Goal Directed Fluid Therapy Revised: Indirect Monitoring of Interstitial Fluid Accumulation During Mini Fluid Challenges with Crystalloids

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Abstract: Goal directed fluid therapy (GDT) implies administration of fluid boluses with the aim of optimizing cardiac performance. There is a major concern that maximization of cardiovascular performance can be achieved in expense of deterioration in body hydration processes. Also, these methods require semi invasive devices. However, monitoring of the whole body hydration status and interstitial fluid accumulation during fluid loading is not possible in everyday clinical practice. A new method, minimum Volume Loading Test (mVLT), uses evaluation of plasma dilution efficacy in small fluid boluses (2.5 – 5.0 ml kg^{-1}) of isoosmotic crystalloid solutions followed by 5 min periods without fluids. The invasively measured arterial and venous hemoglobins, and simultaneous non-invasively measured hemoglobin ($SpHb^{TM}$ from Radical-7, Masimo inc., Irvine, USA) are used for estimation of plasma dilution which serves as an indication of plasma volume expansion.

The objective of this paper was to discuss plasmadilution as a target parameter for goal directed therapy. Could plasma dilution also indicate a degree of interstitial fluid accumulation?

Keywords: Crystalloid solution, interstitial fluid accumulation, fluid therapy, haemoglobin, lymphatics, microcirculation, plasma dilution, pharmacokinetics, volume kinetic analysis.

INTRODUCTION

Intravenous fluid therapy is part of everyday clinical practice in many fields of medicine, particularly in the perioperative setting. An isoosmotic crystalloid solution can be used for many purposes [1] such as treatment for dehydration, resuscitation of hemorrhage or simply for maintenance. Achieving and maintaining of target plasma dilution is of major importance in total intravenous anesthesia (TIVA) and target controlled infusion (TCI). However, the plasma dilution cannot be accurately predicted from the chemical and physical features of a solution, and the physiology of body water balance and fluid distribution among functional fluid compartments. As shown in Fig. (**1**), in addition to the balance of fluid intake and net elimination, the intravascular fluid retention is affected by transcapillary filtration-absorption ratio [2] and lymphatic influx into central veins [3]. The filtration-absorption ratio is thus affected by changes of net transcapillary pressure, and the lymphatic flow by changes of the interstitial hydrostatic pressure [4].Consequently, both pressures are affected by interstitial fluid accumulation. As shown in Fig. (**2**), interstitial expansion by fluids leads to increasing compliance and progressive accumulation of fluid until the anatomical limits are reached. As shown in Fig. (**3**), when the interstitial fluid compliance is maximized (virtually infinite in overhydration), the lymphatic flow does not further increase, because hydrostatic pressure remains constant despite accumulation of interstitial fluid. Thus, even if fluid elimination out of the body is not prominent, the plasma volume expansion efficacy of a crystalloid tends to decrease during infusion because of increasing interstitial fluid compliance Fig. (**4**). If the infusion is targeted to reach and maintain constant plasma dilution or simply to improve hemodynamics, there is a risk of interstitial fluid overload (oedema). Oedema formation deteriorates the turnover of plasma albumin in the lymphatic loop as a result of interstitial trapping of both fluids and proteins [5]. This lowers the plasma protein content leading to a decrease in plasma volume [6]. Oedema prevents the effective delivery of drugs to cells in a swollen tissue and reduces elimination of drugs and metabolites. Thus, for efficacy and safety reasons, any goal directed crystalloid infusion should ideally

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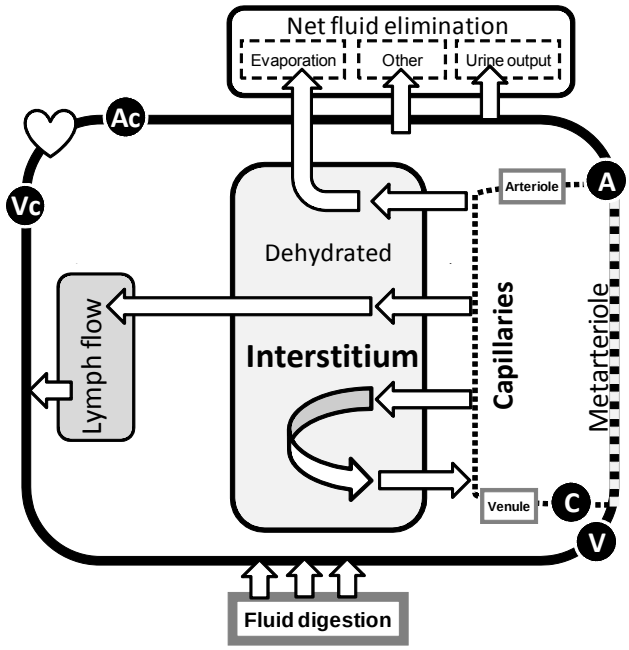


Fig. (1). The model of whole-body fluid handling: the resting state of fluid distribution and elimination in a state of mild dehydration. The digestion origin fluid supply to circulation matches the net whole body fluid elimination. The net lymphatic flow ideally matches the fluid volume which would otherwise accumulate in the interstitium of the whole body. Arrows represent equal fluid volumes.

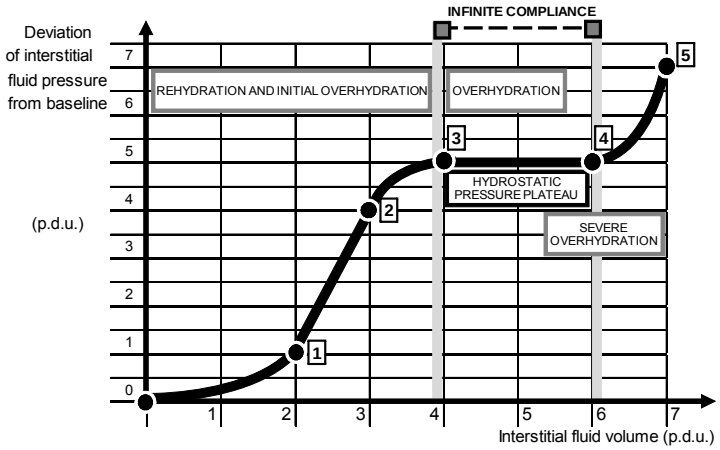


Fig. (2). The theoretical relationship between interstitial fluid volume and hydrostatic pressure in association with different states of hydration in derma and skeletal muscles. Five patterns of relationship can theoretically be reached during five ideally tailored crystalloid infusions separated by the 5 min. periods without fluids (see checkpoints 1-5 in boxes). The model was drawn on the basis of previous studies [57,58].

be monitored for interstitial fluid accumulation with warning signs for detection of edema formation. However, only large deviations from normal interstitial hydration are detectable in current clinical practice [7]. This could lead to undetected complications such as pulmonary edema [8].

In this review, the deficiencies in current perioperative fluid therapy are discussed with emphasis on goal directed fluid therapy and also introducing new methods and techniques.

PERIOPERATIVE FLUID THERAPY: MORE QUESTIONS THAN ANSWERS

It has been shown that critically ill patients and those who undergo major surgery require benefit from precisely-guided and individualized fluid therapy for reduction of

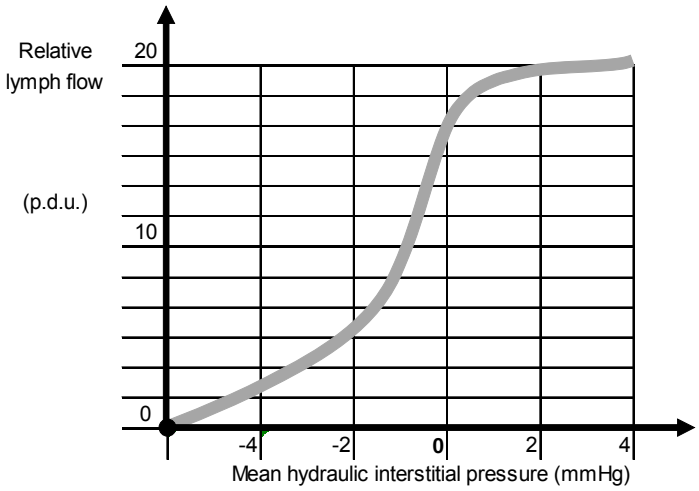
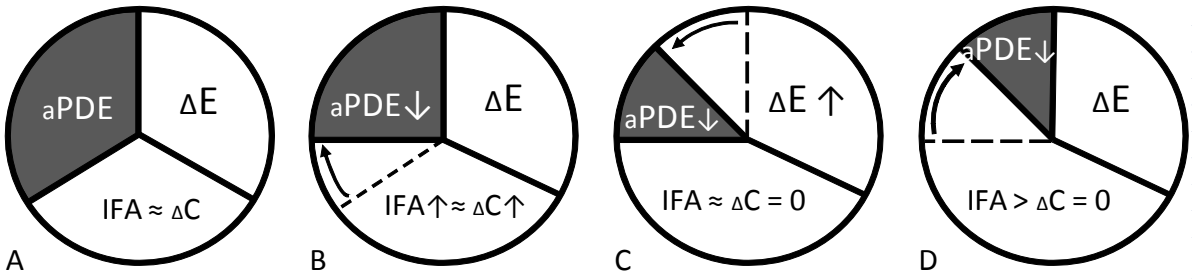


Fig. (3). The dependence of relative lymph flow on the mean interstitial hydraulic pressure. The pressure is negative in severe dehydration. The model was drawn on the basis of the related physiology [5]. **p.d.u.** -- procedure defined unit.



aPDE -- arterial plasma dilution efficacy.

IFA -- the whole body interstitial fluid accumulation:
IFA = ΔV - ΔL, where

ΔE -- deviation of net fluid elimination.
ΔC -- deviation of the whole body interstitial fluid compliance.

ΔV -- deviation of the whole body interstitial volume,
ΔL -- deviation of the whole body lymph flow.

Fig. (4). Theoretical dependency of arterial plasma dilution efficacy (aPDE) on crystalloid infusion induced deviations of the whole body interstitial fluid accumulation (IFA), interstitial compliance (ΔC) and net fluid elimination (ΔE). The aPDE is a single infusion induced fractional deviation of arterial plasma dilution (ΔaPD) which, in turn, is a fractional change of arterial hemoglobin concentration (ΔaHb) in respect to initial baseline Hb before the 1st infusion. Deviations and their ratios are arbitrary and used solely for the explanation of principles in their interaction.

(**A**) All the 1st infusion induced deviations are equal ($0 < aPDE = \Delta E = \Delta C \approx IFA$).

(**B**) The prevailing 2nd infusion induced similar increases of ΔC and IFA are associated with unchanged ΔE and lead to a reduction of aPDE ($0 < aPDE < \Delta C \approx IFA > \Delta E = 0$). (**C**) The prevailing 3rd infusion induced increase of ΔE is associated with unchanged ΔC and IFA leading to a further reduction of aPDE ($0 < aPDE < \Delta E > \Delta C \approx IFA = 0$).

(**D**) The similar reduction of aPDE without an increase of ΔE is caused by the increase of IFA associated with unchanged ΔC.

morbidity [9]. Thus, an individualized fluid management referred to as *goal-directed fluid therapy* (GDT) is now widely used for perioperative fluid management [10]. However, nowadays, there are still more questions than answers [11].

Fluid Deficit

Patients are regarded to be slightly dehydrated before elective surgeries. This is supposedly due to a decrease of circulating blood volume, ongoing urine production, anesthesia, positive pressure ventilation and insensible perspiration [12]. Postoperatively, however, patients are usually over-hydrated [7], while both states can be present in disorders of water balance [13]. However, the exact volume of the body fluid disturbance remains unknown because it is not feasible to measure in the clinical setting. The textbooks [14] recommend several formulae for calculation of fluid deficits, ongoing losses and maintenance requirements. These rules-of-thumb lead to variations among protocols [15]. Mathematical models, are rarely referred to in everyday clinical practice because of complexity, technological limitations and insufficient validation [16]. A pharmacokinetic approach, volume kinetic analysis [17,18], is sometimes used to understand movement of fluids but mainly targets functional volumes [19]. However, the volume kinetic analysis requires frequent blood hemoglobin samples to generate a dilution

curve from which parameters such as distribution volume and elimination can be derived.

Development of Individualized Fluid Administration

Most patients, healthy [21] as well as sick individuals, have efficient physiological reserves to provide substantial tolerance of variations in body hydration [11]. Nevertheless, excessive infusions result in edema and compromised tissue oxygenation, wound healing problems, impairment of coagulation, delayed recovery of gastrointestinal motility and increased risk of cardiac complications [7]. For decades, the strategies of fluid administration were shifting from aggressive (*liberal* which is large overall volume of fluids) to more moderate (*restrictive* - small) [22]. In the last decade concepts of restrictive fluid administration were launched particularly for gastro intestinal surgery [14]. Most likely, the fluid requirements vary according to individual physiology and interventions such as anaesthesia and surgery [7]. It would be more appropriate to look for an individual *responsiveness* to fluid therapy.

Goal Directed Fluid Therapy (GDT): The Basics

The GDT implies stepwise fluid boluses aiming for individual optimization of flow related target parameters such as cardiac stroke volume [23]. Although GDT was first mentioned in the literature about a decade ago [24], the method for guiding volume repletion based on measurements of patient's response to a fluid load has been used for more than 25 years [25]. Its main concept is that fluid administration is justified until it significantly increases the *static* and/or *dynamic* target parameters. Static parameters are those used for the evaluation of *actual response* to the fluid challenge, while dynamic parameters provide a prediction of actual response without administration of fluids [27-29]. Such prediction is referred to as *fluid responsiveness*. Usually fluid boluses are continued until they improve static parameters by the >10 % [23], and/or until such increase is predicted by the >10 % variation of a dynamic parameter during a cycle of mechanical lung ventilation [26].

Fluid Challenge: The Dilemma of Fluid Type and Volume

A fluid bolus has to be minimal but sufficient for the evaluation of induced deviation in static parameters. In GDT therapy, a 150-200 ml volume of colloid is infused over about 5 minutes. This bolus is evaluated before any new decision of subsequent bolus is taken. The question is whether this bolus is evidence based as regards to amount, type and timing? A requirement of the bolus would be that it is large enough to cause a proper identification of response but not contribute to fluid overload. In other words, could a precise determination of plasmadilution be a sufficient replacement for GDT based on deviations in flow-related target parameters. Although crystalloids are primarily the hydrating fluids, in specific clinical settings such as hemorrhage they used as volume expanders. For goal directed therapy, however, morbidity is reduced more effectively when colloids but not crystalloids are deployed [31]. That is related to a lesser development of intestinal edema in patients treated with colloids [32], what is particularly relevant in gastrointestinal surgery, where the fluid restriction leads to better outcomes [33].

The evolving rational strategy for colloid-crystalloid co-administration is the restrictive use of crystalloids and the individualized goal-directed administration of colloids [34, 35]. The minimal effective volume of a colloid that can be used for small volume loading is also unknown. In 2011, Muller and his colleagues specifically addressed the latter issue [36]. In this study, a 100 ml *'mini-fluid challenge'* of colloid was infused over 1 minute. An increased aortic blood flow was sufficient to predict the *fluid response* of an upcoming *fluid load* of 400 ml given over the next 14 minutes. Nevertheless, most likely it would be prudent to continue the 100 ml mini fluid challenges instead of starting the 400 ml fluid loading, because the actual response determined by the mini fluid challenge does not indicate that there is a remaining reserve of myocardial contractility that can be recruited by the upcoming load.

Monitoring of Target Parameters in GDT: The Limitations

In GDT, the evaluation is based on semi- or fully invasive devices. Some are easy to learn, other more difficult [37]. The need for appropriately trained personnel, proper patient positioning, sedation or even general anaesthesia as well as mechanical lung ventilation add up to the limitations in the availability and applicability of appropriate monitoring [38]. Interestingly, any monitoring method or device was never demonstrated as the key factor in improving outcomes [39]. Monitoring alone was found neither sufficient nor beneficial, and was even associated with complications in patients with co-existing cardiac diseases undergoing non-cardiac surgery [40]. Thus, only combining available if not ideal monitoring with appropriate management algorithms is likely to improve outcomes [39].

It has always been a justified need to assess the individual fluid status by simple means, but even nowadays it can be reliably done only when the deviation from normal is quite substantial. Back in 2007, Jacob *et al* wrote that 'we should also be able to provide a rational fluid regimen to the many patients in whom extended monitoring is not possible for logistical or financial reasons' [15]. It seems that not much has changed to this date. In his editorial, Vincent emphasizes that 'there is a need to develop a simple and effective technique by which the response to a fluid challenge can be rapidly and objectively assessed so that fluid loading is reserved only for those who will benefit' [30].

Controversial Outcome Reports in GDT Applications: Need for Re-assessment?

The goal directed fluid therapy guided by static and dynamic target parameters aims for optimization of cardiovascular performance presumably leading to the optimization of tissue perfusion. However, there is a concern that plasma volume expansion by colloids may be achieved at the expense of deteriorated whole body hydration. First, colloids do not provide free water for the needs of hydration. Next, there is evidence for context-sensitive physiologic target blood volume that the body strives to recover soon after the perturbation. Preceding crystalloid [22, 41] and colloid [42]

infusions made the elimination of the later infused crystalloids considerably faster. A speculation would be that elimination of the preceding crystalloid will be faster if it is followed by a colloid solution in normovolemic subjects. The latter hypothesis is based on the fact that excessive colloid-bound water cannot be eliminated similarly to a crystalloid until degradation of infused colloid. Meanwhile, aiming to return to the physiologic target blood volume, free water can be forced out of plasma by being deposited in highly elastic interstitium such as the derma. Theoretically, no matter what is the volume and type of consecutive isoosmotic-isooncotic fluid infusions, the plasma dilution efficacy of a fluid challenge will be minimized after reaching individual physiologic target blood volume.

The above described considerations suggest an explanation for the controversial clinical outcomes reported in association with the use of GDT in the perioperative setting. Considering benefits of GDT, such as improved functional outcomes, there were also reduced hospital stay and morbidity after major surgery [43-47]. However, these data raise concerns [48,49]. For an example, Challand and his colleagues found no advantage of GDT in patients undergoing major colorectal surgery, and additionally - it was even associated with a prolonged hospital stay and time to fitness for discharge [48]. There is a possibility that different outcomes were determined by different states of the whole body hydration. More specifically, optimization of cardiovascular performance by GDT may have induced over- or under-hydration of tissues. Future research with a focus on the investigation of alternative target parameters and the refinement of GDT algorithm itself are therefore encouraged.

Plasma Dilution Efficacy as a Result of Small Fluid Challenge: A New Target Concept

Although infused fluid dissolves in the blood, hemodilution has to be transformed into the corresponding plasma dilution before it is used in calculations related to distribution of fluid, because it is the water in plasma that equilibrates with extravascular fluid spaces. According to the background physiology of GDT, plasma dilution induced increase in circulating volume is a trigger in a chain reaction where, ideally, the increase in blood volume leads to the increase in flow related target parameters. Therefore, *plasma volume expansion efficacy* of a small fluid challenge can serve as target parameter in GDT, especially when evaluation of deviations in flow related parameters is not applicable or available.

The fluid challenge induced *plasma dilution* is the fractional change of hemoglobin in respect to initial baseline which, in consecutive fluid challenges, is the hemoglobin value before the first fluid bolus. The volume expansion in large vessels is most important in the context of possible changes in cardiac preload. Plasma dilution in any site of circulation except the capillaries can be used as an index of plasma volume expansion in large vessels, because hematocrit differences in large and small blood vessels due to the Fahraeus effect can be ignored. Plasma dilution efficacy can be calculated as the fractional change of plasma dilution induced by a fluid challenge. Such calculation avoids the potential errors arising from the use estimated normal blood volume in the conventional equations for the calculation of plasma volume expansion [50-53].

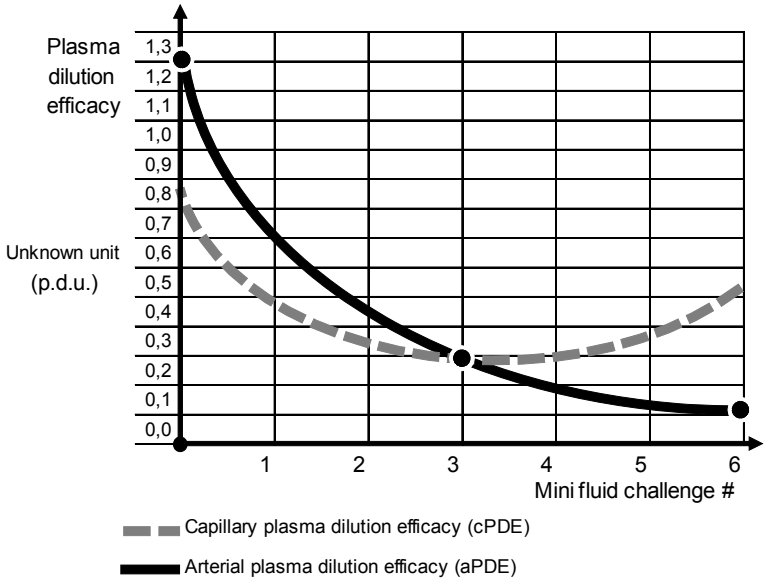
Plasma Dilution and Hemodynamics: Special Considerations

When the heart is fully efficient, it does increase the stroke volume in response to plasma dilution induced preload. External factors can also prevent the improvement in cardiac performance, e.g. increased intrathoracic pressure that lowers responsiveness of preload [28]. That explains why a variability of flow-related parameter response to similar fluid challenges occurs. As an example, from 40% to 72% of intensive care patients with hemodynamic instability responded to a fluid load by a significant increase in stroke volume and cardiac output [54].

The non-responsiveness of flow related parameters may be caused either by a single factor or a combination of several factors such as (a) low plasma volume expanding efficacy of the infused fluid, i.e. due to the activated elimination (Fig. **4**), (b) non-responsiveness of preload, i.e. due to venous pooling or high intrathoracic pressure, (c) non-responsiveness of cardiac stroke volume, i.e. due to preexisting maximized myocardial contractility (location in a flat part of the Frank-Starling's curve). In contrast to colloids, the plasma volume expansion efficacy of crystalloids is more difficult to predict. Studies on volume kinetics show that plasma dilution of crystalloids is about 20% in normovolemic individuals, while it reaches 75% in hypovolemic [55]. The volume kinetic analysis suggested that 54% of the 25 ml kg^{-1} of lactated Ringer's solution resided in the circulation at the end of infusion in subjects who significantly increased cardiac output (*reponders*) compared with intravascular fluid retention of 25% in *non-responders* [56]. These findings suggest that similar crystalloid fluid challenges can be associated with different plasma dilution efficacies, and only the efficacious plasma dilution leads to significant increase in cardiovascular performance (if it has a functional reserve). The clinical implication is that both inefficient plasma dilution and inefficient increase in flow related parameters would indicate refraining from further fluid administration.

Applied Physiology for Interpretation of Plasma Dilution in Consecutive Fluid Challenges

In human physiology, the degree of interstitial tissue expansion by fluid defines the hydration status of the whole organ. Interstitial volume expansion leads to changes of tissue specific elasticity. It is described by interstitial fluid compliance (Fig. **2**) which is the ratio between the deviation of interstitial fluid volume and hydrostatic pressure (Fig. **3**). Interstitial compliance increases during fluid accumulation until the anatomic elasticity of the tissue reaches maximum [57,58]. The increase of compliance facilitates interstitial fluid accumulation, reduces intravascular fluid retention and thus lowers the plasma dilution efficacy in consecutive crystalloid boluses, particularly when net fluid elimination is also activated by the fluid challenge (Figs. **5,6**). Consequently, plasma dilution efficacy of a fluid challenge will be more pronounced in dehydrated individuals than in normally hydrated. That concept serves as background for the Volume



Mini fluid challenge -- relatively small volume (2.5-5.0 ml kg^{-1}) crystalloid infusions followed by 5-minute periods without fluids.

p.d.u. -- procedure defined unit (Confirmed minutes for the meeting in Uppsala 2008-10-23 – 25 (Report). Committee and Subcommittee on Nomenclature, Properties and Units (SC-C-NPU), IUPAC–IFCC. 2008. Retrieved September 10, 2010).

Fig. (5). The theoretical arterial and capillary plasma dilution efficacy during the six mini fluid challenges. The optimized interstitial fluid accumulation is presumably associated with the minimization of capillary plasma dilution efficacy seen in mini fluid challenge #3.

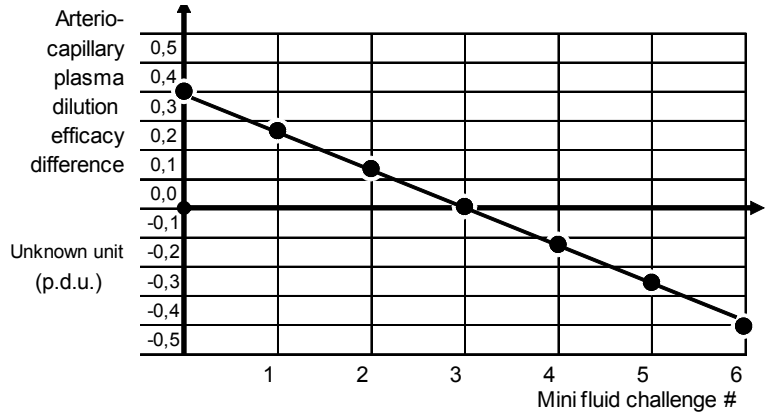


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Fig. (6). The theoretical arterio-capillary plasma dilution efficacy difference during the six mini fluid challenges. The optimized interstitial fluid accumulation is presumably associated with the zero value seen in mini fluid challenge #3.

Loading Test (VLT) [59,60]. However, the plasma dilution efficacy of a crystalloid challenge cannot be used for evaluation of changes in the whole-body interstitial fluid compliance *per se* because plasma dilution is similarly dependent on the changes of interstitial pressure-dependent lymphatic influx, also the changes in net fluid elimination that includes urine production and other routes of the whole-body fluid loss (Fig. **1**). It has been reported that preceding infusions of crystalloid [22,41] and colloids [42] made elimination of a later infused crystalloid considerably faster. However, a reduced lymph flow can have similar impact as increased net fluid elimination, both resulting in a decrease of intravascular fluid retention and plasma dilution efficacy of crystalloid fluid challenge (Fig. **4**). Despite the importance of the lymphatic influx in the regulation of plasma volume [61], the clinical discrimination between the impact of net fluid elimination and net lymphatic influx on plasma dilution cannot be made.

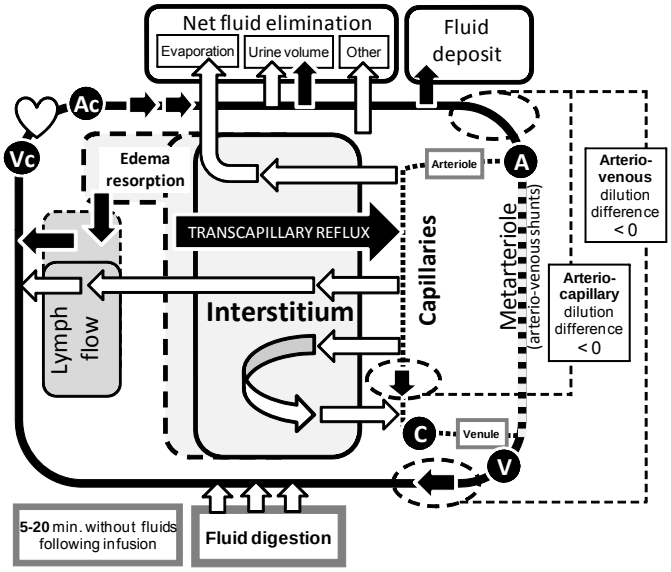
Arterio-venous Plasma Dilution Difference: A dynamic variable

In contrast to arterial, venous plasma dilution is affected by the transcapillary fluid shifts in a vicinity of capillary

beds related to the venous blood flow in the site of measuring. Svensen *et al* reported a significant decrease of arterio-venous dilution difference when it went from positive to negative during a 20 minute period without fluids following a 25 ml kg^{-1} infusion of lactated Ringer's solution in healthy volunteers [62]. It was explained as redistribution of excess interstitial fluid *via* the veins originating in the tissues of a hand. That fluid was eliminated or deposited in more compliant tissues because it did not induce the corresponding arterial plasma dilution. This is clinically important since it emphasizes that, in contrast to conventional assumption of venous hemoglobin concentration being higher than arterial [63,64], it can be reversed during fluid therapy. Thus, arterial but not venous *plasma dilution efficacy* of a crystalloid challenge should be used for evaluation of the *whole-body response* to a fluid challenge. On the other hand, the significant decrease of arterio-venous dilution difference to negative values during the 20 minutes period without fluids after the crystalloid infusion should indicate detection of capillary refill with excessive interstitial fluid. This pattern can serve as a warning sign for interstitial fluid overload. Invasiveness of arterial and venous blood hemoglobin sampling and analysis of the blood samples is the major limitation for its clinical application.

Capillary Plasma Dilution Efficacy: A Marker of Interstitial Fluid Accumulation

The recent advance in the understanding of the anatomy and physiology in transcapillary fluid exchange suggests that integrity of capillary barrier rather than Starling forces has the major importance in the regulation of transcapillary fluid exchange [35]. Only the destruction of endothelial glycocalyx layer by inflammation or circulation overload allows the 'classic' action of Starling forces. Thus, the transcapillary hydrostatic pressure gradient appears to be the major determinant in the transcapillary fluid equilibration if the endothelial glycocalyx layer is intact. In contrast to the predictable *in vivo* osmotic pressure of the crystalloid solution [1] and its impact on the osmolality of plasma [65], the fluid challenge induced deviation in net transcapillary hydrostatic pressure is multi-factorial and dynamically changing. The midcapillary hydrostatic pressure is mainly affected by the changes in the stimulation of arteriolar and venular sphincters, while interstitial hydrostatic pressure is dependent on the interstitial expansion by fluids [2]. Nevertheless, theoretically, the local autoregulation of arteriolar-venular tone ratio in a capillary bed is adjusted in response to the interstitial fluid status. The decrease in arteriolar tone and corresponding increase in venular tone facilitates filtration of the fluid from capillaries into interstitium by increasing the transcapillary filtration-absorption ratio. If it is the case during the rehydration of interstitium, the capillary plasma dilution efficacy will decrease in consecutive fluid challenges. That would lead to positive values of arterio-venous and arterio-capillary plasma dilution efficacy differences. And on the contrary, the increase in arteriolar tone and decrease in venular tone facilitates absorption of interstitial fluid into capillaries by decreasing the transcapillary filtration-absorption ratio. If this is the case during the overhydration of interstitium, the capil-



A -- net arterial blood flow of the whole-body arterioles, **V** -- venous blood flow of the whole-body venules, **C** -- net capillary blood flow of the whole body end-capillaries (venular part of capillaries), **Ac** -- arterial blood flow in pulmonary artery, **Vc** -- venous blood flow in superior vena cava.

A **B**

Fig. (7). The model of whole-body fluid handling: a state of net interstitial overhydration. During 5-20 min. after the excessive fluid infusion, the *transcapillary reflux* of excessive fluid and its redistribution is followed by renal elimination and deposit in more compliant tissues. Arrows represent equal fluid volumes; white arrows reflect the basal fluid shifts, and black arrows are for shifts induced by the previous fluid infusion.

lary plasma dilution efficacy will increase in consecutive fluid challenges due to the *reflux* of excessive fluid from interstitium (Fig. **7**). That would lead to the negative values of arterio-venous and arterio-capillary plasma dilution efficacy differences. However, an increase of renal fluid elimination and/or deposit in more centrally located tissues would lead to the same phenomenon without changes in arteriolar and venular tone and transcapillary filtration-absorption ratio. Nevertheless, this way or another, the capillary plasma dilution efficacy increase in consecutive mini fluid challenges and negative values of arterio-venous and arterio-capillary plasma dilution efficacy differences would signal about the redistribution of fluid from the dependent arm and elimination or deposit in other location.

Specific Clinical Settings: Anaesthesia

Specific clinical settings can have inherent impact on arterio-venous and arterio-capillary plasma dilution efficacy differences. In addition to local autoregulation, the arteriolar to venular tone ratio can be affected by sympathetic stimulation which is known to be simultaneously affecting the systemic arterial tone and arteriolar sphincters in the capillary beds [2]. The splanchnic and cutaneous veins have exceptionally high numbers of α1- and α2-adrenergic receptors, and are highly sensitive to adrenergic stimulation [66]. That makes the cutaneous veins and venulae more sensitive to changes in sympathetic stimulation than arterial resistance vessels and arteriolae [67-70]. Thus, theoretically, anaesthesia-related sympathectomy would affect venular tone more than arteriolar; thus, arteriolar to venular tone ratio would tend to decrease facilitating the decrease of transcapillary filtration-absorption ratio. Along with the anaesthesia-related suppression of fluid elimination it would facilitate the increase in arterial, capillary and venous plasma dilution efficacy of the fluid challenges and decrease the arterio-venous and arterio-capillary dilution differences. However, local control mechanisms can override neural or systemic humoral influences: tissue metabolites can regulate local blood flow in specific vascular beds, independently of the systemic regulation. Because blood flow itself can influence the local concentration of the metabolic intermediates, blood flow in capillary beds tends to oscillate spontaneously over time in a process known as vasomotion. [69].

II REFINEMENT OF GOAL DIRECTED FLUID THERAPY

The Minimal Volume Loading Test (mVLT)

The concepts described in Part I are used in the *minimal Volume Loading Test* (mVLT) that was recently proposed by the authors. The mVLT is a development of its predecessor – the VLT method [59]. The mVLT also uses plasma dilution as a target parameter as well as crystalloid fluid challenges, but in contrast to VLT, the volume of a fluid challenge is smaller and the time course for response evaluation is similar to conventional algorithms for goal directed fluid therapy.

In a clinical validation, three fluid challenges consisting of 5 ml kg^{-1} of acetated Ringer's solution followed by 5 min. periods without fluid were administered in elective orthopedic surgery patients after preoperative overnight fast. The primary hypothesis was that arterial plasma dilution efficacy will decrease in consecutive fluid challenges as a result of net increase in fluid elimination and/or fluid deposit in the compliant tissues such as the derma. Aiming to investigate the applicability of noninvasive measures of plasma dilution, the non-invasive continuous hemoglobin ($SpHb^{TM}$) measurement technique was used to investigate the accuracy of noninvasively derived arterial variables with the laboratory derived arterial values serving as the reference method.

The results of a pilot trial in 12 patients showed that the invasive arterial plasma dilution efficacy of consecutive fluid challenges significantly decreased [66, 67].

The Noninvasive Hemoglobin ($SpHb^{TM}$) Measures: Lack of Accuracy?

The Masimo Corporation introduced its Radical 7 platform as a module of the Rainbow SET® Pulse CO-Oximetry™ in 2009. It was supposed to be an alternative to the invasive blood sampling, and the bed-side or laboratory analysis of arterial and venous hemoglobin. It has set the case for the investigation of its accuracy in various clinical and experimental settings. However, the results are not uniform. A report from the manufacturer's supported trial which evaluated the accuracy of 335 noninvasive and 165 laboratory-analyzed hemoglobins is optimistic in concluding that noninvasive measurement is accurate within 10 g/l during hemodilution in 20 healthy volunteers [68]. That is the accuracy claimed in the manufacturer's brochures. Soon after, Gayat *et al.* reported an independent clinical trial where they evaluated the agreement between invasive and noninvasive hemoglobins in 300 patients and found SpHb as systemically biased and too unreliable to guide the transfusion decision [69]. The accuracy was also insufficient for the clinical applicability in patients undergoing Caesarean section [70]. The non-invasive SpHb values obtained during the crystalloid challenge could not provide useful data for the volume kinetic analysis [20].

Taking into account the results of the previously discussed mVLT validation study, there can be other reasons for the discrepancy of invasive and noninvasive measures other that lack of accuracy.

CONCLUSION

Here the current issues in fluid therapy and also new developments were discussed with a firm emphasis on the possibility of indirect noninvasive real time monitoring of interstitial fluid accumulation by using the Radical-7 Pulse CO-Oximeter. The role of crystalloid induced plasma dilution, a target parameter not used for goal directed fluid therapy, was discussed as part of a new method – the mini Volume Loading Test (mVLT). This method could possibly evaluate hydration status by evaluating the efficacy of plasma dilution induced by consecutive mini fluid challenges with crystalloids. If this method can be validated it opens up a simple way of estimating hydration status and the need for replacement of iv fluids. This could lead to the development of an 'intelligent infusion system' for administration of crystalloid solutions guided by the noninvasive real-time plasma dilution feedback from the capillary beds. It would be a major

breakthrough in fluid therapy, since accurate administration has been shown to be beneficial for patients.

CONFLICT OF INTERESTS

1. US Patent: Andrijauskas A. Systems and method for homeostatic blood states. Issued on 2010-08-31. Patent number US 7,788,045 B2.
2. Provisional US and International patent application: Andrijauskas A. Method for evaluating state of hydration of a subject. 2010, Dkt. No. 81281-PRO/GJG/BJA.

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REFERENCES

[1] Zander, R. Infusion fluids: why should they be balanced solutions? *Eur. J.Hosp. Pharm. Pract.*, **2006**, *12*, 60-62.

[2] Boulpaep, E.L. In: *Medical Physiology;* Boron, W.F.; Boulpaep, E.L., Eds.; Saunders: Philadelphia, **2003**, pp. 463-475.

[3] Aukland, K.; Reed, R.K. Interstitial lymphatic mechanisms in the control of extracellular fluid. *Physiol. Rev.*, **1993**, *73*(*1*), 1-78.

[4] Wiig, H.; Rubin, K.; Reed, R.K. New active role of the interstitium in control of interstitial fluid pressure: potential therapeutic consequences. *Acta. Anaesthesiol. Scand.,* **2003**, *47*(*2*),111-121.

[5] Boulpaep, E.L. In: *Medical Physiology*; Boron, W.F.; Boulpaep, E.L., Eds.; Saunders: Philadelphia, **2003**, pp. 475-477.

[6] Boulpaep, E.L. In: *Medical Physiology*; Boron, W.F.; Boulpaep, E.L., Eds.; Saunders: Philadelphia, **2003**, pp. 425-426.

[7] Holte, K.; Sharrock, N.E.; Kehlet, H. Pathophysiology and clinical implications of perioperative fluid excess. *Br. J. Anaesth.,* **2002**, *89*, 622–632.

[8] Arieff, A.I. Fatal postoperative pulmonary edema. Pathogenesis and literature review. *Chest,* **1999**, *115*, 1371–1377.

[9] Bundgaard-Nielsen, M.; Ruhnau, B.; Secher, N.H.; Kehlet, H. Flow-related techniques for preoperative goal-directed fluid optimization. *Br. J. Anaesth.,* **2007**, *98* (*1*), 38–44.

[10] Bundgaart-Nielsen, M.; Holte, K.; Secher, N.H.; Kehlet, H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta. Anaesthesiol. Scand.,* **2007**, *51*, 331-340.

[11] Hahn, R.G. Fluid therapy might be more difficult than you think. Editorial. *Anesth. Analg.,* **2007**, *105* (*2*), 304-305.

[12] Holte, K.; Kehlet, H. Compensatory fluid administration for preoperative dehydration – does it improve outcome? *Acta. Anaesthesiol. Scand.,* **2002**, *46*, 1089-1093.

[13] Berl, T.; Taylor, J. In: *Critical Care*; Fink, M.P.; Abraham, E.; Vincent, J.L.; Kochanek, P.M., Eds.; Elsevier Saunders: Philadelphia, **2006**, pp. 1085-1096.

[14] Brandstrup, B. In: *Perioperative fluid therapy*; Hahn, R.G.; Prough, D.S.; Svensen, C.H., Eds.; Informa healthcare: New York, **2007**, pp. 436-437.

[15] Jacob, M.; Chappell, D.; Rehm, M. Clinical update: perioperative fluid management. *Lancet*, **2007**, *369*, 1984-1986.

[16] Gyenge, C.C.; Bowen, B.D.; Reed, R.K.; Bert, J.L. Transport of fluid and solutes in the body. I. Formulation of a mathematical model. *Am. J. Physiol.,* **1999**, *277*, H1215-H1227.

[17] Hahn, R.G. The use of volume kinetics to optimize fluid therapy. *J. Trauma*, **2003**, *54*(*5* Suppl), S155-158.

[18] Svensen, C.H.; Rodhe, P.M.; Prough, D.S. Pharmacokinetic aspects of fluid therapy. *Best Pract. Res. Clin, Anaestheiol.,* **2009**, *23*, 213-224.

[19] Hahn, R.G.; Svensen, C. Plasma dilution and the rate of infusion of Ringer's solution. *Br. J. Anaesth.,* **1997**, *79*, 64-67.

[20] Hahn, R.G.; Li, Y.; Zdolsek, J. Non-invasive monitoring of blood haemoglobin for analysis of fluid volume kinetics. *Acta. Anaesthesiol. Scand.,* **2010**, *54*, 1233-1240.

[21] Holte, K.; Jensen, P.; Kehlet, H. Physiologic effects of intravenous fluid administration in healthy volunteers. *Anesth. Analg.,* **2003**, *96*, 1504-1509.

[22] Holte, K.; Klarskov, B.; Christensen, D.S.; Lund, C.; Nielsen, K.G.; Bie, P.; Kehlet, H. Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized, double-blind study. *Ann. Surg.,* **2004**, *240*, 892-899.

[23] Bundgaard-Nielsen, M.; Holte, K.; Secher, N.H.; Kehlet, H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol. Scand.,* **2007**, *51*, 331-340.

[24] Rhodes, A.; Cecconi, M.; Hamilton, M.; Poloniecki, J.; Woods, J.; Boyd, O.; Bennett, D.; Grounds, R.M. Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. *Intensive Care Med.,* **2010**, *36*, 1327-1332

[25] Vincent, J.L.; Weil, M.H. Fluid challenge revisited. *Crit. Care Med.,* **2006**, *34*, 1333-1337.

[26] Wiesenack, C.; Fiegl, C.; Keyser, A.; Prasser, C.; Keyl, C. Assessment of fluid responsiveness in mechanically ventilated cardiac surgica,l patients. *Eur. J. Anaesthesiol.,* **2005**, *22*(*9*), 658-665.

[27] Reuter, D.A.; Goetz, A.E. Differentiating "Volumetric preload monitoring" and assessing "fluid responsiveness". *Anesth. Analg.,* **2006**, *102*(*2*), 651-652.

[28] Lopes, M.R.; Auler, J.O.C.; Michard, F. Volume management in critically ill patients: new insights. *Clinics*, **2006**, *61*(*4*), 345-350.

[29] Berkenstadt, H.; Margalit, N.; Hadani, M.; Friedman, Z.; Segal, E.; Villa, Y.; Perel, A. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth. Analg.,* **2001**, *92*, 984-989.

[30] Vincent, J.L. "Let's give some fluid and see what happens" versus the "mini-fluid challenge". Editorial. *Anesthesiology,* **2011**, *115*, 455-456.

[31] Moretti, E.W.; Robertson, K.M.; El-Moalem, H.; Gan, T.J. Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. *Anesth. Analg.,* **2003**, *96*, 611-617.

[32] Prien, T.; Backhaus, N.; Pelster, F.; Pircher, W.; Bue, H.; Lawin, P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *J. Clin. Anesth.,* **1990**, *2*, 317-323.

[33] Joshi, G.P. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth. Analg.,* **2005**, *101*, 601-605.

[34] Spahn, D.R.; Chassot, P.G. Fluid restriction for cardiac patients during major noncardiac surgery should be replaced by goal-directed intravascular fluid administration. *Anesth. Analg.,* **2006**, *102*, 344-346.

[35] Chappell, D.; Jacob, M.; Hofmann-Kiefer, K.; Conzen, P.; Rehm, M. A rational approach to perioperative fluid management. *Anesthesiology,* **2008**, *109*, 723-740.

[36] Muller, L.; Toumi, M.; Bousquet, P-J.; Riu-Poulenc, B.; Louart, G.; Candela, D.; Zoric, L.; Suehs, C.; de La Coussaye, J.E.; Molinari, N.; Lefrant, J.Y.; AzuRéa Group. Increase in aortic blood flow after an infusion of 100 ml of colloid over one minute can predict fluid responsiveness. The mini-fluid challenge study. *Anesthesiology,* **2011**, *115*, 541-547.

[37] Jhanji, S.; Dawson, J.; Pearse, R.M. Cardiac output monitoring: basic science and clinical application. *Anaesthesia,* **2008**, *63*, 172-181.

[38] Michard, F.; Reuter, D. Assessing cardiac preload or fluid responsiveness? It depends on the question we want to answer. *Intensive Care Med*., **2003**, *29*, 1396.

[39] Arbous, M.S.; Meursing, A.E.; van Kleef, J.W.; de Lange, J.J.; Spoormans, H.H.; Touw, P.; Werner, F.M.; Grobbee, D.E. Impact of anesthesia management characteristics on severe morbidity and mortality. *Anesthesiology,* **2005**, *102*, 257-268.

[40] Polanczyk, C.A.; Rohde, L.E.; Goldman, L.; Cook, E.F.; Thomas, E.J.; Marcantonio, E.R.; Mangione, C.M.; Lee, T.H. Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. *J. A. M. A.,* **2001**, *286*, 309-314.

[41] Svensen, C.; Drobin, D.; Olsson, J.; Hahn, R.G. Stability of the interstitial matrix after crystalloid fluid loading studied by volume kinetic analysis. *Br. J. Anaesth.,* **1999**, *82*, 496-502.

[42] Borup, T.; Hahn, R.G.; Holte, K.; Ravn, L.; Kehlet, H. Intraoperative colloid administration increases the clearance of a postoperative fluid load. *Acta. Anaesthesiol. Scand.,* **2009**, *53*, 311-317.

[43] Pearse, R.; Dawson, D.; Fawcett, J.; Rhodes, A.; Grounds, R.M.; Bennett, E.D. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit. Care,* **2005**, *9*, R687-R693.

[44] Grocott, M.P.; Mythen, M.G.; Gan, T.J. Perioperative fluid management and clinical outcomes in adults. *Anesth. Analg.,* **2005**, *100*, 1093-1106.

[45] Wakeling, H.G.; McFall, M.R.; Jenkins, C.S., Woods, W.G.A., Miles, W.F.A.; Barclay, G.R.; Fleming, S.C. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br. J. Anaesth.,* **2005**, *95*, 634-642.

[46] Noblett, S.E.; Snowden, C.P.; Shenton, B.K.; Horgan, A.F. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br. J. Surg.,* **2006**, *93*, 1069-1076.

[47] Holte, K.; Kehlet, H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *J. Am. Coll. Surg.,* **2006**, *202*(6), 971-989.

[48] Challand, C.; Struthers, R.; Sneyd, J.R.; Erasmus, P.D.; Mellor, N.; Hosie, K.B.; Minto, G. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br. J. Anaesth.,* **2012**, *108*(1), 53-62.

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

[50] Nadler, S.B.; Hidalgo, J.U.; Bloch, T. Prediction of blood volume in normal human adults. *Surgery,* **1962**, *51,* 224-232.

[51] Pearson, T.C.; Guthrie, D.L.; Simpson, J.; Chinn, S.; Barosi, G.; Ferrant, A.; Lewis, S.M.; Najean, Y. Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. *Br. J. Haematol*., **1995**, *89*(4),748-756.

[52] DuBois, D.; DuBois, E.F. A formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.,* **1916**, *17*, 863-871.

[53] Gann, D.S.; Carlson, D.E.; Byrnes, G.J.; Pirkle, J.C.; Allen-Rowlands, C. Impaired Restitution of blood volume after large hemorrhage. *J. Trauma*, **1981**, *21*(8), 598-603.

[54] Hadian, H.; Pinsky, M.R. Functional hemodynamic monitoring. *Curr. Opin. Crit. Care,* **2007**, *13*, 318-323.

[55] Drobin, D.; Hahn, R.G. Volume kinetics of Ringer's solution in hypovolaemic volunteers. *Anesthesiology,* **1999**, *90*, 81-91.

[56] Svensen, C.H.; Olsson, J.; Hahn, R.G. Intravascular fluid administration and hemodynamic performance during open abdominal surgery. *Anesth. Analg.,* **2006**, *103*, 671-676.

[57] Wiig, H. Pathophysiology of tissue fluid accumulation in inflammation. *J. Physiol.,* **2011**, *589*(12), 2945-2953.

[58] Aukland, K.; Reed, R.K. Interstitial lymphatic mechanisms in the control of extracellular fluid. *Physiol. Rev.,* **1993**, *73*(1), 71-78.

[59] Andrijauskas, A. Systems and method for homeostatic blood states. U.S. Patent *7*,788,045 B2, August 31, **2010**.

[60] Hahn, R.G.; Andrijauskas, A.; Drobin, D.; Svensen, C.; Ivaskevicius, J. A volume loading test for the detection of hypovolaemia and dehydration. *Medicina. (Kaunas).,* **2008**, *44*(12), 953-959.

[61] (a) Negrini, D.; Moriondo, A. Lymphatic anatomy and biomechanics. *J. Physiol.,* **2011**; *589*(12): 2927-2934. (b) Huxley, V.H.; Scallan, J. Lymphatic fluid: exchange mechanisms and regulation. *J. Physiol.,* **2011**, *589*(12), 2935-2943.

[62] Svensen, C.H.; Rodhe, P.M.; Olsson, J.; Borsheim, E.; Aarsland, A.; Hahn, R.G. Arteriovenous differences in plasma dilution and the distribution kinetics of lactated Ringer's solution. *Anesth. Analg.,* **2009**, *108*, 128 -133.

[63] Mokken, F.C.; van der Waart, F.J.M.; Henny, C.P.; Goedhart, P.T.; Gelb, A.W. Differences in peripheral arterial and venous hemorheologic parameters. *Ann. Hematol.,* **1996**, *73*, 135-137.

[64] Yang, Z.W.; Yang, S.H.; Chen, L.; Qu, J.; Zhu, J.; Tang, Z. Comparison of blood counts in venous, fingertip, and arterial blood and their measurement variation. *Clin. Lab. Haematol.,* **2001**, *23*, 155-159.

[65] Williams, E.L.; Hildebrand, K.L.; McCormick, S.A.; Bedel, M.J. The effect of intravenous lactated ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth. Analg.,* **1999**, *88*, 999-1003.

[66] Andrijauskas, A.; Svensen, C.H.; Ivaskevicius, J. *Minimum volume loading test to evaluate hydration in patients*, Abstracts of Posters presented at the 2011 Annual Meeting of the International Anesthesia Research Society Vancouver, British Columbia, Canada May 21-24, 2011. *Anesth. Analg.,* **2011**, *112*(5), S232.

[67] Andrijauskas, A.; Svensen, C.H.; Ivaskevicius, J. *Minimum volume loading test to evaluate hydration in healthy volunteers*, Abstracts of Posters presented at the Annual Meeting of the International Anesthesia Research Society Vancouver, British Columbia, Canada May 21-24, 2011. *Anesth. Analg.,* **2011**, *112*(5), S-234.

[68] Macknet, M.R.; Allard, M.; Applegate, R.L.; Rook, J. The accuracy of noninvasive and continuous total hemoglobin measurement by pulse CO-Oximetry in human subjects undergoing hemodilution. *Anesth. Analg.,* **2010**, *111*, 1424-1426.

[69] Gayat, E.; Bodin, A.; Sportiello, C.; Boisson, M.; Dreyfus, J-F.; Mathieu, E.; Fischler, M. Performance evaluation of a noninvasive hemoglobin monitoring device. *Ann. Emerg. Med.,* **2011**, *57*(4), 330-333.

[70] Butwick, A.; Hilton, G.; Carvalho, B. Non-invasive haemoglobin measurement in patients undergoing elective Caesarean section. *Br. J. Anaesth.,* **2012**, *108*(2), 271-277.

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