Fluid therapy and the hypovolemic microcirculation

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Purpose of review
In shock states, optimizing intravascular volume is crucial to promote an adequate oxygen delivery to the tissues. Our current practice in fluid management pivots on the Frank-Starling law of the heart, and the effects of fluids are measured according to the induced changes on stroke volume. The purpose of this review is to evaluate the boundaries of current macrohemodynamic approach to fluid administration, and to introduce the microcirculatory integration as a fundamental part of tissue perfusion monitoring.

Recent findings
Macrocirculatory changes induced by volume expansion are not always coupled to proportional changes in microcirculatory perfusion. Loss of hemodynamic coherence limits the value of guiding fluid therapy according to macrohemodynamics, and highlights the importance of evaluating the ultimate target of volume administration, the microcirculation.

Summary
Current approach to intravascular volume optimization is made from a macrohemodynamic perspective. However, several situations wherein macrocirculatory and microcirculatory coherence is lost have been described. Future clinical trials should explore the usefulness of integrating the microcirculatory evaluation in fluid optimization.

Keywords
fluid therapy, goal-directed therapy, hypovolemia, microcirculation, shock

INTRODUCTION

Shock is recognized as one of the most common life-threatening conditions in critical care patients, affecting about one-third of this population [1]. It is usually defined as the clinical expression of the failure of the cardiovascular system to successfully promote tissue perfusion. This situation may lead to tissue hypoxia resulting in the inability to sustain cellular respiration essential for supporting organ function, and activation of anaerobic metabolism cellular pathways occurs. If maintained over time, this anaerobic state can result into cellular dysfunction, organ dysfunction and finally multiorgan failure that might lead to the death of the individual [1,2].

Over the last years, there has been an increasing interest in the literature on microcirculation, as it is considered to be the final destination of the cardiovascular system responsible for the delivery of oxygen to tissues through red blood cell transport. Furthermore, microcirculation is believed to be mainly responsible for tissue wellness, as it is the limiting factor for oxygen transport to the tissues [3].

Microcirculatory alterations, either caused by primary pathogenic factors and/or as a consequence of global hemodynamic derangements, are remarkably involved in the effects of shock on organ function [4]. A limitation of oxygen transport to cells occurs, secondary to disturbances in convection (blood flow) and/or diffusion (increased distance between cells and oxygen-carrying red blood cell-carrying capillaries) [5]. Microcirculatory cellular alterations may be also present including endothelial dysfunction, red blood cell rheological disturbances, and vascular smooth muscle cell alterations leading to dysfunction of autoregulatory mechanisms, among others. In addition, endothelial glycocalyx shedding is also a major contributor to the equation, as it is responsible for the

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KEY POINTS

- Hemodynamic coherence between the macro and the microcirculation might be lost in shock states, limiting the value of the current Frank-Starling approach to volume administration guidance.
- The final aim of fluid therapy is to improve perfusion at the microcirculatory level, and therefore, evaluating the microcirculation seems mandatory in the management of shock states.
- The ideal type of fluid is still to be determined, and future RCTs need to be performed choosing the right population that may benefit from the intervention and include physiology-based endpoint-guided resuscitation algorithms for fluid therapy.

compromise of the endothelial vascular barrier, with the consequent formation of tissue edema [6].

Although appreciated from a theoretical point of view, the microcirculation has only been clinically accessible over the last 15 years because of the introduction of hand-held microscopes. This technology has allowed direct study of this crucial end station of the cardiovascular system [7]. The development of these technologies has prompted the research for the inclusion of routine microcirculation evaluation for shock detection and its management at the bedside.

HEMODYNAMIC COHERENCE: THE COUPLING BETWEEN GLOBAL HEMODYNAMICS AND MICROCIRCULATION

From a hemodynamic perspective, shock can be the final common consequence of different pathophysiological mechanisms, as classically defined by Weil [4]: cardiogenic failure (primary pump failure), hypovolemia (preload decrease secondary to internal or external fluid loss), and cardiac obstruction (afterload increase, e.g., acute pulmonary embolism or cardiac tamponade). Each of these mechanisms may lead to a common insufficient cardiac output situation and, furthermore, is usually associated with a hemodynamic coherence (coupling) between macro and microcirculation. Restoration of the underlying disease results in a restoration of global blood flow and correction of tissue perfusion. However, the fourth state of shock is referred to as distributive shock (occurring in states of inflammation/infection) and can occur in the presence of normal or even high cardiac output. Tissue hypoxia in such distributive shock states is not caused by an insufficient cardiac output but rather by a (micro)vascular distribution defect causing heterogeneity of flow and resulting in the presence of hypoxic areas in the organ tissue beds. Such a loss of coherence between the macro and microcirculation results in a functional shunting of these hypoxic areas and manifests itself clinically as a reduction in oxygen extraction. It is also this state of shock that is most resistant to fluid therapy and can only be unveiled by observation of the microcirculation [8]. Microcirculatory alterations occurring in such states of maldistributive shock are caused by multiple mechanisms, including a wide number of cellular alterations such as red blood cell rheological alterations and endothelial cell dysfunction [9].

SYSTEMIC HEMODYNAMICS AND MICROCIRCULATORY PROFILE OF HYPOVOLEMIA

Hypovolemia can be defined as a decrease in blood volume resulting from loss of blood, plasma and/or plasma water, causing a loss of intravascular content and resulting in a potential limitation of tissue perfusion. However, the hemodynamic impact of this phenomenon may be variable and complex to evaluate. Depending on the degree of hypovolemia, different clinical scenarios with particular hemodynamic status can be observed: In the first phase, the blood volume that is lost is compensated by an equivalent reduction in unstressed volume (the blood stored in large capacitance veins that is not contributing to venous return), thereby maintaining venous return and consequently cardiac output. This situation, known as compensated hypovolemia, may be not associated to tissue hypoperfusion markers. As blood volume lost increases, the described compensatory mechanisms become insufficient, resulting in decreased venous return and consequently decreased cardiac output. This situation has been termed as uncompensated hypovolemia, and usually will be clinically expressed with parameters of tissue hypoperfusion such as hypotension. Furthermore, vasodilation secondary to inflammatory or septic states leads to a special hemodynamic situation wherein a blood volume shift occurs from the stressed to the unstressed compartment, termed as relative hypovolemia. Finally, the end stage of decreased preload and cardiac output secondary to uncompensated and/or relative hypovolemia can be also worsened by impairment in venous return secondary to an increase in intrathoracic pressure in those patients undergoing positive pressure ventilation. This situation has been termed central hypovolemia, and is

considered to be one of the main causes of shock in critically ill and anesthesia patients [10].

As previously mentioned, the microcirculation is the ultimate destination of blood flow to the tissues, to deliver oxygen through red blood cell transport to parenchymal cells for their metabolic demands. In hypovolemic shock, oxygen delivered to cells may be compromised, primarily because of a reduction in microcirculatory blood flow rather than a limitation in oxygen-carrying capacity (which only becomes a problem in really severe hemorrhagic states) [11]. Furthermore, in hypovolemic shock, these alterations in microvascular perfusion seem to be homogeneous in contrast to distributive shock where the core problem is a misdistribution of microvascular flow, and the consequent presence of microcirculatory shunting [12].

When hypovolemia is accompanied by impairment in tissue perfusion, resuscitation interventions should start immediately. In this regard, fluid therapy is considered to be one of the key interventions to correct this condition. But how can fluid therapy be guided?

MANAGEMENT OF HYPOVOLEMIA: FLUID THERAPY

The aim of fluid therapy during hemodynamic resuscitation is to increase global blood flow, and doing so, increase tissue perfusion and thus oxygen availability for cellular respiration [13]. As most common causes of shock have some degree of hypovolemia, volume expansion with fluids is recognized as the first step of resuscitation. However, managing fluid administration to optimize intravascular filling appears extremely complex, and both underfilling and fluid overload should be avoided, as both situations are hazardous and might compromise patients' outcome. Therefore, an accurate assessment of fluid therapy is mandatory, aiming at correcting tissue perfusion without causing harm.

Triggers for fluid therapy

Independently of the underlying disease, in critically ill patients, the clinical scenario of tissue hypoperfusion must be assessed. To confirm the situation of tissue dysoxia at the bedside, monitoring global indirect parameters of tissue perfusion, such as venous oximetry and/or lactate, is recommended [2,13]. Despite each of these global parameters having its own limitations, their incorporation in quantitative resuscitation strategies has demonstrated beneficial effects on survival [14]. However, during the last decade, with the introduction of new technologies capable of evaluating tissue perfusion and oxygenation at a local or microcirculatory level, novel parameters related to tissue perfusion have emerged. Importantly, many of these parameters have repeatedly shown their prognostic value, independent of conventional global markers of hypoperfusion [15–19]. Evaluation and management of shock is now evolving from global endpoints to regional and/or microcirculatory endpoints, but this process is still ongoing, and requires further research. To date, the lack of prospective studies assessing the effect on outcome of microcirculatory endpoints-based strategies is the major limiting factor for the incorporation of these parameters to clinical practice.

Current practice: the macrohemodynamic approach

Independent of the chosen trigger, when tissue hypoperfusion is suspected, the clinician has to decide whether fluid administration will be able to restore tissue wellness. Currently, volume expansion aims at increasing global blood flow, with the expectation that such an increase will also improve flow to the microcirculation and, thereby, increase oxygen availability to the tissues. At the bedside, when deciding whether giving fluids will augment global flow, the decision is made according to the Frank-Starling principle of cardiac performance [20]. Briefly, considering that there is a positive relationship between preload and stroke volume, and this relation follows a curvilinear shape, for a given increase in preload, a significantly greater increase in stroke volume will be observed on the steep ascending portion of the curve, defining a preload-dependent area. On the opposite flat part of the curve, a preload-independent area can be defined, where volume expansion will not produce significant changes in stroke volume (Fig. 1) [11]. In daily practice, the clinician evaluates several hemodynamic variables that indicate whether the patient is located at the preload-dependency area or at the preload-independent area of the Frank-Starling curve. These tools allow the prediction of the macrohemodynamic effect of volume expansion. When prediction is cumbersome, a fluid challenge or a passive leg-raising maneuver is performed, and its effects on cardiac output evaluated. Fluid-responsiveness is arbitrarily defined as a 15% or higher increase in cardiac output in response to a fluid challenge, and patients are divided into responders and nonresponders, accordingly. Patients considered to be nonresponders, either predicted or directly measuring changes in cardiac output after a fluid challenge, should not receive fluids but instead require other hemodynamic interventions

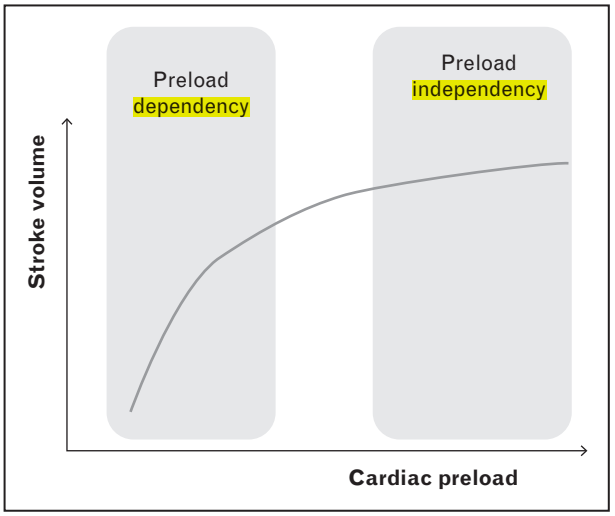

FIGURE 1. The Frank-Starling approach. Current clinical practice pivots on the evaluation of stroke volume changes, either predicted or observed, related to changes in preload. Accordingly, a preload-dependent and a preload-independent area are defined, and volume infusion is indicated only in the preload-dependent part of the cardiac performance curve.

if further resuscitation is necessary [20]. Despite this macrocirculatory Frank-Starling-based approach being recommended in several international guidelines and expert panels, it is well known that in real practice fluid administration remains highly empirical, and a large proportion of clinicians do not practice preload-assessment or cardiac output monitoring.

Integrating the microcirculation

As the ultimate goal of hemodynamic resuscitation is to restore tissue perfusion, introduction of technologies aimed at exploring and quantifying the status of microcirculatory perfusion has given rise to the possibility of using microcirculatory parameters as a tool to select and evaluate the effect of interventions directly on the microcirculation. But, how can these parameters be used? Are they superior to the macrohemodynamic approach? Or should a combination of both approaches be used? As already pointed out, the current view of fluid administration is focused on the condition wherein administration of fluids is expected to result in rises of cardiac output. When fluid-responsiveness is not predictable, the effect of fluid administration on cardiac output is closely monitored until cardiac output does not further increase. This macrocirculatory view pivots on the hypothesis that microcirculatory effects of volume expansion will parallel changes in cardiac output. In other words, it is assumed that increasing global oxygen transport (global flow) will actually mean an increased delivery of oxygen at the cellular level (local flow). However, several authors have pointed out that microcirculatory effects of volume expansion might be relatively independent of their macrocirculatory effects. In preload-responsive patients, Pottecher *et al.* [21] observed that changes in cardiac output and microvascular variables after volume expansion were disproportionate, suggesting that mechanisms involved in the regulation of microvascular perfusion and changes in cardiac output might not be equal. Even more relevant than these observed differences in the magnitude of response to fluid administration, several authors have shown that the macrocirculatory effects of volume might not be associated with a parallel effect at the microcirculatory level. Using videomicroscopic techniques, Ospina *et al.* [22] and Pranskunas *et al.* [23▪] reported similar results, when analyzing simultaneous macrocirculatory and microcirculatory effects of fluid administration. Both studies showed that improvement in microcirculatory indices of perfusion was not related to increases in cardiac output, and this could happen according to not only the magnitude of the observed changes, but also their direction. Similar observations were also reported by Silva *et al.* [24] when using a surrogate of tissue perfusion, such as gastric mucosal pCO_2. Interestingly, the effect of volume expansion on microcirculatory variables was not predictable by means of macrocirculatory variables, but only by baseline values of the microcirculatory parameter itself. When analyzing whether these observed differences might have impact on patients' evolution, Pranskunas *et al.* showed that only fluid administration that resulted in improved microcirculatory flow resulted in a reduction in clinical parameters of hypovolemia – such as tachycardia, oliguria, high lactate or low $ScvO_2$, whereas fluid administration that did not affect microcirculatory flow was not effective in correcting clinical parameters of hypovolemia, independently of changes in cardiac index [23▪]. On the whole, these observations collide with current fluid administration strategies, based on the macrocirculatory Frank-Starling approach.

In summary, it can be concluded that fluid administration in conditions wherein microcirculatory perfusion is already restored will not result in an additional improvement in microcirculatory performance and importantly, this can also hold true for preload-responsive patients. However, when microcirculation is impaired, the effect of volume expansion on microvascular perfusion might not always be in coherence with its macrocirculatory

effect. This implies that chasing global oxygen delivery does not ensure microcirculatory improvement *per se*. Of note, in volume-responder patients, despite achieving an increase in global flow, and thus, in the convective component of systemic oxygen delivery, volume overload could actually result in a decrease of oxygen availability at the cellular level because of several mechanisms. Firstly, important reductions in the oxygen-carrying capacity of blood because of hemodilution might be responsible for a decrease in oxygen availability. Such an effect would not be identified when considering the patient as a fluid-responder, and highlights the difference between increasing global oxygen 'delivery' and the oxygen that is actually delivered to the tissues. A second condition wherein optimization of systemic indicators of oxygen delivery does not ensure sufficient tissue oxygenation occurs in increased capillary leak states. Tissue edema associated to capillary leak might be aggravated when fluids are infused, dramatically worsening the diffusive component of the oxygen trail at the tissue level. Such a condition can occur for example in malaria [25], and may explain the deleterious effects of fluid administration in the Feast trial [26]. A third condition wherein there is a lack of coherence between systemic optimization and microcirculatory oxygen delivery is the condition wherein fluid administration targeting elevated central venous pressure can result in impaired microcirculatory blood flow, derived from congestion owing to an outflow pressure increase [27]. This detrimental effect might be amplified when using strategies pointing at achieving predetermined values of venous pressures, as currently recommended in international guidelines [28]. A fourth condition wherein increased systemic perfusion may not ensure adequate oxygen transport to vulnerable microcirculatory areas can be caused by disturbed regulation of microcirculatory blood flow causing loss of regional matching of oxygen supply to demand, resulting in shunting of microcirculatory weak units, and manifesting itself clinically as an oxygen extraction deficit [12,29]. Such a condition is referred to as distributive shock [4] in which loss of (micro)vascular regulation can be caused by the action of inflammatory mediators and/or infectious agents such as occurs in sepsis.

Globally, the existing data suggest that the effects of fluid administration are complex, and microcirculatory effects are not always predictable from a macrocirculatory approach. The integration of microcirculatory parameters would provide a helpful complement to systemic hemodynamics in order to optimize tissue perfusion and to be able to identify conditions in which there is a loss of hemodynamic coherence between systemic and microcirculatory determinants of oxygen delivery. Therefore, a functional microcirculatory approach has been proposed [11], and the concept of microcirculatory fluid-responsiveness seems desirable when assessing the effects of volume expansion. A conceptual framework of functional microcirculatory hemodynamics is depicted in Fig. 2. This representation seeks to integrate the concepts of hypovolemia and fluid overload with their microcirculatory equivalents, convection limitation and diffusion limitation, respectively. The recent development of new-generation hand-held videomicroscopes able to automatically analyze functional microcirculatory parameters is expected to contribute to the diagnosis of hypovolemia and implement procedures related to microcirculatory-guided fluid therapy at the bedside [30].

Choosing the right amount of resuscitation fluid

It should be stressed that the total amount of volume administered during fluid resuscitation is believed to be a major determinant of outcome in critically ill shock patients [31]. Fluid balance will depend on the selected triggers for fluid therapy (which will depend on how tissue hypoperfusion is being assessed), and the chosen resuscitation endpoints (misleading endpoints such as CVP have proven to be associated with excessive positive fluid balance and poor outcome). Whether fluid balance independently affects outcome or it is just a confounder remains unclear, but aggravating fluid balance by using the wrong tools and the wrong endpoints should not take place in the context of current knowledge. More physiological endpoints for resuscitation, probably including microcirculatory parameters, should be developed to allow a more individualized approach regarding the amount of resuscitation fluid volume.

Choosing the right timing of fluid administration

Timing of fluid therapy is also a relevant key point. When analyzing some failed goal-directed studies, it was noted that resuscitation interventions did not result in outcome improvements when initiated too late in the time course of the disease [32,33], once tissue damage was presumably present. The EGDT study carried out by Rivers *et al.* [34] highlighted the importance of time. Early fluid-loading strategies have been adopted in sepsis management guidelines, with apparently favorable results [14]. However, compliance with current volume loading

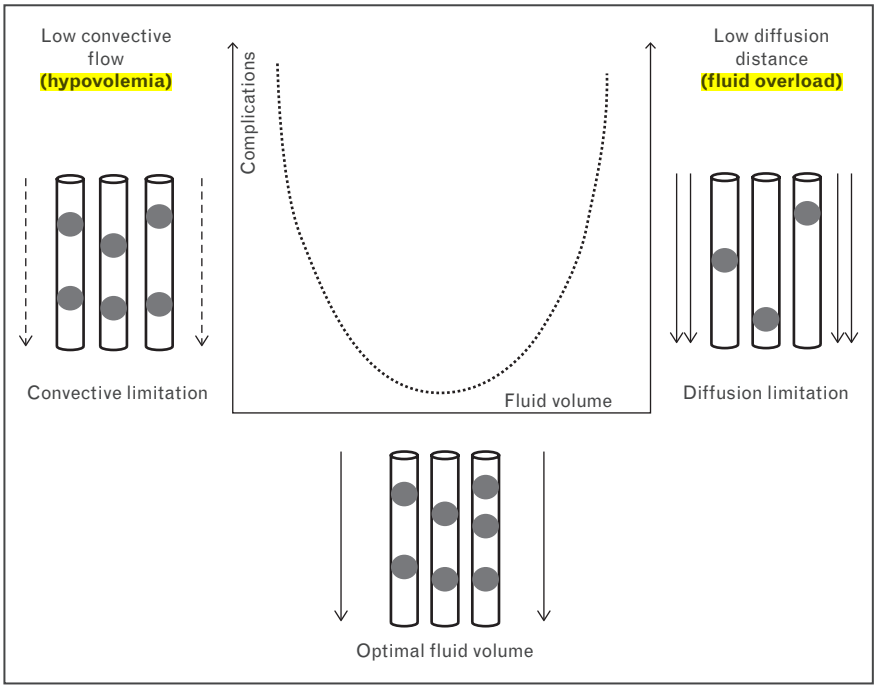

FIGURE 2. Conceptual framework of microcirculatory functional hemodynamics. Inadequate oxygen delivery to the tissues might be observed either in low convective flow states or in states with impaired diffusion. Both situations would represent a limitation to cellular metabolism, deriving in organ dysfunction and higher rate of complications. Direct evaluation of the microcirculation would allow defining the real volume status of the capillary network, and doing so, would provide fundamental information for guiding fluid therapy. Adapted from [11].

recommendations has not been independently associated to increased survival rates [35]. Evidence appears more consistent when evaluating the effect of fluids administered late in the time course of the disease. On this behalf, several authors have reported the negative effect on outcome derived from initial positive fluid balance [31,34,36]. The significance of the time factor has been endorsed by observations at the microcirculatory level, where the response to fluid administration has proven to differ according to the elapsed time since the onset of the disease. Using sublingual videomicroscopy, Ospina-Tascon *et al.* [22] detected improvements in perfusion of small vessels in response to volume expansion only when fluids were administered early after diagnosis of septic shock. Importantly, this effect was again independent from those at the global hemodynamic level.

Choosing the right type of resuscitation fluid

In a critical care and anesthesia setting, choosing the type of fluid to resuscitate patients has become a difficult decision. Robust evidence for the choice of fluids is lacking [37], and the selection of fluids for resuscitation is usually dictated more by local practice patterns [38]. In the last years, an intense debate between colloids and crystalloids for fluid resuscitation has emerged in the literature [39,40].

Current evidence supporting the use of colloids, especially with low-molecular-weight hydroxyethyl starches (HES), is based primarily in mechanistic and short-term physiological endpoint studies. Multiple clinical and experimental studies show that using fluid resuscitation with colloids, predefined hemodynamic endpoints (whatever are chosen) are achieved earlier and with less quantity of volume infused than with crystalloids [41–44]. Furthermore, these findings are maintained when microcirculatory endpoints are evaluated [45]. This evidence prompted the extensive use of HES as a more efficient intravascular expander than crystalloid solutions in critically ill patients. However, series of studies with semisynthetic colloids started to report some deleterious effects that seem to be dose-related, such as coagulopathy, accumulation in skin and liver, inflammation and induction of oxidative stress, and development of acute kidney injury [46,47]. Although the precise mechanism for this renal toxicity remains to be elucidated, in-vitro studies suggest that HES and gelatin reduce human proximal tubular cell viability [48]. Of note is that these hemodynamic beneficial results with semisynthetic colloids have not translated into better

patient-centered outcomes in the randomized controlled clinical trials (RCTs) developed in the last years, where a tendency to more mortality, acute renal failure, and need for renal replacement therapy has been reported [49,50]. What reason may explain this disconnection between the results from mechanistic and physiological studies opposed to the results from clinical outcome-centered RCTs? The key seems to be again in a physiological approach. One of the most criticized 'flaws' of these large-sized RCTs was the fact that patients included in those studies were not necessarily in shock (so in need of fluid therapy resuscitation) and, furthermore, fluid administration (either using colloid or crystalloid) was not guided by a defined goal-directed hemodynamic algorithm [37]. This may be one of the major causes, as discussed earlier in this review, that could explain this disconnection from 'bench to bedside' in the use of colloids versus crystalloids for fluid resuscitation. Moreover, in a recent multicenter international RCT wherein fluids (colloids versus crystalloids) were given only to patients with hypovolemic shock in need of fluid resuscitation, use of colloids (the majority of which were HES solutions) gave a benefit in terms of mortality in comparison with crystalloid solutions [51]. Nevertheless, the controversy about the use of colloids continues with uncertainty about how to perform volume expansion in critically ill populations [52,53,54▪]. It seems clear that further future RCTs investigating the impact of different types of resuscitation fluid on patient outcomes should be performed with more focus on precise criteria for choosing the right population that may benefit from the intervention (shocked patients in need of fluid resuscitation) and include physiology-based endpoint-guided resuscitation algorithms for fluid therapy [55].

Following the recent drawbacks for colloids as resuscitation fluids, current interest is turning back to crystalloids. Saline (0.9% NaCl) is still by far the most commonly used fluid for resuscitation, it has the lowest price of all fluids, it is relatively well tolerated, and clinicians have an extended experience with its use at the bedside [56]. Regrettably, increasing evidence on the deleterious effects of saline is starting to show in the last decades. One of the most important issues is owing to the relatively high chloride content of crystalloid solutions that may lead to hyperchloremic metabolic acidosis [57]. Adverse effects such as immune and renal dysfunction have been attributed to this phenomenon, although the clinical consequences of these are still unclear [56–58]. On this behalf, development of crystalloid solutions with less chloride (with acetate, lactate or gluconate) and with a chemical composition that approximates extracellular fluid has been developed in the last decades. These solutions have been termed 'balanced' salt solutions. However, they also have their own adverse effects such as hyperlactatemia, metabolic alkalosis, inflammation and oxidative stress, hypotonicity, and cardiotoxicity [39]. Still, the use of balanced salt solutions in preference to 0.9% saline is just supported by the absence of harm in large observational studies. Thus, development of studies examining safety and efficacy of balanced salt solutions versus saline seems to be one of the next steps on the great fluid debate [38].

Currently, clinicians have to face the fact that the ideal resuscitation fluid does not exist. What seems clear is that every type of fluid has its problems, and that future research of new-generation fluids should be developed on the basis of an understanding of physiology of hypovolemia. There is a need to focus this fluid research on improving oxygen-carrying capacity [59], by using, for example, Hb-based oxygen carriers [60], and moreover limiting the pro-inflammatory effects of fluids [61].

CONCLUSIONS

In summary, the sole purpose of fluid therapy can arguably be defined as improving cardiac output with the aim of promoting tissue perfusion and oxygenation. Such goal can be achieved by targeting systemic variables of oxygen delivery under the condition that coherence between global hemodynamics and the microcirculation is maintained. However, as observed in states of distributive shock, the underlying problem might associate a loss of the hemodynamic coherence, and therefore, guiding fluid therapy according to its macrocirculatory effect might not only be ineffective, but also cause harm. In such conditions, monitoring fluid responsiveness from a Frank-Starling perspective will not result in the optimal volume being administered, inviting either microcirculatory hypoperfusion or fluid overload.

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Healthcare, Deerfield, Illinois and AM-Pharma, Bunnik, The Netherlands. C.I. has developed SDF imaging and is listed as inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past, but has not been involved with this company for more than five years now, except that he still holds shares. Braedius Medical, a company owned by a relative of C.I., has developed and designed a hand held microscope called CytoCam-IDF imaging. C.I. has no financial relation with Braedius Medical of any sort, i.e., never owned shares, or received consultancy or speaker fees from Braedius Medical.

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- ■ of special interest
- ■■ of outstanding interest

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