



## REVIEW

# The Extended Starling principle needs clinical validation

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The Revised (or "Extended") Starling principle is based on highly controlled laboratory-based frog and rodent experiments and remains a hypothesis awaiting clinical validation. A key point is that the endothelial glycocalyx layer moves the oncotic gradient from being between the plasma and the interstitium to between the plasma and a virtually protein-free space between the glycocalyx and the endothelial cell membrane, which dramatically changes the prerequisites for fluid absorption from tissue to plasma. However, many experimental and clinical observations in humans agree poorly with the new microcirculatory proposals. The most troubling aspect of the explanation regarding the role of the glycocalyx in the Revised Starling principle is the effective reabsorption of fluid by skeletal muscle when the capillary filtration pressure is acutely reduced. Other issues include the plasma volume effects of hypertonic saline, iso-oncotic and hyper-oncotic albumin, fluid distribution during cardio-pulmonary bypass, and the virtually identical capillary leakage of plasma and albumin despite marked inflammation found in our fluid therapy studies. The Revised Starling principle deals mainly with steady-state conditions, but the circulatory system is highly dynamic. Second to second vasomotion is always operational and must be considered to understand what we observe in humans.

The works of Levick, Michel and other microcirculatory researchers on "The Revised Starling Principle" were popularized for a broader anesthesiology readership by Tom Woodcock in a review article in the *British Journal of Anaesthesia* in 2012.<sup>1</sup> The interpretation presented by Woodcock received much attention and has been the subject of numerous lectures in anesthesiology courses and at congresses. The arguments and perceived clinical implications have been further developed in two books.<sup>2,3</sup>

We have great respect for microcirculatory researchers and do not question their results, but we would like to be convinced that their hypotheses are valid in living human beings before they are used as the basis for recommending clinical management of patients. For example, one claim is that hyper-oncotic albumin is not useful for treating peripheral edema, as this therapy cannot recruit fluid from

the interstitial fluid space.<sup>1</sup> This proposal runs contrary to clinical experience and needs data from humans before this indication for albumin treatment is abandoned. Findings made during short periods of time (seconds to a few minutes) in very primitive experimental systems, like isolated frog mesenteric venules or rat venules, should be tested in larger animals and then in volunteers and patients before changes in clinical fluid therapy are even considered.

## 1 | WHAT DOES THE REVISED STARLING PRINCIPLE IMPLY?

The Revised (or "Extended") Starling principle remains a hypothesis that deals mainly with steady-state conditions, but the circulatory

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system is highly dynamic, so one has to ask: is it ever at steady state, or is steady state something achieved in the laboratory by holding multiple parameters constant so a single variable can be measured with great precision? While these laboratory approaches help us to understand basic relationships, in the intact mammal multiple parameters are changing simultaneously and the best we can do is to measure the integrated response, like arterial pressure and cardiac output.

Based on Woodcock's statements, most clinicians have understood the "Revised Starling principle" to imply that the transvascular exchange of fluid no longer occurs according to a simple gradient of hydrostatic and oncotic pressures across the capillary wall. The reason is the endothelial glycocalyx layer, which moves the oncotic gradient from being between the plasma and the interstitium to between the plasma and a virtually protein-free space between the glycocalyx and the endothelial cell membrane. This represents a major change and not an extension of the Starling principle.

The glycocalyx layer is said to be quickly degraded due to inflammation, ischemia, and even surgery to cause a rapid increase in the capillary leakage of proteins. This would reduce the intravascular persistence of infusion fluids. A frightening example was given by Rehm et al in 2001, when only 40% of a brisk volume load with iso-oncotic albumin solution and hydroxyethyl starch remained in the vascular system shortly after induction of general anesthesia before open abdominal hysterectomy.<sup>4</sup> This result has been re-published many times, even in the *Lancet*.<sup>5</sup>

The new views did not agree with our findings of how colloid fluid behaves in the body. In both volunteers<sup>6,7</sup> and patients,<sup>8</sup> we did not observe an unexpected and large capillary leakage of colloid fluid volume, although hypervolemia had been induced. Our contrary results made us begin to wonder whether the new "Revised Starling" needed to be considered in the clinic, and if so, how should it be considered? Does it add anything? The Starling equation had been corrected by the "reflection coefficient" years before the era of intensive research about the glycocalyx layer,<sup>9</sup> and it was already known that capillary leakage of albumin increases in septic patients.<sup>10</sup>

## 2 | SEARCH FOR CLINICAL EVIDENCE

The first challenge was to critically review the study by Rehm et al.<sup>4</sup> The poor clinical efficacy of colloids seemed to be due to overlooking the transit time for their blood volume tracer, indocyanine green. On correction for this error, close to 100% of the infused colloid volume appeared to have been retained, and the same result was obtained based on the dilution of the to both these questions.<sup>11</sup> Tracer kinetics is a difficult field and is hampered by a host of potential errors.

The second step was to study whether degradation of the glycocalyx and increased capillary leakage really occur after volume loading and the induction of anesthesia for open abdominal

### Editorial Comment

In this special article, which is one of a pair of invited narrative reviews, the author group focuses on clinical validation of intravascular fluid kinetics, particularly related to developing thought concerning the theoretical framework for trans-capillary fluid filtration.

hysterectomy. Based on a research collaboration with Riga Stradins University, we can now answer "no" to both these questions.<sup>12</sup> The rates of capillary leakage of albumin and fluid were normal. Damage to the glycocalyx, which is often assessed by measuring plasma levels of syndecan-1 and heparan sulfate, did not occur.

The third step was to study the "non-absorption rule," which says that raising the oncotic pressure in the plasma cannot recruit fluid from the interstitial volume.<sup>1</sup> This is another claim that changes the prerequisites for the traditional Starling equation. We found that infusing 20% albumin in volunteers increased the plasma volume by twice the infused amount and increased urinary excretion. The same clinical efficacy was observed after major surgery lasting for a mean of 6 hours, despite the fact that the postoperative patients showed a marked inflammatory response.<sup>13</sup> The capillary leakage of albumin and fluid was virtually identical in these two groups, and no elevation of glycocalyx degradation products was seen. The same findings were made with Ringer's lactate in patients undergoing surgery for appendicitis and cholecystitis.<sup>14</sup>

So far, we have spent a great amount of time and money in trying to reproduce the key mechanisms of the "Revised Starling principle" in living humans, but with disappointing results. Degradation of the glycocalyx does not seem to be an issue in routine surgery, except perhaps after cardiac operations. Whether increased plasma concentrations of degradation products shorten the intravascular persistence time of infusion fluids is unproven. Ince et al have also tried to validate that the glycocalyx is a barrier for fluid distribution, but with a negative result.<sup>15</sup> Our enthusiasm for measuring degradation products has further decreased after finding that 3-4-fold elevations can be explained by changes in kidney function, which is common in severe disease and during surgery.<sup>16</sup>

## 3 | FLUID RE-ABSORPTION IN MUSCLE

Many experimental and clinical observations in humans agree poorly with the new microcirculatory proposals. The most troubling aspect of the explanation regarding the role of the glycocalyx in the Revised Starling principle is the effective reabsorption of fluid by skeletal muscle when the capillary filtration pressure is acutely reduced. Woodcock<sup>1</sup> has indicated that fluid cannot be recruited to the plasma across the capillary wall in muscle because the capillaries are of the continuous type. However, an extensive literature exists

on capillary refill and the reabsorption of clinically significant volumes of interstitial fluid, and these are sustained over many minutes to hours.<sup>17,18</sup>

We believe that single post-capillary venules in the mesentery of frogs and rats are structurally incapable of reproducing the prerequisites for the effective transcapillary reabsorption in muscle. The small volume of interstitial fluid surrounding a single microvessel assures that interstitial oncotic pressure increases rapidly during reabsorption, and makes the process short-lived.<sup>19</sup> Conversely, the large volume of skeletal muscle and skin, accounting for 40% of the body mass in humans, underlies its importance in transcapillary refill and yet, this important point has apparently been overlooked.<sup>20,21</sup>

The mechanistic components required for the no-reabsorption state of the Revised Starling—for example, a low-protein sub-glycocalyx fluid layer, a long and tortuous intercellular cleft (filled with low protein filtrate), and sporadic junctional breaks that increase in filtrate velocity up to 10-fold—are employed to explain the inability of plasma oncotic forces, indeed, “the sum-of forces”, that cannot reverse filtration.<sup>21</sup> Fluid reabsorption is said to be possible for a few minutes in hypovolemic states,<sup>1,19</sup> although the time frame has been extended to hours in their recent review, but whether this claim also involves muscle tissue is unclear. Moreover our findings of a rapid reversal of the arterio-venous difference in plasma dilution in the hand already at 2 min after ending crystalloid volume loading shows that fluid can also be recruited from muscle even in the hypervolemic state.<sup>22</sup>

We cannot help but hypothesize that the “transient” nature of the filtration–reabsorption relationship is a function of the experimental preparation and may not be as widely applicable as may be inferred by numerous reviews. In an intact circulation with an intact sympathetic nervous system, minute to minute and second to second vasomotion is always operational; therefore, “transient” reabsorption must be occurring all the time.

## 4 | TROUBLESOME CLINICAL CORRELATES

Another setting where fluid seems to be recruited across the capillary wall is offered by experiments with hypertonic saline (4 × the infused volume) and hypertonic saline dextran (7.2 × the infused volume).<sup>23</sup> Here, the large volumes of recruited fluid can hardly stem from the glycocalyx layer, which Woodcock is convinced to be the source of hyper-oncotic recruitment.<sup>1</sup>

Connecting the patient to the circuit after cardiopulmonary bypass means that the hydrostatic pressure is kept constant while the plasma oncotic pressure is dramatically reduced by dilution with the crystalloid fluid in the circuit. Our analysis showed that the priming solution (Ringer’s) had a perfectly normal distribution half-life of 8 min in this setting.<sup>24</sup> No distribution at all would have occurred if the subglycocalyx region had been protein free.

Many attempts have been made to “explain” clinical findings using the Revised Starling principle that are easier to explain using

traditional concepts. One example is why colloids show no advantage over crystalloid fluids in expanding the plasma volume when the circulatory pressure is acutely reduced.<sup>1</sup> However, an acute reduction of both the hydrostatic and colloid osmotic pressures in the vascular system would interrupt the capillary filtration, even with the traditional Starling equation. This interruption makes the clinical efficacy of colloid and crystalloid the same, at least until a new Starling equilibrium develops.

A modified version of this proposal is that the Revised Starling principle is claimed to account for the observation that crystalloid fluids are retained intravascularly to a greater extent in hypovolemia.<sup>25</sup> Interestingly, they are not, at least not in hemorrhagic hypovolemia, as long as the arterial pressure is maintained.<sup>26</sup>

The Revised Starling principle is also said to explain why crystalloid and colloid fluid have the same clinical efficacy when studied over long periods of time, such as days, in intensive care. These comparisons are extremely time-dependent,<sup>27</sup> and the similar long-time clinical efficacy can actually be explained by volume kinetics based on data from young healthy volunteers with a presumed intact glycocalyx layer.<sup>28</sup>

## 5 | VALIDATION IN HUMANS IS NEEDED

Woodcock and colleagues are to be congratulated for having greatly increased attention on the role of microcirculation in anesthesia in general and in fluid therapy in particular. However, we believe the novel views more fundamentally change the way the traditional Starling mechanism operates than they admit themselves. What is needed now is to demonstrate their clinical validity in living human beings.

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