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Jean-Louis Vincent
Editor

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Distribution of Crystalloids and Colloids During Fluid Resuscitation: All Fluids Can be Good and Bad?

I. László, N. Öveges, and Z. Molnár

Introduction

Early fluid resuscitation remains the cornerstone of the treatment of severe hypovolemia, bleeding and septic shock. Although during these circumstances fluid administration is a life-saving intervention, it can also exert a number of adverse and potentially life-threatening effects; hence fluid therapy by-and-large is regarded a "double-edged sword" [1]. Unfortunately, for the three fundamental questions of: 'when', 'what' and 'how much', there are no universally accepted answers. Nevertheless, not giving enough volume may result in inadequate cardiac output and oxygen delivery (DO_2) and hence severe oxygen debt; while fluid overload can cause edema formation both in vital organs and in the periphery, hence impairing tissue perfusion. Despite broad acceptance of the importance of using appropriate parameters to guide treatment during resuscitation, current practice seems rather uncoordinated worldwide as was recently demonstrated in the FENICE trial [2]. In addition to using appropriate hemodynamic parameters to guide fluid resuscitation, the type of the infusion fluid should also be chosen carefully.

Fundamentally, crystalloids *or* colloids are suitable for fluid resuscitation. Theoretically, colloids have better volume expansion effects, therefore they restore the circulating blood volume and hence DO_2 faster than crystalloids do. The natural colloid, albumin, is very expansive compared to crystalloids, but the cheaper synthetic colloids have several potential adverse effects. Ever since colloids appeared on the scene the 'crystalloid-colloid debate' started, which seems like a never-ending story. At present, the gigantic pendulum that swings our opinion between 'good' and 'bad' based on current evidence, points more to the latter where synthetic colloids are concerned.

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According to Starling's '3-compartment model', crystalloids, with their sodium content similar to that of the serum, are distributed in the extracellular space, while colloids should remain intravascular because of their large molecular weight. Therefore, theoretically one unit of blood loss can be replaced by 3–4 units of crystalloid and one unit of colloid solution [3]. This theory has a long history and has been widely accepted worldwide since the 1960s [4]. However, several clinical trials including thousands of critically ill patients seemed to disapprove this principle as there were no large differences in the volumes of crystalloids versus colloids needed to stabilize these patients.

Understanding physiology, especially the role of the recently discovered multiple functions of the endothelial glycocalyx layer, may cast a different light on these controversies. The purpose of this chapter is to highlight several issues, which should be taken into account when we are interpreting the results of recent clinical trials on crystalloid and colloid fluid resuscitation.

Starling's Hypothesis Revisited in the Context of the Glycocalyx

Fundamentally, there are three infusion solutions that can be administered intravenously: water, in the form of 5% dextrose; crystalloids, containing sodium ions in similar concentration to that of the plasma; and colloids, which are macromolecules of either albumin or synthetic colloid molecules, such as hydroxyethyl starches (HES), dextrans or gelatin solutions.

According to the classic Starling view, the main determinants of fluid transport between the three main fluid compartments of the intracellular, interstitial and intravascular spaces are determined mainly by the two semipermeable membranes: the endothelium and the cell membrane (Fig. 1). Water and glucose molecules can pass freely from the vasculature to the cells, hence they are distributed in the total body water. Sodium containing crystalloids can pass the endothelium but not the cell membrane, hence these are distributed in the extracellular space, proportionally to the volume of the interstitial and intravascular compartments to the total extracellular fluid volume (Fig. 2). Colloids, because of their large molecular weight should remain intravascularly (Fig. 3).

The filtration rate per unit area across the capillary wall is mainly determined by hydrostatic and colloid osmotic pressures as indicated by the classic Starling's equation:

$$J_v = K_f((P_c - P_i) - \sigma(\pi_i - \pi_c))$$

where J_v is the fluid movement; $(P_c - P_i) - \sigma(\pi_i - \pi_c)$ is the driving force; P_c is the capillary hydrostatic pressure; P_i is the interstitial hydrostatic pressure; π_i is the interstitial oncotic pressure; π_c is the capillary oncotic pressure; K_f is the filtration coefficient; and σ is the reflection coefficient.

However, there is some evidence that in most tissues lymphatic flow would be insufficient to handle the extravasation of the amount of fluid as predicted by Starling, a phenomenon also termed the "low lymph flow paradox" [5, 6]. It has

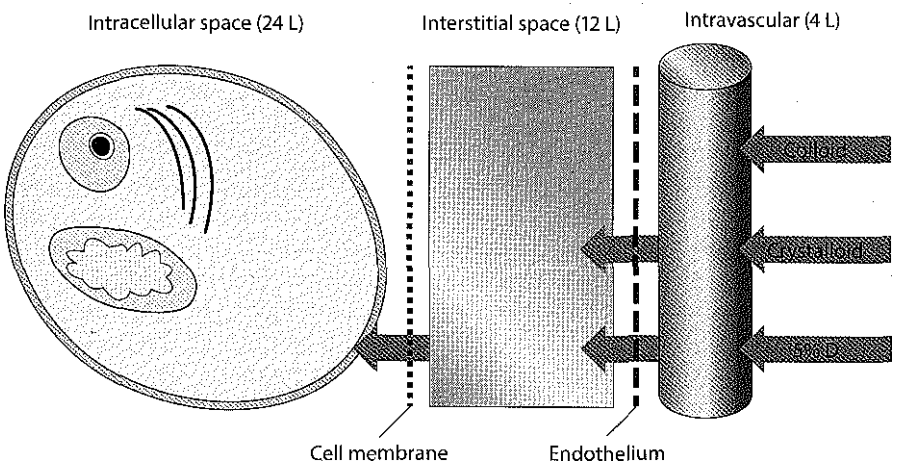

Fig. 1 Fluid distribution in the three main fluid compartments. In a normal (70 kg) adult, the total body water is about 60% of the total body weight, approximately 40 L, divided into intracellular (~ 24 L), interstitial (~ 12 L) and intravascular (~ 4 L) spaces separated by the endothelium and the cell membrane. According to Starling's classic '3 compartmental model' fluid distribution is mainly determined by these semipermeable membranes. Therefore, colloids stay in the intravascular compartment, crystalloids are distributed in the extracellular space, and water, in the form of 5% dextrose (5%D), is distributed in total body water

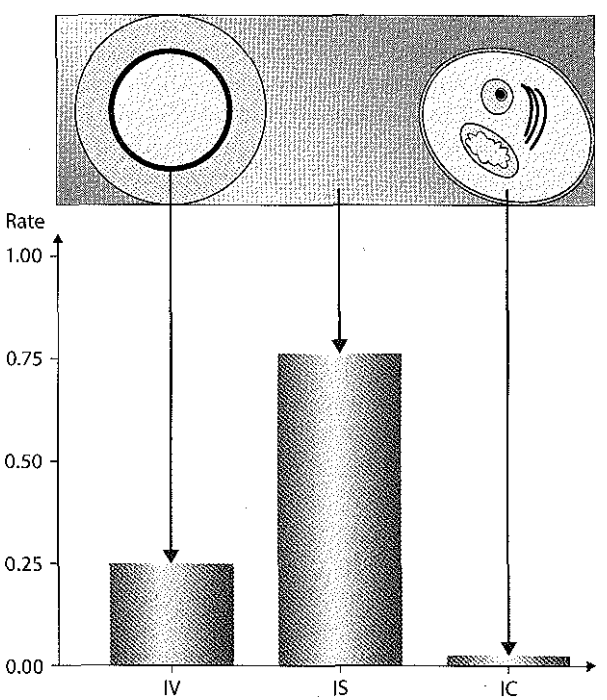

Fig. 2 Crystalloid distribution between the 3 compartments in normal subjects. Crystalloid solutions can pass the endothelium freely, but not the cell membrane because of their sodium ion content, hence they cannot enter the intracellular (IC) compartment. Therefore, they are distributed in the intravascular (IV) and the interstitial (IS) compartments. The rate of distribution between these two compartments is determined by how each relates in volume to the total extracellular fluid volume (12 + 4 = 16 L in our example in Fig. 1). Accordingly, for every unit of infused crystalloid, one fourth will remain intravascularly and three fourths interstitially

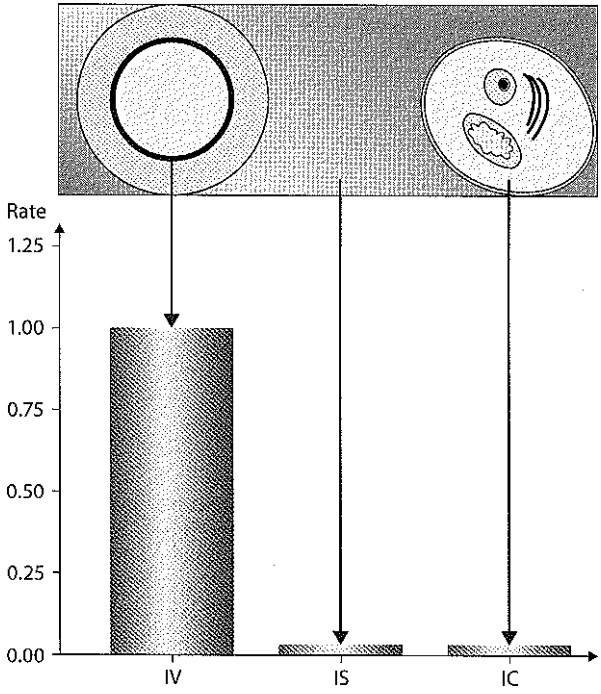

Fig. 3 Colloid distribution in normal subjects. Theoretically, due to their molecular weight, colloids should remain in the intravascular space. *IV*: intravascular; *IS*: interstitial; *IC*: intracellular spaces

been proposed that it is the endothelial glycocalyx layer that plays a pivotal role as a primary molecular filter and also provides an oncotic gradient, which was not included in Starling's hypothesis [7]. A web of membrane-bound glycoproteins and proteoglycans on the luminal side of endothelium has been identified to form the glycocalyx layer. This compartment consists of many highly sulfated glycosaminoglycan chains providing a negative charge for the endothelium. Due to these electrostatic properties, the subglycocalyx space produces a colloid oncotic pressure that may be an important determinant of vascular permeability and thus fluid balance [8]. The structure and function of the endothelial glycocalyx varies substantially among different organ systems, and it is also affected by several inflammatory conditions [9].

In a recent experiment on isolated guinea pig heart, Jacob et al. observed a very interesting phenomenon [10]. They perfused the coronaries with colloid free buffer, isotonic saline, albumin and HES solution, and measured extravascular transudate and edema formation. The experiment was then repeated when the glycocalyx was stripped from the vessel wall by treating it with heparinase. With intact glycocalyx, the net transudate, measured as hydraulic conductivity, was found to be 9.14 µl/min/g tissue for colloid free perfusion, which was dramatically reduced to 1.04 µl/min/g when albumin was added in physiological concentration to the perfusate. It was also attenuated by HES supplementation but to a significantly lesser degree, to 2.67 µl/min/g. The observation that adding colloids to the perfusate re-

this effect did not correlate with the colloid osmotic pressure: albumin, which is a much smaller molecule than HES, had significantly better effects in preventing transudate formation. This phenomenon is termed the "colloid osmotic pressure paradox", and cannot be fully explained by Starling's hypothesis and equation. One of the possible explanations is that the charges exposed by molecules forming the glycocalyx are mainly negative, whereas albumin carries molecules such as arginine and lysine with positive charges. There is some experimental evidence that these arginine groups are responsible for the effects of albumin on vascular permeability. By contrast, HES molecules are uniformly negatively charged, which may explain the significant difference in hydraulic conductivity observed by Jacob and coworkers [10].

These authors also suggested modifying the Starling equation to:

$$J_v/A = L_p((P_c - P_t) - (\pi_e - \pi_g))$$

where J_v/A is the filtration rate per unit area; L_p the hydraulic conductivity of the vessel wall; $P_c - P_t$ the difference in hydrostatic pressure between the capillary lumen (c) and tissue (t); π_e the colloid osmotic pressure in the endothelial surface layer; and π_g the colloid osmotic pressures directly below the endothelial surface layer in the glycocalyx.

Nevertheless, under normal circumstances, when the glycocalyx is intact, the Starling concept is still valid and fluid transport is determined by the 'Starling forces' (Fig. 4a), and the volume-replacement ratio should be several times higher for colloids compared to crystalloids. Indeed, several experimental studies mainly in bleeding-resuscitation animal models reported the volume-replacement ratios

Table 1 Experimental studies

Trial	Modell	Type of Fluids	VRR	Comments
Kocsi (n = 13) [12]	Controlled bleeding on pigs	Voluven (6% HES)	1:1	The 1:1 blood loss:colloid VRR maintained baseline GEDV throughout the experiment
Simon (n = 25) [11]	Controlled animal study in septic shock in pigs	– RL – HES 700/6:1 – HES 130 – HES 700/2.5:1	1:1 1:1.12 1:3.08 1:2.97 1:3.78	In comparison to RL, all HES solutions were more effective at maintaining plasma volume
Ponschab (n = 24) [13]	Bleeding-resuscitation pig model	Balanced crystalloid, in 1:1 or 1:3 replacement ratio	1:1.08 1:2.85	High volume (1:3) caused more pronounced cooling and impaired coagulation
Fodor (n = 25) [14]	Bleeding-resuscitation in rats	– Blood – HES 6% – NaCl 0.9%	1:1	No difference between colloids and crystalloids on pulmonary function. However, detailed invasive hemodynamic assessment was not performed

VRR: volume-replacement ratio; *GEDV*: global end diastolic volume; *HES*: hydroxyethyl starch; *RL*: Ringer's lactate

for colloids as predicted by Starling's hypothesis [11–14]. These are summarized briefly in Table 1. The explanation could be that, in animal models, because of the relatively short experimental time, and because most models investigated hypovolemia, bleeding and resuscitation, the glycocalyx has no time for degradation. Nevertheless, these studies had different aims than to test Starling's hypothesis, and this should be performed in the future.

The glycocalyx has a pivotal role not just in regulating endothelial permeability but in several others functions: it modulates shear force induced nitric oxide

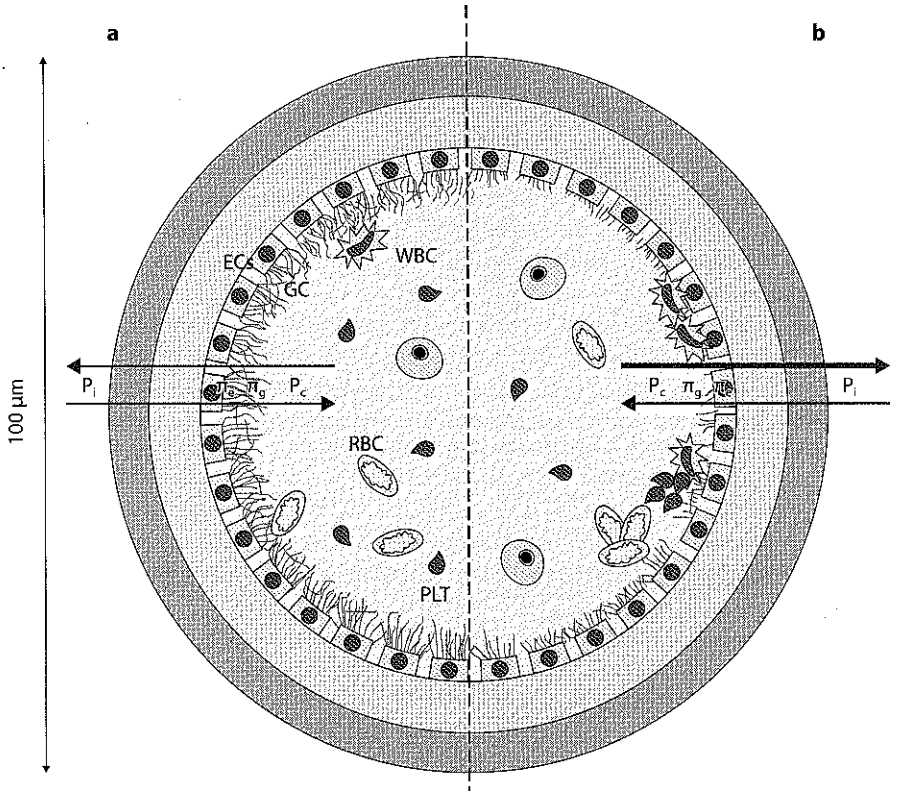

Fig. 4 Schematic transection of a capillary. **a** In normal subjects, the glycocalyx (GC) is intact and Starling's concept is more-or-less valid so that fluid transport is mainly determined by the Starling equation (see text). **b** In several critical illness conditions, both the glycocalyx and the endothelium become damaged. During these conditions, the regulating functions of the endothelium and glycocalyx are partially or totally lost. These will affect fluid transport across the vessel walls with excessive fluid and protein extravasation, will cause leukocyte adherence and platelet adhesion, further impairing capillary blood flow, and the complex function of the endothelium and the microcirculation. *ECs*: endothelial cells; *RBC*: red blood cells; *PLT*: platelets; *WBC*: white blood cells; *Pi*: interstitial hydrostatic pressure; π_e: colloid osmotic pressures in the endothelial surface layer; π_g: colloid osmotic pressures directly below the endothelial surface layer in the glycocalyx

(NO)-synthesis and dismutation of oxygen free radicals in the endothelial cells and controls coagulation and inflammation by preventing platelet adhesion and leukocyte adherence to the vessel walls [15]. It is, therefore, not surprising that whenever the glycocalyx layer is damaged, important pathophysiological changes take place, which can have serious effects on the function of the affected organ, or organs.

The Glycocalyx in the Critically Ill

There is mounting evidence that the glycocalyx becomes impaired or destroyed in several critical illness conditions, including inflammation (both infectious and non-infectious), trauma, sepsis, ischemia-reperfusion injuries, but also persistent hypo-, and hypervolemia [16]. During these conditions, the regulating functions of the endothelium and glycocalyx are lost, which can have serious effects on permeability and hence fluid transport across the vessel walls with excessive fluid and protein extravasation (Fig. 4b), but other functions like leukocyte adherence and platelet adhesion are also affected. There is experimental evidence that during these conditions, the interstitial space becomes overwhelmed with colloid molecules [10]. Although albumin seemed to be somewhat more able to interact with these conditions than HES, nevertheless it could not prevent colloid extravasation, which was also enforced by increasing hydrostatic pressures. These experimental findings are in agreement with the results of our clinical study, in which patients with septic shock and acute respiratory distress syndrome (ARDS) were administered either HES (molecular weight of 250 kDa) or gelatin (30 kDa) to treat hypovolemia. We used detailed hemodynamic monitoring and observed no difference in the volume-replacing effects of these colloids, and no change in the extravascular fluid volume, despite the huge difference in their molecular weight and colloid osmotic pressure [17]. This was possibly due to the very severe and long-standing (several days) condition of these patients, when it is highly likely that the glycocalyx was already severely damaged, hence 'size' (i. e., molecular weight) no longer mattered.

These observations are important when we try to interpret the results of recent large clinical trials comparing crystalloids and colloids in the critically ill.

Volume-replacement Effects of Crystalloids and Colloids in the Critically Ill

Although most recent large clinical trials had end-points of 28-day mortality or organ dysfunction, it is worthwhile analyzing the results from a different perspective. One of the landmark trials was the SAFE study, published in 2004, in which investigators compared the safety of albumin to normal saline in ICU patients (n = 6,997). The results showed no significant differences between the groups in hemodynamic resuscitation endpoints, such as mean arterial pressure (MAP) or heart rate, although the use of albumin was associated with a significant but clinically small increase in central venous pressure (CVP). The study showed no significant differ-

ence between albumin and normal saline regarding 28-day mortality rate or development of new organ failure [18]. The SAFE study was followed by the VISEP [19], CHEST [20] and 6S [21] trials, all reaching a more or less similar conclusion. Results showed a strong association between acute kidney injury, increased use of renal replacement therapy (RRT) and the use of HES solution, which was also accompanied with unfavorable patient outcome [19–21]. By contrast, in the CRISTAL trial, which was designed to test mortality related to colloid and crystalloid based fluid replacement in ICU patients, investigators detected a difference in death rate after 90 days, favoring the use of colloids. Furthermore, patients spent significantly fewer days on mechanical ventilation and needed shorter durations of vasopressor therapy in the colloid group than in the crystalloid group [22].

There are several common features in these studies. First of all, the ratio of the administered volume of crystalloid and colloids was completely different to what would have been expected according to the Starling principle (Table 2). In general, 30–50% more crystalloid seemed to have the same volume-expanding effect as colloids. Based on these results, a common view was formed that HES does not have higher potency for volume expansion than crystalloids, but carries a greater risk of renal dysfunction and mortality [18–25].

However, it is important to note that none of these trials used detailed hemodynamic monitoring, which is the second common feature of these studies. The administration of intravenous fluids was mainly based on clinicians' subjective decision [18, 19, 21, 22, 25], or on parameters such as heart rate [20], blood pressure [19, 21, 23], CVP [19, 21, 23], urine output [18–21, 23], lactate levels [20] or central venous oxygen saturation [19, 21, 23]. Cardiac output and stroke volume were not measured in most of the trials, which is essential to prove volume responsiveness, and none of the applied indices listed above are good monitoring tools of fluid therapy [1, 26]. Therefore, it is possible that a considerable number of these patients was treated inappropriately. Although it is not the task of the current review, it is important to note that the methods used as indications for fluid administration, also reflect our everyday practice, as was nicely confirmed in a recent observational study [2]. In this large international survey, it was revealed that fluid therapy is mainly guided by inadequate indices during our daily clinical routine. Therefore, one cannot exclude that in these trials a considerable proportion of patients were not hypovolemic at all. Indeed, in the CHEST trial the mean values of the target parameters were as follows: heart rate of 89/min, MAP 74 mmHg, CVP 9 mmHg and serum lactate 2 mmol/l. [20] None of these values suggests hypovolemia, or at least it is highly unlikely that any of us would commence fluid resuscitation based on these values. There is some evidence that in healthy male subjects colloid solutions provided a four times greater increase in blood volume compared to saline, and extravasation was significantly higher after saline infusion [27]. Therefore, if we consider that a considerable proportion of these patients were critically ill, hence their glycocalyx was impaired, and although they were not hypovolemic they still received colloids, this may have led to excessive extravasation. Furthermore, if fluid was administered to normovolemic patients, this could have caused increased hydrostatic pressures in the microcirculation leading to excessive HES extravasation

Table 2 Human randomized controlled trials

Trial	Population	Types of fluid	Cr/Co	Invasive hemodynamic monitoring
Finfer (n = 6,933) [18]	ICU patients	Albumin, saline	1.32	No
Brunkhorst (n = 537) [19]	ICU patients with severe sepsis	HES, RL	1.32	No
Myburgh (n = 7,000) [20]	ICU patients	HES 130/0.4, saline	1.20	No
Guidet (n = 174) [23]	Patients with severe sepsis	HES 130/0.4, saline	1.23	No
Perner (n = 798) [21]	ICU patients with severe sepsis	HES 130/0.42, Ringer's acetate	1.00	No
Annane (n = 2,857) [22]	ICU patients with hypovolemic shock	Colloids (gelatins, dextrans, HES, 4 or 20% albumin), crystalloids (isotonic or hypertonic saline, Ringer's lactate)	1.5	No
Yates (n = 202) [24]	High-risk surgical patients	HES 130/0.4, Hartman's solution	1.69	No
Caironi (n = 1,810) [25]	Severe sepsis, septic shock	20% albumin, crystalloid	1.02	No
Lobo (n = 10) [27]	Healthy male subjects	Gelofusin or HES 6%, saline	1.00	No

Cr/Co: ratio of crystalloid/colloid; *HES*: hydroxyethyl starch; *ICU*: intensive care unit

and deposit of colloid molecules in the tissues, further amplifying its adverse/toxic effects.

Clinical Implications

These observations can have an important impact on our daily clinical practice. These results suggest that, in addition to global and regional hemodynamic parameters, the role of the glycocalyx should be taken into account during the management of fluid resuscitation. Measuring several degradation markers (Table 3) in the blood [28–33] and even visualizing the microvasculature (Table 4) has now become pos-

Table 3 Glycocalyx degradation markers

Trial	Model	Methods	Conclusions, comments
Johansson (n = 75) (n = 80) [28, 29]	Prospective observational study in trauma patients	syndecan-1 (ng/ml); ELISA	Trauma is associated with endothelial damage, glycocalyx degradation
Ostrowski (n = 29) [30]	Experimental human endotoxemia (n = 9) and septic patients (n = 20)	syndecan-1 (ng/ml); ELISA	Endotoxemia did not but sepsis did cause endothelial damage, indicated by biomarkers that correlated with disease severity
Steppan (n = 150) [31]	Septic patients (n = 104), major abdominal surgery (n = 28), healthy volunteers (n = 18)	syndecan-1 (ng/ml); ELISA HS (μg/ml); ELISA	Significant flaking of the endothelial glycocalyx occurred in patients with sepsis, and to a lesser extent in surgical patients
Yagmur (n = 225) [32]	Critically ill patients (n = 164) and healthy controls (n = 61)	HA (μg/L); automated latex agglutination assay	Authors suggest that HA might have implications in the pathogenesis of critical illness and sepsis
Schmidt (n = 17) [33]	Mechanically ventilated ICU patients	CS (μg/ml) HS (μg/ml) Mass spectrometry	Circulating glycosaminoglycans may provide insight into respiratory pathophysiology

CS: chondroitin sulfate; *ELISA*: enzyme-linked immunosorbent assay; *HA*: hyaluronic acid; *HS*: heparan sulfate; *ICU*: intensive care unit

Table 4 Techniques to visualize the endothelial glycocalyx

Trial	Model	Method	Conclusions
Donati (n = 66) [34]	Septic patients (n = 32) Non-septic ICU patients (n = 18)	Sublingual sidestream dark field (SDF)	Correlation between PBR and number of rolling leukocytes postcapillary, confirming that glycocalyx shedding enhances leukocyte-endothelium interaction
Reitsma (n = 22) [15]	Endothelial glycocalyx structure in the intact carotid artery on C57B16/J mouse	Electron microscopy	The EG can be adequately imaged and quantified using two-photon laser scanning microscopy in intact, viable mounted carotid arteries
Gao [35]	Male Wistar rats, weighing 200–300 g	Brightfield images	The removal of heparan sulfate may cause collapse of the glycocalyx
Yen [36]	Ex vivo experiment on rat and mouse aortas	High resolution confocal microscopy	The surface glycocalyx layer is continuously and evenly distributed on the aorta wall but not on the microvessel wall

EG: endothelial glycocalyx; *EM*: electron microscopy; *PBR*: perfused boundary region; *RL*: rolling leukocyte

sible [15, 34–36], and may become part of bedside routine in the not too distant future. Theoretically, for example in an acutely bleeding patient in the emergency room or in the operating room, the glycocalyx may be intact, which could be proven by novel investigations, and fluid resuscitation with colloids may be more beneficial and more effective compared to crystalloids. By contrast, during circumstances when the glycocalyx is impaired, colloids should be avoided. However, rather than just assuming the condition of the glycocalyx, its routine measurement could have an important impact on our daily practice and even on patient outcome.

Conclusion

Transport of fluids across the vessel wall was first described by Ernest Starling. Although his hypothesis is predominantly still valid, especially under physiological circumstances, the "low lymph flow paradox" and the "colloid osmotic pressure paradox" cannot be explained by simply applying the Starling equation. The discovery of the glycocalyx and its multiple roles in maintaining an intact and appropriately functioning endothelial surface layer has shone new light on vascular physiology. Therefore, in the future a paradigm shift will become necessary in order to appropriately assess and better guide fluid therapy. Without a detailed evaluation of the global effects of hypovolemia and fluid resuscitation, and assessment of the function of the microcirculation and the function of the glycocalyx, one cannot give adequate answers to the questions of 'when, what and for how long' should we administer fluids to our patients. We have to accept that, despite the significant results of large trials that are valid for the majority of the investigated population, at the bedside we should take an appropriate physiological parameter-based individualized approach. Thus, it turns out that all fluids can be good *and* bad depending on the specific circumstances.

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