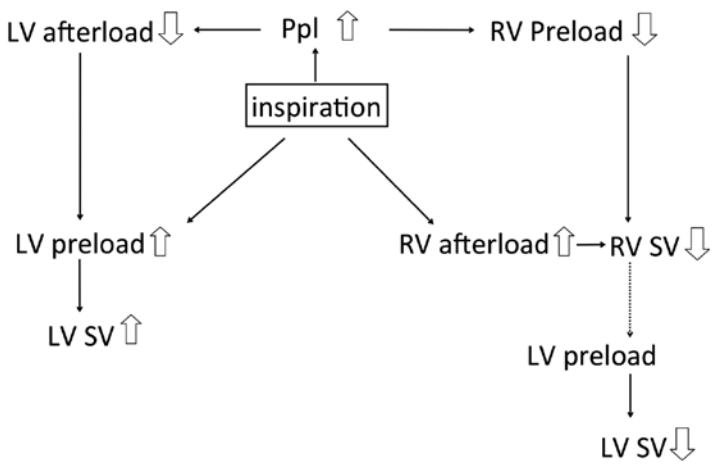


Figure 5

Mechanism of arterial pressure variations.



LV indicates left ventricle; RV, right ventricle; Ppc, pericardial pressure.

The resultant calculation of arterial pressure variations can be performed in multiple ways. First, the variation in systolic arterial pressure can be calculated (systolic pressure variation). Second, the pulse-pressure variation can be calculated by taking the changing difference of systolic minus diastolic pressure. Finally, when a continuous arterial pressure wave–based CO device is used, the variation in SV can be calculated. Calculations are all based on the same formula (Table 1). Respiratory tidal volume, cardiac arrhythmias, and the ratio of the respiratory rate to heart rate all influence the magnitude of arterial pressure variations.[62] Although the magnitude of the Δ up seems to depend on left ventricular performance, the magnitude of the Δ down is specifically influenced by hypovolemia. Therefore, apart from systolic pressure variation and pulse-pressure variation, Δ down can also be used to establish fluid responsiveness.[63] In small children, variation in blood-flow velocity in the aorta using echocardiography can serve as a surrogate for arterial pressure variations.[51, 52]

Arterial pressure variations are a reliable indicator of fluid responsiveness in adults.[53, 64, 65] However, reliability decreases with spontaneous respiration, nonsinus rhythm, pulmonary hypertension, right heart failure, low tidal volume, or open-chest conditions.[66-69] Also, in children or experimental pediatric animal models, arterial pressure variations and variation in blood-flow velocity in the aorta seem to predict fluid responsiveness, but specific cutoff values have not been established yet.[6, 19, 51, 52, 56, 70] The passive leg-raising test is a reliable indicator of fluid responsiveness in adult patients regardless of whether it is done during mechanical ventilation or spontaneous breathing.[71] However, there are currently no study results from children available. In our experience, in small children the passive leg-raising test seems to provide limited information, perhaps because of the relatively low blood volume in their legs (unpublished data).

Lung water

Pulmonary edema can be quantified by measuring EVLW. The extravascular fluid of the lung can be present in the interstitium and/or the alveolar compartment.[72] Alveolar flooding probably occurs after an initial increase of EVLW of ≈100% and is enhanced by the disruption of the alveolar membrane.[72, 73] Only when alveolar flooding appears will the oxygenation be seriously impaired and clinical signs become apparent.[74] Because fluid overload is a risk factor for mortality in critically ill adults and children and a restrictive fluid policy might reduce complications after major surgery, using a tool for detecting and quantifying fluid overload might be advantageous.[11, 75]

EVLW can be measured at the bedside by using the transpulmonary thermodilution technique, which is incorporated in the PiCCO device and is indexed to body weight

(EVLWI).[61, 76-78] Transpulmonary thermodilution also tracks fast changes in EVLW.[79] For the adult population, an EVLWI between 3 and 7 mL/kg is considered normal, and levels of > 10 mL/kg are associated with pulmonary edema.[78]

In adults, EVLWI measurement has been validated in many studies[78, 80-83]; in children, results of only 1 validation study have been published.[61] EVLWI cannot currently be measured reliably in patients with a significant left-to-right or right-to-left shunt. Measurement of EVLWI in children or pediatric animal models has revealed higher values compared with adult normal values.[7, 18, 25, 26, 61] As a result, the validity of these measurements in children has been questioned.[84] There is still no solid explanation why EVLW values are higher in young children. There are 3 possible explanations: (1) the greater body water content in young children, although this only explains a small part of the higher EVLW[85]; (2) the method of calculation of EVLWI[61, 78]; and (3) younger children have relatively more lung tissue mass and less air volume compared with older children; the larger tissue volume indicates that there is more interstitial tissue in the lung and might result in a larger quantity of fluids (eg, lung water).[57]

In both adults and children EVLWI is related to disease severity and outcome, especially when indexed to predicted body weight instead of actual body weight.[86-88] Furthermore, EVLWI divided by GEDVI might distinguish between pulmonary edema caused by increased capillary permeability or increased hydrostatic pressure.[89] Therefore, EVLWI might be a useful tool for guiding fluid or diuretic therapy. Until the results of a currently executed trial are available, there is only circumstantial evidence from adults to support this theory (ClinicalTrials.gov, identifier NCT00624650).[90, 91] EVLW could be used as a tool for evaluating therapies for reducing pulmonary edema.[92]

The clinical value of lung-water estimation in children is unclear. A recent clinical study in a general population of critically ill children that compared EVLWI with a chest radiograph score of pulmonary edema revealed no correlation between the two. Also, there was no correlation between the PaO_2/fraction of inspired oxygen ratio or A–a gradient and EVLWI or the chest radiograph score. However, EVLWI was indeed significantly higher in younger compared with older children.[26]

Discussion

To date, several advanced hemodynamic parameters in critically ill children are available for clinical use. Unfortunately, like in adults, evidence that these devices might reduce mortality rates is lacking. However, measurement of CO and venous oximetry have been adequately validated and could be incorporated in clinical guidelines. Besides the clinical use of the mentioned variables, they can also serve a research purpose for studying, for example, the effects of various inotropic agents.

Many pediatric hemodynamic parameters must be interpreted in relation to age.[93, 94] Therefore, normal pediatric values should be adapted accordingly. Until normal values for these parameters are established, their use is limited to individual changes in relation to interventions or their course over time. Furthermore the relation of organ weight and, among others, blood volume with body weight or body surface area changes with human growth, which might have important consequences for indexing hemodynamic parameters such as lung water or CO.[57] Also, many technologies are not adapted for use in children or are still insufficiently validated. Because the pediatric market is less commercially interesting, it remains uncertain if these problems will be solved in the near future.

Because fluid therapy is the mainstay of hemodynamic treatment in critically ill children, the determination of fluid responsiveness seems to be essential.[2, 9] For the majority of critically ill children in shock, the initial approach will remain the prompt administration of fluid up to 40 mL/ kg.[10, 95] Hereafter, predicting fluid responsiveness could prevent fluid overload and its deleterious effects.[11] Therefore, the value of static and dynamic parameters in children should be elucidated in the near future.

One should bear in mind that hemodynamic monitoring by itself will never be of benefit to critically ill children. The advantageous effects must be the result of correct interpretation of monitoring results coupled with a treatment strategy that is beneficial.[96] As long as it is unknown what the precise effects of certain vasoactive drugs on critically ill children are, advanced monitoring will not achieve its maximum beneficial effect. However, advanced hemodynamic monitoring is indispensable for evaluating these drugs.

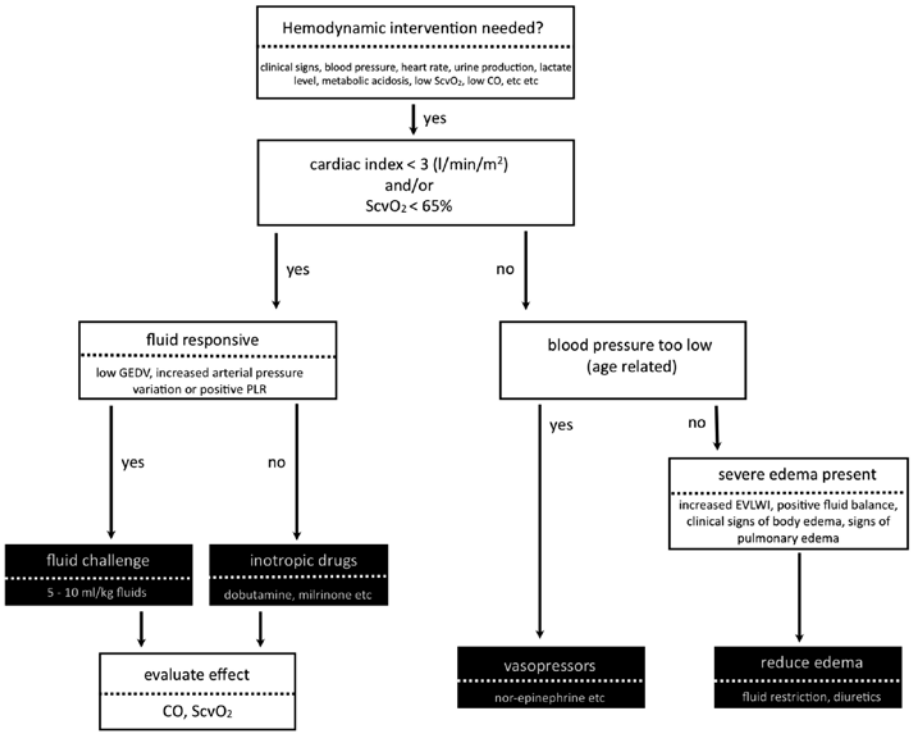
Figure 6 serves as an illustration of the interpretation of hemodynamic variables with subsequent treatment actions. Other algorithms might also be possible, and some patients have both low CO and low blood pressure. Therefore, it is debatable what treatment options should be used first. This algorithm can also be used repeatedly as long as circulatory conditions require it. Because hemodynamic parameters reflect cardiac function and/or blood flow to the whole body, monitoring of specific organ oxygenation or microcirculation could be useful. Therefore, 2 technologies might become useful in the near future. Near infrared spectroscopy (NIRS) provides the clinician with a quantification of tissue oxygenation in the brain or muscle.[97] More experimentally, microcirculation can be quantified in buccal mucosa by using orthogonal polarization spectral imaging or side-stream dark-field imaging.[98] Because many hemodynamic strategies aim to improve tissue oxygenation, both technologies seem rational. However, because these techniques only measure microcirculation or oxygenation in a specific organ or part of the body, it is likely that they will supplement advanced hemodynamic monitoring but not replace it completely.

Conclusion

Advanced hemodynamic monitoring in pediatric patients is feasible, and many important parameters of the circulation can be quantified, which might result in more rational and effective hemodynamic treatment protocols.

Figure 6

Example of a hemodynamic treatment protocol. Note that a low $ScvO_2$ could be replaced by a high OER in cases of a low SaO_2 (as in right-to-left shunts). Also, the algorithm can be used repeatedly as long as there is a need for hemodynamic intervention. PLR indicates Passive Leg raising.



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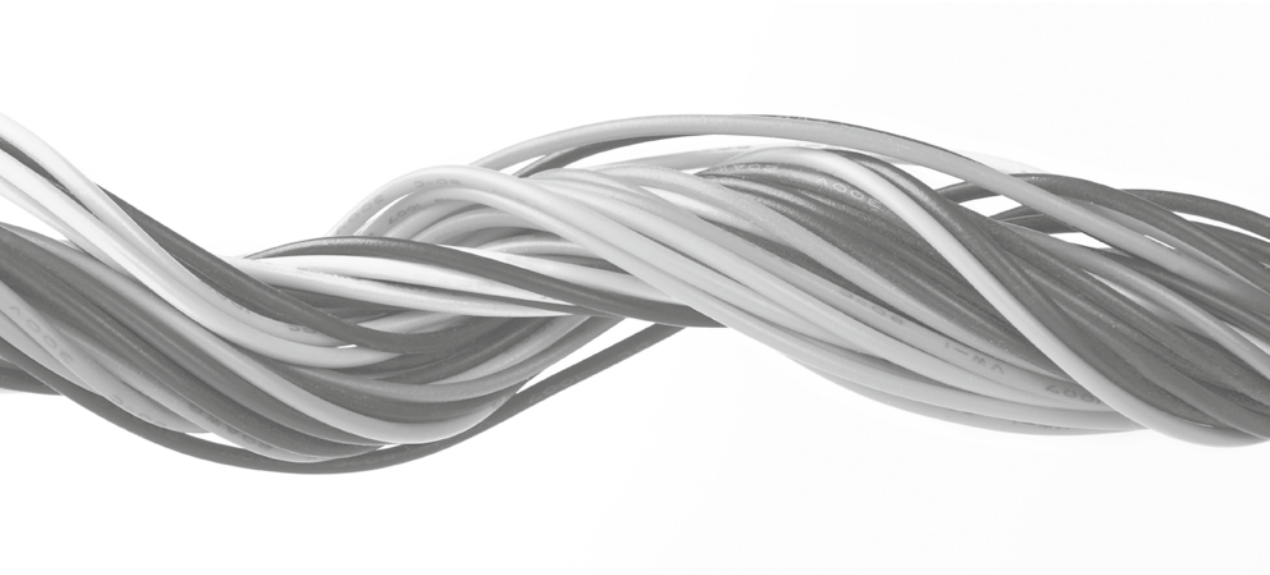

Cardiac output monitoring in pediatric patients

3

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Abstract

Cardiac output (CO) measurement is becoming increasingly important in the field of pediatric intensive care medicine and pediatric anesthesia. In the past few decades, various new technologies have been developed for the measurement of CO. Some of these methods are applicable to pediatric patients and some are already being used in children. The devices and methods have their advantages and limitations and, therefore, it is difficult for the clinician to decide which technique should be used. This article focuses on the currently available minimally invasive and noninvasive monitoring devices for CO measurement in children. A brief explanation of the technical aspects of each method and clinical use will be followed by the knowledge, gained from infant animal and clinical pediatric studies. The goal of this article is to give an update of the various CO measurement technologies in children.

Introduction

Cardiac output (CO) measurement is the cornerstone of advanced hemodynamic monitoring and provides invaluable information for the circulatory management of critically ill patients. Measurement of CO at the bedside in adults started with the introduction of the pulmonary artery catheter (PAC) in 1967.[1] With the PAC, CO can be measured by employing the thermodilution technique, but it requires an invasive right-heart catheterization. The technical aspects and the risks involved make the PAC less applicable for children and unsuitable for neonates and young children. As a result, CO monitoring and concomitant hemodynamic management evolved strongly in adults, while the development in children lagged behind.

During the last decade more technologies have become available for measurement of CO and additional hemodynamic variables. Since the newer methods do not require the same degree of invasiveness as the PAC they are called less or minimally invasive. However, some of these minimally invasive technologies still need arterial and central venous catheters, but by also using these catheters for standard treatment and pressure measuring purposes, one has two birds with one stone. The new technologies have replaced the need for usage of the invasive PAC for almost all, except some specific, clinical indications, such as pulmonary hypertension. Examples of these newer technologies are several types of transpulmonary dilution techniques, Doppler measurements and arterial pressure curve-based CO estimates. These new devices are in part also suitable for measuring CO in young children, first studied a decade ago.[2, 3] As a result, hemodynamic monitoring in children is now slowly evolving in the pediatric critical care and anesthesia arena.

One of the problems for the pediatric intensivist and anesthesiologist is to decide which technique should be used in pediatric patients.[4, 5] Not all methods are properly validated in children, and conclusions of studies, reviews and editorials concerning adult hemodynamic monitoring cannot be extrapolated to pediatric patients.[6-13]

This article gives an update on available technologies of minimally invasive and noninvasive CO monitoring in pediatric patients.

Clinical importance of measuring CO

Cardiac output is the amount of blood pumped by the heart every minute, expressed in liters per minute. It is the product of cardiac stroke volume and heart rate. Stroke volume is determined by preload, contractility and afterload. Given that children vary widely in weight and height, CO is normally indexed to body surface area (l/min/m^2), but can also be indexed to body weight (l/min/kg). Indexing of CO enables clinicians to compare measured CO values between individuals and to established normal values.

According to Ohms law, blood pressure is related to CO and systemic vascular resistance. Therefore, a low blood pressure is the result of a low CO, a low peripheral resistance or both. Since blood pressure is essential for the perfusion of organs and tissues, it is maintained by several regulating systems in the body, the most important being the baroreflex. While blood pressure is important as the driving perfusion pressure, CO is important for delivering oxygen to the tissues. This oxygen delivery is reflected by the multiplication of CO, hemoglobin level and oxygen saturation. When indicated, CO can be increased by various measures, for instance volume therapy to increase preload, vasoactive medication to increase contractility and vasodilating agents to decrease systemic vascular resistance.

Clinical estimation of CO, although still frequently practiced, poorly correlates with the true value of CO.[14, 15] Measurement of CO is, therefore, imperative to determine the hemodynamic status of the patient, to initiate the appropriate therapy, to follow the patient's response to therapy and, thereby, to prevent organ dysfunction.

How to interpret studies comparing different CO techniques

The number of studies validating CO measurement in children is limited and almost all include small numbers of patients or animals. Additionally, the methodology varies between several studies. To clarify the differences between these studies, we will briefly mention two general aspects of the methods used: which reference method is used and how the results are analyzed.

When validating a CO technique, the new technology should be compared with a gold standard reference technique. This reference technique should be accurate in measuring true values, should have a small variability and should provide reproducible results. Finally, the reference method itself should not influence the method being tested. To our knowledge, the best *in vivo* method of measuring CO is the use of ultrasound transit-time flow probes. These flow probes should preferably be positioned around the pulmonary artery, since positioning the probe around the ascending aorta will result

in a CO value not including flow to the coronary arteries.[16] Ultrasound flow probes have a documented variability less than 10%, provide real-time continuous CO values and do not need calibration. Measured values closely resemble true CO.[17-19] Flow probes, being highly invasive, are normally only feasible in animal models. Therefore, when studying CO measurements in humans, other less reliable methods are used for validation. Comparing CO measuring devices using a less reliable reference method can therefore lead to erroneous results.
The clinical standard in adults for measuring CO is the pulmonary artery thermodilution (PATD) technique. In pediatric patients, methods such as the Fick technique and transpulmonary thermodilution (TPTD) have been regarded as sufficiently precise and accurate to act as a clinical gold standard.[3, 20, 21]

The appropriate statistical analysis for comparing two measurement technologies is well described but not always sufficiently practiced. Correlation coefficient and regression analyses are inappropriate statistical techniques for comparing two methods measuring the same physiological variable, such as CO. In 1986 Bland and Altman proposed a new statistical method.[22] This method delivers graphical information in which the difference between the two methods is plotted against the mean values of the two methods. Using this statistical analysis, the agreement between two methods is quantified by calculating bias, limits of agreement and percentage error. The bias is the mean difference between the two methods, while the limits of agreement are calculated by multiplying the standard deviation of the difference between the methods by 1.96. The limits of agreement reflect the boundaries between 95% of all measurement values that are positioned in the plot.
Additionally, Critchley and Critchley recommended using the percentage error to compensate for the relationship between the magnitude of CO measurements and the size of the error, especially important for pediatric patients, who have lower absolute CO values compared with adults.[23]
The percentage error can be calculated by taking the percentage of the limits of agreement in relation to the mean CO measurement value of the reference technique. The percentage error can be used as cutoff value for accepting a new technique. The basis of this approach is that, in order to accept the new technology, the level of accuracy and precision should be at least equal to the reference technique. They suggest acceptance of a new method judged against the ±20% precision of the reference method and consequently accept the percentage of error of agreement between the new and the reference technique of up to ±30%. This shows that the precision of the reference technique is extremely important when assessing the combined error of the two. Therefore, the precision of the reference method should always be mentioned and any validation study should start with a definition of acceptable percentage error (using the error-gram of Critchley and Critchley) prior to the data analyses.[23, 24]

By using the method proposed by Critchley and Critchley in pediatric studies there might be an important drawback. The percentage error is calculated by using the mean of a range of absolute CO values. When the limits of agreement (e.g., the errors in measurement) are proportional to the mean CO value, the percentage error will be comparable between high and low CO samples. For instance, in comparing a pediatric and an adult study validating the transpulmonary thermodilution technique, the mean CO value was 2.55 l/min in the pediatric study and 8.8 l/min in the adult study. The limits of agreement were 0.49 l/min in the pediatric and 2.2 l/min in the adult study.[3, 25] Thus, the percentage error was even smaller in the pediatric study. However, due to technical reasons, errors in the measurement may also have an absolute character and may not solely be proportional to the measured value. In these cases, the limits of agreement would be relatively larger compared with the mean value, resulting in a larger percentage error in subjects with lesser weight or lesser size.

Besides analyzing the accuracy of a new technique to reflect absolute values of CO, the ability to track directional changes should be carefully studied.[26] This is becoming more important since changes in CO as a result of therapeutic interventions are frequently considered more valuable than single measurements.

Indicator dilution methods

Indicator dilution methods are based on measuring the change of concentration over time of an indicator at a point downstream following a venous injection. In doing so, the flow is inversely proportional to the area under the concentration–time curve for the indicator as shown in the Stewart–Hamilton equation:

$$\text{Flow} = \text{mass of indicator} / \int C(t) \times dt$$

Indicator dilution methods, regardless of what indicator is used, have to fulfill the following conditions: constant blood flow, no or minimal loss of indicator between injection and detection point, complete mixing of the indicator with blood and the indicator must pass the detection point only once.[27] Almost all indicator dilution methods require a central venous catheter and an arterial catheter. Sequential injections of the indicator are performed as soon as the dilution curve is back to baseline. This prevents recirculation bias between separate measurements. During a single thermodilution, the dilution curve is interrupted at the downslope part based upon a specific algorithm to prevent the effects of recirculation.[28] Subsequently, the curve is extrapolated from the interrupted point to the baseline in order to calculate the area under the curve (AUC).[29, 30]

Transpulmonary thermodilution CO

The TPTD technique uses thermal energy as an indicator. In contrast to PATD, the transpulmonary approach uses a large (mostly femoral) systemic artery in which the temperature change is detected. Since TPTD does not require the insertion of the pulmonary artery catheter, this method is considered 'less invasive'. Moreover, no extra catheters have to be inserted because this special thermistor-equipped arterial catheter can also be used as an arterial catheter for continuous blood pressure measurement and blood sample drawing. A central venous catheter for the injection of an ice-cold indicator is needed, but is often already employed in patients where CO monitoring is indicated. The minimum size of the thermistor tipped arterial catheter is 3-French, which makes it accessible for infants weighing as little as 3.5 kg.[31, 32] Furthermore, a special device is needed to compute the measured values pulse-contour CO (pulse-induced contour CO; PiCCO™) (Table 1).

Several pediatric or juvenile animal studies showed TPTD to be a reliable technique for CO measurement. Lemson et al. validated TPTD CO measurements, with ultrasound perivascular flow probes serving as the standard reference, under various hemodynamic conditions.[20] The study was performed in newborn lambs as a surrogate for infants. CO measurement was also reliable in a low CO state with a percentage error of ±14.7%. Besides measuring absolute values, the TPTD method was also reliably capable of tracking changes in CO. Ruperez et al. compared TPTD with PATD in juvenile animals and demonstrated moderate agreement (percentage error of ±33%).[33] Clinical pediatric studies demonstrated the mean of a series of three TPTD measurements, spread randomly over the respiratory cycle, to be a reliable and validated method for estimating CO in children.[34] Pauli et al. used the direct Fick method as the clinical reference standard and found a percentage error of ±11%. Other pediatric clinical studies used the indirect Fick method (indirect calorimetry) and PATD as a reference method for CO measurements.[2, 3] They demonstrated acceptable agreement (Table 2). In addition, these studies confirmed that TPTD slightly overestimates CO. In conclusion, the TPTD appears to be accurate and can be considered as a reference standard for CO measurement in children.[21] In the presence of cardiac shunts, the PiCCOplus device is capable of detecting and quantifying right-to-left shunts (Pulsion Company. PiCCO operational manual, software version 7.0, part 8.4.5. 2005). However, validation of this method has not been published and the method has not been incorporated in the successor of this device. Studies on the reliability of thermodilution CO measurement in the presence of left-to-right shunts are not conclusive.[35, 36]

Besides CO measurement, the TPTD technique also allows for assessment of global end diastolic volume and extravascular lung water. Global end diastolic volume is related to preload and extravascular lung water is a quantification of pulmonary edema.[37, 38] The results of intrathoracic and intracardiac volumes and extravascular lung water volume in juvenile animals and children are different from adult reference values.[39, 40] Further studies are needed to define normal values in the pediatric range and clarify the

clinical value of these measurements.[39-42] When using the PiCCO device, additional continuous CO measurement is possible using pulse contour analysis (see later).

When using the TPTD technology some points are of importance. A femoral venous catheter can be used for indicator injection.[27, 39, 43] However, the use of venous and arterial femoral catheters on the same side of the body and of the same length should be avoided. Local extravascular distribution of the thermal indicator can reach the arterial thermistor before the temperature change by blood does. This phenomenon is called 'crosstalk' and is blood-flow dependent.[44, 45] Finally, the absolute values of CO are always slightly, but consistently, overestimated because of temperature loss.

Lithium dilution CO

The transpulmonary lithium dilution CO method (TPLD) uses an isotonic solution of lithium chloride (LiCl) as the indicator and requires a venous and arterial catheter, usually already in place, and a specially developed lithium sensor.[46] After venous injection of LiCl, arterial blood is withdrawn by means of a mechanical device through a lithium sensor, and CO is derived from the lithium concentration–time curve. Each measurement requires approximately 3 ml of blood. The sensor consists of a lithium-selective electrode. When the lithium-selective membrane is in contact with blood, the voltage across it is related to plasma lithium concentration following the Nernst equation together with a correction for plasma sodium concentration. The TPLD technique is incorporated in the lithium dilution CO (LiDCO™) device (see Table 1).

There is currently one study in pediatric patients validating TPLD CO measurements. Using TPTD as the reference technique, the results demonstrate its safety and feasibility in patients who weigh as little as 2.6 kg. From the data the percentage error could be recalculated, which was quite acceptable (±32%) with a percentage of the bias of 5%.[47] The TPLD method does not require a special arterial or venous catheter. Like the PiCCO, the LiDCO device offers the advantage of continuously monitoring CO using an arterial pressure-based CO technique (see later). Several points should be considered. Each measurement takes approximately 3 ml of blood, which is a significant amount for small infants. Since the mean of two to three measurements is needed, this would take up to 10 ml of blood loss for each CO measurement, which is not acceptable for small children. TPLD cannot be used in the presence of some non-depolarizing neuromuscular blocking agents and the baseline lithium level at the start of the measurement should not exceed 0.2 mEq/l.[48] The current intravenous LiCl dose recommendation for adults is 0.15 mmol for every single CO measurement, with a maximum cumulative dose of 3 mmol. The dose used in children for a single CO measurement is 0.002–0.009 mmol/kg, which has no known pharmacological effect.[48, 49] In some countries, the use of LiCl as an indicator is prohibited by law, and the device has not yet acquired a US FDA registration for children weighing less than 40 kg.

Pulse dye densitometry

With pulsed dye densitometry, intermittent CO measurements can be obtained at the bedside by using a finger or nose clip device and a dye densitogram analyzer (DDG2001 analyzer, see table 1).

Table 1

Devices for measuring cardiac output in children

Name (Manufacturer)	Technology	Invasiveness	Equipment	Reliability in children	Remarks
PiCCO (Pulsion, Munich, Germany)	TPTD + APCCO	+++	special AC + CVC	+++	Multiple hemodynamic parameters, continuous, gold standard in children
LidCO (LidCO, London, UK)	TPLD + APCCO	++	AC + CVC or PVC	+++	Continuous, requires injection of lithium, not for children < 40 kg
DDG 2001 analyzer (Nihon Kohden, Tokyo, Japan)	PDD	+/-	PVC Finger/ nose clip	?	Non-invasive, intermittent, no validation in children
COstatus (Transonic, Ithaca, USA)	TPUD	+++	AC + CVC	?	Intermittent, no validation in children
Flowtrac/Vigileo Edwards Lifesciences, Irvine, USA)	APCCO	+	AC	?	Continuous, calibration not possible. No validation in children
MostCare (Vytech, Padova, Italy)	APCCO	+	AC	+/-	Continuous, calibration not possible
CardioQP (Deltex, Chichester, UK)	Oesophageal doppler	+/-	oesopagus probe	+/-	No intravascular catheters needed. difficult in small children
USCOM (Uscom, Sydney, Australia)	Trans- cutaneous Doppler	-	external doppler probe	+/-	Non-invasive, intermittent, operator dependent
NICO2 (Respironics, Paris, France)	CO2 Fick rebreathing	+/-	endo- tracheal tube	?	Non-invasive, only in intubated patients with Tv > 300 ml
Aesculon (Osypka medical, Berlin, Germany)	Electrical impedance cardiometry	-	surface electrodes	+/-	Non-invasive, continuous
NICOM (Cheetah Medical, Tel Aviv, Israel)	bioreactance	-	surface electrodes	?	Non-invasive, continuous
Nexfin (BMEYE, Amsterdam, Netherlands)	APCCO	-	finger cuff	?	Non-invasive, also measures continuous blood pressure, no calibration incorporated, not for small children

+ and - symbols represent the degree of invasiveness or reliability (e.g., +++ = reliable or invasive, - = not invasive or less reliable).

AC = arterial catheter; APCCO = arterial pressure based continuous cardiac output; CVC = central venous catheter; PDD = pulse dye densitrometry; PVC = peripheral venous catheter; TPTD = transpulmonary thermodilution; TPUD = transpulmonary ultrasounddilution.

This technique is based on a dye (indocyanine green) dilution technique with a transcutaneous signal detection adapted from pulse oximetry.[50] In contrast to the conventional dye dilution method, this technique does not require blood sampling after the venous injection of indocyanine green. CO and circulating blood volume can be calculated by analyzing the pulsatile change in indocyanine green concentration in the arterial blood by placing a probe over arterial vessels. Appropriate signal detection is mandatory and high heart rate, poor peripheral circulation, interstitial edema and movement artifacts negatively influence this.
Studies in adults are limited, and recent data regarding reproducibility and validity of the pulsed dye densitometry method are conflicting.[51-53] Although the first (experimental) studies in pediatric animals and patients applying blood volume and CO measurements are published, the technique has not been validated.[54-57] The applicability in clinical practice is, therefore, as yet unknown.

Ultrasound dilution method
The ultrasound dilution technology was first introduced in adult patients during hemodialysis and is still under development. The method uses an extracorporeal arterial–venous tubing loop, connected to existing intravascular central venous and arterial catheters, in which the indicator is injected. A roller pump provides a constant blood flow through the loop and the system needs to be primed once at the beginning of every series of CO measurements. Normal isotonic saline, heated to body temperature, is used as the indicator. The difference of velocity of ultrasound between blood and isotonic saline induces a decrease in ultrasound velocity, which is used to obtain a dilution curve.[58] The average of two to three consecutive injections spread randomly over the respiratory cycle is advised for obtaining an accurate value of CO.[59] The volume of the injectate is 0.5 ml/kg, with a maximum of 30 ml. Operator errors are reduced because flow sensors measure exactly the injectate volume, whereas dilution sensors in the arterial part measure ultrasound velocity.

The technique was accurate and precise in the CO range of less than 1.5 l/min in a piglet study.[59] The first data of pediatric use are available, but more human studies are needed to further assess the reliability of this method in various clinical situations for infants and children.[60]
The use of a nontoxic, low volume and warmed injectate makes it attractive for infants and children, as well as for patients who are at risk for fluid overload. As with the TPTD technique, this method also provides static hemodynamic variables, such as central blood volume, total end-diastolic volume and active circulation volume, for all of which the clinical utility has yet to be evaluated.

Table 2

Technologies for measuring cardiac output

Reference	technology	reference method	subjects	weight of subjects	number of subjects	range of CO	bias	limits of agreement	PE	r^2
				kg		l/min	l/min	l/min	%	
Lemson et al [20]	TPTD	UFP	lambs	4.2 - 12.5	11	0.4 - 3.1	0.2	0.24	14.7	0.95
Ruperez et al. [27]	TPTD	PATD	Pigs	9 - 16	16	0.9 - 5.6	0.28	0.63	30	0.86
Pauli et al. [28]	TPTD	O2 Fick	humans	4.3 - 88	18	0.4 - 6.2	0.06	0.38	10.7	0.99
Tibby et al. [3]	TPTD	O2 Fick	humans	2.5 - 60	24	0.24 - 8.7	0.03	0.49	19	0.99
Mcluckie et al [2]	TPTD	PATD	humans	9.8 - 23.7	9	3 - 5.3	0.19	0.42	9.5	NA
Piehl et al. [29]	TPTD	PATD	pigs	24-37	10	0.8 - 6.0	0.14	0.47	11.6	0.96
Linton et al. [41]	TPLD	TPTD	humans	2.6 - 34	17	0.4 - 6.0	-0.10	0.62	31.8	0.96
Taguchi et al. [51]	PDD, prototype	UFP	pigs	7.5 - 14.0	15	NA	0,034	0,59	65&	NA
de Boode et al. [53]	TPUD	UFP	pigs	3.5 –7.0	9	0.46 – 1.9	0.04	0.26	26,9	NA
Lopez-Herce et al. [56]	APCCO (PiCCO)	TPTD	pigs	9-16	51	0.52-4.22	0.04	1.10	62.7	0.41
Piehl et al. [29]	APCCO (PiCCO)	PATD	pigs	24-37	10	0.8 - 6.0	0.11	0.45	11	0.97
Mahajan et al. [57]	APCCO (PiCCO)	TPTD	humans	>10	16	1.4-9.7 (indexed)	0.08	1.98	54	0.53
Fakler et al. [58]	APCCO (PiCCO)	TPTD	humans	10.6-35.6	24	1.86-7.04 (indexed)	0.05	0.8	20&	0.86
Kim et al. [59]	APCCO (LiDCO)	TPLD	humans	13-77	20	1.9-5.9 (indexed)	0.19	0.28	8.8	0.88
Calamandrei et al. [66]	PRAM	transthoracic echo doppler	humans	2 - 45	48	0.89 – 7.48	0.12	0,6	20.3	0.98
Tibby et al. [75]	Oesophageal doppler	TPTD	humans	3 - 70	100	0.32 – 9.19	NA	NA	NA	0.82
Schubert et al. [77]	Oesophageal doppler	transthoracic echo doppler	humans	2.6 - 47	26	2.3 (SD ±1.4)	0.36	1.67	77.7	0.72
Knirsch et al. [78]	Oesophageal doppler	PATD	humans	3.4 - 59.4	40	1.2 – 7.1	0.66	1.79	54.3	0.65

Critchley et al. [84]	TCDU (USCOM)	UFP	dogs	11-22	6	0.9-5.6	-0.01	0.33	13	0.87
Knirsch et al. [80]	TCDU (USCOM)	PATD	humans	3.4 - 51	24	1.3 – 5.3	-0.13	1.34	36	NA
Botte et al. [87]	CO_2 Fick	transthoracic echo doppler	humans	15-60	21	1.82-9.96	-0.61	0.94	20	0.85
Levy et al. [88]	CO_2 Fick	PATD	humans	9.2 – 47.4	37	1.2 – 5.4	-0.27	1.49	53&	0.69
de Boode et al. [90]	modified CO2 Fick	UFP	lambs	2.9 – 6.4	7	0.2 – 1.4	0.08	0.25	35&	0.86
Osthaus et al. [93]	EV	TPTD	pigs	11.2 – 13.8	5	0.29 – 4.5	-0.63	1.28	83	0.67
Tomaske et al. [94]	EV	PATD	humans	0.5-16.5	50	0.6 – 7.2	0.66	1.49	43.8	0.79
Tomaske et al. [95]	EV	transthoracic echo doppler	humans	3.4-59.4	36	0.62-6.27	0.31	1.92	67.7	0.56
Norozi et al. [96]	EV	O2 Fick	humans	2.7 - 54	32	0.4 - 4	0.01	0.46	38&	0.94
Schubert et al. [77]	EV	transthoracic echo doppler	humans	2.6 - 47	13	2.3 (SD 1.4)	0.87	3.26	159&	0.77

Note: when interpreting validation data we advise to use mainly the Bland Altman method (looking at bias and limits of agreement) and the percentage error.

APCCO = arterial pressure based continuous cardiac output; TPTD = transpulmonary thermodilution; TPLD = transpulmonary lithiumdilution; TPUD = transpulmonary ultrasounddilution; PDD = pulse dye densitrometry; PRAM = pressure recording analytical method; UFP = ultrasound flow probe; EV = electrical velocimetry; TCDU = Transcutaneous continuous wave Doppler ultrasound.
NA = not available; PE = percentage error; & = value not provided in article but deducted from graphical data.

Arterial pressure-based CO measurement

Arterial pressure-based continuous CO measurement (APCCO) converts the arterial pressure wave into CO. It is based upon the principle that the stroke volume of one heartbeat generates a corresponding arterial pressure wave. Using an APCCO method, the pressure wave is converted back into stroke volume.

Several different algorithms for converting the pressure waveform to stroke volume exist; different methods are also employed for taking the mean value of several heartbeats and for converting stroke volume to CO.[61] Several facts regarding the APCCO systems for use in children are of importance. First, the pressure waveform is largely dependent on the Windkessel function of the aorta. This function is influenced by the aortic compliance, which changes over time due to patient-related factors, but also by changes in blood pressure itself. Second, the arterial pressure waveform changes from central (aorta) to peripheral (radial) positions. In general, the systolic pressure increases and the diastolic pressure decreases going downstream, while the mean pressure remains the same as a result of the reflection of the arterial waveform. This effect is also dependent on patient-related (static) factors, such as age and medication (dynamic), by influencing vascular tone. Third, these systems have to rely on an optimal arterial pressure waveform. Therefore, an optimal arterial pressure transducing system has to be used with low compliant tubing, fast-reacting pressure heads and careful calibration. Especially in small children, kinking of catheters, damped waveforms and movement artifacts often exist due to the small size of the arterial catheters in these patients. Fourth, cardiac rhythm disturbances will influence these systems. Fifth, all algorithms used are designed for adults and do not address specific vascular properties that are applicable to a growing and developing vascular system.[62] Owing to these variables, it is challenging to measure CO reliably by only converting an arterial waveform to volume without knowing the individual patient-related factors.

The available APCCO systems are PiCCO, PulseCO (LiDCO), FloTrac/Vigileo™ system, pressure recording analytical method (PRAM; MostCare®) and Nexfin (formerly Modelflow) (Table 1). They all use their own specific algorithms and methods for converting the pressure wave to volume. Pulse-contour and pulse CO use a second CO technique for calibration. The FloTrac/Vigileo system uses a stored database of many patients as reference for calibration. The other systems (PRAM, Nexfin) are independent of patient characteristics or calibration. The systems incorporating a second calibrating CO measuring technique have the advantage over other methods that they also provide volumetric data, which may be helpful in targeting fluid therapy. However, the techniques used for calibration have their own (technical) limitations.

Pulse-contour

The pulse-contour analysis of the PiCCO system requires an initial calibration using TPTD. Furthermore, periodic recalibration is necessary on a regular basis, at least every 8 h, or more frequently when patient-related factors change.[63, 64]

Lopez-Herce et al. studied the correlation between CO measured by TPTD and PiCCO in an infant animal model.[65] Based on the correlation coefficient, the authors concluded that there was a good agreement, but on recalculating the percentage error (±63%) the method should have been rejected. Piehl et al. demonstrated in a piglet hemorrhagic shock model a percentage error of 11% between PiCCO and PATD under stable hemodynamic conditions.[66] On the other hand, PiCCO's utility in the setting of rapidly changing hemodynamics was limited unless recalibration with TPTD was frequently performed.

A study in pediatric cardiac surgery patients showed no good agreement (percentage error ±54%) between CO measured by TPTD compared with PiCCO.[67] Part of the explanation is found in their study population. Some patients had intracardiac shunts and valvular diseases, which makes both CO measurement techniques unreliable. However, the weak agreement persisted even after the congenital defects were corrected. From another pediatric study, the results for accuracy and precision cannot be reliably recalculated.[68]

In our opinion, the pulse-contour analysis algorithm has to been refined, especially for use in pediatric patients and in changing hemodynamic conditions. The small patient size with small absolute CO values, very high heart rates, abrupt changes in blood pressure and the greater compliance of the child's aorta, affects the accuracy and precision of PiCCO analysis. Therefore, using the PiCCO system in children, the continuous pulse-contour system can be used as a rough estimate of CO. However, important therapeutic decisions should be based on the more reliable TPTD CO measurements.

PulseCO

The PulseCO method, incorporated in the LiDCO device, converts the arterial waveform to a nominal stroke volume using a pressure-volume transformation.[48] By using the entire pressure waveform rather than just the systolic portion of the curve, the PulseCO system incorporates the influence of peripheral resistance and the reflected wave from the periphery. The CO estimations are periodically calibrated by the TPLD technique, comparable to the pulse-contour method.

The method has been validated in a pediatric study comparing pulse CO against PATD under hemodynamically stable conditions.[69] This resulted in very precise (percentage error of 8.8%) and accurate (relative bias 6%) measurements. The method seems promising, but further studies under various hemodynamic conditions are warranted. Like the PiCCO system, the accuracy and precision are dependent on the frequency of recalibration. Also with this method, we would like to advise that important clinical decisions are based upon the more reliable TPLD technique.

FloTrac/Vigileo system

The FloTrac/Vigileo system is a CO-monitoring system based on analysis of the systemic arterial pressure wave, which does not require calibration. The stroke volume is derived by the application of a proprietary algorithm, using the patient's vascular resistance and arterial compliance based on sex, height, weight and age, and the pulse pressure waveform characteristics.[70] The pulsatility is derived from continuous analysis of the shape of the arterial pressure waveform. The technique involves determination of the area under the arterial pressure curve, thus quantifying the relationship between the amount of blood flow and the pressure wave associated with it. This relationship can vary widely from one individual to another, but also in a single individual as clinical conditions change. By using the aforementioned system, the second-generation operating FloTrac/Vigileo system recalculates its calibration constant every 60 s and does not provide a beat-to-beat CO result.

Contradictory results have been obtained in adult, hemodynamically unstable patients.[71-73] However, the algorithm has been modified, which may improve the reliability of the device.[74] Arterial wave artifacts, aortic regurgitation and an irregular pulse influence the measurements unfavorably. As far as we know, no pediatric or infant animal studies have been published using this method.

PRAM

The pressure recording analytical method analyzes the systemic arterial pressure waveform morphology.[75] The results of this beat-to-beat analysis allow for determination of the stroke volume, which provides CO by multiplying stroke volume by heart rate. This recently developed method has been studied in children by Calamandrei et al.[76] The PRAM CO measurements were compared with transthoracic Doppler echocardiographic measurements. Recalculation of their data shows a percentage error of 20.3%. The method may be valuable in pediatric patients, but more clinical validation studies are warranted.

Ultrasound techniques

Transthoracic echocardiography

Transthoracic echocardiographic assessment of CO can be divided into volumetric and Doppler-based methods.[77, 78] Using volumetric measurements of the left ventricular volume performed at the end systolic and end diastolic phase, the stroke volume (end-diastolic minus end-systolic volume), and hence the stroke volume, can be estimated.[79] The two main limitations of this volumetric method are resolution and geometry.[80] The resolution of echocardiography is approximately 1 mm.[77] But a variation of 1 mm in the

size of the ventricle radius of an infant heart can influence the stroke volume estimation to an important extent. The geometric limitations rely on the assumptions of circular or elliptical shape of the ventricles and on the uniform contractions of the ventricles. In clinical practice, this is often not the case.

Doppler-based methods require accurate measurement of the pulmonary or aortic valve annulus and the velocity profile of systolic flow through the valve.[81] The velocity–time integral is known as stroke distance, which is the distance that a column of blood will travel along the aorta in one cardiac cycle. Stroke distance can be converted to stroke volume, and hence CO. The major difficulty is the measurement of the aortic dimensions for the calculation of the cross-sectional area. This may cause large variations in CO data between the reference method and Doppler echocardiography.[82]

Both these techniques require training in echocardiography, which makes it less useful to many intensive care unit practitioners. Another problem is the need for the constant realignment of handheld probes. On the other hand, transthoracic echocardiography supplies a vast amount of functional, morphological and thus diagnostic information, including indices of diastolic dysfunction, regional wall abnormalities, valve regurgitation, pericardial effusion, chamber dilatation, cardiac chamber interdependence, systemic and pulmonary blood flow (Qp/Qs ratio), superior caval vein flow (neonates) and organ flow.

Lu et al. evaluated the accuracy, reproducibility and efficacy of various methods of volumetric echocardiographic assessment of left ventricular indices in children. In this study, M-mode, 2D and 3D echocardiographic algorithms were compared with cardiac magnetic resonance measurements. The 3D echocardiography was superior to the other methods in accuracy and reproducibility for quantification of the LV indices in children.[80] Chew et al. published a 20-year literature review for Doppler CO measurement in children, focusing on its reliability, bias and precision in comparison to standard reference methods such as thermodilution, dye dilution and Fick techniques. [82] They concluded that Doppler CO measurements are reasonably precise, with a percentage error of ±30% and a percentage bias of less than 10% (range: -37–16%) in the majority of studies. However these results are operator and thus experience dependent.

Echocardiographic estimation of CO in the intensive care unit has several limitations, such as technical problems, examiner variability and costs. Furthermore, transthoracic echocardiography is, by definition, a non-continuous measure of cardiac function and filling status, and not useful as a trend monitor over hours and days. As such, echocardiography cannot be considered to be a CO monitoring device. However, it is has become an indispensable diagnostic tool for critically ill adults and children in many intensive care units.

Transesophageal Doppler ultrasound method

The transesophageal Doppler ultrasound technique (TED) measures the descending aortic blood velocity. The Doppler probe is positioned in the esophagus at the midthoracic level and placed in the direction of flow in a blind fashion and is subsequently adjusted to obtain the optimal Doppler signal.[83] Murdoch and Tibby derived blood flow velocity in mechanically ventilated children in the descending aorta without the need for direct aortic cross-sectional area measurement, which is a major source of error of Doppler flow measurement.[84, 85] They used signal minute distance as a surrogate for CO, which is a time–velocity integral multiplied by heart rate. Compared with the TPTD technique, in both studies the signal minute distance was able to track changes in CO under various hemodynamic conditions. This property makes TED a very useful method for guiding fluid management in children.[86] However, percentage error could not be recalculated from their data for CO measurements. Mohan et al. studied tracking changes in CO with suprasternal Doppler ultrasound and TED in children.[87] Their data support that TED seems to be a clinically useful tool in monitoring trends in CO. Chew et al. reviewed several pediatric studies of ultrasound Doppler CO measurement, and concluded that transesophageal Doppler measurements seem to be more reproducible than transthoracic echocardiography, with an interobserver repeatability of 2.5–8% and an intraobserver repeatability of ±3%.[82] Schubert et al. compared TED (CardioQP™; see Table 1) with transthoracic echocardiography for CO measurement in postcardiac surgery infants and children.[88] TED seemed to underestimate CO and recalculation of the percentage error resulted in an unacceptably high value of ±78%. The Working Group on Noninvasive Haemodynamic Monitoring in Pediatrics compared the CardioQP™ esophageal Doppler technique in children during heart catheterization with the PATD method.[89] They conclude that CO values cannot be reliable measured with the CardioQP™ calculating a percentage error of ±54%.

Technical aspects, such as probe size, fixation and patient tolerance, are limitations for the use of TED. With the provision of special pediatric probes, the technique seems safe for children and infants.[88] On the other hand, in small children it is difficult to position the Doppler probe optimally and, owing to its size, the probe cannot be left in place for a long period of time in small children. Furthermore, the nasogastric tube can negatively influence the quality of the obtained signal. The absolute CO measurements should not be interpreted, as they almost always underestimate the true value. This can be explained by the assumption that the insonation angle (the angle between the ultrasound beam and the aortic blood flow) is supposed to be approximately the same as the fixed angle between the probe and the transducer. Even small deviations of the actual from the assumed angle will result in erroneous velocity calculations, because of the nonlinear character of the cosine function in the Doppler equation.[90]

Continuous wave Doppler ultrasound

The ultrasonic CO monitor (USCOM) (see Table 1) is a new, easy to handle portable apparatus for measuring CO. It provides a transcutaneous CO measurement based upon continuous wave Doppler ultrasound. The Doppler flow is measured using a handheld probe positioned on the thorax. A nomogram, based on the subject's height, incorporated into the software, estimates the valve cross-sectional area, so that the CO can be calculated from the measured flow across the aortic or pulmonary valve.[91-94]

The reliability found in animal studies compared with ultrasound flow probes around the ascending aorta were acceptable, with a percentage error of 13%.[95] It has been used in adults, as well as in children and neonates, for assessment of serial CO measurements and changes in CO. The only validation study in children has been performed by Knirsch et al. against the PATD.[91] With a percentage error of ±36%, they concluded that the USCOM does not reliably represent absolute CO measurements compared with PATD. A pilot study in healthy newborns and preterm neonates showed a good inter-operator (rater) agreement.[92] The study of Phillips et al., comparing USCOM versus 2D echo Doppler in 37 preterm neonates, showed good agreement between the two intermittent CO measurement methods.[96]

The USCOM CO measurements are rather dependent on the skills of the operator and on the quality of the Doppler flow signal. The nomogram-based estimates of the cross-sectional area of the aorta and pulmonary values are bound to introduce some systematic error into the measurement of CO in the clinical setting. The validity of this technique requires further studies. Its clinical use seems especially beneficial in settings of emergencies for a quick and global estimation of CO.

Fick principle technique

The direct oxygen Fick method is a gold standard for the measurement of CO. The Fick equation relates CO to oxygen consumption and the arterial–venous oxygen content difference[3, 97, 98]:

$CO = VO_2/(CaO_2 – CvO_2)$

where VO_2 is oxygen consumption; CaO_2 is arterial oxygen content; and CvO_2 is mixed venous oxygen content. However, this method requires the precise and simultaneous measurement of VO_2 (using calorimetry), hemoglobin level and arterial and mixed venous oxygen saturation. This renders the method not practical for bedside measurement.

The equation may also be modified using carbon dioxide (CO_2) elimination and the difference between the venous and arterial CO_2 blood content. The NICO2TM monitor (see Table 1), designed for CO measurement, utilizes the indirect Fick principle for CO_2, based on a partial rebreathing method, which obviates the need to measure CO_2 in the blood stream.[99-101] However, this technique needs further adjustments for use in younger children and is dependent on the assumed amount of pulmonary shunt.[99, 102] One of the major disadvantages of this Fick derived method is that the measurement of CO requires a period of steady state. Furthermore, its use is restricted because of the many potential technical problems, such as sampling, air leak, high inspiratory oxygen concentrations and death space. Currently, it can only be used in patients ventilated with tidal volumes more than 300 ml. Consequently, the technique is often not applicable in critically ill patients who require extreme ventilatory conditions, using high fractions of inspired oxygen. The technique will also fail in conditions that affect the intra alveolar distribution of the gas, for instance in the presence of severe interstitial or obstructive lung disease.[12]

Besides the rebreathing CO_2 Fick method, a modified CO_2 Fick method is also applicable in children. Like the oxygen Fick method, it requires arterial and central venous blood sampling. Instead of determination of VO_2, VCO_2 measurement is necessary. VCO_2 can be measured using volumetric capnography. Although reliable, this technique is still complicated and shares many disadvantages with the oxygen Fick method, but it has the advantage of being validated in small subjects.[103]

Bio-impedance techniques

The noninvasive thoracic bio-impedance technique for measuring CO was introduced more than 40 years ago with impedance cardiography.[104] In the last decades two

successors of the impedance cardiography technology have been developed: electrical velocimetry (EV) and bioreactance.

The first method relates the maximum rate of change of thoracic electrical impedance to peak aortic blood acceleration, and derives the mean aortic blood velocity using a transformation.[105] This technique measures changes in the transthoracic impedance during cardiac ejection caused by volumetric changes of the aorta and by conductivity changes of the blood in the aorta. The basic equation of the algorithm, in contrast to former approaches, focuses on the compartment with the greatest contributing factor to conductivity changes, being the blood in the aorta. Minor changes in high-resistance low-conductivity compartments, such as the lung, gas and surrounding tissues, are neglected. This technique requires four disposable surface electrodes, two placed at the left side of the neck and two placed on the left lateral side of the thorax at the level of the xiphoid process. The device emits a small sinusoidal, low current (2 mA) with high frequency (50 kHz) through two electrodes on both sides. The other two electrodes record the thoracic electrical bio-impedance (Z). Changes of the basic impedance are averaged over ten cardiac cycles. The first study to validate EV in an infant-simulated model, was a piglet study comparing CO measurements of EV with TPTD under various hemodynamic conditions.[106] Although the EV method could track changes of more than 15% in CO, the percentage error was markedly higher (83%), which they attributed to the morphology differences between humans and piglets. Four human studies have been published in pediatric patients since the commercial availability of the Aesculon® (see Table 1). Tomaske et al. compared EV with PATD in pediatric patients with congenital heart disease without shunts, under hemodynamic stable conditions. [107] They could not assess reliable CO measurements with EV and found a percentage error of ±44%. Recently, the same group published a similar study, this time comparing CO measurements of EV with transthoracic echocardiographic Doppler flow.[108] Again, agreement between the two methods was low. Two other clinical studies also showed an unacceptable percentage error.[88, 109]
Although the EV method is potentially attractive, being noninvasive, continuous and easily applicable, at this stage it cannot be used in clinical practice for reliable measurement of absolute CO values in children. New approaches for optimizing electrode position on the patient's surface have been suggested for improvement.

Bioreactance, the second technique, is the analysis of the variation in the frequency spectra of a delivered oscillating current that occurs when the current traverses the thoracic cavity. This is different from the traditional bioimpedance technique that analyses only the changes in signal amplitude. Although promising results in adults have been published, there are currently no pediatric data available.[91, 110-112]

Noninvasive continuous finger arterial pressure & CO monitoring

Blood pressure and CO can be obtained using a continuous, noninvasive, finger arterial pressure measurement technique. This method requires an inflatable finger cuff that incorporates a photoplethysmographic sensor, a rapid-reacting pneumatic servo system and a special device (Nexfin; see Table 1). This method is based upon the vascular clamp principle of Penaz and is the successor of the former Finapres device.[113-115]

In short, the plethysmographic signal drives the servo system in a way that the finger arterial wall is constantly kept unloaded. Thereby, the cuff pressure is a reflection of the finger arterial pressure. After application of a software algorithm, a brachial pressure curve is generated.[116] The blood pressure measurement is reliable and complies with the Association for the Advancement of Medical Instrumentation standards in adults[117-119]. In children, a beta-type device has been shown to be feasible and accurate in measuring blood pressure.[120-122]

The Nexfin device incorporates an APCCO method that can be applied to the arterial waveform from the finger artery. Patient parameters (weight, length, gender, age) are needed to track changes in CO more reliable. Using a separate calibration method is possible but is not required. This continuous noninvasive CO method has only been studied in adults so far, and has shown been to be reasonably accurate.[123-127] At present, only finger cuffs for children from 6 to 8 years of age are commercially available. Application for younger children will be available in the future.

Expert commentary

The ideal CO monitor should be accurate, reproducible, continuous, noninvasive, easy to apply, operator-independent, cost effective and should have a rapid response time (beat-to-beat) (4). Unfortunately, no such technique exists for CO measurement in either pediatric or adult practice.

In this article, we discussed the available CO monitoring devices that are currently available and, in part, applicable in pediatric patients. The choice is mainly determined by the clinical indication and situation. Thereafter, the balance between invasiveness, risks, instrumentation, user expertise and additional parameters that can be collected, together with cost, will finally be decisive. In choosing a device the physician should consider the following three questions: is a reliable absolute measurement of CO required or is tracking changes more appropriate? In the first case a more invasive approach is required. In the latter, a continuous technique should be applied. Is an invasive measurement feasible or does the clinical situation require noninvasiveness? When noninvasiveness is required, the physician should be aware that the obtained

results are often less reproducible. Are other hemodynamic measurements also required (such as extravascular lung water or arterial pressure variations)?
In clinical practice, invasive dilution techniques should be considered for hemodynamic monitoring of septic and other (postoperative) circulatory compromised pediatric patients during pediatric intensive care unit treatment. The CO value may help the clinician to guide inotropic, vasopressor or fluid therapy. In the setting of perioperative hemodynamic monitoring, continuous CO measurement, such as an APCCO method or TED, is probably more convenient. Tracking changes in these situations is particularly informative and in some systems there is no need for intermittent recalibrations. Noninvasive methods, such as echocardiography and other ultrasound techniques, can be very useful in the first phase of treatment of an acute patient, because it can be available quickly and can guide the direction of treatment in the first phase. Depending on the severity of the circulatory insufficiency, continuous and more invasive monitoring should be considered thereafter.
In general, a more invasive technique produces a more reliable absolute measurement. Most importantly, the physician should have the knowledge of the technical background and pitfalls that are associated with the use of the chosen technology.

Five-year view
Data from adult studies cannot be extrapolated to small children. More research is needed to further adapt algorithms and technologies for the pediatric population. Unfortunately, industrial interest is generally directed towards adult critical care medicine and anesthesiology. Besides that, technical difficulties and ethical constraints to perform clinical validation studies in children also play a role. We believe that the combination of transthoracic echocardiography and a fast and continuous CO monitoring technology (with or without calibration) will be the most ideal combination in the near future.

With every new device comes the need for validation and evaluation of its usefulness in the clinical setting. In this regard there is a growing need for standardized validation methods for CO monitoring tools.

Besides validation studies, randomized trials of CO guided hemodynamic therapy should demonstrate whether CO monitoring is a useful adjunct to the existing clinical arsenal with respect to morbidity and mortality in critically ill children.

Key issues
- Measurement of cardiac output (CO) is imperative to determine the hemodynamic status of the patient, to initiate the appropriate therapy, to subsequently follow the patient's response to instituted therapies and thereby trying to prevent organ dysfunction.

- In the last decade, more technologies have become available for measurement of CO, in part applicable in pediatric patients. As a result hemodynamic monitoring in children is now slowly evolving in the pediatric critical care and anesthesia area.
- The ideal CO monitor does not exist.
- The choice of CO measuring device in children is mainly determined by the clinical indication and situation. Thereafter, the balance between invasiveness, risks, instrumentation, user expertise, additional parameters that can be collected and costs will finally be decisive.
- More research is needed to further adapt algorithms and technologies for the pediatric population.

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Part II

Transpulmonary thermodilution cardiac output monitoring

Cardiac output can be measured with the transpulmonary thermodilution method in a pediatric animal model with a left-to-right shunt

4

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Abstract

Background

The transpulmonary thermodilution technique for measuring cardiac output has never been validated in the presence of a left-to-right shunt.

Methods

In this experimental, pediatric animal model nine lambs with a surgically constructed aorta-pulmonary left-to-right shunt were studied under various hemodynamic conditions. Cardiac output was measured with closed and open shunt using the transpulmonary thermodilution technique (CO_{TPTD}) with central venous injections of ice-cold saline. An ultrasound transit time perivascular flow probe around the main pulmonary artery served as the standard reference measurement (CO_{MPA}).

Results

Seven lambs were eligible for further analysis. Mean weight was 6.6 kg (± SD 1.6). The mean CO_{MPA} was 1.21 l/min (range 0.61 – 2.06 l/min) with closed and 0.93 l/min (range 0.48 – 1.45 l/min) with open shunt. The open shunt resulted in a mean Qp/Qs ratio of 1.8 (range 1.6 – 2.4). The bias between the two CO methods was 0.17 l/min (limits of agreement (LOA) ± 0.27 l/min) with closed shunt and 0.14 l/min (LOA ± 0.32 l/min) with open shunt. The percentage errors were 22% with closed shunt and 34% with open shunt. The correlation between the two methods was r= 0.93 ($p<0.001$) with closed shunt and r=0.86 ($p<0.001$) with open shunt. The correlation between the two methods in tracking changes of CO (Δ CO) during the whole experiment was r = 0.94 ($p<0.0001$).

Conclusions

The transpulmonary thermodilution technique is a feasible method of measuring cardiac output in pediatric animals with a left-to-right shunt.

Introduction

Clinical hemodynamic assessment in critically ill children is considered unreliable.[1] Therefore, several invasive and non-invasive methods of measuring CO are increasingly applied in infants and children.[2, 3] Of these the transpulmonary thermodilution (TPTD) technique is considered the gold standard.[4-7]
TPTD measures CO by analyzing the thermodilution curve in the femoral artery after injection of ice-cold saline in a central vein. However, in the presence of congenital intra- and/or extra-cardiac shunts, the TPTD method is considered inaccurate. The systemic blood flow in the presence of a shunt is usually evaluated by clinical signs and intermittent echocardiography.[8-10] Heart catheterization using oximetry (Fick's principle) and several other methods accurate detect, localize and quantify left-to-right shunts.[11-15] However, a continuous bedside CO measurement, reliable in a shunt circulation seems not available.
The transpulmonary thermodilution method may, however, be more reliable in case of a left-to-right shunt than previously considered. In general, indicator dilution methods have to fulfill four conditions: 1) steady blood flow, 2) no or minimal loss of indicator between injection and detection point, 3) complete mixing of the indicator with blood, and 4) the indicator must pass the detection point only once.[16] In the presence of a left-to-right shunt, CO measurement using the TPTD technique, may meet all these conditions.
We evaluated the reliability of the TPTD technique in a pediatric animal model with a surgically constructed aorta-pulmonary left-to-right shunt. Measurements were performed under various hemodynamic conditions of hemorrhagic shock with open and closed shunt and resuscitation with closed shunt. We also studied the possibility to track changes in the CO.

Methods

General. This experiment was performed in accordance with Dutch national legislation concerning guidelines for the care and use of laboratory animals and was approved by the local ethics committee on animal research of the Radboud University Nijmegen Medical Centre (RUNMC Licence number RU-DEC 2008-117; CDL-projectnumber 33047). Nine lambs were studied under general anesthesia. Premedication consisted of the intramuscular administration of midazolam 2 mg/kg and ketamine 10 mg/kg and intravenous administration of propofol 2 mg/kg. General anesthesia was maintained using inhalation of isoflurane 1-1.5 volume% and continuous intravenous administration of sufentanil 20 µg/kg/hr, midazolam 0.2 mg/kg/hr, ketamine 10 mg/kg/hr, and pancuronium 0.05 mg/kg/hr after a loading dose of 0.05 mg/kg. During

the experiment continuous intravenous glucose 10% 2 ml/kg/hr was administered. The lambs were orotracheally intubated using a 5 to 6 mm (inner diameter) cuffed endotracheal tube (Kruse, Marslev,Denmark). The lungs were mechanically ventilated in a pressure-controlled mode using tidal volumes of approximately 10 ml/kg (Datex-Ohmeda anesthesia machine). Normocapnia, guided by capnography with the CO_2SMO Plus Respiratory Profile Monitor (Model 8100, Respironics, Pittsburgh, USA), was achieved by adjusting the respiratory frequency to maintain an end-tidal CO_2 tension between 30 and 41 torr (4.0–5.5 kPa). A servo-controlled heating mattress and an external heating lamp were used to maintain rectal temperature between 38 and 40°C. At the start of the shunt construction, anticoagulation therapy was instituted with unfractioned heparin with a loading dose of 100 IU/kg and a continuous intravenous infusion of 50 IU/kg/hr. At the end of the experiment, the animals were sacrificed.

Instrumentation. Immediately after induction of anesthesia the animals received a femoral artery catheter (3Fr 7 cm, PV2013L07,Pulsion, Germany), a femoral central venous catheter (5Fr 2lumen 13 cm, Arrow, Germany) and a Pediasat Oximetry Catheter (4,5F 5 cm, Edwards Lifesience LLC, USA) positioned in the external jugular vein with the tip positioned in the superior vena cava. All intravascular catheters were inserted by surgical cut-down. A left-sided thoracotomy was performed and the remains of the native ductus arteriosus were ligated. A 4 to 6 mm pediatric shunt (Gore-Tex® Vascular Grafts, Gore Medical, USA) was constructed between the descending aorta and the left pulmonary artery. Ultrasound transit time perivascular flow probes (PAX series, Transonic Systems, Ithaca, NY) were placed around the main pulmonary artery (Q_{MPA}, probe 10 mm) to measure reference cardiac output (CO_{MPA}). Two 8 mm flow probes were positioned around the descending aorta, proximal (Q_{pre}) and distal (Q_{post}) of the aorta-pulmonary shunt. The flow probes were checked for zero flow value directly postmortem. Ultrasound transit time flow probes use a two-way ultrasound technique. By calculating the difference between transit times upstream and downstream, the blood flow is measured. Care was taken to avoid air within the flow probe by applying sufficient quantities of acoustic gel. During the whole experiment the thorax was left open enabling opening and closure of the shunt with a clip.

Transpulmonary Thermodilution. Transpulmonary thermodilution cardiac output (COTPTD) was measured by injecting ice-cold saline into the jugular venous catheter. Temperature changes were detected by the thermistor tipped catheter inserted in the femoral artery connected to a commercially available device (PiCCOplus, software version 6.0, Pulsion, Munich, Germany). We used the mean value of three bolus injections of 3 ml of ice-cold (<10°C) saline. The venous injection point was not in proximity to the arterial femoral catheter thermistor tip, thereby avoiding the cross-talk phenomenon in case of low cardiac output.[17, 18] Measurements were stored on a computer using specially designed software (PiCCO-Volef Data Acquisition version 6.0, Pulsion, Munich, Germany). Before a series of thermodilution measurements, the central venous catheter

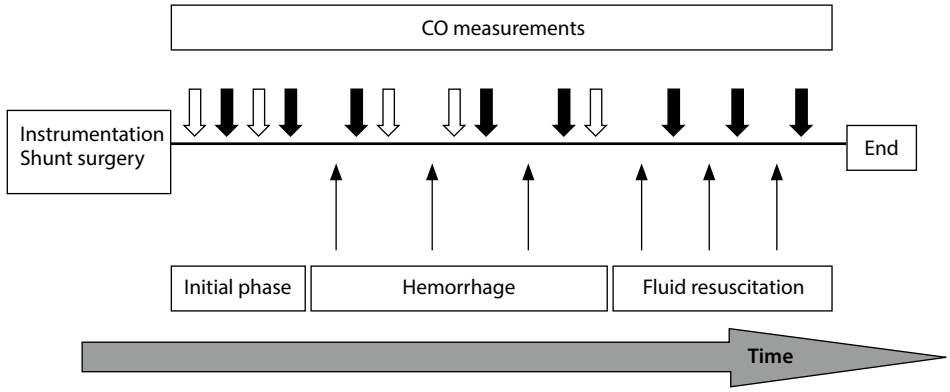
was flushed with 1–2 ml of ice-cold saline. Afterwards, each thermodilution measurement was visually inspected to assure that it was technically correct.
Other Measurements. We measured invasive arterial pressure and central venous pressure, electrocardiogram, heart rate, arterial oxygen saturation, end-tidal CO_2, respiratory frequency, tidal volume, airway pressure, and body core temperature. During CO_{TPTD} measurement, all other hemodynamic variables, including CO_{MPA}, were recorded simultaneously with a 200-Hz sampling rate using a computer system with special biomedical registration software (Poly, Inspektor Research Systems, Amsterdam, The Netherlands). The exact time span of the thermodilution measurement was marked in the registration. The difference between CO_{TPTD} and CO_{MPA} was calculated using the mean value of three consecutive TPTD measurements and the mean value of CO_{MPA} measurements over the same three periods. To analyze whether changes in CO_{MPA} are adequately reflected by changes in CO_{TPTD}, we included all measurements over the entire experiment.

For technical reasons, direct measurement of the shunt flow is not possible, therefore shunt flow was calculated as the difference between Q_{pre} and Q_{post}.
The Qp/Qs ratio was calculated using the following equation:
$Qp/Qs = (Q_{MPA} + (Q_{pre} - Q_{post})) / Q_{MPA}$
In open shunt conditions we only included measurements with a Qp/Qs ratio of > 1.5.

Protocol. The CO measurements were performed during three phases of the experiment as shown in figure 1. The aorta-pulmonary shunt was alternately opened and closed with a clip. The hemorrhage was performed by three periods of withdrawal of blood from the venous catheter to obtain a decrease in mean arterial blood pressure of 10 mmHg each step. After the hemorrhagic phase, the shunt remained closed and the animals were resuscitated with three fluid challenges of 20 ml/kg of either homologous whole blood transfusion or hydroxyethyl starch HES 130/0.4 6% (VoluvenTM), depending on the hemoglobin content of the blood, analyzed after each volume loading. Blood transfusions were stopped as soon as the initial hemoglobin content was reached.
In case of serious hemodynamic insufficiency at the time of the experiment a continuous infusion of epinephrine was administered to prevent the animal from dying.

Figure 1

Protocol of the 3 phases of the experiment. Cardiac output is measured with alternately open (not padded arrow) and closed shunt (solid broad arrow).



Statistical analysis. Comparison between absolute values of CO_{TPTD} and CO_{MPA} and changes in CO was performed using correlation statistics (Pearson correlation) after confirming normal distribution of the data. In addition, data were analyzed using the method described by Bland and Altman.[19] As the number of measurements per animal did not vary (1x12, 6x13) we did not correct for the repeated measurements. The difference between the two methods (bias) was calculated by subtracting the value of CO_{MPA} from CO_{TPTD}. The bias was plotted against the mean CO ($[CO_{MPA} + CO_{TPTD}]/2$). The limits of agreement (LOA) were calculated by multiplying the standard deviation (SD) of the bias with 1.96. The percentage error was calculated using the following formula: (1.96 x SD of the bias)/mean Q_{MPA} x 100%, using mean Q_{MPA} as being the reference.[20] The coefficient of variance (CV) of the CO is calculated by dividing the SD of the mean by the mean of all the CO measurements of each technique and lamb separately. The results are expressed as percentages (=100% x SD/mean). Calculations and data management were performed using Excel for Windows (Office 2007, Microsoft, Seattle, WA). Statistical calculations were performed with MedCalc (Med-Calc Software, Mariakerke, Belgium).

Table 1

Characteristics, hemodynamic parameters and procedures of each lamb separately.

lamb	weight	age	shuntsize	Mean shuntflow	mean	Mean CO_{MPA}	Mean CO_{MPA}	Mean MAP	total
nr	(kg)	(days)	(mm)	(l/min)	Qp/Qs	Closed shunt	Open shunt	(mmHg)	blood withdrawal
					Ratio (range)	(l/min)	(l/min)	(range)	(ml/kg)
1	3.5	12	4	0.7	1.9 (1.7-2.1)	0.87	0.80	46 (36-54)	21
2	6.2	5	6	0.6	1.6 (1.3-1.8)	1.23	0.98	40 (29-53)	21
3	8.7	10	6	0.9	1.7 (1.6-1.8)	1.65	1.31	44 (35-58)	22
4	6.4	11	6	0.6	2.0 (1.4-2.4)	1.06	0.67	34 (25-51)	17
5	7.3	28	6	0.7	1.6 (1.3-1.8)	1.49	1.19	43 (32-54)	15
6	7.7	28	6	0.6	1.6 (1.4-1.9)	1.15	1.00	55 (115-47)	14
7	6.4	29	6	0.8	2.4 (2.1-2.6)	0.93	0.61	46 (33-53)	22

Table 2

Coefficient of variation in cardiac output (CO) measurements of each lamb separately.

Lamb	mean CO TPTD	SD TPTD	CV TPTD	mean CO MPA	SD MPA	CV MPA
(number)	(l/min)		(%)	(l/min)		(%)
1	0.90	0.05	5	0.84	0.01	1
2	1.19	0.08	7	1.13	0.01	1
3	1.65	0.12	7	1.52	0.02	1
4	0.98	0.07	8	0.91	0.01	1
5	1.51	0.09	6	1.37	0.01	1
6	1.50	0.18	12	1.09	0.02	2
7	1.06	0.08	8	0.81	0.01	1

Mean CO TPTD resp. MPA= mean cardiac output of all transpulmonary thermodilution resp. main pulmonary artery measurements; SD TPTD resp. MPA = standard deviation of the mean CO TPTD resp. MPA; CV TPTD resp. MPA = coefficient of variation (100 x SD/mean) of the TPTD resp. MPA measurements expressed in percentages.

Results

One lamb died during the surgical procedure due to an intractable bleeding before the first measurement was performed. In another lamb the aorta-pulmonary shunt was insufficient with a maximum Qp/Qs ratio of 1.2. Data from this lamb were excluded from the study. As a result seven lambs with a mean body weight of 6.6 kg (± SD 1.6) and a mean age of 17.6 days (± SD 10.3) were included. The mean CO_{MPA} with a closed shunt was 1.21 l/min (range 0.61 – 2.06 l/min) and with an open shunt 0.93 l/min (range 0.48 – 1.45 l/min). Hemodynamic data for each individual lamb are shown in table 1. The open shunt resulted in a mean Qp/Qs ratio of 1.8 (range 1.6 – 2.4) with a mean aorta-pulmonary shunt flow of 0.7 l/min (range 0.6 – 0.9 l/min).

Calculations of the coefficient of variance (CV) are shown for each technique per lamb in table 2. The median CV for the TPTD technique and flow probe (MPA) respectively is 6% (min. 0% and max. 33%) respectively 1% (min. 0% and max. 6%). An example of a change in the thermodilution curve induced by opening the shunt is depicted in figure 2. The shunt opening induced a Qp/Qs ratio of 1.8. The measurement results are shown in table 3. The increase in mean transit time (MTt) was almost half the increase in down slope time (DSt): 52% and 92% respectively. The influence of the Qp/Qs ratio on the change in MTt and DSt is depicted in figure 3. The inverse correlation between the percentage changes of Qp/Qs and CO is shown in the same figure ($r = -0.84$; $p<0.0001$).

Differences between the CO_{TPTD} and the CO_{MPA} with a closed and open shunt are shown in figure 4a and 4b respectively. The higher number of paired CO measurements in Figure 4b is explained by the fact that during the resuscitation phase the shunt remained closed. The mean bias was 0.17 l/min (LOA ± 0.27 l/min) with the shunt closed and 0.14 l/min (LOA ± 0.32 l/min) with an open shunt. The bias was not influenced by epinephrine administration or the magnitude of the Qp/Qs ratio (not shown). The Spearman's coefficient of rank correlation (rho) between the shunt ratio (Qp/Qs) and the difference between CO values by the two techniques was -0.2 (95%CI -0.392 to 0.00646; $p = 0.057$). The percentage errors were 22% with a closed shunt and 34% with an open shunt. The correlation coefficient between the two methods was 0.93 ($p<0.001$) with a closed shunt and $r = 0.86$ ($p<0.001$) with an open shunt.

The correlation between the two methods in tracking changes in CO (Δ CO) for the whole experiment was $r = 0.94$ ($p<0.0001$)(figure 5).

Figure 2

Transpulmonary thermodilution curves of lamb 1 with a closed and open shunt during stable hemodynamics.

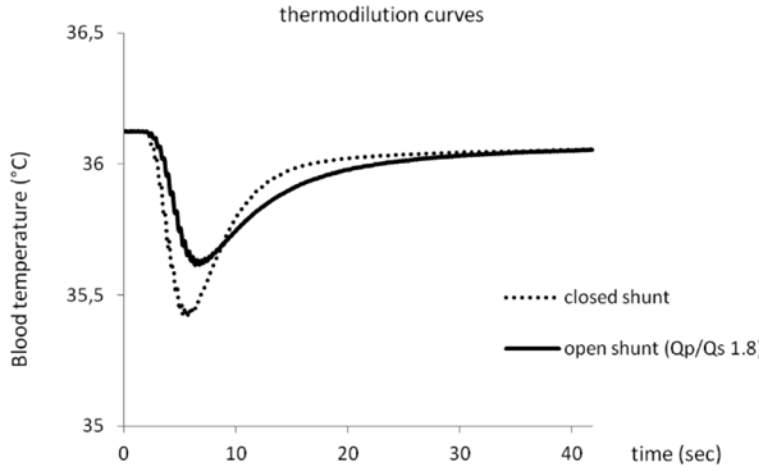


Table 3

The absolute values of two single TPTD measurements with a closed and open shunt in lamb 1, graphically illustrated in figure 2.

shunt	CO_{TPTD} (l/min)	MTt (sec)	DSt (sec)	EVLW (ml)	GEDV (ml)	MAP (mmHg)
closed	0.96	8.9	4.8	61	65	55
open	0.83	13.5	9.2	113	59	46

Figure 3

The percentage change in Qp/Qs ratio compared to the percentage change in mean transit time (MTt)(solid circle) and down slope time (DSt)(open square) with an open and closed shunt. The linear correlation is r=0.95 (p<0.001) for the MTt and r=0.96 (p<0.0001) for the DSt. The inverse correlation between the percentage change of Qp/Qs and CO (open triangle) is r = -0.84 (p<0.0001).

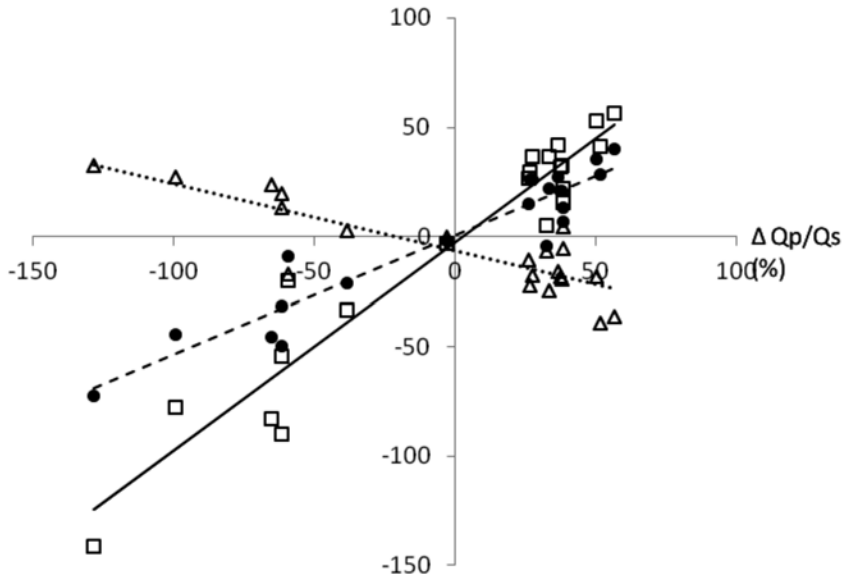


Figure 4a

Bland Altman plots with closed (4a) and open shunt (4b).

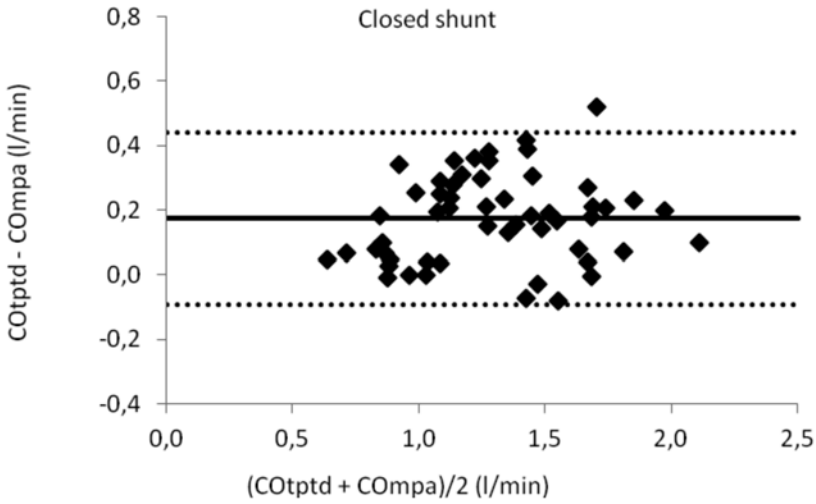


Figure 4b

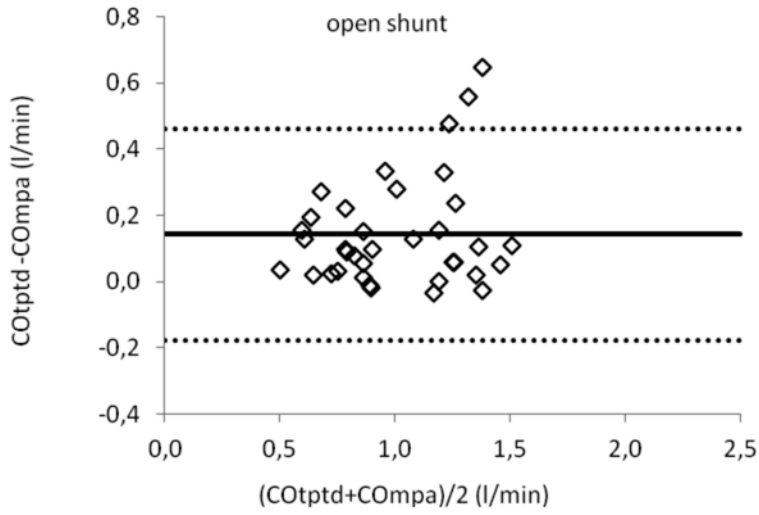
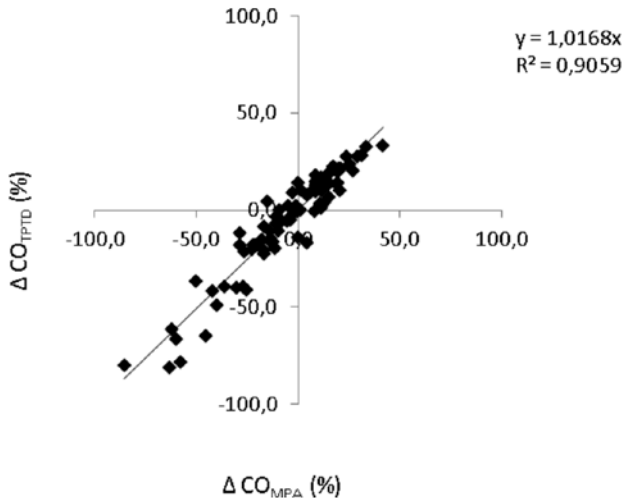


Figure 5

Correlation between changes in CO_{TPTD} and changes in CO_{MPA} for the whole experiment with sequential open and closed shunt.



Discussion

For the first time we demonstrate that the transpulmonary thermodilution cardiac output measurement is feasible in the presence of a significant left-to-right shunt. There was a significant correlation r = 0.94 ($p<0.0001$) between the two methods in tracking changes of CO including the results over the whole experiment. The experiment order made it impossible to separate the results for tracking changes of CO merely in the open situation.

The precision of TPTD for measuring CO with a closed shunt is in agreement with earlier studies from our group with a percentage error well within the acceptable limits of 30% as described by Critchley and Critchley.[4, 20] However, the percentage error for measuring CO with an open shunt was significantly larger (34 versus 22%). This can be explained by the lower cardiac output with an open shunt condition and the increased limits of agreement. Probably the shunt flow itself may cause this measurement error. The longer passage time of the thermal indicator in the extra circuit may cause a loss of indicator by diffusion into the surrounding tissue resulting in an overestimation of the CO.

The calculations of CV of the CO measurements show more deviations with the TPTD method compared to the flow probe (MPA) technique (table 2). The low CV values of

our reference technique (flow probe) confirm assessment of CO measurements in stable conditions. The measurements by the TPTD method fluctuated more during the same time-interval, which explains the difference in agreement between the two methods, although it is not possible to deduce from these calculations, which measurement contains the true value.

We used the flow through the main pulmonary artery as the reference value of the systemic blood flow. We consider this the only valid reference method, since shunt flow entered the pulmonary circulation distal to the measurement site and it also includes the coronary blood flow. The descending aortic blood flow distal from the shunt does not represent systemic blood flow, as it excludes the blood going to the upper part of the body and the coronaries.

CO_{TPTD} measurement in the presence of a left-to-right shunt has, to our knowledge, not been validated before although the technique was described in several case reports.[21, 22] Silove et al. measured systemic CO by thermal (room temperature) dilution technique in pediatric patients with a left-to-right shunt and compared the results with the reference Fick method.[23] Measuring the output of the left and right ventricles separately, the issue of recirculation was circumvented. The relation between the outputs of the two ventricles correlated closely to the Qp/Qs ratio based on the Fick method.

A left-to-right shunt prolongs the indicator pathway by recirculation. Broadbent et al. described in 1954 the typical alterations in the peripheral (= transpulmonary) dye dilution curve of a centrally located left-to-right shunt in 16 subjects with a patent ductus arteriosus.[24] They showed a decrease in the maximal dye concentration and a prolongation of the disappearance time of the curve. We confirmed these findings in our experiment (Figure 3).

The distortion of the TPTD curve can also be quantified by calculating the mean transit time (MTt) and down slope time (DSt) as shown in table 3. MTt is the time interval between the moment of injection and time of appearance of half of the amount of the injectate at the detector and DSt describes the extrapolated decay of the curve. Dye dilution studies showed a relation between the concentration curve and presence and magnitude of a shunt.[24, 25] As shown in figure 3, our study revealed a significant correlation between Qp/Qs and changes in MTt and DSt. Therefore, MTt and DSt related to cardiac output may be useful for quantifying the magnitude of the shunt.

The presence of a shunt also effects the measurement of the global end diastolic volume (GEDV) and extravascular lung water (EVLW). Since DSt increases with greater magnitude compared to MTt, the pulmonary thermal volume (PTV) will increase more than the intrathoracic thermal volume (ITTV). Therefore, GEDV will decrease and extra vascular lung water (EVLW) will increase. This has been confirmed in clinical patients.[22] These results show that in cases of a left-to-right shunt, volumetric variables like GEDV and EVLW are inaccurate.

The commonly used techniques for CO evaluation in the presence of a left-to-right shunt are arterial and venous oximetry and transthoracic echocardiography. Unfortunately these techniques are either invasive, or need trained and experienced performers. Recent studies of other (non-invasive) methods like the modified carbon dioxide Fick method and electric velocimetry show promising results but need further research.[26, 27] In our opinion, the TPTD method is a valuable alternative. Although, the precision is less with an open shunt, the ability to track changes in CO is clinically acceptable.

Our study has several limitations. First we only studied a limited number of animals. Second, although this experiment was carefully controlled, we cannot be sure that the model adequately reflects the human situation. Third, it was not possible to close the shunt consistently for 100% in all animals, which is of minor importance for our study. Still we can't rule out that the measurements in the closed shunt situation were influenced by residual shunt flow, although the results of TPTD for measuring CO with a closed shunt correlated well with the reference method and were in agreement with earlier studies from our group. Fourth, we introduced an uncertain amount of inaccurateness by using a syringe of 10 ml to determine 3 ml injections. It is advisable to choose the size of syringes to the volume amount of indicator. Fifth, the experiment required the frequent opening and closing of the shunt. As a result is was not possible to study consecutive hemodynamic changes (following fluid therapy for instance) with the shunt left open. Sixth, this model resembles the situation with a patent ductus arteriosus with a unidirectional left-to-right blood flow. In case of a bi-directional or mainly right-to-left shunt blood flow these results will be different.

In conclusion, our study shows that cardiac output measurement using the transpulmonary thermodilution technique is feasible in the presence of a centrally located left-to-right shunt. However, volumetric values like GEDV and EVLW are strongly influenced by and dependent on the amount of shunt flow.

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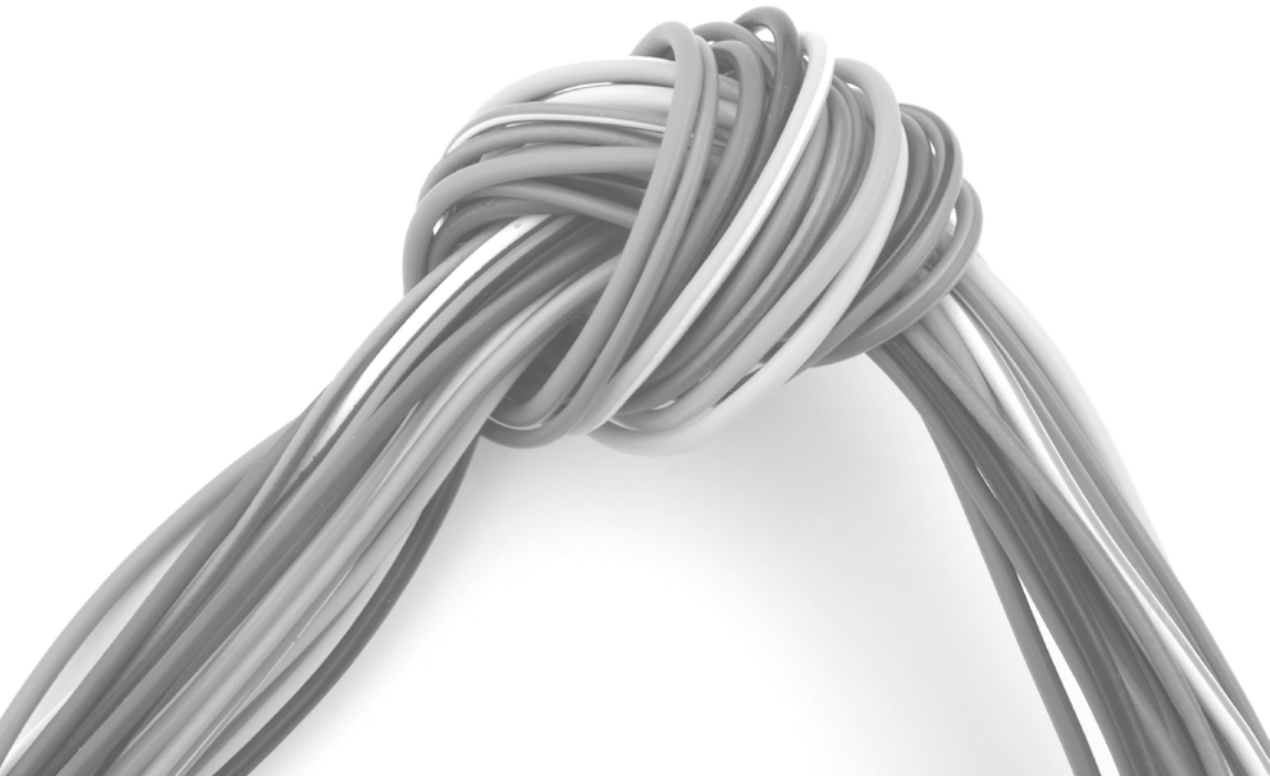
Appendix

Calculation of EVLW and GEDV

Intrathoracic thermal volume (ITTV)	=	CO x MTt x 1000 / 60 [ml]
Pulmonary thermal volume (PTV)	=	CO x DSt x 1000 / 60 [ml]
Global end diastolic volume (GEDV)	=	ITTV – PTV [ml]
Intrathoracic blood volume (ITBV)	=	GEDV x 1,25 [ml]
Extra vascular lung water (EVLW)	=	ITTV – ITBV [ml]



Interpretation of the transpulmonary thermodilution curve in the presence of a left-to-right shunt

5

Intensive Care medicine 2011; 37(3): 550-1

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Abstract original article

Transpulmonary thermodilution curves for detection of shunt.
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The transpulmonary thermodilution (TPTD) with integrated invasive arterial pulse contour analysis monitoring system operates via a single thermal indicator technique to determine extravascular lung water (EVLW), cardiac output (CO) and volumetric variables. The impact of intracardiac shunt on volumetric variables derived from the TPTD curve has not previously been studied. The present two case reports, describe the impact of ventricular septal defect (VSD) and aorto cava fistula (ACF) on the TPTD curve and EVLW measurements in critically ill patients monitored with TPTD.

This report describes two cases of systemic-venous circulation shunt generating early recirculation of thermal indicator with overestimation of EVLW. Haemodynamic measurements in the first patient showed a CO at 4.8 l/min with an increased extravascular lung water indexed value (EVLWI, 31.7 ml/kg), despite absence of hypoxaemia (FiO2 30%) and normal lungs on chest ray. Because, of these conflicting monitoring results, a transthoracic echocardiography was performed that displayed an apical VSD with a gradient measured at 30 mmHg. After surgical repair of the VSD, CO was 5.7 l/min and EVLWI decreased to 14.3 ml/kg. The second case describes a diagnostic dilemma in a hemodynamic instable patient with abdominal pain. Haemodynamic measurements showed decreased global end diastolic volume (GEDV) and increased EVLWI value, despite absence of hypoxaemia. The thermodilution curve was characterized by an early recirculation of the cold indicator which resulted in premature flattening of the descending portion of the curve, indicating a left-to-right shunt. Additional examinations showed an aorto-cava fistula related to an aortic aneurysm at the level of the bifurcation of the aorta.

In conclusion, in the case of recirculation of thermal indicator, the observed overestimated EVLW in absence of gas exchanges abnormality could be an indicator suggesting the search for a circulatory shunt.

To the editor

In a recent article by Giraud et al. the effect of a left-to-right shunt on the transpulmonary thermodilution (TPTD) curve and the subsequent calculation of extravascular lung water (EVLW) and intra thoracic blood volume (ITBV) is described.[1] The authors conclude that a left-to-right shunt generates recirculation of thermal indicator, which induces a change in the dilution curve. Although we support their observation their explanation may lead to confusion.

The transpulmonary thermodilution method must fulfill the following conditions: 1) constant blood flow, 2) no or minimal loss of indicator between injection and detection point, 3) complete mixing of the indicator with blood, and 4) the indicator must pass the detection point only once.[2] To satisfy condition 4, the dilution curve is interrupted at the down slope part based upon a specific algorithm to prevent the effects of recirculation.[3] Subsequently the curve is extrapolated from the interrupted point to the baseline in order to calculate the area under the curve.[4]

The cases described by Giraud et al. both had a left-to-right shunt (ventricular septal defect (VSD) and aorto-cava fistula (ACF). The (pulmonary) "recirculation" that occurs in a left-to-right shunt is an extra "short" circuit. The observed TPTD curve is the result of a delay in delivery of the indicator to the systemic circulation and will subsequently show a lower initial peak, followed by a slow re-approximation to the baseline.

Unfortunately the authors do not provide the values of the mean transit time (MTt) and downslope time (DSt), but these numbers are easily deduced from Figure 1 on page 1084. The recalculations are explained in table 1 and show that the left-to-right shunt induces an increase of both time intervals. The increase of the DSt (51%) is twice the increment of the MTt (25%). Recirculation of the indicator passing the detecting point for a second time is excluded by the fact that true recirculation will not occur before approximately 60 seconds (≈ 2*MTt in the normal situation). This is long after the interruption of the down slope part.

Increment of the DSt and, to a lesser extent, of the MTt can also be observed in the presence of a large volume of lung water. Both situations are the consequence of delayed delivery of indicator to the systemic circulation. In conclusion it can be stated that a left-to-right shunt induces an increase in DSt and, to a lesser extend MTt as a consequence of delayed delivery of indicator to the systemic circulation, due to the presence of an extra circuit. This phenomenon should not be confused with true recirculation.

Table 1

Recalculations case 1

Case 1	VSD present	VSD closed
CO	4.79	5.68
ITBVI	857	1334
EVLWI	31.7	14.3
BSA	1.8	1.8
weight	75	75
Calculations		
ITBV (ml)	1542.6	2401.2
EVLW (ml)	2377.5	1072.5
GEDV (ml)	1234.1	1921.0
ITTV (ml)	3920.1	3473.7
MTt (sec)	49.1	36.7
PTV (ml)	2686.0	1552.7
DSt (sec)	33.6	16.4

Formulas

ITTV = CO * MTt * 1000 / 60

PTV = CO * DSt * 1000 / 60

GEDV = ITTV - PTV

ITBV = GEDV * 1,25

EVLW = ITTV - ITBV

Reference

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Transpulmonary thermodilution cardiac output measurement is not affected by severe pulmonary edema. Results of a newborn animal study

6

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Abstract

Background

The transpulmonary thermodilution (TPTD) technique is widely used in clinical practice for measuring cardiac output (CO). This study was designed to investigate the influence of various amounts of pulmonary edema on the reliability of CO measurements by the TPTD method.

Methods

In 11 newborn lambs pulmonary edema was induced using a surfactant washout technique. Serial CO measurements using TPTD (CO_{TPTD}) were performed at various amounts of lung water. Simultaneously, CO was measured by an ultrasound flow probe around the main pulmonary artery (CO_{MPA}) and used as the standard reference. CO was divided by the body surface area to calculate cardiac index (CI). Data were analysed using correlational statistics and Bland-Altman analysis.

Results

One lamb died prematurely. A total of 56 measurements in 10 lambs were analysed with a median CI_{MPA} of 2.95 (IQR 1.04) litres min^{-1} m^{-2}. Mean percentage increase in extravascular lung water (EVLW) between the start and the end of the study was 126.4 % (SD ± 40.4). Comparison of the two CO methods showed a mean bias CI of -0.16 litres min^{-1} m^{-2} (limits of agreement (LOA) ±0.73 litres min^{-1} m^{-2}) and a percentage error of 23.8%. Intraclass correlation coefficients were 0.91 (95% CI 0.81-0.95) for absolute agreement and 0.92 (95% CI 0.87-0.95) for consistency. Acceptable agreement was confirmed by a tolerability-agreement ratio of 0.39. The within-subject correlation between the amount of EVLWI and the bias between the two methods was not significant (-0.02; $p = 0.91$).

Conclusions

Cardiac output measurements by the transpulmonary thermodilution technique over a wide range of CI values are not affected by the presence of high EVLWI. The slight underestimation of the CO is independent of the amount of pulmonary edema.

Introduction

Cardiac output (CO) is measured reliably in newborn animals and children using the transpulmonary thermodilution (TPTD) technique.[1, 2] Furthermore, this technology can be used at the bedside to measure cardiac volumes and to quantify the amount of pulmonary edema, expressed as extravascular lung water (EVLW).[3-5] However, both in adults and in children, the TPTD method slightly overestimates the true CO value.[6-8] Loss of indicator because of the longer distance of the thermal indicator traversing the heart, lungs and great vessels is suggested as an explanation of the difference in the CO when comparing pulmonary artery with (transpulmonary) femoral artery thermodilution. In addition, there may be other factors that negatively influence the reliability of the TPTD technique. These include indicator loss because of low blood flow or the presence of a left-to-right shunt.[9-11] However, the effect of pulmonary edema on the reliability of CO measurements is only scarcely studied. Theoretically, an increased loss of indicator in the presence of a high amount of pulmonary edema may occur because a thermal indicator diffuses much more easily through water than through air. Consequently, more temperature will be lost into the surrounding tissues. Only a few studies in adults analysed the dependency of CO measurements on the amount of lung edema.[9, 12, 13] However, as infants and young children have a much higher EVLW indexed to body weight (EVLWI) than adults, the impact of these increased amounts of lung edema may be more pronounced.[14-16] Pediatric studies are, to our knowledge, not available. Therefore this newborn animal experiment was designed to investigate the influence of various levels of pulmonary edema on the reliability of CO measurements.

Methods

General. This experiment was performed in accordance with Dutch legislation concerning guidelines for the care and use of laboratory animals and was approved by the local ethics committee on animal research of the Radboud University Nijmegen Medical Centre (RUNMC Licence number RU-DEC 2010-034; CDL-project number 33078). Eleven lambs were studied under general anaesthesia. Premedication consisted of the i.m. administration of midazolam (0.2 mg kg^{-1}), ketamine (10 mg kg^{-1}) and i.v. administration of propofol (2 mg kg^{-1}). General anaesthesia was maintained using inhalation of isoflurane (1-1.5 vol%) and the continuous i.v. administration of sufentanyl (20 µg kg^{-1} hr^{-1}), midazolam (0.2 mg kg^{-1} hr^{-1}), ketamine (10 mg kg^{-1} hr^{-1}), and pancuronium (0.02 mg kg^{-1} hr^{-1}) after a loading dose of 0.05 mg kg^{-1}. The depth of anaesthesia was repeatedly assessed by pain stimuli and clinical parameters such as heart rate, spontaneous ventilation, and elevated arterial pressure. The depth of anaesthesia was adjusted when necessary. During the experiment, continuous i.v. dextrose 10% 2 ml kg^{-1} hr^{-1}

was administered. The lambs were intubated orotracheally using a 4 to 6 mm (inner diameter) cuffed tracheal tube (Kruse, Marslev, Denmark). The lungs were mechanically ventilated in a pressure-controlled mode using tidal volumes of approximately 10 ml kg^{-1} (Datex-Ohmeda anaesthesia machine) and an inspiratory-to-expiratory ratio of 1:2. Normocapnia, guided by capnography with the CO_2SMO Plus Respiratory Profile Monitor (Model 8100, Respironics, Pittsburgh, USA), was achieved by adjusting the minute volume ventilation to maintain an end-tidal CO_2 tension between 4.0 and 5.5 kPa. Impaired oxygenation was treated by adjusting the positive end expiratory pressure (PEEP) and the fraction of inspired oxygen (FiO_2) to maintain the oxygen saturation > 95%. A servo-controlled heating mattress and an external heating lamp were used to maintain core temperature between 38 and 40°C. At the end of the experiment, the animals were killed with pentobarbital (150 mg kg^{-1} i.v.).

Instrumentation. Immediately after induction of anaesthesia a thermal-dye-dilution probe (PV2023, Pulsion, Germany) equipped with a thermistor for detection of changes in blood temperature and a fiber optic to detect plasma levels of green dye, was inserted in the femoral artery. In the contra lateral femoral vein a central venous catheter (5Fr, 2lumen, 13 cm, Arrow, Germany) was inserted for the administration of fluid and drugs. At the same site a femoral artery catheter (20 Ga, single lumen, 12 cm, Arrow, Germany) was introduced for arterial pressure monitoring and blood sampling. All intravascular catheters were inserted by a surgical cut-down technique. A left-sided thoracotomy was performed and the remains of a native ductus arteriosus were ligated. An ultrasound transit time perivascular flow probe (10 or 12 mm) (PAX series, Transonic Systems, Ithaca, NY) was placed around the main pulmonary artery to measure reference CO (CO_{MPA}). The flow probe signal was checked for zero flow values directly postmortem. Ultrasound transit time flow probes use a two-way ultrasound technique. By calculating the difference between transit times upstream and downstream, the blood flow (Q_{MPA}) is measured. Care was taken to avoid air within the flow probe by applying sufficient quantities of acoustic gel. After the placement of the flow probe the thorax was closed. The animals were positioned either supine or lying on the right side throughout the experiment.

Pulmonary edema was induced using a surfactant washout lavage model.[17] In short, lambs underwent repetitive saline lavages (10-35 ml kg^{-1} $lavage^{-1}$ 37°C NaCl 0.9%) of the lung in order to induce surfactant depletion and provoke acute lung injury (ALI). Before the lavages the lambs were pre-oxygenated using an FiO_2 of 1.0. After the lavages, the animals were stabilized for 30 minutes before measurements of ventilatory and hemodynamic parameters and blood gases were obtained. Between lavages the PEEP and minute volume ventilation were increased to maintain oxygen saturation and end-tidal CO_2 within the normal range.

Transpulmonary thermodilution. Transpulmonary thermodilution CO (CO_{TPTD}) was measured by rapid injection of 5 ml ice-cold saline (NaCl 0,9%) into the femoral venous catheter. Changes in temperature were detected by the thermistor connected to a COLD monitor (Pulsion, Munich, Germany). The theoretical background of measuring CO by analysis of the dilution curves and calculation using the Steward Hamilton equation is described elsewhere. [18] Besides CO, blood volumes and extravascular lung water can be calculated from the measurement of the mean transit time (Mts) and downslope time (Dst) of the dilution curves.[5, 19] Before a series of thermodilution measurements, the central venous catheter was flushed with 1–2 ml of ice-cold saline. Each thermodilution curve was visually inspected for artefacts or signs of an inadequate measurement. We used the mean value of three bolus injections of 5 ml of ice-cold (<10°C) saline.

Other Measurements. We measured invasive arterial pressure and central venous pressure, continuous electrocardiogram, heart rate, arterial oxygen saturation, end-tidal CO_2, respiratory frequency, tidal volume, airway pressures, and body core temperature. During the thermodilution measurements, all other hemodynamic variables, including CO_{MPA}, were recorded simultaneously with a 200-Hz sampling rate using a computer system with special biomedical registration software (Poly, Inspektor Research Systems, Amsterdam, The Netherlands). The exact time span of the dilution measurement was marked in the registration system. The reference CO was calculated using the mean value of CO_{MPA} measurements over the same three periods as the mean value of three consecutive TPTD measurements.

Protocol. After instrumentation, baseline measurements of CO (TPTD and CO_{MPA}) respiratory and hemodynamic parameters and blood gases were obtained. Repetitive saline lavage procedures were performed in either one or two subsequent sessions of 10-30 ml kg^{-1}, depending on the recovery of the lambs during the procedure. After each lavage procedure, a pause of 30 minutes was instituted for cardiorespiratory stabilization, followed by repeated measurements of the above-mentioned parameters. A blood transfusion was administered if the hemoglobin (Hb) was < 3.5 mmol $litre^{-1}$. Dobutamine or epinephrine was administered when indicated.

Statistical analysis. The CO values were indexed (CI) to body surface area (BSA). The BSA of the lambs was calculated using the following formula: BSA = $weight^{2/3}$ x 0.121.[20] The statistical variability in the CO during the measurement periods is expressed as the coefficient of variance (CV). This is calculated by dividing the standard deviation (SD) of the mean by the mean of the CO_{MPA} results during each separate measurement period. The results are expressed as percentages (=100% x SD/mean). We defined a CV of ≤ 5 % as acceptable for reliable CO_{TPTD} measurements. Intraclass correlation coefficients, using the two-way mixed model, were calculated for consistency and absolute agreement between

the CO measurement methods. In addition, data were analysed using the method described by Bland and Altman.[21] The difference between the two methods (bias) was calculated by subtracting the value of CI_{MPA} from CI_{TPTD}. The bias was plotted against the mean CI ({CI_{TPTD} + CI_{MPA}}/2). The limits of agreement (LOA) were calculated by multiplying the SD of the bias with 1.96. The percentage error was calculated using the following formula: {(1.96 x SD of the bias)/mean CI_{MPA}} x 100%, using mean CI_{MPA} as the reference.[22] As the number of measurements per animal varied, we corrected for the repeated measurements.[23] The strength of agreement was also calculated by the agreement-tolerability-interval ratio, with acceptable agreement defined as a ratio <1.[24] The tolerability interval is estimated from the 95% range of the observed CI data. The agreement interval is calculated from the range of the LOA. Differences between the bias of low/high CI (</≥ 3.0 litres min^{-1} m^{-2}), lowest/highest quartile of EVLWI groups and low/high (</≥ 8cmH_2O) PEEP were analysed by the Mann-Whitney test. Differences between the LOA were analysed by comparison of standard deviations test (F-test). Differences between the start and final results of EVLWI, PaO_2/FiO_2 ratio and PEEP were analysed by the Wilcoxon signed-rank test. The percentage bias of the CO_{TPTD} compared with the reference CO is calculated by (bias/mean CO_{MPA}) x 100%. Within-subject correlation statistics were used in the comparison of PEEP, EWLWI and PaO_2/FiO_2 ratio with the bias by analysis of covariance for repeated measurements. [25] Calculations and data management were performed using Excel for Windows (Office 2007, Microsoft, Seattle, WA). Statistical calculations were performed with MedCalc (MedCalc Software, Mariakerke, Belgium).

Table 1

Lamb	Weight	Age	Total lavages	CO measurements	Mean CO_{MPA} (±SD)	Mean CI_{MPA} (±SD)
	(kg)	(days)	(ml kg^{-1})	(n)	(litres min^{-1})	(litres min^{-1} m^{-2})
1	8.1	21	125	7	1.89 (0.13)	3.86 (0.27)
2	7.4	21	303	5	1.06 (0.29)	2.31 (0.63)
3	4.1	7	293	6	1.00 (0.09)	3.24 (0.29)
4	7.4	14	68	2	2.48 (0.81)	5.39 (1.77)
5	10.2	17	294	6	2.06 (0.49)	3.62 (0.86)
6	9.4	18	191	4	2.05 (0.14)	3.81 (0.26)
7	died				excluded	excluded
8	8	15	420	8	1.01 (0.26)	2.08 (0.54)
9	9.9	16	242	3	1.61 (0.25)	2.89 (0.45)
10	11.5	19	184	7	1.82 (0.25)	2.95 (0.40)
11	12.3	22	98	8	1.61 (0.23)	2.50 (0.36)

Characteristics of the lambs.

Results

One lamb died soon after the first lavage before reliable CO measurements could be performed. Ten lambs with an age between 1 and 3 weeks and with a median weight of 8.8 kg (interquartile range IQR 2.8) were studied. The characteristics of the lambs are shown in table 1. The pulmonary lavages and high ventilator pressures induced cardio respiratory instability in all animals. We excluded four CO measurements, each from a different lamb, because of CV > 5%.

A total of 56 measurements were analyzed with a median CO_{MPA} of 1.63 (IQR 0.71) l min^{-1} and CI_{MPA} of 2.95 (IQR 1.04) litres min^{-1} m^{-2}. Intraclass correlation coefficients were 0.91 (95% CI 0.81-0.95) for absolute agreement and 0.92 (95% CI 0.87-0.95) for consistency. Differences between the two CO methods are shown in the Bland-Altman plot (Figure 1). The mean bias of the CI was -0.16 litres min^{-1} m^{-2} (LOA ±0.73 litres min^{-1} m^{-2}). The percentage error was 23.8%. Correction for unequal repeated measurements per lamb revealed LOA in the same range (± 0.75 litres min^{-1} m^{-2}) and a percentage error of 24.4%. The tolerability interval was 1.7 – 5.4 litres min^{-1} m^{-2} and the agreement-tolerability-interval ratio revealed 0.39.

Separate analysis of the lower and higher CI measurements showed comparable percentage errors 22% (CI < 3.0 litres min^{-1} m-2; n=28; mean bias -0.06 (LOA ± 0.51) L min^{-1} m^{-2}) and 23% (CI ≥ 3.0 litres min^{-1} m^{-2}; n=28; mean bias -0.27 (LOA ± 0.85) litres min^{-1} m^{-2}). We subsequently determined the bias and level of agreement of the CI measurements for different amounts of EVLWI and showed a mean bias of -0.28 (LOA ± 0.57) litres min^{-1} m^{-2} and percentage error of 16.1% in the lowest quartile of EVLWI versus -0.27 (LOA ± 0.33) litres min^{-1} m^{-2} and percentage error of 21.8% in the highest quartile of EVLWI. Differences in the bias and LOA were significant in the low/high CI (p=0.014 and p=0.008) groups, but not in the low/high EVLWI (p=0.75 and p=0.84) groups.

The initial median EVLWI was 16.0 ml kg^{-1} (IQR 3.8), which increased after multiple lung lavage procedures to a final median EVLWI of 34.3 ml kg^{-1} (IQR 9.1). The mean percentage increase of EVLWI between the start and the end of the study was 126.4 % (SD ± 40.4). The increment of EVLWI worsened oxygenation. The median PaO_2/FiO_2 ratio decreased from 403 (IQR173) to 73 (IQR 54). The median PEEP had to be increased during the experiment from 5 cmH_2O (IQR 0) up to 16 cmH_2O (IQR 10). The differences in these parameters between the start and final measurements were analysed by the Wilcoxon signed-rank test (all p = 0.02) and are shown in figure 2abc. The overall CO_{TPTD} measurements underestimated slightly the CO with 6%, increasing up to 7% bias in the highest (> 30 ml kg^{-1}) EVLWI values. When we compared the bias and LOA between the two CO measurements during low PEEP (n=22) and high PEEP (n=32), these differences were not statistically significant (p=0.98 and p=0.11). The within-subject correlations between the amount of EVLWI, PaO_2/FiO_2 ratio, or the PEEP and the bias between the two CO measurement methods were r = -0.02 (p = 0.91), r = 0.09 (p = 0.56) and r = 0.10 (p = 0.5) respectively and are illustrated in figures 3abc.

Figure 1

Bland-Altman plot comparing the cardiac index values by the TPTD method (CI_{TPTD}) and the peri-vascular flow probe around the main pulmonary artery (CI_{MPA}).

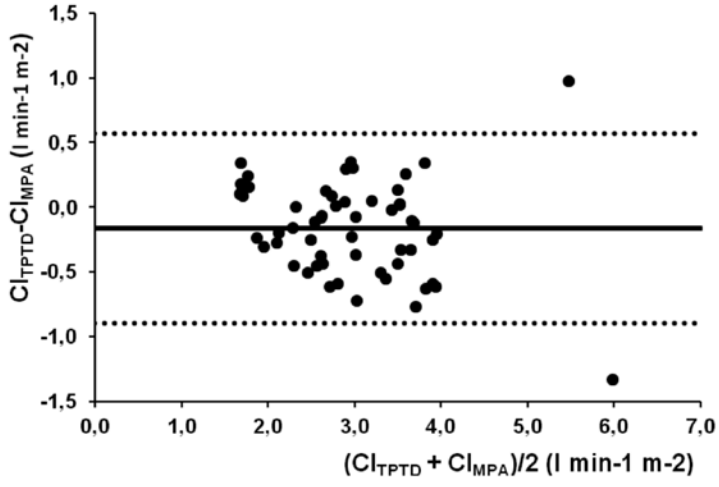


Figure 2abc

Wilcoxon signed-rank test plot comparing the change in indexed extra vascular lung water (EVLWI; ml kg^{-1}) (a), PaO_2/fiO_2 ratio (b) and PEEP (cmH_2O) (c) from the start to the end of the experiment for each lamb separately.

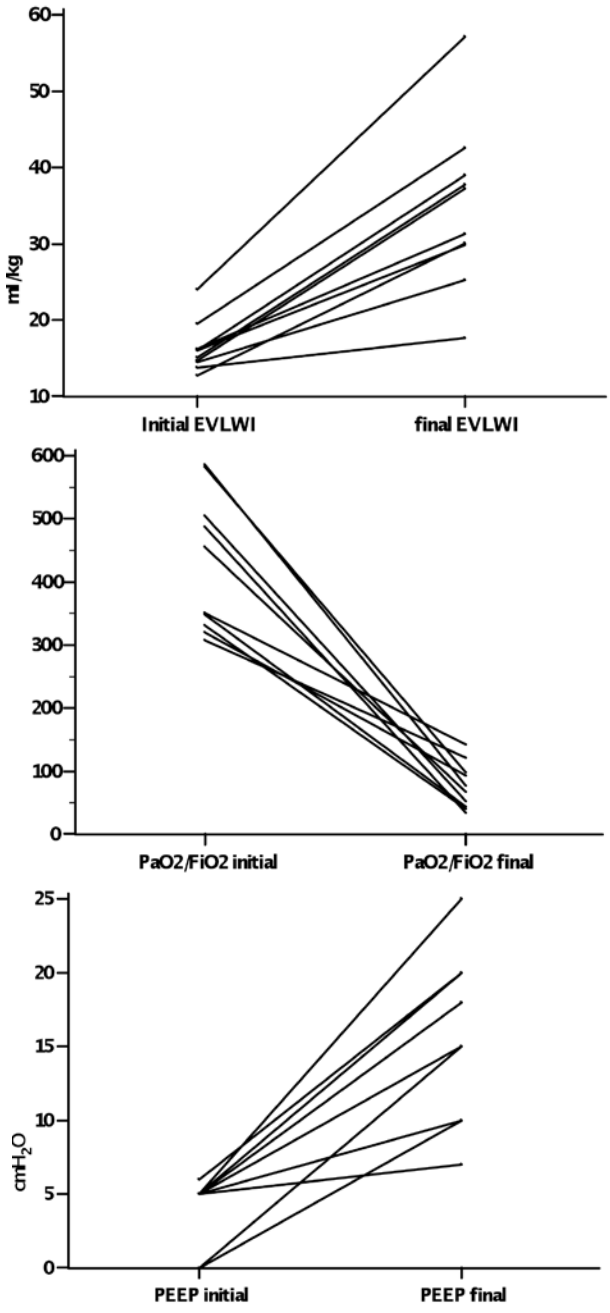
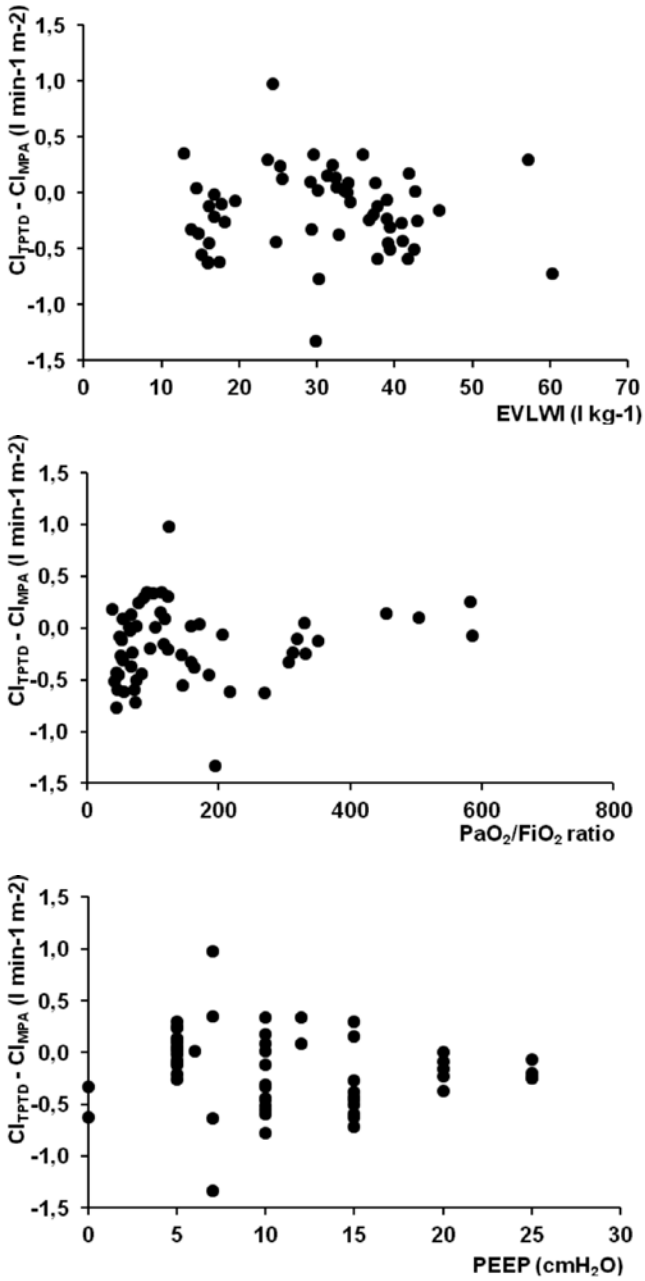


Figure 3 abc.

Scatter plots of the bias of CI measurements by the TPTD method (CI_{TPTD}) and the peri-vascular flow probe around the main pulmonary artery (CI_{MPA}) on the y-axis and EVLWI (a)(within-subject r = -0.02), PaO_2/FiO_2 ratio (b)(within-subject r = 0.09) and PEEP (c)(within-subject r = 0.10) on the x-axis.



Discussion

In this newborn animal model the TPTD method accurately measured CO in the presence of severe pulmonary edema (increase more than 125%). The bias and LOA were small and the percentage error around 24% is within the range of acceptance.[22] The high intraclass correlation coefficient and the low (< 0.5) agreement-tolerability-interval ratio, taking the reference range of the observed data of the study as tolerability interval into account, support the acceptable strength of agreement and imply the EVLWI to be irrelevant in this study.[24] The initial EVLWI values in our pediatric animal model were higher than normal indexed EVLW values known from adult studies, but in agreement with the high EVLWI found in young children.[14-16, 26] Our results show no important dependency of the bias between the two CO methods and the amount of EVLW, but rather a scatter of differences that need to be considered.

It has been estimated that with the TPTD method up to 9% of the thermal indicator may be lost during passage through the pulmonary circulation.[27] In critically ill pediatric patients without pulmonary edema, TPTD overestimates the CO up to 4.4% compared with pulmonary artery thermodilution.[6] This is in agreement with adult studies.[6-10, 28] Our results didn't show overestimation of the CO_{TPTD}. An explanation for this discrepancy could be that, in contrast to others, we used an ultrasound flow probe as reference method, which is not influenced by other factors. Most human studies use the pulmonary artery thermodilution as the reference method, which is influenced by the traversing distance of the indicator and the transient effect of ice water on the heart rate.[29, 30]

Only a few adult studies focus on the influence of pulmonary edema on the reliability of CO measurements using the TPTD technique. A retrospective study in adult surgical intensive care patients showed no dependency of the bias between TPTD and pulmonary artery thermodilution CO measurements on the amount of pulmonary edema.[12] In this study however, the amount of EVLWI was relatively low (mean 9.1 (SD ± 5.8 ml kg^{-1}) compared with the much higher EVLWI values in children. Another adult study in ARDS patients with a high mean EVLWI of 20.2 ml kg^{-1} showed the same results.[13] This may be explained by re-entry of the lost cold thermal indicator into the flowing blood. An older study found a decrease in thermal loss as EVLW accumulates with a negative correlation between the bias and the EVLW.[9] The measured values of EVLWI in this adult study ranged from 1.9 up to 27.5 ml kg^{-1}. In our study, the EVLWI values ranged from 12.8 up to 60.2 ml kg^{-1}. In agreement with the latter study, our results also show a slight (6%) underestimation of the mean CO_{TPTD}.

These findings suggest that in the presence of severe pulmonary edema, other factors compensate for the possible loss of the thermal indicator. Factors governing the temperature exchange between blood and interstitial fluid are the **velocity of diffusion** of the cold indicator, the **surface area for exchange**, the **volume of the interstitial fluid**

into which cold diffuses, and the **flow of blood**, which determines the time during which temperature exchange must occur.[31] So, as a result of perfusion alterations induced by pulmonary edema, PEEP or both, the surface area for exchange is reduced compensating thermal indicator loss in edematous lung tissue. However, our study couldn't demonstrate an effect of PEEP level on the bias between CO measurements. Blood flow alteration is another factor influencing the loss of thermal indicator. High CO states may not allow sufficient time for equilibration with the extra vascular fluids and therefore less thermal indicator may be lossed.[9] On the other hand, low CO values result in more indicator loss at lower flow rates.[32, 33] This influence of the blood flow on the bias is confirmed in our study comparing low with high CO values. However, fractionally the error margin of the measurements remains the same. The higher the CO the wider the LOA and vice versa, resulting in comparable percentage errors in the high and low CO values.

Limitations

Despite variable hemodynamic circumstances, we included only measurements during stable blood flow. We corrected for the unequal and repeated CO measurements per lamb. Our animals were either lying supine or on their right side, which could influence the distribution of pulmonary edema, atelectases, and ventilation-perfusion mismatch and may have influenced our measurements in the comparison between the animals. We had no clinical indication to assume intracardiac shunting. We used a common model to induce EVLW increment with well-described pathophysiological and morphological characteristics.[17, 34, 35] However this surfactant depletion model does not share all features of ALI/ARDS in humans. Finally, the difference in normal values of EVLWI between children and adults may not be real but the result of a difference in age-related changes in the ratio of lung weight to body weight ratio.[36]

Conclusions

Haemodynamic monitoring plays a crucial role in the treatment of critically ill patients. Especially patients with capillary leakage and ALI require tight fluid management avoiding risk of overzealous fluid administration while maintaining sufficient intravascular volume status. The transpulmonary thermodilution technique provides reliable CO monitoring over a wide range of clinical conditions. This study shows that the CO measurements are not affected by severe pulmonary edema.

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Part III

Extravascular lung water

Validation of extravascular lung water measurement by transpulmonary thermodilution in a pediatric animal model

7

Submitted

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Abstract

Background

The measurement of extravascular lung water (EVLW) using the transpulmonary thermodilution (TPTD) technique enables the bedside quantification of the amount of pulmonary edema. Children have higher indexed values of EVLW (EVLWI) compared to adults. TPTD measurements of EVLW in children have not yet been validated. The purpose of this study was to validate the EVLW measurements with the TPTD method over a wide range of lung water values in a pediatric animal model.

Methods

In eleven lambs pulmonary edema was induced using a surfactant washout model. Between the lavages, EVLWI was estimated using transpulmonary single (TPTD) and double (TPDD) indicator dilution. Two additional lambs were used to estimate EVLWI in lungs without pulmonary edema. The final EVLWI results were compared with the EVLWI estimations by post-mortem gravimetry (EVLWIG). The results were analysed using both correlation and Bland Altman statistics.

Results

EVLWITPTD correlated significantly with either $EVLWI_G$ (r^2=0.87) and with $EVLWI_{TPDD}$ (r^2=0.96). The mean bias with EVLWIG was 12.2 ml kg^{-1} (limits of agreement (LOA) ± 10.9 ml kg^{-1}) and with $EVLWI_{TPDD}$ 2.4 ml kg^{-1} (LOA ± 3.8 ml kg^{-1}). The percentage errors were 41% and 14%, respectively. The bias became more positive when the mean of $EVLWI_{TPTD}$ and $EVLWI_G$ increased (r^2 =0.72 (p=0.003)).

Conclusions

$EVLWI_{TPTD}$ was significantly correlated to the post-mortem gravimetric gold standard, although a significant overestimation was demonstrated with increasing pulmonary edema.

Introduction

The measurement of extravascular lung water (EVLW) enables the bedside quantification of pulmonary edema. Therefore monitoring of EVLW is increasingly used as a parameter for diagnosis and treatment of critically ill adults with acute lung injury (ALI). EVLW measurement may allow the clinician to optimize fluid management and prevent further impairment of pulmonary function. In adults, mortality is closely related to the amount of EVLW.[1-6] Only a few studies have investigated the value of extravascular lung water measurement in children.[7, 8] Interestingly, these reports showed consistently higher normal EVLW values when indexed to bodyweight, specifically in young children. In pediatric patients the use of lung water measurement to guide fluid therapy seems to have a positive effect on outcome as well, but is not yet integrated in therapeutic guidelines.[9, 10]

Measurement of EVLW has been studied for many years. The gold standard reference method is gravimetry.[11-13] The gravimetric method compares the wet and dry weight of the lungs and corrects for the amount of blood. Unfortunately it is only feasible post mortem.

Among the clinical methods, the most frequently used at the bedside is the transpulmonary indicator dilution technique. The transpulmonary double indicator dilution (TPDD) technique, using ice-cold indocyanin green (ICG), has been validated against the reference gravimetric method and is widely accepted as the clinical gold standard.[14-17] The difference between the mean transit times of both indicators is used to calculate the extravascular lung water (see Appendix 1). The system is no longer commercially available.

Meanwhile, a single transpulmonary thermodilution (TPTD) technique has been developed for the routine bedside estimation of EVLW in patients (PiCCO (Pulsion, Germany) (see Appendix 1).[18] This system is a reliable bedside method to measure EVLW in young children without clinical signs of pulmonary edema.[7] However, TPTD estimation of EVLW may be influenced by regional lung perfusion, type of lung injury and amount of EVLW.[19-22] Children have higher indexed values of EVLW compared to adults, up to more than 30 ml kg^{-1}. TPTD measurements of EVLW in these patients has not yet been validated.

The purpose of this study was twofold. First, we aimed to validate EVLW measurements with TPTD (using PiCCO) against gravimetry over a wide range of lung water values in a pediatric animal model. Second, since sequential gravimetric measurements are impossible, we compared subsequent TPTD with TPDD measurements in the same animal model in order to test the ability of the TPTD measurements to track changes in EVLWI.

Methods

General. This experiment was performed in accordance with Dutch legislation concerning guidelines for the care and use of laboratory animals and was approved by the local ethics committee on animal research of the Radboud University Nijmegen Medical Centre (RUNMC Licence number RU-DEC 2010-034; CDL-projectnumber 33078). Thirteen lambs under general anaesthesia were studied. Premedication consisted of the intramuscular administration of midazolam (0.2 mg kg^{-1}), ketamine (10 mg kg^{-1}) and intravenous administration of propofol (2 mg kg^{-1}). General anaesthesia was maintained using inhalation of isoflurane (1-1.5 volume%) and the continuous intravenous administration of sufentanil (20 µg kg^{-1} hr^{-1}), midazolam (0.2 mg kg^{-1} hr^{-1}), ketamine (10 mg kg^{-1} hr^{-1}), and pancuronium (0.02 mg kg^{-1} hr^{-1}) after a loading dose of 0.05 mg kg^{-1}. The depth of anaesthesia was repeatedly assessed by pain stimuli and clinical parameters such as heart rate, spontaneous ventilation or arterial blood pressure and was adjusted when necessary. During the experiment continuous intravenous dextrose 10% 2 ml kg^{-1} hr^{-1} was administered. The lambs were intubated orotracheally using a 4 to 6 mm (inner diameter) cuffed endotracheal tube (Kruse, Marslev, Denmark). The lungs were mechanically ventilated in a pressure-controlled mode using tidal volumes of approximately 10 ml kg^{-1} (Datex-Ohmeda anaesthesia machine) and an inspiratory-to-expiratory ratio of 1:2. Normocapnia, guided by capnography with the CO_2SMO Plus Respiratory Profile Monitor (Model 8100, Respironics, Pittsburgh, USA), was achieved by adjusting the minute volume ventilation to maintain an end-tidal CO_2 between 30 and 41 torr (4.0–5.5 kPa). Impaired oxygenation was treated by adjusting the positive end expiratory pressure (PEEP) and the fraction of inspired oxygen (FiO_2) to maintain the oxygen saturation > 95%. A servo-controlled heating mattress and an external heating lamp were used to maintain core temperature between 38-40°C. At the end of the experiment, the animals were killed with pentobarbital (150 mg kg^{-1} i.v.).

Instrumentation. Immediately after induction of anaesthesia a thermal-dye-dilution probe (Pulsiocath PV2023, 3 Fr, Pulsion, Germany) equipped with a thermistor for detection of changes in blood temperature and a fiber optic to detect changes in ICG concentrations in the blood was placed in the lower abdominal aorta via the femoral artery. In the contralateral femoral vein a central venous catheter (5Fr, 2lumen, 13 cm, Arrow, Germany) was inserted for the administration of fluid and drugs. At the same site a femoral artery catheter (20 Ga, single lumen, 12 cm, Arrow, Germany) was introduced for arterial blood pressure monitoring and blood sampling. All intravascular catheters were inserted by a surgical cut-down technique.

Acute lung injury was induced using a surfactant washout model resulting in pulmonary edema.[23] In short, 11 lambs underwent repetitive saline lavages (10-35 ml kg^{-1} $lavage^{-1}$ 37°C NaCl 0.9%) of the lung in order to induce surfactant depletion and provoke acute

lung injury (ALI). Prior to the lavages the lambs were pre-oxygenated using a FiO_2 of 1.0. After the lavages, the animals were stabilized for 30 minutes. Between lavages the PEEP and minute volume ventilation were adjusted to maintain oxygen saturation and end-tidal CO_2 within the target range. To include also the EVLWI measurements of minimal injured lungs, in 2 additional lambs no lavages were performed and only baseline measurements were performed before they were killed.

TPDD measurements were performed by rapid injection of 5 ml ice-cold (<10°C) ICG injectate (1 mg ml^{-1} in glucose 5%) into the femoral venous catheter with the catheter tip close to the right atrium. Changes in both temperature and ICG concentration were detected by the thermal-dye-dilution probe connected to a COLD monitor (Pulsion, Munich, Germany). In the last three animal experiments the COLD system was defective. Alternatively, a thermistor tipped arterial catheter (3Fr, 7 cm, PV2013L07, Pulsion, Germany) connected to a PiCCOplus monitor (software version 6.0, Pulsion, Munich, Germany) was used, with which EVLWI can be estimated only by the TPTD technique. TPTD measurements were performed by rapid injection of 5 ml ice-cold saline (NaCl 0,9%) into the femoral venous catheter with the catheter tip close to the right atrium. Cardiac output (CO), blood volumes and EVLWI can be calculated from the analysis of the dilution curves and measurement of the mean transit time (MTt) and downslope time (DSt) (Appendix 1).[18, 24, 25] Before a series of measurements was performed, the central venous catheter was flushed with 1–2 ml of ice-cold saline. Each dilution curve was visually inspected for artifacts or other signs of inadequate measurement. EVLWI was determined by the average of three consecutive EVLWI measurements by TPDD/TPTD.

Gravimetric technique. Immediately prior to killing the animal, a 50 ml sample of central venous blood was obtained. Subsequently, a median sternotomy was performed and the lungs were removed and drained passively. The gross weight of each lung, with its residual blood, was determined. The lungs were homogenized with an equal weight of water to induce hemolysis using a commercial blender and homogenizer. The homogenate was centrifuged at 6000 rpm for 1 hour at 4°C to separate a clear supernatant. Haematocrit from whole blood and haemoglobin from whole blood and lung supernatant were measured. The wet and dry weights of the samples of blood, homogenate and supernatant were determined before and after 4 days incubation in a heat chamber at 70°C until the weight stabilized. Postmortem EVLWI was calculated by the formulas as previously described (see Appendix 2).[11-13]

Determination of the relationship between ITBV and GEDV. To establish the relation between ITBV and GEDV, we used the TPDD technique to determine the ITBV, which is the calculation of the distribution volume of the non-diffusible indicator ICG (equation

6 in Appendix 1). From the same data, the results of the thermal indicator dilution curve were used in the calculation of the GEDV (equations 1 till 3 in Appendix 1).

Protocol. After the instrumentation, baseline dilution measurements, respiratory parameters and blood gases were obtained. Repetitive saline lavage procedures were performed in either one or two subsequent sessions of 10-30 ml kg^{-1}, depending on the recovery of the lambs during the procedure. Halfway and final measurements of the above mentioned parameters were repeated after a post-lavage stabilization period. We also included two lambs without lung lavage to measure EVLWI in minimal injured lungs. In all lambs postmortem EVLWI measurements were performed by gravimetry ($EVLWI_G$). A blood transfusion was administered if the haemoglobin concentration was < 3.5 mmol l^{-1}. Dobutamine or epinephrine was administered when indicated.

Statistical analysis. The EVLW values were indexed (EVLWI) to actual bodyweight (kg). Variables were summarized as frequencies for categorical data, means and standard deviations for continuous normally distributed variables, or medians and interquartile ranges otherwise. Correlation between $EVLWI^{TPTD}$, $EVLWI^{TPDD}$ and $EVLWI_G$ was tested by Spearmans's coefficient of rank correlation. Data were compared using the method described by Bland and Altman.[26] The difference between two methods (bias) was calculated by subtracting the reference value of EVLWI (either gravimetry or TPDD) from $EVLWI_{TPTD}$. The bias was plotted against the mean EVLWI ({$EVLWI_{TPTD}$ + $EVLWI_{(TPDD\ or\ G)}$}/2). The limits of agreement (LOA) were calculated by multiplying the standard deviation (SD) of the bias with 1.96. The percentage error was calculated using the following formula: {(1.96 x SD of the bias)/mean $EVLWI_{(TPDD\ or\ G)}$} x 100%.[27] Comparisons between the bias of EVLWI between TPTD and the two reference methods, and final PEEP, final PaO_2/fiO_2 ratio, age, mean EVLWI and CO were analysed by Spearmans's coefficient of rank correlation. Changes in consecutive EVLWI measurements by TPTD and TPDD were calculated by subtracting the preceding from the succeeding result. Comparison of these changes in EVLWI was analysed by Spearmans's coefficient of rank correlation.
The relationship between GEDV and ITBV, expressed as the linear regression equation ITBV = a x GEDV + b (Appendix 2), was analysed using the $EVLWI_{TPDD}$ results. Additionally, the $EVLWI_{TPDD}$ results were separated into two subgroups ($EVLWI_{TPDD}$ < / > 20 ml kg^{-1}) to demonstrate the influence of the amount of $EVLWI_{TPDD}$ on the coefficients a and b.
Calculations and data management were performed using Excel for Windows (Office 2007, Microsoft, Seattle, WA). Statistical calculations were performed with MedCalc (Med-Calc Software, Mariakerke, Belgium).

Table 1.

Characteristics and extravascular lung water index (EVLWI) results of the lambs.

Lamb	Weight	Age	Total lavage volume	Initial EVLWI TPTD	Final EVLWI TPTD	Final EVLWI TPDD	EVLWI G	PEEP final	PaO_2/ FiO_2 final
	(kg)	(days)	(ml kg^{-1})	(ml kg^{-1})	(ml kg^{-1})	(ml kg^{-1})	(ml kg^{-1})	(mmHg)	
1	8.1	21	125	13.8	17.7	15.8	15.1	7	143
2	7.4	21	303	14.5	NA	NA	19.4	18	93
3	4.1	7	293	19.5	42.6	38.6	28.5	10	122
4	7.4	14	68	16.0	NA	NA	18.8	10	53
5	10.2	17	294	12.8	30.1	29.9	17.1	20	78
6	9.4	18	191	15.1	33.8	34.1	20.1	20	68
7	7.1	14	135	19.1	NA	NA	16.5	16	7
8	8.0	15	420	16.2	31.3	30.4	21.5	25	98
9	9.9	16	242	24.0	NA	NA	18.2	20	35
10	11.5	19	184	16.0	53.5	49.1	29.8	15	41
11	12.3	22	98	14.7	37.3	NA	24.3	15	44
12	5.6	4	0	24.2	24.2	NA	13.3	5	NA
13	6.7	4	0	21.4	21.4	NA	11.8	5	NA

(EVLWI = extravascular lung water index by either transpulmonary thermodilution (TPTD), or transpulmonary double indicator dilution (TPDD) or gravimetry (G), PEEP = positive end expiratory pressure, PaO_2/FiO_2 ratio = ratio between arterial partial pressure of oxygen and inspired oxygen fraction, NA = not available)

Results

Thirteen newborn lambs with a postnatal age between 4 and 21 days and a mean weight of 8.3 kg (range 4.1 – 12.3 kg) were studied. The characteristics and results of the EVLWI measurements of the lambs are shown in Table 1. Four lambs (lambs 2,4,7,9) died during or after a lavage session before reliable final $EVLW_{TPTD}$ measurements could be performed, leaving 9 lambs to compare $EVLWI_{TPTD}$ with $EVLWI_G$. Only 10 lambs could be used comparing $EVLWI_{TPTD}$ with $EVLWI_{TPDD}$ as the COLD device was out of order in the last three experiments.

A total of 25 measurements were analysed comparing $EVLWI_{TPTD}$ versus $EVLWI_{TPDD}$ with a median $EVLWI_{TPDD}$ of 24.0 (IQR 20.7) ml kg^{-1}. For the comparison of $EVLWI_{TPTD}$ with $EVLWI_G$ 9 measurements were analysed with a median $EVLWI_G$ of 20.1 (IQR 10.7) ml kg^{-1}. In the lambs undergoing saline lavages, the initial median $EVLWI_{TPTD}$ was 16.0 ml kg^{-1} (IQR 5.3), which increased after multiple lung lavage procedures to a final median $EVLWI_{TPTD}$ of 31.3 ml kg^{-1} (IQR 14.6). The increase of EVLWI worsened oxygenation as illustrated in Table 1 by a final median PaO_2/FiO_2 ratio of 73 (IQR 54) and a final median PEEP level of 16.5 cmH_2O (IQR 10).

Figure 1ab

Spearman rank correlation between extravascular lung water index by transpulmonary thermodilution ($EVLWI_{TPTD}$) versus gravimetry ($EVLWI_{G}$)(a), and $EVLWI_{TPTD}$ versus transpulmonary double indicator dilution ($EVLWI_{TPDD}$)(b). ····· line of identity

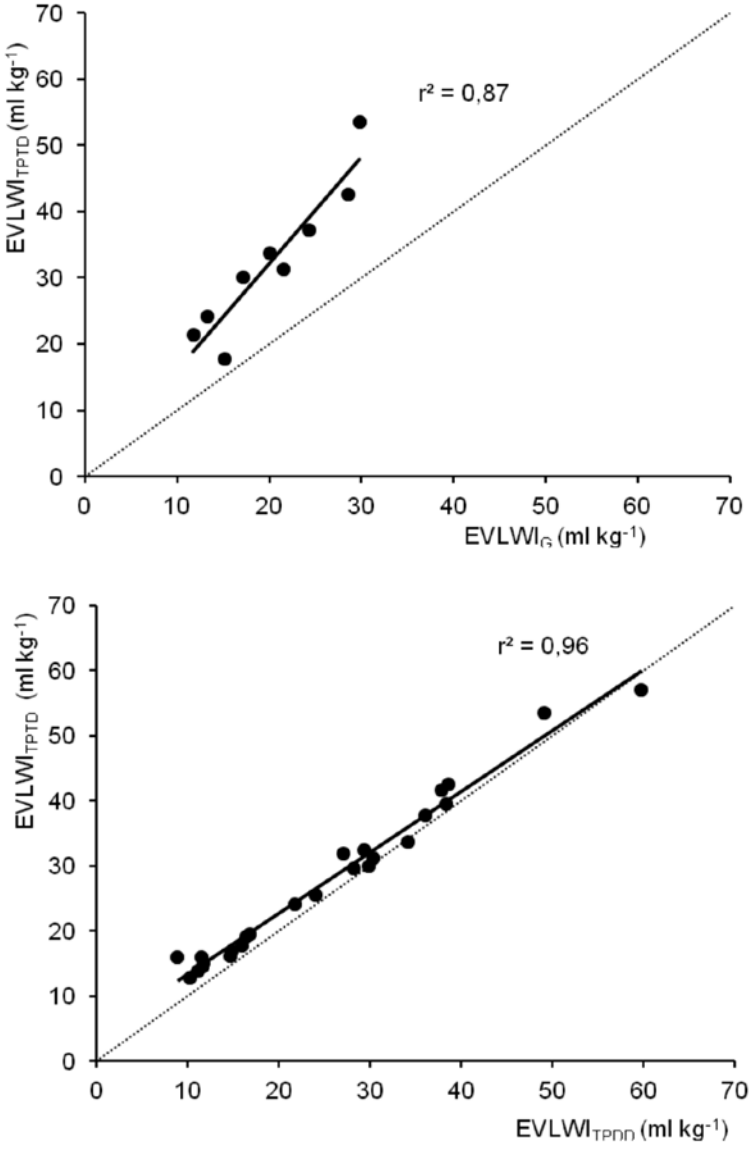
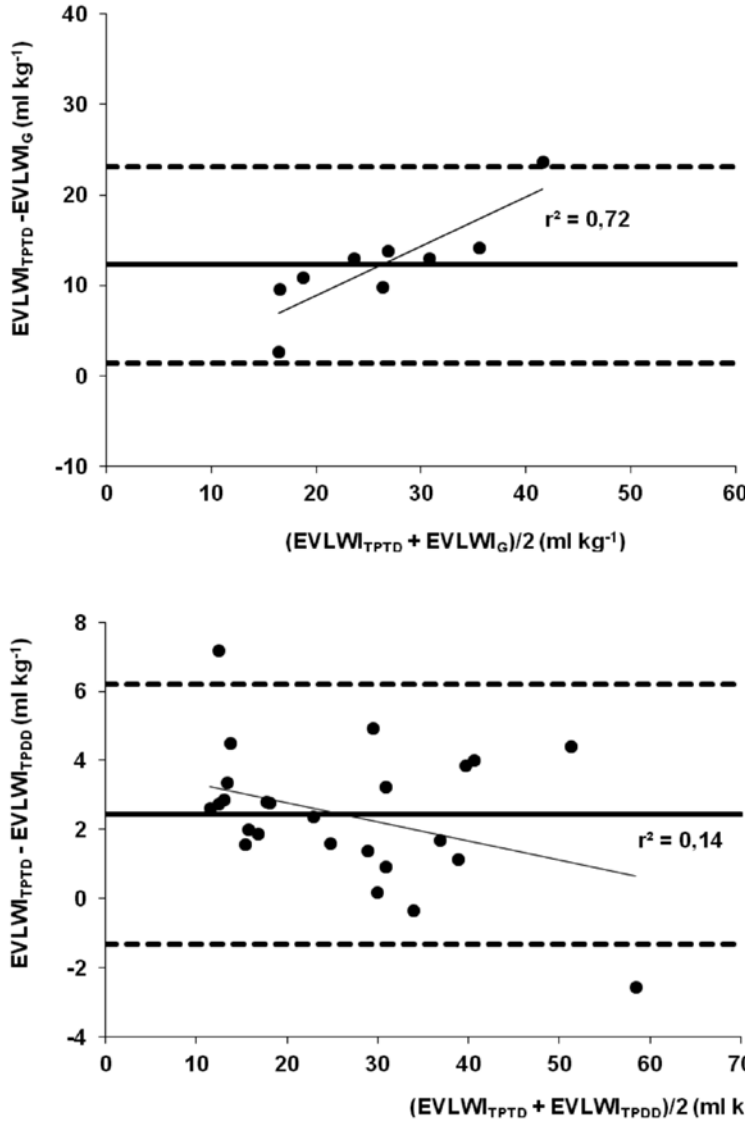


Figure 2ab

Bland Altman plot comparing extravascular lung water index measurements by the transpulmonary thermodilution ($EVLWI_{TPTD}$) with gravimetry ($EVLWI_G$)(a) and transpulmonary double indicator dilution ($EVLWI_{TPDD}$)(b). —— = linear regression line with regression coefficient r^2



Figures 1a and 1b illustrate the correlation between $EVLWI_{TPTD}$ and $EVLWI_{G}$ (r2=0.87, p<0.0002, 95% CI 0.71-0.99) and between $EVLWI_{TPTD}$ and $EVLWI_{TPDD}$ (r^2=0.96, p=<0.0001, 95% CI 0.95-0.99), respectively. Differences between $EVLWI_{TPTD}$ and the two reference methods are shown in the Bland-Altman plots (Figures 2a and 2b). The mean bias with $EVLWI_{G}$ was 12.2 ml kg^{-1} (LOA ± 10.9 ml kg^{-1}) and with $EVLWI_{TPDD}$ was 2.4 ml kg^{-1} (LOA ± 3.8 ml kg^{-1}). The percentage errors were 41% and 14%, respectively. The bias between $EVLWI_{TPTD}$ and $EVLWI_{G}$ was not related to the final PEEP (r^2 = 0.09 (p = 0.44)), final PaO_2/FiO_2 ratio (r^2 = 0.14 (p = 0.3)) or age (r^2 = 0.008 (p = 0.8). The bias became more positive when the mean EVLWI of both techniques increased (r^2 =0.72 (p=0.003))(Figure 2a). The bias between the $EVLWI_{TPTD}$ and $EVLWI_{TPDD}$ did not correlate with the amount of mean EVLWI (r^2 = 0.14 (p = 0.06)) (Figure 2b). Bias of EVLWI between TPTD and the two reference methods was not influenced by cardiac output (r^2 = 0.2; p = 0.23 (G) and r^2 = 0.02; p=0.4(TPDD), respectively). The correlation of change in EVLWI (Δ EVLWI) between consecutive measurements by TPTD and TPDD is shown in Figure 3.

The coefficients a and b in the regression analysis of the relationship between GEDV and ITBV diverge depending on the data used, either all or the two subgroups of $EVLWI_{TPDD}$ < / > 20 ml kg^{-1} (Table 2, Figure 4).

Figure 3

Spearman rank correlation between the change in extravascular lung water index (Δ EVLWI) of transpulmonary thermodilution (TPTD) and transpulmonary double indicator dilution (TPDD) method (p < 0.001). —— = linear regression line with regression coefficient r^2.

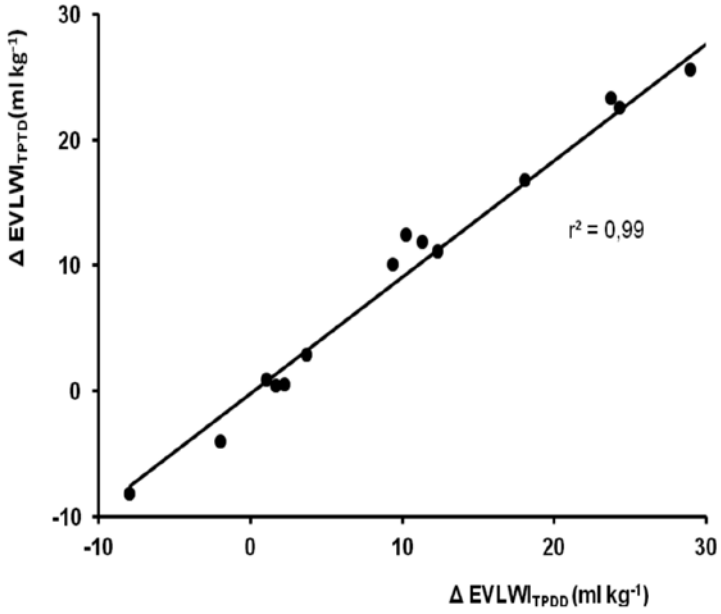


Figure 4

Linear regression analysis of the relationship between intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV): ---- linear regression line of ○ EVLWI < 20 ml kg^{-1}; —— linear regression line of ■ EVLWI > 20 ml kg^{-1}; ····· line of identity

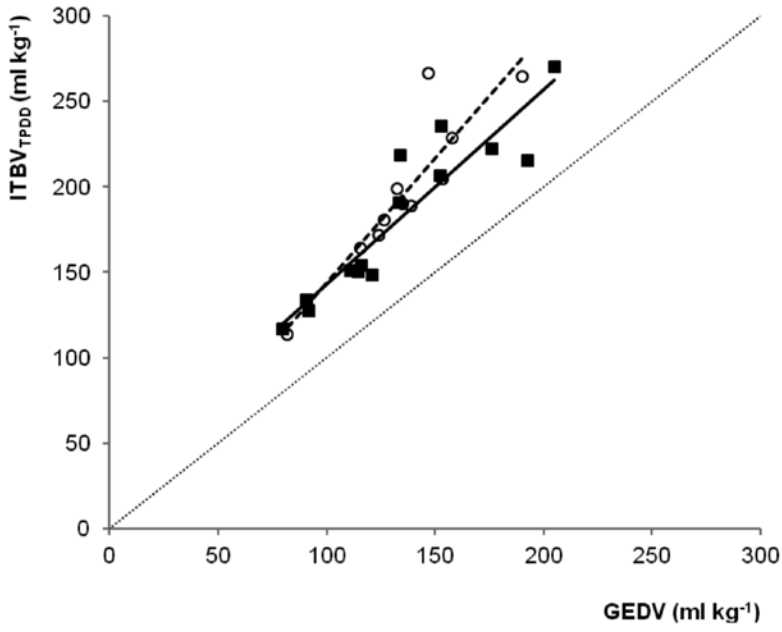


Table 2

*The regression equation ITBV = a x GEDV + b, with a and b as coefficients derived from linear regression analysis using different TPDD data: either all or in subgroups EVLWI < or > 20 ml kg^{-1}. * = p < 0.001.*

TPDD data	n	a	b	r^2	95%CI for slope	95%CI for y intercept
All	25	1.24	21	0.81*	0.98-1.50	14 – 57
EVLWI < 20 ml kg^{-1}	11	1.46	-2	0.81*	0.93-1.99	-76 – 71
EVLWI > 20 ml kg^{-1}	14	1.14	29	0.85*	0.84 – 1.44	-12 – 70

Discussion

Our results show that the EVLWI measurements using the TPTD technique are closely related to both the gravimetric method and the TPDD technique. However, $EVLWI_{TPTD}$ seems to overestimate lung water considerably compared to $EVLWI_{G}$.

Comparing $EVLWI_{TPTD}$ versus $EVLWI_{G}$. Our results are consistent with other experimental studies in which the $EVLWI_{TPTD}$ overestimates gravimetric estimates of EVLWI.[28-31] This is explained by equilibration of the thermal indicator with dry lung mass and non-pulmonary structures such as the hilar vessels and mediastinum.[28, 29, 31] Overall, studies using gravimetry as reference method show good linear correlations with TPTD.[28-31] In agreement with a recent study in humans and a validation study in immature pigs, the overestimation is more pronounced with higher EVLWI measurement values.[30, 32] However, opposite results were found in an experimental study with sheep.[33]

Comparing $EVLWI_{TPTD}$ versus $EVLWI_{TPDD}$. Our results showed a good accuracy and precision over the whole range of pulmonary edema, which is in agreement with previous reports comparing $EVLWI_{TPTD}$ measurements with TPDD as reference technique.[7, 18] Clinical studies in adults show, that in patients with high EVLWI (> 12 ml kg^{-1}), the TPTD technique tends to underestimate lung edema in contrast to the low to normal range (<7 ml kg^{-1}), where there is an overestimation.[18, 22] This may partly be explained from the deviations of the coefficients in various amounts of pulmonary edema in equation 4 (Appendix 1) from the default setting in the PiCCO device, as elucidated in the next paragraph. Our results show the same trend in Figure 2b.
Changes in $EVLWI_{TPTD}$ closely relate to changes in $EVLWI_{TPDD}$, which makes $EVLWI_{TPTD}$ suitable for trend monitoring of pulmonary edema (Figure 3).

Relationship GEDV and ITBV. Using the TPTD method it is assumed that GEDV has a constant and predictable relationship to ITBV, even in the presence of several physiological derangements seen in critical ill patients, which might introduce a potential error. With the TPTD technique, ITBV and EVLW are not obtained directly, but are derived from the measurements of CO, ITTV and PTV using equations 1 till 5 in Appendix 1. The PiCCO device uses a simplified formula, namely ITBV = 1.25 x GEDV (equation 4 in Appendix 1), to estimate ITBV and hence EVLW. This formula is based on a study in adult patients.[18] The coefficients in this linear regression analysis vary among different lung conditions and species.[28, 29, 31, 34-37] Coefficient 'a' calculated from our results of the whole experiment was 1.24, which is close to the PiCCO default setting, and is exactly the same as the results from a pediatric study.[7] Nevertheless, it is too premature to conclude, that age does not influence the estimation of $EVLWI_{TPTD}$.

Factors influencing EVLW measurements using dilution techniques. We clearly demonstrate the influence of the amount of lung water on dilution derived EVLW measurements. We showed a changing relation between GEDV and ITBV depending on the amount of EVLW (Figure 4, Table 2). In other studies this influence is explained by reduced pulmonary blood flow and hence underestimation of the $EVLWI_{TPTD}$ in edematous lung areas compared to $EVLWI_{TPDD}$.[22, 38]
From both experimental and clinical studies, various other factors have been analysed that influence the estimations of EVLWI with the indicator dilution method, including PEEP and cardiac output.[22, 39-41] Overall, these studies illustrate the limitation of the dilution techniques, as they are vulnerable to perfusion variations.[19-21] In our study, there was no relationship between the final PEEP levels, PaO_2/FiO_2 ratio or cardiac output and the bias of EVLWI, although our experiment was not designed to study the influence of these factors.

Limitations

We used an experimental pediatric animal model. The relationship between ITBV and GEDV is species dependent and requires reconsideration when applied to humans.[34] The type of lung injury does affect the EVLW measurements.[35, 38] The results of this surfactant washout model cannot be applied to all other types of acute lung injury, as it doesn't share all features of acute lung injury or acute respiratory distress syndrome in humans.[23] Some of the lambs were treated with epinephrine, which may have affected the measurements.

Conclusions

In conclusion, the $EVLWI_{TPTD}$ was significantly correlated to the post-mortem gravimetric gold standard although a significant overestimation was demonstrated, specifically in the higher lung water range. Secondly, changes in $EVLWI_{TPTD}$ closely relate to changes in $EVLWI_{TPDD}$, which makes $EVLWI_{TPTD}$ suitable for trend monitoring of pulmonary edema.

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Appendix 1

Transpulmonary thermodilution (TPTD)

Analysis of the TPTD curve yields the cardiac output (CO), the mean transit time of the indicator (MTt), and the exponential downslope time of the curve (DSt).

Multiplication of the CO by the MTt gives the volume in which this thermal thermal indicator is dissolved, i.e., the intrathoracic thermal volume (ITTV).

1. ITTV = CO x MTt (ml)

Multiplication of the CO by the DSt gives the largest individual mixing volume in a series of indicator dilution mixing chambers, i.e., the pulmonary thermal volume (PTV).

2. PTV = CO x DSt (ml)

Subtraction of the PTV from the ITTV reflects a volume that represents the global end-diastolic volume (GEDV), i.e., the sum of the diastolic volumes of the right and left heart.

3. GEDV = ITTV – PTV (ml)

There is a linear relationship assumed between intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV) and used as a default setting in the PiCCO[18]:

4. ITBV = (1.25 x GEDV) – 28.4 (ml)
   (PiCCO uses the simplified formula: ITBV = (1.25 x GEDV))

The differences between the ITTV and ITBV yield an estimate of extravascular lung water (EVLW):

5. EVLW = ITTV – ITBV

Transpulmonary double indicator dilution (TPDD)

In the double indicator dilution technique two different indicators are injected simultaneously, using cold indocyanine green (ICG). While the cold equilibrates with the extra vascular space, the dye is rapidly bound to proteins and remains intravascularly. The distribution volume of the cold yields the ITTV, the distribution volume of the dye yields the intrathoracic blood volume (ITBV). Multiplying the CO by the MTt of the strictly plasma bound indocyanin green (ICG) equals the ITBV:

6. $ITBV_{TPDD} = CO \times MTt_{ICG}$

The difference of the thermal and blood volume is the extravascular lung water.

7. $EVLW = ITTV_{TPTD} - ITBV_{TPDD}$

Appendix 2

Formulas used in the gravimetric calculation of EVLW

[1] $Fw_s = \frac{Ww_s - Wd_s}{Ww_s}$

[2] $Fw_h = \frac{Ww_h - Wd_h}{Ww_h}$

[3] $Q_r = Q_h \times \frac{Hb_s}{Hb_b} \times \frac{Fw_h}{Fw_s} \times Hct$

[4] $Q_b = Q_r + \{Q_r(\frac{1-Hct}{Hct})\}$

[5] $Fw_b = \frac{Ww_b - Wd_b}{Ww_b}$

[6] $EVLW = Q_h \times Fw_h - Q_b \times Fw_b - Qw_t$

EVLW	extravascular lung water
Fw	fraction water
b	blood
h	homogenate
s	supernatant
Hct	haematocrit
Hb	haemoglobin concentration
EVLW	extravascular lung water
Ww	wet weight
Wd	dry weight
Q	weight
Q_{wt}	weight of added water
Qb	residual blood content in lungs
Qr	red cell mass of lung

Near Normal Values of Extravascular Lungwater in Children

8

Submitted

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Abstract

Introduction

Extravascular lung water (EVLW) can be measured at the bedside using the transpulmonary thermodilution method and reflects the amount of pulmonary edema. In children unusual high body weight indexed EVLW (EVLWI) have been described, which seems to be related to growth and development. Lack of age related normal values makes the interpretation and clinical use of this parameter impracticable at the pediatric intensive care unit (PICU). Goal of this study was to define "near normal" values of EVLWI in children.

Methods

This international multi-centre study prospectively collected EVLW measurements from children admitted to a PICU after resolution of their illness. The obtained values were indexed to predicted body weight and to height and subsequently related to age.

Results

58 children with heterogeneous PICU admission diagnoses were included in this study. EVLW indexed to predicted body weight correlated with age ($r^2 = 0.7$) and could be categorized in three age groups that consisted of significantly different median EVLWI values (5-95 percentile) < 1 year 10-35 ml/kg, 1-5 year 7-22 ml/kg and 5-17 year 6-12 ml/kg. EVLW indexed to height did not correlate to age and resulted in an age-independent "near normal" value of < 200 ml/m.

Conclusions

Younger children have higher "near normal" values of EVLW indexed to predicted body weight. Age categorized normal EVLWI values are presented for clinical use. Furthermore we suggest to index EVLW to height, which seems to be age-independent.

Introduction

Extravascular lung water (EVLW) can be measured at the bedside using the transpulmonary thermodilution method incorporated in the PiCCO device (Pulsion, Munich, Germany). EVLW reflects the amount of pulmonary edema with acceptable accuracy, predicts mortality in both adults and children and can be used to guide fluid therapy.[1-7]

EVLW is traditionally indexed using body weight (EVLWI, ml/kg). For the adult population values below 10 ml/kg are considered normal. Unusual high values of EVLWI have been described in young children.[8, 9] Since EVLW is related to lung mass the reason for these high values of EVLWI are in part explained by the changing relation between lung mass and body weight during human growth and development, specifically in the first years of life. In the young, the ratio of lung mass (and thus the amount of lung water) to body weight is higher.[10] Up to now, there are still no age related normal values available making the interpretation and clinical use of this parameter impracticable in pediatric patients.[11]

Adult studies have shown that indexing EVLW to predicted body weight produces a more physiological and useful value.[7, 12] Others suggest that indexing EVLW to height is superior to the aforementioned weight-based methods.[13]
This study was designed to collect EVLW values measured by the PiCCO system from children, admitted to a PICU after resolution of their illness. The obtained values were used to define age related "near normal" values of indexed lung water in children.

Methods

In this prospective study EVLW values were collected from routinely performed PiCCO measurements near the end of PICU treatment. Since this study was strictly observational, the medical ethical committee of the Radboud University Nijmegen Medical Centre waived the need for informed consent in concordance with Dutch legislation. Data were collected by PICU's in Tunis (Tunisia), Rome (Italy), Santa Barbara (USA), Hamburg (Germany) and Nijmegen (The Netherlands).

We included children (0 tot 18 years) admitted to a PICU and connected to a PiCCO monitor for hemodynamic monitoring. EVLW values were eligible for the study if they were measured under stable hemodynamic condition and after resolution of the acute illness. Breathing was either spontaneous or with minimal supportive ventilation (pressure support max 10 cmH_2O or likewise, PEEP =< 5 cmH_2O and FiO_2 =< 40%).

Patients were hemodynamically stable including normal sinus rhythm, normal blood pressure, normal renal function and either no or minimal vasoactive support (dopamine or dobutamine ≤ 5 ug/kg/min, epinephrine or nor-epinephrine < 0,1 ug/kg/min and milrinone <0,25 ug/kg/min or enoximone < 10 ug/kg/min).
Exclusion criteria were clinical signs of (pulmonary) edema or increased work of breathing and an abnormal chest x-ray. Additionally, measurements in the presence of an intra- or extra-cardiac left-to-right or right-to-left shunt were excluded as well as measurements with technical defects or abnormal thermodilution curves.

The PiCCO system requires a central venous catheter and a special thermistor equipped arterial catheter inserted in the femoral artery. The three main recorded parameters are cardiac output (CO), global end-diastolic blood volume (GEDV) which reflects preload, and extravascular lung water (EVLW). The technical background of the PiCCO system and the calculation of the various hemodynamic parameters have been described in detail elsewhere.[11] The mean value of multiple (at least 3) measurements was taken. Measurements were performed using various PiCCO devices (PiCCOplus, $PiCCO_2$ or PiCCO module for use with HP/Philips monitoring system). Other recorded data included among others, heart rate, blood pressure, central venous pressure (CVP), respiratory rate, saturation and blood gas results. Apart from a basic description of the hemodynamic status, some of these results were used to determine, the patient had values consistent with a patient in a normal hemodynamic state or resolution of illness.

Predicted body weight based upon height was calculated using published WHO data that reflect the ideal body weight of children ranging from birth to 18 years.[14] Body surface area (BSA) was calculated by the Haycock method using actual weight.[15] CO and GEDV were indexed using BSA (CI = CO/BSA [l/min/m^2]; GEDVI = GEDV / BSA [ml/m^2]). EVLW was indexed either using predicted body weight (EVLWI = EVLW / weight [ml/kg]) or height (EVLWIh = EVLW / height [ml/m]).
All data were tested for normality. In case of normal distribution a t-test (or when appropriate ANOVA) was used, otherwise Mann Whitney U testing was performed. A p-value < 0.05 was considered significant. Normal values were constructed using the 5 to 95 percentile values.

Table 1

Patient data (n = 58)

	Median value (range)
Age (year)	4 (0.04 - 17)
Weight (kg)	19 (3.7 - 80)
Predicted body weight (kg)	18.6 (3.1 – 77.4)
Length of stay PICU (days)	7 (2 - 21)
BSA (m^2)	0.77 (0.23 – 1.96)
FiO_2 (%)	30 (21 - 40)
PaO_2 (mmHg)	98.1 (62.3 - 204)
SaO_2 (%)	97 (92 - 100)
PaO_2/FiO_2 (mmHg)	395 (171 - 661)
$PaCO_2$ (mmHg)	35.6 (21 – 45)
A-a gradient (mmHg)	34 (0-174)
pH	7.44 (7.33 – 7.60)
PEEP (cmH_2O)	5 (4-5)
HR (bpm)	110 (62 - 169)
MAP (mmHg)	78 (48 - 131)
Respiratory rate (resp/min)	21 (11 - 46)
CO (l/min)	3.48 (0.56 – 10.9)
CI ($l/min/m^2$)	4.61 (2.15 – 13.91)
SV (ml)	34.13 (6.44 – 100.48)
SVI (ml/m^2)	40.23 (20.4 – 98.1)
GEDV (ml)	348 (70 - 1120)
GEDVI (ml/m^2)	479 (186 - 772)
EVLW (ml)	216 (71 - 544)
EVLWI (ml/kg)	10.3 (4.7 – 34.6)

BSA = body surface area
MAP = mean arterial pressure
CO = cardiac output
CI = cardiac index = CO/BSA
SV = stroke volume
SVI = stroke volume index = SV/BSA
GEDV = Global end diastolic volume
GEDVI = global end diastolic volume index = GEDV / BSA
EVLW = Extra vascular lungwater
EVLWI = Extra vascular lungwater index = EVLW / body weight

Results

58 children were included in this study of which 42 were breathing spontaneously while 16 were being mechanically ventilated. Admission diagnoses were heterogeneous and included among others sepsis (14 children), pulmonary infection (12 children), Trauma (10 children), neurological disorders (5 children), organ transplant (4 children) and various other diseases (14 children). Patient characteristics are depicted in table 1. The mean body mass index (BMI) was 16.9 (SD 3.4, range 11.7 to 27.7) kg/m^2. Only four children had a BMI value above 22 kg/m^2.

Figure 1 shows the relation between EVLW and weight. Figure 2 shows the relation between age and EVLW indexed to predicted body weight. Figures 3ab reflect EVLW indexed to either predicted body weight or height divided per age group.

There were no differences between mechanically ventilated or spontaneous breathing children with regard to PaO_2/FiO_2 ratio, EVLWI, CI or GEDVI (data not shown). There were also no differences between boys and girls with respect to age, weight, height, CI, GEDVI or EVLWI. We couldn't demonstrate any influence of the site of the central venous line (internal jugular, subclavian or femoral vein) on the results of the PiCCO measurements concerning CO, EVLW and GEDV.

The additional results of the PiCCO measurements, GEDVI and CI, are shown in Table 2. There were no differences between the CI values in the different age categories. However, the GEDVI values of the youngest age group were lower compared to the oldest group ($p < 0.05$). The median value of EVLWIh for the entire cohort was 200 ml/m (5-95 percentile 125-315 ml/m).

Figure 1

The relation between EVLW and weight

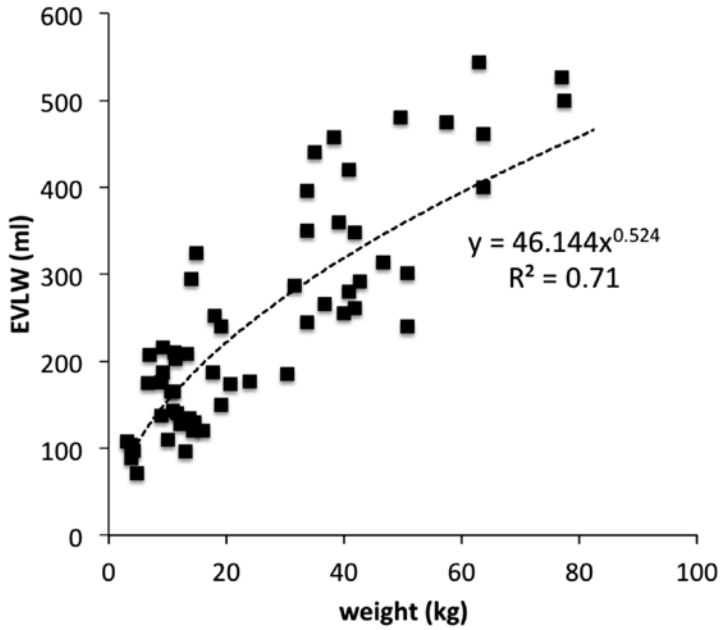
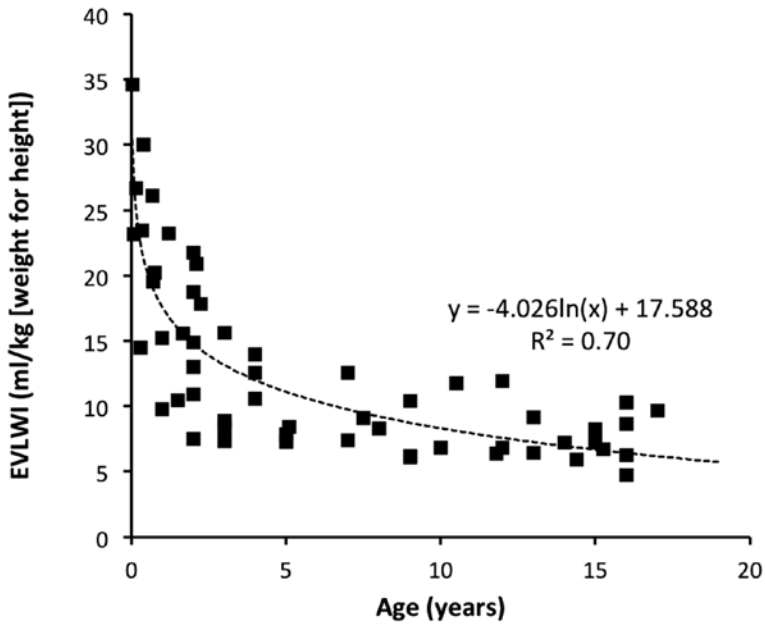


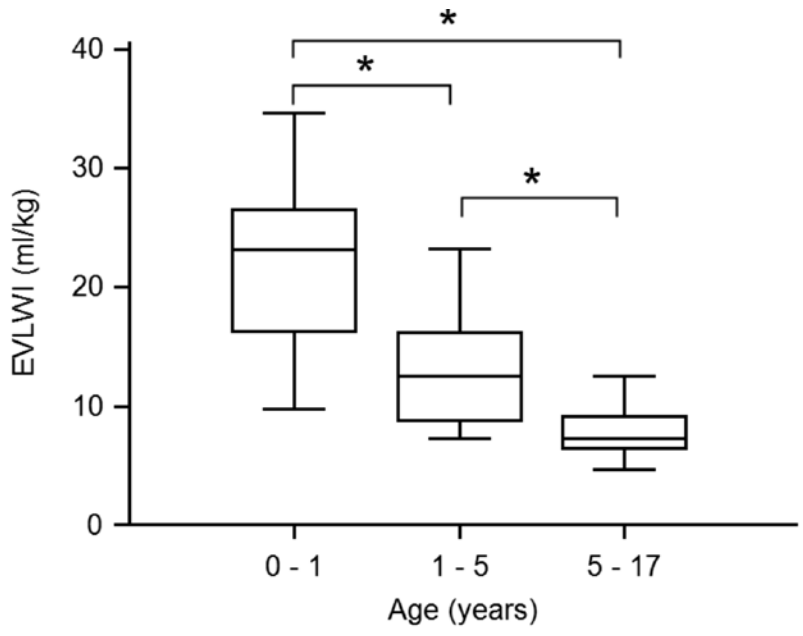
Figure 2

The relation between age and EVLW indexed to predicted body weight



Figures 3a

reflect EVLW indexed to predicted body weight divided per age group



Figures 3b

reflect EVLW indexed to height divided per age group

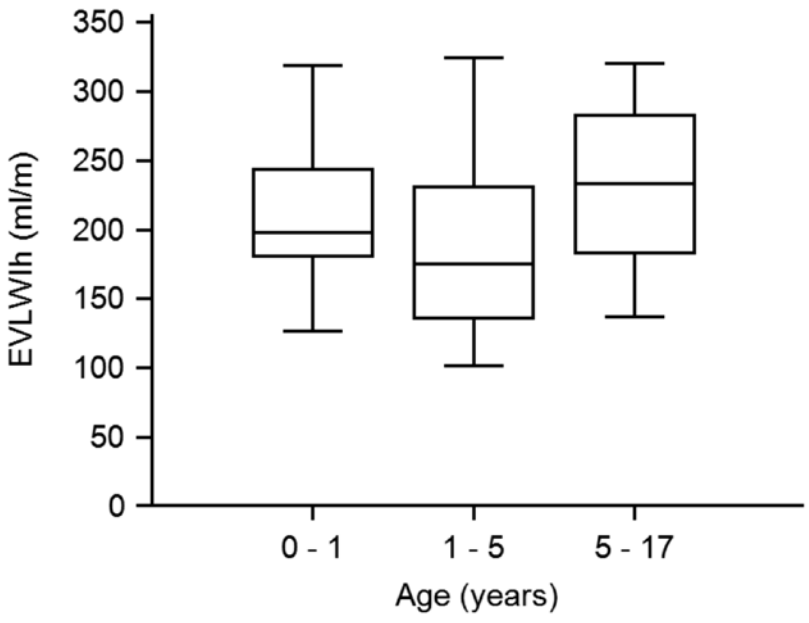


Table 2

Measurement results (median and 5-95 percentile) of EVLWI, GEDV and CI categorized in three age groups

Age (year)	EVLWI [ml/kg] Median (5-95 percentile)	EVLWIh [ml/m] Median (5-95 percentile)	GEDVI [ml/m^2] Median (5-95 percentile)	CI [l/min/m^2] Median (5-95 percentile)
0 – 1	23 (10 – 34)	198 (142-313)	420 (270-510)	4.7 (2.2-13.7)
1 – 5	13 (7 – 22)	175 (127-316)	510 (260-680)	4.5 (2.6-6.2)
5 - 17	7 (6 – 12)	234 (142-313)	515 (340-690)	4.6 (2.7-6.7)
All	10 (6-26)	201 (124-315)	476 (305-701)	4.6 (2.5-6.6)

Discussion

Our study confirms that young children have higher values of indexed lung water compared to older children or adults. The collected data enable, for the first time, the design of age related normal values for EVLWI.

High levels of lung water in young children have been described in the past and our results are in conjunction with these results.[4, 9, 16] However these studies reflect critically ill children with predominant pulmonary abnormalities and frequently severe edema. This is the first study to describe measurements after these pulmonary abnormalities have been resolved, and therefore the results can be regarded as "near normal".
We propose the following "near normal" values in children based upon predicted body weight. For children under one year of age EVLWI values below 34 ml/kg can be considered normal. For children between 1 and 5 years normal values are below 22 ml/kg. Between 5 and 17 years levels should be below 12 ml/kg. Above 17 years adult values (< 10 ml/kg) should be used.

In a former study, we explained the high lung water values in children by the altered relation between body weight and lung mass of children compared to adults[10]. Also, the relation between GEDV and intra thoracic blood volume (ITBV) is not constant in all ages, and may vary even among individuals and species [17]. Yet the PiCCO system assumes a constant relationship and uses an adult-based calculation algorithm of EVLW values.[18, 19]

In general, indexing requires a linear (and 1:1) relation between the physiologic variable and the indexing parameter over an age range from newborns to adults. The question

is, which body parameter is most suitable for indexing hemodynamic variables. Several adult studies have shown predicted body weight to be superior over actual body weight in predicting severity of illness.[12, 13, 20] For that reason we primarily choose to use that same method in our study. Besides, in the software versions of the newer $PiCCO_2$ devices predicted body weight is used for indexing EVLW in both adults and children. However, with regard to lung mass, it seems that height is the most suitable parameter since lung volume is importantly related to height. [21] Recent studies in adults suggest that height seems to be superior to weight as indexing variable.[13, 22] Our study results confirm that indexing to height might be more useful compared to the default indexing to predicted body weight, which makes age-dependent adjustments unnecessary. Our study results suggest normal values of EVLWIh below 315 ml/m.

In the present study CO indexed to BSA was age independent, which suggests the possibility of extrapolating adult normal values to children. In contrast, GEDVI appears to be age dependent and in accordance to an earlier study, lower in young children [10].

There are several limitations to our study. First data were collected at various PICU's and with various PiCCO devices without a uniform treatment protocol. On the other hand the PiCCO measurements were routinely performed as advised by the manufacturer. Furthermore we collected absolute values to prevent indexing differences based upon various algorithms incorporated in the subsequent software versions of the PiCCO devices. Second the sample size is small. Third, the children were primarily selected based on a normal pulmonary condition and not on normal preload and cardiac output conditions. Therefore CI and GEDVI values from this study may not be entirely interpreted as normal. Fourth, we cannot rule out underlying pulmonary pathology, as no additional pulmonary examinations were included. On the other hand, the presented oxygenation and respiratory variables point to a near normal pulmonary condition. Therefore, the values of EVLWI should be interpreted as "near" normal. Unfortunately measurements of healthy children will ethically not be possible or at least very difficult to perform due to the invasive nature of these measurements.

Conclusion

We conclude that in younger children, even after resolution of critical illness, values of predicted body weight indexed extravascular lung water are higher compared to published adult values. We present age related normal EVLWI values for possible clinical use. Furthermore we advise to index EVLW to height, which seems to be age-independent.

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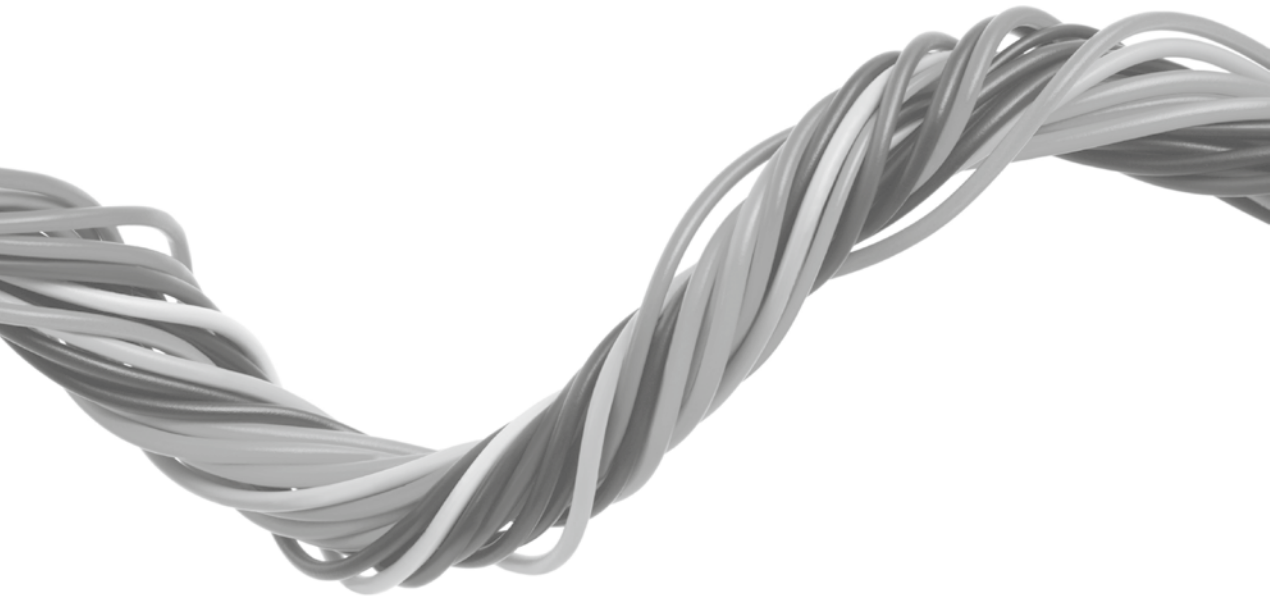
Part IV

Summary



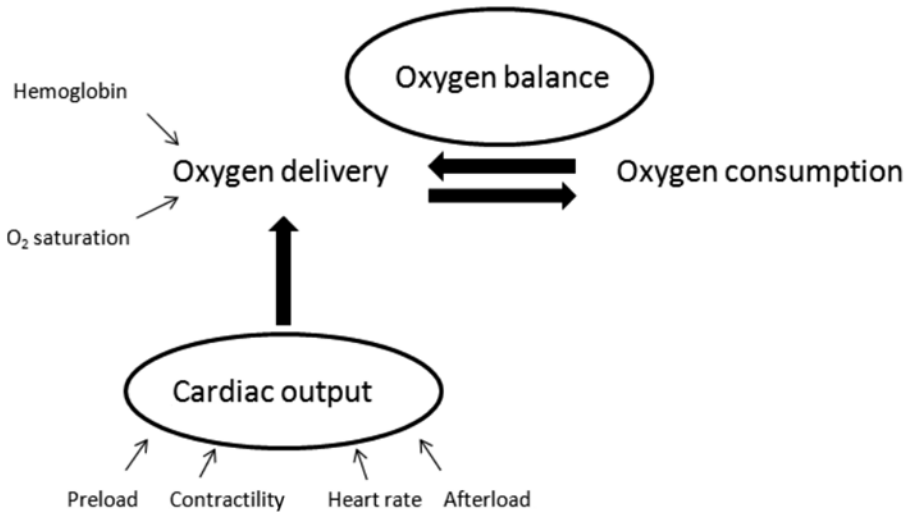
General discussion, summary and future perspectives

9

General discussion

Circulatory failure is a life-threatening condition that is associated with tissue hypoperfusion and cellular hypoxia leading to organ dysfunction.[1] The optimal method of guiding therapy with the use of hemodynamic monitoring in these critically ill children is still under discussion. Assessment of the hemodynamic state is often not based on a single measurement but a continuous evaluation of oxygenation, cardiac function and volume status over time during disease progression. In this chapter we will discuss the role of advanced hemodynamic monitoring in critically ill children in clinical practice.

Figure 1
Principle hemodynamic determinants



The main component of interest in monitoring the hemodynamic status is the oxygen balance. Figure 1 shows the physiological determinants of hemodynamics. The oxygen delivery, the product of cardiac output (CO) and O_2 blood content, must satisfy the O_2 consumption to keep a positive O_2 balance in the body and prevent tissue hypoxia. Blood flow or CO, necessary for oxygen transport, depends on the interplay of heart rate, preload, contractility and afterload. Advanced hemodynamic monitoring quantifies the components pertaining to oxygen balance. These measurements help to evaluate adequacy of the circulation and can be used as end-points in guiding therapies. Physical examination and routine hemodynamic variables, such as blood pressure and heart rate, play only a minor role in hemodynamic management of critically ill patients as they are unreliable estimating (changes in) cardiac output.[2, 3].

End-points

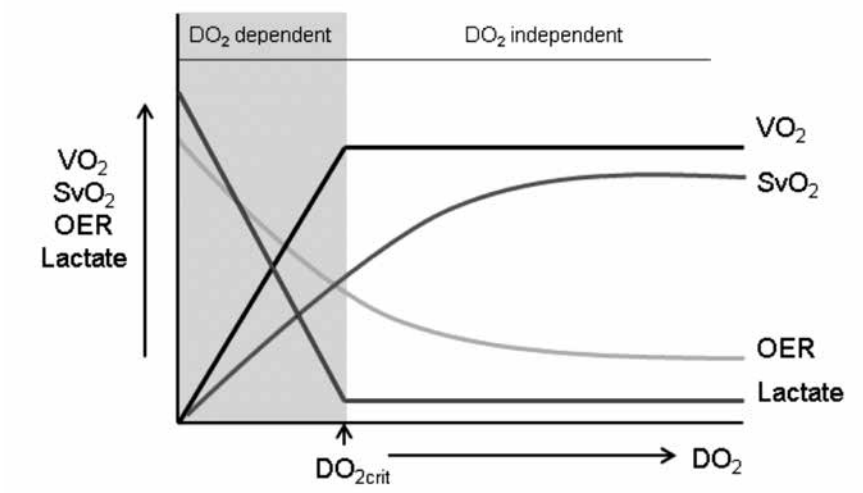
The recommendations of the pediatric sepsis guidelines, based on adult studies, direct the intensive care hemodynamic support to goals of central venous oxygen saturation ($ScvO_2$) ≥ 70% and cardiac index (CI) between 3.3 and 6.0 L/min/m^2 after the initial resuscitation of septic shock.[4, 5] These and other advanced hemodynamic end-points will be discussed in the next paragraph.

Oxygen balance related end-points

The balance of oxygen delivery and consumption can be assessed by measuring the oxygen extraction ratio (OER) as described in **chapter 2** of this thesis. Monitoring of the mixed venous oxygen saturation (SvO_2) is used as a surrogate for the balance between systemic oxygen delivery (DO_2) and consumption (VO_2). The relationship between DO_2 and VO_2 is biphasic as shown in Figure 2. The VO_2 is independent of oxygen delivery over the upper range of DO_2 due to the body's ability to increase the OER. This is reflected by a decrease in SvO_2. However, VO_2 will become dependent on DO_2 when the enhanced OER fails to compensate for the decreased DO_2. Below the point of critical DO_2 (DO_{2crit}), oxygen demands exceed oxygen availability. At this point VO_2 falls, anaerobic metabolism ensues and lactate accumulates in the blood. The DO_{2crit} changes in parallel to changes in oxygen requirements. The associated critical OER, which is approximately 70%, remains constant regardless of changes in oxygen demand or cause of the inadequate DO_2.[6, 7] A significant elevated OER is an indicator of (impending) inadequate tissue oxygenation.

Figure 2

Schematic relationship of oxygen delivery (DO_2) and oxygen consumption (VO_2), mixed venous oxygen saturation (SvO_2), oxygen extraction ratio (OER) and lactate concentration in the blood.



Mixed venous oximetry is often not available as placement of a pulmonary arterial catheter is difficult in neonates and infants. Alternatively, central venous oxygen saturation ($ScvO_2$) is monitored in or nearby the right atrium. The agreement between SvO_2 and $ScvO_2$ has been investigated in numerous studies with controversial conclusions.[8-12] Sampling from the superior vena cava reflects the venous blood from the upper part of the body and neglects venous blood from the lower body. The opposite applies to the inferior vena cava. In general, all the organs have different OER and consequently different regional venous oxygen saturations. In normal conditions, the lower body extracts less oxygen than the upper body, which is reflected by a higher inferior vena cava oxygen saturation. However, septic shock and other critically ill settings will change regional ratios of oxygen supply to demand. This effects the $ScvO_2$ values depending on the sampling site and effects the relationship between SvO_2 and $ScvO_2$, which differs from normal conditions. This makes the interpretation of $ScvO_2$ in critical conditions more complex. Furthermore, a drop in $ScvO_2$ does not necessarily mean that tissue hypoxia occurs. Only when the VO_2 becomes dependent on DO_2, indicating an oxygen debt, the corresponding $ScvO_2$ reflects inadequate tissue oxygenation. To make it even more complex, also an elevated (>70%) $ScvO_2$ may be indicative of inadequate oxygenation, as a result of impairment of oxygen extraction. A beneficial effect of fluid administration on VO_2 in potential fluid responders, seems to be more reliable predicted by lactate than $ScvO_2$.[13] Right-to-left shunting will influence the absolute values of arterial and venous oximetry. This will however not be of influence of the calculation and interpretation of the OER. In conclusion, $ScvO_2$ should not be used as an individual marker in the assessment of tissue oxygenation but combined with other variables.[14]

Anaerobic markers like serum lactate levels and the respiratory quotient (CO_2 production (VCO_2)/ O_2 consumption (VO_2) ratio) are elevated once aerobic metabolism cannot be maintained.[15] Therefore lactic acidosis may, at an advanced stage of circulatory failure, indicate inadequate DO_2 leading to impaired oxygen utilization. Under conditions of tissue hypoxia the total VCO_2 should be less reduced than VO_2, as CO_2 is also produced under anaerobic conditions. Thus the VCO_2/VO_2 ratio, equal to the veno-arterial CO_2 tension difference/arteriovenous O_2 content difference ratio, will be increased. These two anaerobic metabolism markers can be used to diagnose global tissue hypoxia and to monitor whether therapy will reduce oxygen debt assessed by an increase in VO_2. A possible advantage of the respiratory quotient above lactate would be, that it is a pure marker of anaerobic metabolism, as lactate levels may also be elevated as a result of impaired clearance.[16] Lactate clearance (> 10%) seems to have prognostic value and may be a potential goal in early sepsis resuscitation.[17, 18] However, future studies are needed to prove that targeting these indicators of anaerobic metabolism improves outcome. It seems logical that targeting therapy by achieving a rapid decline of lactate levels will benefit patient in shock. On the other hand an increased lactate level is a non-

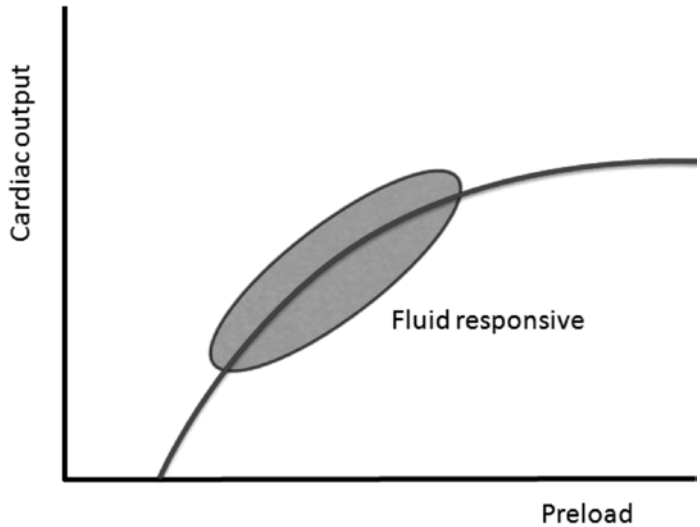
specific indication of tissue hypoxia. It does not guide the clinician into what specific therapy (e.g. fluids, vaso-active drugs etc) is most beneficial.
In summary, from the available oxygen balance related parameters, serum lactate levels may be used as a prognostic marker in critically ill patients. Furthermore, $ScvO_2$ and OER can be considered as therapeutic end-points in critically ill children.

Cardiac output related end-points
Blood flow, responsible for the transport of oxygen, can be quantified by measuring CO. An outline of all the modalities for CO measurements in children is described in **chapter 3** of this thesis. In general, more invasive measurements of CO are more reliable. CO as an end-point to guide therapy can be used either to target normal values or to monitor changes over time. The first option is only useful if a reliably estimate of CO can be obtained. In **Part II** of this thesis we show that the transpulmonary thermodilution (TPTD) method is a reliable method of CO measurement under various conditions of critical illness and its use in children can be advised. The second option, CO trend monitoring, can be applied with less accurate methods with advantages of being less invasive and easy to apply.[19-22] In critically ill patients the first approach may be preferred above the latter as an accurate estimation of the CO may give a better insight of the etiology of the circulatory failure. High CO values in combination of inadequate oxygenation may indicate hyperdynamic shock and should be treated differently from a low CO state. In this context it is also important to realize which optimal values should be targeted.
CO should be integrated into therapeutic guidelines as an end-point in critically ill children. Furthermore, separate estimations of one or more determinants of CO (heart rate, preload, afterload and contractility) may help to direct medical decisions to improve specifically these variables. Examples are fluid responsiveness (preload) to guide fluid administration and systemic vascular resistance index (afterload) to institute vasodilators.

Fluid status related end-points
The relation between CO and preload is reflected by the Frank-Starling curve (Figure 3). The steep part of the curve demonstrates fluid responsiveness. Estimating fluid responsiveness is often used as an indicator of preload. Dynamic indices of fluid responsiveness can be obtained by tracking changes in stroke volume and blood pressure continuously, making use of the heart-lung interaction.[23, 24] These functional hemodynamic parameters, like pulse pressure variation and stroke volume variation, can be provided by various advanced hemodynamic monitoring devices, estimating variations in arterial pulse pressure, systolic pressure, stroke volume and changes in central venous pressure, aortic flow and variability of plethysmographic measurements. [25] However, these parameters are limited in their use because the patients require positive pressure ventilation under strictly defined conditions.[26, 27] Several studies

in children have evaluated these parameters.[28-39] It may reduce the amount of inappropriate fluid administration and may potentially improve outcome from critical illness, but further research is needed to validate these indices. At present, they cannot be used as therapeutic end-points yet.

Figure 3
Frank Starling curve



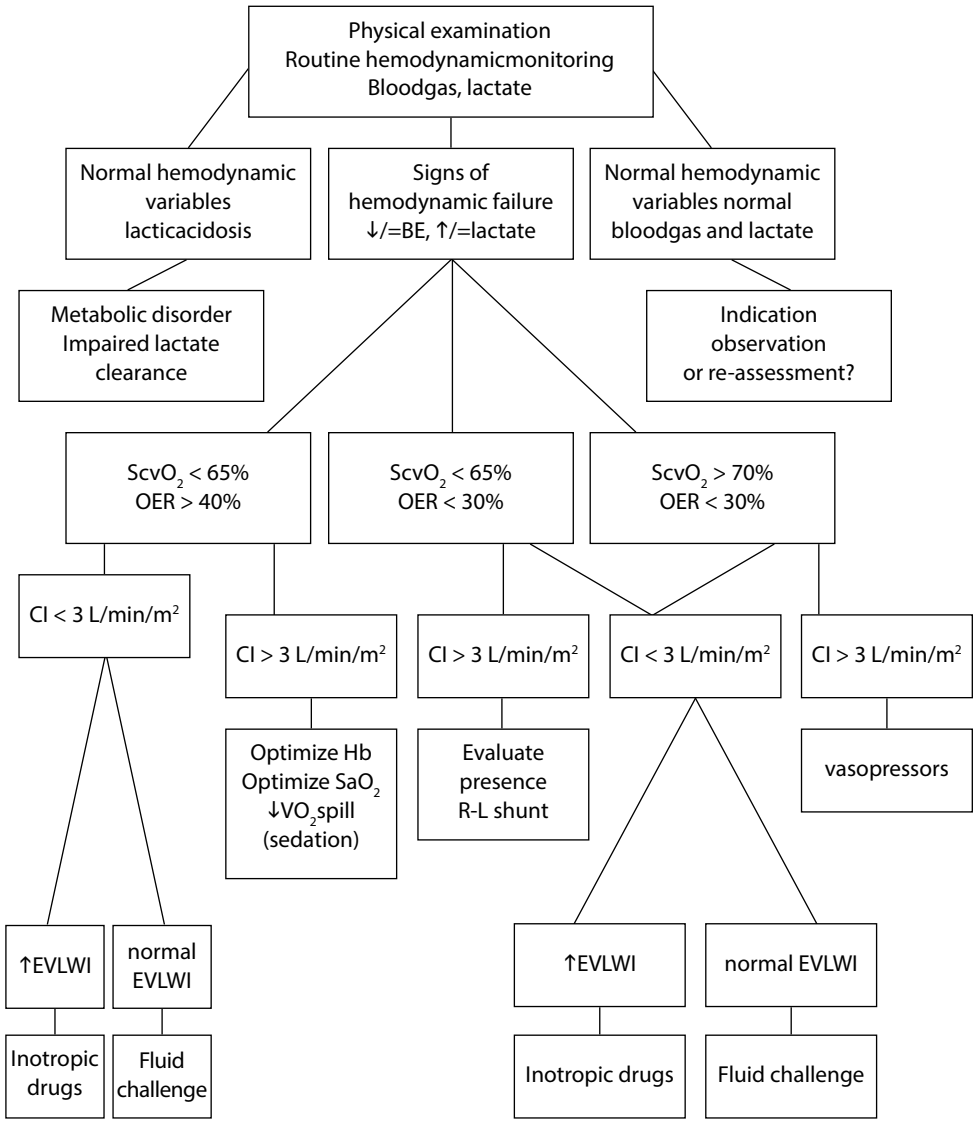
Instead, monitoring extravascular lung water (EVLW) may help to diagnose fluid overload. This parameter quantifies pulmonary edema and can be measured at the bedside by the TPTD technique. In **chapter 7** we describe a validation study of measuring EVLW over a wide range of pulmonary edema. Changes over time are reliably estimated. However, this parameter seems to be related to growth and development and age related normal values are lacking. In **chapter 8** we present age categorized normal EVLWI values for clinical use. We also suggest an even more practical age-independent EVLW indexed-to-height value. Targeting EVLWI end-points may prevent overzealous fluid administrating and may be used in titrating fluid and diuretic therapy.[40]

Algorithm

Having summarized various potential therapeutic end-points to be targeted in critically ill children, the next step should be a practical advice for clinical use. The proposed flow diagram is similar to the treatment algorithm in **chapter 2**, supplemented with end-point targets.

Figure 4

Algorithm of end-points hemodynamic monitoring.



BE base excess, = normal value, $ScvO_2$ central venous oxygen concentration, OER oxygen extraction ratio, CI cardiac index, EVLWI extravascular lung water index, Hb hemoglobin concentration, SaO_2 arterial oxygen saturation, VO_2 oxygen consumption, R-L shunt right-to-left shunt.

CO and the other measurements are not mandatory for every child admitted to the PICU. So the first step in the flow diagram (figure 4) should discriminate these children, using physical examination, routine hemodynamic monitoring and blood gas analysis and serum lactate concentration.

In the flow diagram target values are suggested. But normal values are not always optimal endpoints and moreover, target values need adjustments over time and have to be interpreted in relation to the underlying pathophysiologic process.

Timing of applying advanced hemodynamic monitoring is important. Should we wait until all other measures have failed to start monitoring cardiac output? Looking at the sepsis algorithm of the stepwise management of hemodynamic support in infants and children, cardiac output monitoring is only suggested in persistent catecholamine refractory shock.[4] Of course, inserting catheters or applying special monitoring equipment can be time consuming and inconvenient in the very first minutes of resuscitation. But waiting until fluid administration seems to be ineffective, risking overzealous fluid administration with detrimental effects on morbidity and mortality, may be the other extreme.

Conclusion

In conclusion, advanced hemodynamic monitoring can provide essential information of the hemodynamic status of a patient in order to ensure adequate tissue oxygenation. Today, various devices are available, also in children, to estimate cardiac output and other hemodynamic parameters using different techniques. We have validated CO and EVLW measurements using the TPTD method in various critically ill conditions in pediatric animal models. This relatively invasive technique is able to estimate CO and EVLW reliably even in extreme conditions, although there are also limitations.
However, simply measuring advanced hemodynamic parameters will not change patient outcome unless it is coupled with therapies, that by itself are associated with improved patient outcomes. A treatment algorithm for clinical practice is suggested using end-point targets like CI and EVLWI to guide medical decisions.

Future perspectives

The next step to be taken are prospective clinical studies in critically ill children, to study the following research questions:

- Do we need different treatment protocols during the acute and chronic phases of critical illness in children? In the acute phase of septic shock most patients will be treated aggressively with fluid administration. Targeting the same end-points values in the chronic phase, fluid administration could be detrimental. Maybe by that time fluid restriction and vasoactive drugs or even diuretics could be beneficial, which is often instituted with delay. A more patient- and disease-course-tailored approach may be needed.

- Because overzealous fluid administration appears to be detrimental, can we define an optimal point on the Starling curve where we should stop further fluid administration even though the patient appears to be fluid responsive? Being fluid responsive surely doesn't mean fluids should be administered if clear signs of aerobic metabolism are present.

- Can we use less invasive methods to obtain CO, EVLW and $ScvO_2$? At present, EVLW can only be measured invasively using dilution techniques. It would be very useful to quantify pulmonary lung edema in a non-invasive way, for example by using ultrasound techniques. Continuous non-invasive measurement of $ScvO_2$ may be possible by pulse oximetry in pulmonary tissue.[41] Validation studies of non-invasive CO measurement techniques in children are needed, using standardized reference methods. Special attention should be paid to the underlying algorithms which should be adapted to children. The different body proportions in children should be taken into account formulating normal values and indexing parameters.

- More research is warranted to explore the microcirculation. Assessment of the adequacy of oxygen balance by markers like $ScvO_2$, OER and lactate reflect the global body oxygen balance, yet may not recognize regional mismatch. Indices of tissue perfusion may be used as early indicators of impaired tissue oxygenation. We may even go one step further, looking at the cellular level. Most of the body's oxygen consumption is used by mitochondria. Mitochondrial function monitoring may be ultimately the optimal method monitoring the adequacy of organ perfusion.

Summary

Chapter 2 reviews the clinical assessment of various hemodynamic variables in pediatric critical care. The goal of monitoring is to guide clinicians in their management and anticipate on hemodynamic changes. The relationships between specific hemodynamic variables are complex and only a thorough understanding of the (patho) physiology will help interpreting the values in making clinical decisions. There is no one single variable on which medical decisions can be based, but a combination of clinical assessment and (advanced) hemodynamic monitoring parameters is probably the most reliable.

As long as we do not routinely estimate the oxygen balance on cellular or tissue level (monitoring microcirculation), we have to rely on variables derived from the macrocirculation. Cardiac output measurement quantifies systemic blood flow, which can be estimated by the transpulmonary thermodilution technique, which is considered as one of the gold standards in pediatric patients. The use of the central venous oxygen saturation is hampered by different normal values under specific patient conditions. The presence of a right-to-left shunt for example, makes a great difference in the absolute value, but shouldn't influence the oxygen extraction ratio. Several tests and measurement parameters are suggested to evaluate fluid responsiveness, although the application of functional hemodynamic monitoring in pediatric patients is only scarcely studied. Relatively unknown is the estimation of extravascular lung water in children to guide fluid or diuretic therapy. Further pediatric studies need to be done to evaluate the potential beneficial impact on outcome in critically ill children and how to index these values and estimate normal values for infants and children.

In **chapter 3** an overview is provided of the available cardiac output monitoring systems that can be used in infants and children. The systems are reviewed listed in order of degree of invasiveness, from the invasive dilution techniques to the completely non-invasive bioreactance/bioimpedance technique, continuous finger cardiac output monitoring and ultrasound. Pediatric (animal) studies are used to provide scientific evidence to support their application in infants and children. Comparing all these systems is difficult as several different reference standards are applied instead of using one valid gold standard.

Choosing the right monitoring system out of all the available monitoring devices is difficult as the ideal hemodynamic monitoring system doesn't exist (yet). Furthermore, none of the devices can be generally applied to all individuals, as patients and their underlying disease processes are very heterogeneous. It is more appropriate to employ an individualized approach and select the system most suitable for each individual patient and for each type of problem. For a patient-tailored monitoring it is however essential to be familiar with the available technologies with all its advantages and limitations. Even

more important is the understanding and interpretation of the measurement results. In general, a more invasive technique produces a more reliable absolute estimation of cardiac output. The same applies to a system that needs calibration.

Validation studies are needed before an advanced hemodynamic monitoring system can be applied into clinical practice. The transpulmonary thermodilution (TPTD) technique is considered to be a pediatric clinical gold standard in normal conditions and hypovolemic shock.[42, 43]
In **chapter 4** we have validated the TPTD technique in the presence of a left-to-right shunt. Overall, a left-to-right shunt is more frequently seen in infants than in adults. Shunts can be present in patients born with congenital heart and/or vascular diseases or with a persistent ductus arteriosus. The manifestation of a left-to-right shunt can be associated with (cardiogenic) shock, depending on the seriousness of the defect. Frequently these patients will be admitted to an intensive care for stabilization and pre-/ postoperative monitoring
In our study we demonstrated that the transpulmonary thermodilution cardiac output measurement is feasible in the presence of a significant left-to-right shunt. A left-to-right shunt prolongs the indicator pathway by recirculation and distorts the dilution curve. The longer passage time of the thermal indicator in the extra circuit causes loss of indicator by diffusion into the surrounding tissue, resulting in some overestimation of the CO. The distortion of the TPTD curve can also be quantified by calculating the mean transit time (MTt) and down slope time (DSt). Both may be useful for quantifying the magnitude of the shunt. The presence of a shunt also effects the measurement of the global end diastolic volume (GEDV) and extravascular lung water (EVLW), both becoming inaccurate.

Most of congenital shunt anomalies are corrected by the time of adolescence, which make (intra)cardiac shunts rare in adults. Sometimes acquired or congenital shunts are found in adults, detected by coincidence e.g. a different shape of the TPTD curves. In **chapter 5** we comment on two adult case-reports by Giraud et al., both having a left-to-right shunt diagnosed by an abnormal TPTD curve. We tried to explain what influence the presence of a shunt has on the various TPTD derived parameters extracted from the dilution curve, focusing on cardiac output, extravascular lung water and global end-diastolic volume. We concluded that a left-to-right shunt induces an increase in DSt and, to a lesser extend MTt as a consequence of delayed delivery of indicator to the systemic circulation, due to the presence of an extra circuit. This phenomenon should not be confused with true recirculation.

Another critically ill condition in which we have validated the transpulmonary thermodilution technique is acute lung injury. Respiratory insufficiency based

primarily on injured lungs is often associated with a compromised circulation, either directly caused by lung edema or indirectly induced by positive pressure ventilation. Especially patients with capillary leakage and acute lung injury require tight fluid management avoiding overzealous fluid administration while maintaining a sufficient intravascular volume status. These patients may benefit from advanced hemodynamic monitoring

Chapter 6 describes a validation study of the TPTD technique in a surfactant wash-out model to induce acute lung injury (ALI). Although the TPTD technique measures cardiac output reliably, it slightly overestimates the true CO value, both in adults and children. This may be explained by loss of the thermal indicator during the passage through the heart, lungs and great vessels. Presence of pulmonary edema may cause even more loss as a thermal indicator diffuses much more easily through water than through air. Since infants and young children have a much higher EVLW indexed to body weight (EVLWI) than adults, the impact of these increased amounts of lung edema may be more pronounced.

Our study showed however that the TPTD method remained accurate in measuring CO in the presence of severe pulmonary edema (increase over 125%). The results showed no important influence of the amount of extravascular lung water on the reliability of CO measurements. These findings suggest, that in the presence of severe pulmonary edema, other factors compensate for the possible loss of the thermal indicator, like the velocity of diffusion of the cold indicator, the surface area for exchange, the volume of the interstitial fluid into which cold diffuses, and the blood flow, which determines the time during which temperature exchange must occur.

Chapter 7 describes a validation study of extravascular lung water (EVLW) measurements using TPTD in a pediatric animal model. The measurement of EVLW enables the bedside quantification of pulmonary edema and is increasingly used as a parameter for diagnosis, treatment and optimized fluid management of critically ill adults with acute lung injury (ALI). It is a relatively new parameter, not yet integrated in pediatric therapeutic guidelines, and only a few studies have investigated the value of EVLW measurement in children. Interestingly, these reports show consistently higher normal EVLW values, indexed to bodyweight, specifically in young children. Among the clinical methods estimating EVLW, the most frequently used at the bedside is the TPTD technique. However, the reliability of this technique may be influenced by the amount of EVLW itself. The TPTD measurement of EVLW hasn't been validated yet in critically ill children with extremely high amounts of lung water. The purpose of our study was to validate the EVLW measurements by TPTD against two gold standards, the gravimetric method and the transpulmonary double indicator dilution (TPDD) technique, using ice-cold indocyanin green (ICG).

We used eleven lambs in which pulmonary edema was induced using a surfactant

washout model. Indexed EVLW by TPTD correlated significantly with both reference measurements. The percentage errors with gravimetry and TPDD were 41% and 14%, respectively. A significant overestimation was demonstrated comparing EVLW measurements by TPTD and gravimetry, specifically in the higher lung water range. Secondly, changes in $EVLWI_{TPTD}$ were closely related to changes in $EVLWI_{TPDD}$, which makes $EVLWI_{TPTD}$ suitable for trend monitoring of pulmonary edema.

In **chapter 8** an international multi-centre study is presented in which EVLW measurements, reflecting the amount of pulmonary edema, were collected from children admitted to a PICU after resolution of their illness. These data reflect near 'normal' values in children. Lack of age related normal values makes the interpretation and clinical use of this parameter impracticable in critically ill children. The obtained values were measured at the bedside, using the transpulmonary thermodilution method. They were indexed to predicted body weight and to height and subsequently related to age. The unusual high body weight indexed EVLW (EVLWI) compared to adults seems to be related to growth and development. Goal of this study was to define 'near normal' values of EVLWI in children. 58 children with heterogeneous PICU admission diagnoses were included in this study. EVLW indexed to predicted body weight correlated with age ($r^2 = 0.7$) and could be categorized in three age groups with significantly different median EVLWI values (5-95 percentile) < 1 year 10-35 ml/kg, 1-5 year 7-22 ml/kg and 5-17 year 6-12 ml/kg. EVLW indexed to height did not correlate to age and resulted in an age-independent "near normal" value of < 315 ml/m.
In conclusion, younger children have higher "near normal" values of EVLW indexed to predicted body weight and age categorized normal EVLWI values are presented for clinical use. Additionally, we suggest to index EVLW to height, which seems to be age-independent.

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Nederlandse samenvatting, conclusies en toekomst perspectieven

10

Samenvatting, conclusie en toekomst perspectieven voor niet ingewijden

Inleiding

Op een kinder intensive care (PICU) worden onder anderen de ademhaling en de bloedsomloop van patiënten bewaakt. De focus van dit proefschrift ligt op het monitoren van de bloedsomloop bij kinderen, ook wel het hartminuutvolume of circulatie (Engels: cardiac output) genoemd. Het hartminuutvolume is afhankelijk van de hartfunctie (contractiliteit), hartfrequentie, de bloedvaten (afterload) en de vullingstatus (preload) van de patiënt. Het hartminuutvolume zorgt ervoor dat alle lichaamscellen, al naar gelang de behoefte, van voldoende bloed met zuurstof en voedingsstoffen worden voorzien. Bij een verminderde bloedsomloop kan zuurstoftekort in de cellen ontstaan, dat uiteindelijk zal leiden tot orgaanschade.
Het doel van het monitoren van de bloedsomloop is drieledig: in de eerste plaats om gealarmeerd te worden van een achteruitgang van de circulatie, ten tweede om de juiste therapeutische keuzes te maken ter voorkoming van (verdere) orgaanschade. Tenslotte om het effect van de ingezette therapie te evalueren en te sturen richting een bepaalde streefwaarde van een parameter, de zogenaamde doelgerichte therapeutische benadering.

Parameters die gebruikt worden in de praktijk om een indruk te krijgen van de kwaliteit van de bloedsomloop zijn bijvoorbeeld bloeddruk, hartfrequentie, bewustzijn en kenmerken van de huid (temperatuur verschil op verschillende plaatsen in het lichaam (Δ temp) en doorbloeding van de huid (capillary refill time)). Bovendien wordt extra informatie verkregen uit aanvullend bloedonderzoek. Ondanks de vanzelfsprekendheid waarmee dit allemaal wordt gedaan, blijkt de waarde die er aan gehecht kan worden voor het inschatten van de bloedsomloop slechts zeer beperkt. Dit heeft voor een groot deel te maken met het feit dat deze parameters slechts indirect afgeleide waarden zijn van het hartminuutvolume en beïnvloed kunnen worden door compensatie mechanismen van de circulatie en externe factoren, die niets met de bloedsomloop te maken hebben. Bij een zieke patiënt bijvoorbeeld kan aanvankelijk de bloeddruk hoog zijn door angst en koorts, terwijl tegelijkertijd de bloedsomloop al ernstig tekort schiet. In dit geval maskeert een goede bloeddruk een slechte circulatie. Andersom kan ook: als de omgevingstemperatuur koud is, is de huid vaak ook koud en bleek en zal de doorbloeding slecht zijn. Dat betekent echter nog niet, dat de patiënt in shock is.

Concluderend: er is behoefte aan parameters, die de bloedsomloop en de zuurstofbalans in het lichaam betrouwbaar weergeven, zodat een circulatoire achteruitgang eerder

wordt opgemerkt en orgaanschade mogelijk kan worden voorkomen. In de afgelopen decennia zijn er daarom geavanceerde hemodynamische monitoring technieken ontwikkeld, die het hartminuutvolume direct kunnen bepalen en daarnaast nog aanvullende waarden van bloed volumina en zuurstof saturaties kunnen weergeven. Het is belangrijk om de fysiologische achtergrond van de circulatie goed te begrijpen voor een juiste interpretatie van deze geavanceerde parameters. Centraal staat hierin de balans van zuurstof aanbod en zuurstof verbruik in het lichaam.
Bij volwassen intensive care patiënten zijn deze geavanceerde monitoren inmiddels uitgebreid bestudeerd en worden al ruimschoots toegepast. De ervaringen die hiermee zijn opgedaan zijn helaas niet 1 op 1 te extrapoleren naar kinderen aangezien zij geen kleine volwassen zijn. Zij verschillen van volwassenen op basis van hun anatomie, lichaamsverhoudingen en (patho)fysiologie met andere compensatie mechanismen en response op therapieën.
Geavanceerde hemodynamische monitoren worden bij kinderen nog niet routinematig in de praktijk gebruikt. Dit kan onder anderen worden verklaard door onbekendheid met de technieken, ongeschiktheid van de apparatuur voor kinderen (grootte van probes en katheters) en gebrek aan validatie studies en normaalwaarden bij kinderen. Daarnaast is er ook nog geen wetenschappelijk bewijs, dat de toepassing van geavanceerde hemodynamische monitoring ook uiteindelijk een positief effect heeft op het ziektebeloop en de mortaliteit van kritisch zieke kinderen.

Doel van het onderzoek

Het onderzoek beschreven in dit proefschrift is gericht op het valideren van hartminuutvolume metingen middels de transpulmonale thermodilutie techniek (TPTD) bij kinderen in aanwezigheid van diverse ziektebeelden. Er is hierbij gebruik gemaakt van diermodellen als surrogaat voor kinderen. De TPTD techniek wordt beschouwd als een goud standaard bij kinderen onder normale omstandigheden. Het eerste diermodel simuleert een links-rechts shuntcirculatie, waarbij een aangeboren hartafwijking is nagebootst met een extra omleiding van de bloedsomloop tussen de grote lichaamsslagader (aorta) en de longslagader. In het tweede diermodel zijn de longen ziek gemaakt, waardoor zich een grote hoeveelheid vocht ophoopte in de longen.

Het tweede deel van het onderzoek is gericht op de bepaling van een relatief nieuwe parameter, die de hoeveelheid vocht in de longen kan kwantificeren: longwater of longoedeem of extravasculair longwater (EVLW). De mate van longoedeem wordt bij volwassen patiënten gebruikt als voorspeller van overvulling. Het is een potentieel bruikbare maat voor het titreren van het vochtbeleid bij patiënten. Er zijn echter nog

veel onduidelijkheden, voordat deze parameter in de klinische praktijk bij kinderen kan worden toegepast. Gebruik makend van het tweede diermodel met ziek gemaakte longen en grote hoeveelheden longoedeem, zijn EVLW metingen middels de TPTD techniek gevalideerd. Ten slotte is middels een klinische studie getracht, indexeringen en normaalwaarden voor EVLW te definiëren voor kinderen.

Samenvattingen van de studies

Hoofdstuk 2 geeft een overzicht van de fysiologische achtergronden en gebruik van hemodynamische parameters voor de beoordeling van de circulatie bij kinderen. Er wordt ingegaan op de eventuele toegevoegde waarde van geavanceerde hemodynamische monitoring. Aan de orde komen het meten van hartminuutvolume, het voorspellen van positieve reactie van het hartminuutvolume op extra vocht toediening (fluid responsiveness), het berekenen van zuurstof aanbod in relatie tot zuurstof verbruik in het lichaam en het kwantificeren van vocht in de longen. De specifieke fysiologische verschillen tussen kinderen en volwassenen worden toegelicht.
Het meten van cardiac output is technisch inmiddels betrouwbaar mogelijk, ook bij kinderen. Het kan een belangrijke bijdrage leveren in het beoordelen van de hemodynamische status van een patiënt. Dit geldt ook voor het bepalen van de centraal veneuze saturatie, al moet bij de interpretatie van de absolute uitslag altijd rekening worden gehouden met eventuele congenitale hartafwijkingen, zoals een shuntcirculatie.
Met de opkomst van nieuwe technologieën, worden ook nieuwe volumetrische en dynamische parameters verkregen. Volumetrische parameters zoals GEDV, ITBV en EVLW zijn potentiële waarden, die een inschatting kunnen geven van de mate van onder- en overvulling van de patiënt. Dynamische parameters zijn afgeleid van variaties tijdens de ademhalingscyclus die ontstaan in de bloeddruk en slagvolume van het hart. Deze parameters worden gebruikt voor het voorspellen van fluid responsiveness.
Ondanks de verschillende mogelijkheden voor geavanceerde hemodynamische monitoring bij kinderen, zullen toekomstige studies moeten aantonen of dit uiteindelijk ook een verbetering zal geven op de morbiditeit en mortaliteit. Naast validatie studies zullen in de toekomst studies moeten worden verricht, waarin cardiac output en andere geavanceerde parameters geïntegreerd zijn in behandelingsprotocollen.

Hoofdstuk 3 geeft een overzicht van alle klinisch beschikbare methoden om het hartminuutvolume bij kinderen te kunnen meten. Helaas bestaat de ideale hemodynamische cardiac output monitor vooralsnog niet. De meest invasieve methoden zijn de transpulmonale dilutie technieken. Deze geven het meest betrouwbaar het hartminuutvolume weer. Minder en niet-invasieve methoden zijn pulse contour analyse technieken, echocardiografie en echo doppler, bioreactance/bioimpedance technieken

en continue vinger cardiac output monitoring. Ongekalibreerde technieken zijn onbetrouwbaarder dan gekalibreerde technieken, maar zijn vaak wel makkelijker en sneller toe te passen. De keuze van de methode wordt meestal bepaald door de klinische situatie van de individuele patiënt. Tevens zou men zich kunnen afvragen 1. Is een betrouwbare meting noodzakelijk of is het volgen van cardiac output (trendmonitoring) voldoende, 2. Zijn invasieve metingen haalbaar of moet voornamelijk niet invasief worden gemeten 3. Zijn ook andere hemodynamische metingen gewenst (zoals EVLW, GEDV)? Bij deze keuzes dient men bekend te zijn met de eigenschappen en beperkingen van de verschillende hemodynamische monitoren om de uitslagen goed te kunnen interpreteren.

De transpulmonale thermodilutie techniek wordt beschouwd als een goud standaard voor cardiac output metingen bij kinderen. Deze is gevalideerd voor normale omstandigheden en bij hypovolemische shock.
In **hoofdstuk 4** hebben we een validatie studie uitgevoerd naar de cardiac output metingen in de aanwezigheid van een links-rechts shuntcirculatie. De studie is uitgevoerd in een pediatrisch diermodel, waarbij een artificiële shunt is aangelegd tussen de aorta en de longslagader. Dit diermodel simuleert een links-rechts shuntcirculatie zoals in de praktijk gezien wordt bij een persisterende open ductus Botalli of diverse aangeboren hartafwijkingen. Aangezien een dergelijke shunt hemodynamisch belangrijke consequenties kan hebben, kan het van groot belang zijn, de circulatie betrouwbaar te monitoren bij deze kinderen.
Onze studie toont aan dat het meten van het hartminuutvolume mogelijk is in aanwezigheid van een belangrijke links-rechts shunt. Hoewel de circulatietijd van de indicator verlengd wordt met veranderingen van de vorm van de dilutie curve tot gevolg, blijven de cardiac output waarden acceptabel in vergelijking met de referentie methode (ultrasound flow probe). Er ontstaat enige overschatting van het hartminuutvolume bij toename van de shuntgrootte. De verandering van de vorm van de dilutie curve heeft wel invloed op de bepalingen van GEDV en EVLW. Deze worden hierdoor onbetrouwbaar en niet interpreteerbaar.

Hoofdstuk 5 is een commentaar op een gepubliseerd artikel van Giraud, waarin twee case reports worden besproken van volwassen patiënten met een links-rechts shunt. Door de afwijkende vorm van de TPTD dilutie curve en onlogische uitslagen van de cardiac output, werden de artsen getriggerd om aan de aanwezigheid van een shunt te denken. Deze toevalsbevinding werd middels aanvullende diagnostiek in beide gevallen bevestigd. Wij hebben aan de hand van de gepresenteerde data een logische verklaring gegeven voor de sterk afwijkende CO, EVLW en GEDV uitslagen. Deze case reports illustreren fraai het belang van het goed interpreteren van data die door de monitor gegeven worden. Het is belangrijk de vorm van de dilutie curve steeds te controleren en

niet te berusten in afwijkende uitslagen, maar actief op zoek te gaan naar een plausibele verklaring.

Een veel voorkomend ziektebeeld bij kritisch zieke patiënten is ALI (acute lung injury), waarbij patiënten respiratoir insufficiënt worden en afhankelijk zijn van mechanische beademing. Meestal zijn deze patiënten tevens circulatoir instabiel en moeten hemodynamisch bewaakt worden.
Hoofdstuk 6 beschrijft een validatie studie van cardiac output metingen middels TPTD in een pediatrisch diermodel, waarbij in de longen een ALI wordt geïnduceerd door middel van longspoelingen. Tijdens deze experimenten ontstaat een toename van longoedeem, bepaald aan de hand van EVLW metingen. De betrouwbaarheid van de cardiac output metingen met de thermodilutie techniek zou theoretisch beïnvloed kunnen worden door de hoeveelheid vocht in de longen. Temperatuurverlies treedt namelijk makkelijker op in water dan in lucht, waardoor meer verlies van de thermo-indicator zou optreden in longen met grote hoeveelheden longoedeem. Deze studie resultaten zijn vooral van belang voor kinderen, aangezien met name zieke jonge kinderen veel hogere geïndexeerde EVLW waarden hebben dan volwassenen.
De resultaten van onze studie toonden echter geen grote invloed van de hoeveelheid EVLW op de betrouwbaarheid van de cardiac output metingen. Mogelijk zijn er andere factoren, die het eventuele verlies van de thermo-indicator compenseren. Theoretisch zijn dit de invloed van de snelheid van diffusie van de thermo-indicator, de grootte van het oppervlak van uitwisseling, het volume van het interstitiele vocht waarin gediffundeerd kan worden en de bloeddoorstroming in de longen.

Hoofdstuk 7 beschrijft een validatie studie van EVLW metingen middels de TPTD techniek in hetzelfde pediatrische diermodel als de studie in hoofdstuk 6. EVLW is een relatief nieuwe parameter, die gebruikt kan worden voor het kwantificeren van vocht in de longen en een richting kan geven aan het vochtbeleid bij patiënten. Kritisch zieke kinderen kunnen extreem grote hoeveelheden longoedeem hebben. In deze omstandigheden zouden de EVLW bepalingen middels TPTD onbetrouwbaarder kunnen worden, maar dit is echter nooit eerder onderzocht.
In het diermodel werd het beeld van acute lung injury (ALI) middels longspoelingen geïnduceerd, waardoor een forse toename van het EVLW ontstond. De TPTD techniek werd vergeleken met twee goud standaarden voor EVLW metingen: de postmortale gravimetrie methode en de transpulmonale double indicator dilution (TPDD) techniek. Ondanks een goede correlatie van de EVLW metingen middels TPTD ($EVLW_{TPTD}$) met beide referentie methoden, ontstond er wel een trend van overschatting van het $EVLW_{TPTD}$ vergeleken met de gravimetrie tijdens de toename van het longoedeem. Aangezien het tevens klinisch van belang is, om het EVLW in de tijd te vervolgen, hebben we in onze studie ook nog gekeken naar de veranderingen van EVLW gedurende het beloop van

het experiment. De veranderingen in $EVLW_{TPTD}$ metingen blijken betrouwbaar als trend monitoring vergeleken met de veranderingen in $EVLW_{TPDD}$ metingen.

Hoofdstuk 8 beschrijft een internationale klinische studie bij kinderen, opgenomen op de PICU met een medische indicatie voor een PiCCO katheter, waarmee TPTD metingen van cardiac output en EVLW kunnen worden verricht. Prospectief zijn EVLW metingen verzameld op het moment, dat de kinderen vrijwel helemaal opgeknapt waren van hun opname diagnose. We hebben deze waarden als 'bijna' normaal beschouwd, aangezien in de inclusie criteria stabiele respiratoire en hemodynamische voorwaarden werden gesteld. De klinische toepassing van EVLW bij kinderen is nog niet goed onderzocht. Dit komt mede door het gebrek aan normaalwaarden en onduidelijkheid rondom optimale indexering.
Kinderen hebben opvallend hoge EVLW waarden geïndexeerd naar lichaamsgewicht vergeleken met volwassenen. Dit werd bevestigd met onze studie. Dit heeft naar alle waarschijnlijkheid te maken met groei en ontwikkeling. Uit de metingen van in totaal 58 kinderen hebben we normaalwaarden voor 3 leeftijd-categorieën gecreëerd, met mediane EVLWI (5-95 percentile) waarden die onderling significant van elkaar verschillen: < 1 jaar 10-35 ml/kg, 1-5 jaar 7-22 ml/kg en 5-17 jaar 6-12 ml/kg. EVLW geïndexeerd naar lengte blijkt een leeftijd onafhankelijke maat te zijn, met een normaalwaarde van < 200 ml/m.

Circulatoir falen is een levensbedreigende situatie die gepaard gaat met zuurstoftekort in de cellen en geassocieerd is met orgaan uitval. Geavanceerde hemodynamische bewaking kan een toegevoegde waarde hebben voor het starten en sturen van therapie bij ernstig zieke kinderen. De parameters die middels geavanceerde hemodynamische monitoring worden verkregen, kunnen vervolgens gebruikt worden als streefwaarden in een doelgericht therapie algoritme (zie **hoofdstuk 9**, figuur 4). Hiervoor komen in aanmerking: centraal veneuze zuurstofsaturatie ($ScvO_2$), zuurstof extractie ratio (OER), serum lactaat concentratie, base excess (BE), hartminuutvolume (CO) en extra vasculair longwater (EVLW). Een advies voor de meest optimale monitor voor het verkrijgen van deze hemodynamische parameters bij kinderen kan vooralsnog niet worden gegeven.
Het beoordelen van de circulatie is een dynamisch proces, waarbij niet op een enkele parameter of een enkele meting gevaren kan worden. Het lijkt het meest betrouwbaar om regelmatig een combinatie van bovengenoemde parameters gedurende verschillende fasen van het ziekteproces te interpreteren. Hierbij kan het effect worden gemeten van therapie en een trend worden vervolgd van het ziekteproces. De streefwaarden zullen gaandeweg mogelijk moeten worden aangepast afhankelijk van het ziektebeloop.

Conclusies en toekomstperspectieven

Geavanceerde hemodynamische monitoring kan essentiële informatie geven over de circulatoire conditie van de patiënt en is toenemend ook beschikbaar voor kinderen. Met onze studies hebben we een bijdrage willen leveren aan het valideren van CO en EVLW metingen bij kinderen. De transpulmonale thermodilutie methode lijkt onder verschillende condities betrouwbaar, maar er zijn ook beperkingen.

Toekomstig onderzoek zal zich met name richten op prospectieve klinische studies bij kinderen met de volgende onderzoeksvragen:

- Kunnen we toekomstige behandelingsprotocollen van hemodynamisch instabiele patiënten nog meer individualiseren en rekening houden met het stadium van het ziekteproces?
- Kunnen we een optimaal eindpunt definiëren voor het toedienen van vaatvulling ter preventie van overvulling?
- Welke minder invasieve meetmethoden kunnen (betrouwbaar) gebruikt worden bij kinderen voor het beoordelen van de circulatie? Mogelijk door uitbreiding van validatie studies bij kinderen van reeds bestaande technieken, mogelijk door nieuw te ontwikkelen meetmethoden.
- Welke methoden en parameters kunnen worden gebruikt voor onderzoek naar de microcirculatie. Mogelijk geeft onderzoek op weefsel, cellulair of zelfs mitochondrieel niveau een betrouwbaardere weergave van de zuurstofbalans.

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Curriculum vitae

Anneliese Nusmeier was born on the 30th of November 1967 in Losser, the Netherlands. She obtained her secondary school diploma at the Ichthus College in Enschede in 1986. That year she started Medical School at the State University of Groningen. Her medical degree was obtained in 1993, after which she worked as a resident at the Department of Pediatrics of the Emma Children's Hospital of the Academic Medical Centre (AMC) of Amsterdam. In 1994 she participated in a project of cerebral malaria in children in the Gambia, West Africa under supervision of Dr. M. Boele van Hensbroek. Her training in Pediatrics commenced in 1995 at the pediatric departments of the Jeroen Bosch Hospital (location Groot ZiekenGasthuis) in 's-Hertogenbosch (head Dr. J.H. Hoekstra). She completed her training in 2000 at the AMC (head Prof. Dr. C.J. de Groot and Prof. Dr. H.S.A. Heymans) and subsequently completed her fellowship of Pediatric Intensive Care Medicine at the same hospital in 2002 (head Prof. Dr. A.P. Bos). In 2003 she became a staff member at the Department of Intensive Care of the Radboud University Nijmegen Medical Centre (head Prof. Dr. J.G. van der Hoeven) working as a pediatric intensivist on the Pediatric Intensive Care Unit.

Anneliese is happily married to Gert Visch. They live in Beek Ubbergen together with their two sons: Ruben (1999) and Maurits (2001).

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