



# Do Intensivists Need to Care About the Revised Starling Principle?

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R. G. Hahn

## 11.1 Introduction: Concerns Among Clinicians

Microcirculatory researchers have recently re-evaluated the principles of transvascular fluid exchange. The new aspects were summarized for anesthetists and intensivists in an influential and widely cited review article by Woodcock and Woodcock in 2012 [1]. The new evaluations have been transmitted via numerous lectures and articles worldwide and have even been the leading topic of a book [2]. Those who are popularizing the new concepts provide explanations for how fluid therapy works in humans and even give recommendations, despite the fact that the revised physiology rests primarily on experiments on mesenteric capillaries of primitive animals, such as frogs.

A multitude of “pro” articles claim a clinical importance for the revised Starling and glycocalyx principles. The present “con” article points out that the new concepts are sometimes difficult to reconcile with actual studies in humans.

## 11.2 Glycocalyx Degradation

The luminal side of the endothelium is covered with a layer of loose tissue containing glycoproteins and glycosaminoglycans called the glycocalyx layer. Beyond any doubt, this layer is relevant to many functions in the vascular system [3], but the key issue for anesthetists and intensivists is how easily injury or fragmentation (shedding) of the glycocalyx occurs, and to what degree this type of injury impairs the intravascular persistence of infusion fluids.

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R. G. Hahn (✉)

Research Unit, Södertälje Hospital, Södertälje, Sweden

Karolinska Institutet at Danderyds Hospital (KIDS), Stockholm, Sweden

e-mail: [robert.hahn@sll.se](mailto:robert.hahn@sll.se)

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Glycocalyx shedding is suggested to result from hypervolemia, surgery, ischemia, and severe infection [1]. Several hundred published clinical studies have reported acute elevations of the plasma concentration of glycocalyx layer constituents, implying damage to the endothelium. However, the observed three- to four-fold elevations of syndecan-1 and heparan sulfate can also be explained by changes in kidney function [4], which is often affected after surgery, trauma and intensive care.

Acute shedding probably needs to be associated with at least a tenfold elevation of the plasma concentrations of glycocalyx components to exclude the kidney as a confounder, but it most certainly occurs in cardiac surgery and in severely ill patients. Importantly, several key scenarios have been studied that show only minimal, if any, signs of glycocalyx shedding. These include cholecystitis, appendectomy [5], hysterectomy [6], hypervolemia [5, 6] and lengthy (6 h) abdominal surgery [7, 8]. However, the occurrence of acute shedding seems unlikely in most situations encountered in routine hospital work.

Correction of the plasma concentration of degradation products for plasma albumin has occasionally been applied, but its validity is unproven due to a lack of pharmacokinetic characteristics for these substances [9].

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### 11.3 Increased Capillary Leakage?

A fourfold increased rate in the capillary leakage of albumin has been found in septic patients [10]. However, we do not know whether the increased loss was replaced by albumin from an increased lymphatic flow, or if the intravascular persistence of infusion fluid was affected. Severe disease is always associated with hypoalbuminemia, but it does not seem to be coupled with impaired intravascular persistence of infusion fluid or albumin [8].

Capillary leakage resulting from glycocalyx fragmentation has been difficult to demonstrate in complex biological systems. Rehm et al. [11] pointed out this possibility by using indocyanine green to demonstrate massive capillary leakage immediately after induction of general anesthesia for abdominal hysterectomy, where hypervolemia was induced with colloid fluid. Only 40% of the infused volume remained after a short equilibration time [12, 13].

Inspired by this finding, Nemme et al. induced hypervolemia with a rapid infusion of Ringer's in the same setting, but found no increase in glycocalyx shedding products in the bloodstream at all [6]. At the same time, the possibility was raised that Rehm's widely cited finding was due to overlooking the transit time of the indocyanine green tracer between the site of injection and the site of elimination (the liver) [14].

Rehm's group used an isolated heart model to convincingly demonstrate increased leakage of fluid upon administration of natriuretic peptides, which cause glycocalyx shedding, but the glycocalyx layer was unlikely to have remained intact after such a complex manual preparation [15].

Later, the occurrence of increased capillary leakage of albumin or fluid due to glycocalyx shedding was refuted in cholecystitis, appendectomy [5] and abdominal surgery [7, 8]. In the rat, Can Ince's group could not find any evidence that the glycocalyx serves as a barrier to fluid distribution [16].

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## 11.4 “Non-absorption Rule”

Another claim is that an increased intravascular oncotic pressure cannot reverse fluid filtration in the capillaries because of the existence of a presumed colloid-free spatium below the glycocalyx layer (the “non-absorption rule”). This is said to explain why one cannot successfully treat edema by infusing colloid fluids. Naturally, the clinician then begins to question whether infusing 20% albumin is meaningful for that purpose.

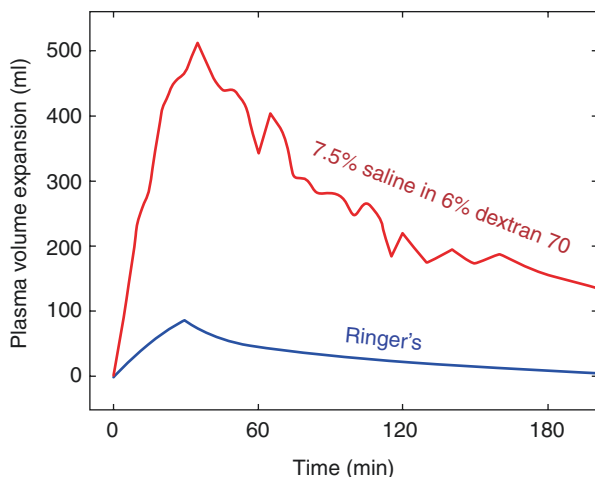
A recent study by my group shows that infusion of 20% albumin results in allocation of three times as much fluid to the circulating plasma than the infused volume [17], which degree is expected because recruitment of fluid also concentrates the albumin concentration of the interstitium. Moreover, the same recruitment was shown in volunteers and in postoperative patients who had undergone surgery with a mean operating time of 6 h, and who had a much lower plasma albumin concentration at baseline [8].

These findings do not support the “non-absorption rule,” although the possibility remains that the recruited fluid stems from the lymph rather than from the interstitial fluid. Recruitment of fluid from the glycocalyx layer has been claimed to occur, but is unproven [1] and further would be expected to cause some disintegration of this structure (shedding), which does not occur as a result of fluid recruitment with 20% albumin [17].

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## 11.5 Capillary Filtration

A finding in primitive animals related to the “non-absorption rule” is that fluid is filtered throughout the length of most capillaries. No absorption occurs at the distal end, except transiently in hypovolemic states. This claim creates difficulties in understanding how hypertonic (7.5%) saline can greatly increase the plasma volume when given to normovolemic volunteers [18]. Infusion of 7.5% saline in 6% dextran 70 increases the plasma volume even more, by twice as much as 7.5% saline alone, which is consistent with the idea that osmotically withdrawn intracellular fluid is further transported to the plasma by a transendothelial absorption process [18] (Fig. 11.1). The reversal of the arteriovenous difference in plasma dilution in the hand only 2 min after the end of an infusion of crystalloid fluid is also difficult to reconcile [19]. This latter finding suggests that filtered fluids in the hand muscles become absorbed locally, despite the fact that the filtration pressure must be markedly raised.



**Fig. 11.1** Plasma volume expansion based on hemoglobin dilution. Red curve: in a representative male volunteer receiving 250 ml of 7.5% saline in 6% dextran 70 over 30 min. Blue curve: the same amount of Ringer's solution in a group of 10 volunteers simulated by volume kinetics (data from [18])

The revision of the traditional models for transvascular fluid exchange emphasizes filtration while downplaying, in particular, the impact of the interstitial colloid pressure, since the colloid gradient is claimed to exist between the plasma and an almost protein-free “protected region” of the subglycocalyx space [1]. This model scarcely agrees with our results from cardiopulmonary bypass (CPB), where the priming solution (Ringer's) had a normal distribution half-life of 8 min [20]. Connecting the patient to the circuit would then imply that the hydrostatic pressure is kept constant while the intravascular colloid pressure is dramatically reduced by dilution with the crystalloid fluid in the circuit. In this setting, no distribution at all would have occurred if the subglycocalyx region had been protein free.

## 11.6 Are Colloids and Crystalloids Equal?

Microcirculatory researchers claim that the traditional Starling principle predicts that crystalloid fluid has only a transient effect on the blood volume in hypovolemic humans [21]. This is actually the case, and rebound hypovolemia is therefore an expected but widely overlooked problem [22]. However, these researchers now propose an alternative interpretation, the revised Starling principle, which predicts that crystalloids are retained to a greater extent in the hypovolemic setting. This is said to explain why crystalloids are far more effective in the operating room and in trauma than in volunteers [21].

In clinical patients, an excess intravascular accumulation of crystalloid fluid has been known for almost 30 years to require the development of arterial hypotension,

i.e., relative or absolute hypovolemia is not sufficient [23, 24]. In humans, a reduction in the mean arterial pressure (MAP) to a steady state 20% below baseline temporarily arrests the distribution of crystalloid fluid to the interstitium, making it an effective plasma volume expander [25]. This effect is easy to explain by the traditional Starling equation, since a reduction in the intravascular pressure should create difficulties for infused fluid to distribute against an interstitial fluid at a normal pressure. However, the effective plasma volume expansion is likely to last only until the infusion has built up a new Starling equilibrium. Thereafter, the distribution function is the same as that observed in conscious volunteers [26].

Kinetic analyses in humans do not support a more than transient slowdown of the rate of distribution of fluid in extrarenal capillaries in this setting. The increased effectiveness of crystalloid fluid in lengthy surgery or intensive care is not due to a slow distribution but due to renal fluid retention, which is proportional to the patient's age and inversely to the MAP [27]. Therefore, the rate of elimination is the main factor that determines plasma volume expansion during long observation times, and this fact has cast doubts over the relative potency of these fluids in several intensive care studies [28].

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## 11.7 Hemodilution and the Glycocalyx

Objections to the use of hemoglobin (Hb) concentration to estimate the distribution of infused fluid are usually based on microcirculatory considerations. Hb concentration is claimed to be a misleading index of plasma volume change because red blood cells (RBCs) do not pass into the glycocalyx layer; therefore, Hb only indicates the circulating blood volume [13, 29].

This consideration is not valid because the Hb concentration is only the inverse of the blood water concentration and has nothing to do with the blood volume. The glycocalyx will be indicated by the Hb concentration as long as infused water passes into the glycocalyx. This can be understood from the following example:

Assume that we infuse two fluids on separate occasions that distribute into different body fluid compartments (let us say the plasma and the total body water). Naturally, the hemodilution will be greater for the first and smaller for the second infusion. Nevertheless, a correct volume of distribution for the infused fluid will be obtained in both cases by dividing the infused volume with the Hb dilution. The fact that RBCs cannot distribute into the total body water is not relevant as long as the infused water volume does distribute there. Hence, the hemodilution reflects how the infused water is distributed, and whether this is occurring inside or outside the circulating blood does not matter.

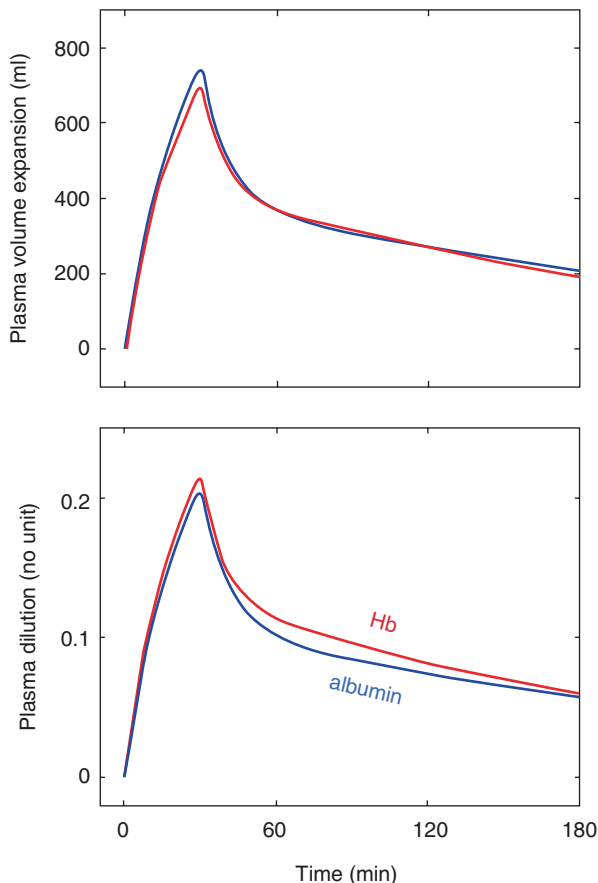
Microcirculatory researchers also discredit the use of Hb because RBCs circulate at a different rate than the plasma [21]. This objection might be valid for radioactive tracers but not for hemodilution, which will be the same even if the RBCs are transported at a rate of zero. The blood Hb concentration mirrors the blood-water concentration and nothing else.

## 11.8 Volume Kinetics

The most sophisticated use of Hb dilution is to apply volume kinetics to serial measurements and calculate the distribution and elimination of an infusion fluid [27]. This analysis detects a “wall” between a central compartment (the plasma) and a peripheral compartment (probably the interstitium) and indicates where the infused fluid is located, regardless of the degree of hemodilution. Hence, if hemodilution is doubled, the plotted fluid distribution will be the same, although a scaling factor between the hemodilution and the volume change (i.e.,  $V_c$ , the plasma volume) will be cut in half.

The example shown in Fig. 11.2 compares the modeled plasma volume expansion and the plasma dilution as derived by population volume kinetics, based on four published studies where blood Hb and plasma albumin were measured at precisely timed intervals during and after infusion of a crystalloid fluid [6, 26, 30, 31]. Both albumin and Hb show practically identical intravascular fluid volumes (Fig. 11.2, upper). The scaling factor between the volume change and dilution was

**Fig. 11.2** Plasma volume expansion (upper) and the corresponding plasma dilution (lower) when 1.5 l of crystalloid fluid is infused over 30 min. Computer simulations based on population kinetic data from 128 infusion experiments (2009 data points), where blood hemoglobin (Hb) concentration and plasma albumin had been measured at precisely timed intervals. Compilation of measurements from four studies [6, 26, 30, 31] using methods described in [27]



3.25 l for Hb and 3.63 l for albumin, and this is the closest we can get to an estimate of the plasma volume using dilution kinetics. Figure 11.2 (lower panel) indicates a somewhat smaller plasma dilution for plasma albumin than for Hb, which agrees well with the “f-cell ratio”, or “hematocrit factor”, (usually 0.88–0.92; here, it is  $3.25/3.63 = 0.895$ ), which is reported when the blood volume is measured using radioactive tracers.

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## 11.9 Conclusion

The relevance of the revised Starling principle and the glycocalyx model to clinical work is not yet proven, and their use can even create difficulties in explaining the results of some studies in humans. Acute degradation of the glycocalyx apparently requires the occurrence of a more severe physiological insult than was previously believed. Misinterpretation of elevated plasma concentrations of glycocalyx degradation products due to changes in kidney function can be suspected. Shortened intravascular persistence of infusion fluids after shedding of the glycocalyx layer has not yet been demonstrated in humans. Lastly, the author argues against objections raised by microcirculatory researchers regarding the use of hemodilution to study fluid distribution.

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