VL-DUAL SHORT REVIEW

# Notes on the revised Starling principle

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**Abstract** Many researchers are more accustomed to the traditional Starling principle (SP) interpretation in capillary exchanges, compared to the revised Starling principle (RSP), owing to its friendly formulation and its apparently greater adherence to the reality. However, the simplification holds if and only if SP is limited just to the hydrostatic and osmotic pressures in the vascular compartment, omitting the action of the analogous pressures in the interstitial tissue (simplified traditional Starling principle or sSP). This omission allows the elegant interpretation of a fluid exchange symmetry along the capillary, from the arteriolar to the venular end, which is at the base of the Filtration-Absorption Model of capillary exchanges. However, if the interstitial factors are not negligible instead, even SP capillary fluid balance shifts asymmetrically towards filtration, instead of absorption. This asymmetry is the same of the revised Starling principle (RSP), thus the simpler assumption of SP is a clear misinterpretation, due to an erroneous simplification with no historical basis. Indeed, already in 1968 Zweifach and Intaglietta documented an incomplete absorption at the venular end of the capillaries. The current short review underlines the differences between the traditional and the revised Starling principles, with the aim of providing a simpler and clear comparison between the two models of capillary fluid exchanges.

**Keywords** Starling principle, Revised Starling principle, Filtration-Absorption model, Excess of capillary filtration, Lymphatic drainage.

## I - Introduction

I and many other participants already started to discuss about the Starling Principle[1] during the VL-DUAL online Vasculab Event (Nov 2023)[2], having the opportunity to read very interesting remarks.

Anyway, it's better to **restart from the basic knowledge**, in order to help people to overcome any conceptual difficulties.

Indeed, many specialists think that the faced topics were very theoretical ones, with no real practical use, as in the old as well as in the revised form.

A simple variant of this behaviour consists in accepting the old principle, because it is simpler and explains the facts more easily.

Really, this point of view is faulty, because not always simpler arguments are true and generally **the MODELS-WHICH-EXPLAIN often can be just an "ad hoc" hypotheses, while a good model should be predictive, i.e. able to foresee interesting developments**.

In addition, what is a good model depends on the **time period** when you value it.

For instance, the traditional Starling principle (**SP**) was excellent at the end of the XIX century, while today the revised Starling principle (**RSP**)[3] is more adaptive and promising.

As to the practical use, consider both principles in action in pathology:

- in excess filtration as in acute inflammation or superficial or deep thrombosis;
- in excess absorption as in post-haemorrhage hemo-dilution.

## II - The traditional Starling principle

EH Starling[1] formulated the principle in 1896, considering two compartments (intra-capillary and interstitial) separated by a homogeneous semipermeable membrane and then in 1898 suggested the hypothesis of a fluid exchange symmetry along the capillary, from the arteriolar to the venular end.

The mathematical form of the principle however appeared later in the Landis and Pappenheimer[4] chapter (1962) and was then refined in 1993 by Muscarella[5]. The osmotic reflection coefficient for semipermeable membranes was introduced instead in 1974 by Michel[6].

The first measurements of the parameters involved in the principle were effected in 1994 by Bates, Levick and Mortimer[7], who confirmed many of the Starling and Landis forecasts, however providing no support for the symmetric fluid exchange.

Nowadays, the principle is reported generally as follows:

$J_v = L_p A\{(P_c - P_i) - \sigma(\pi_p - \pi_i)\}$;

where

$J_v$ : capillary filtration rate;

$L_p$ : capillary conductance;

A : area;

P : pressure;

$\sigma$ : (also sigma) the Staverman's reflection coefficient [0-1] for semipermeable membranes, which quantifies the osmotic effect;

$\pi$ : (also COP) colloid osmotic pressure

and the subscripts c, i, p refer to capillary, interstitium and plasma.

The above equation can be rearranged, in order to group together the reabsorbing parameters, as follows:

$J_v = L_p A\{P_c - (P_i + \sigma(\pi_p - \pi_i)\} =$

$J_v = L_p A(P_c - P_0)$;

Where $P_0 = P_i + \sigma(\pi_p - \pi_i)\}$ resumes the reabsorbing forces towards the capillary lumen.

A simplified application of the Starling principle assumes that the interstitial forces are negligible, i.e. $P_0$ is worth just the osmotic action of plasma proteins.

On the contrary, applying the complete formula, the result is much lower and towards filtration, instead of absorption.

## III - The revised Starling principle

Let's introduce the revised Starling model[3], underlining its differences from the traditional one (Table I).

Using differences, it would be simpler to understand also the different behaviour of both models.

### III.a - Comments

Owing to chronological reasons, the old model couldn't of course rely on the glycocalix model.

In addition, the old two compartments model is widened to three, adding the space in the intercellular cleft, i.e. plasma and ISF are not in contact with each other, because the cleft space places itself between them.

Practically, the cleft substitutes the interstitium and the net reabsorbing force is replaced by $P_0 = P_i + \sigma(\pi_p - \pi_g)\}$ instead of $P_0 = P_i + \sigma(\pi_p - \pi_i)\}$, where the cleft COP is $\pi_g$ instead of $\pi_i$.

Furthermore, the interstitial forces are considered fixed in the old model, while they change according to the capillary pressure in the revised model.

The simple and homogeneous semipermeable membrane becomes dis-homogeneous, adding also a new type of large pores, which allow the flow of proteins.

Finally, the *Filtration – Absorption Model* was not confirmed as in the old as well as in the new model, according to Bates' paper[7] and others.

All people who became fans of the old model to safeguard the venular absorption, should definitely change their mind, because the old model fails too in explaining the absorption in the venular capillary end.

## IV - Final remarks

### IV.a - Humans and animals

Almost all research experiments on the Starling principle were effected on animals, with the exception of the Landis experiment on capillaries in human nails and the one of Bates.

Comparing the traditional and the revised Starling principle

| | Traditional | Revised |
|---|---|---|
| Glycocalix | NO | YES |
| N. of compartments | 2 Plasma, ISF | 3 Plasma, Cleft, ISF |
| Semipermeable membrane | Homogeneous, 1 type of pores | Dis-homogeneous, 2 type of pores |
| N. of flows | 1 [Fluid ($J_v$)] | 2 [Fluid ($J_v$), Proteins ($J_p$)] |
| $P_i$ and $\pi_i$ | Fixed | Change with capillary flow ($J_v$) |
| Adopted COP | $\pi_i$ Interstitial COP | $\pi_g$ Sub-glycocalyx COP |
| Filtration – Absorption Model | Not working | Not working |

*Table I - See the text for explanation of the adopted terms.*

## IV.b - A remark on data from Bates.

The short review from Levick and Michel[3] on the revised Starling principle reports many data taken from Bates[7], thus a few observations about could be very informative.

Bates collected measurements from women with post-mastectomy (PMO) oedema. In these patients, plasma proteins were less than normal, thus lowering one of the reabsorbing forces, as in the diseased as well as in the healthy control arm.

As another important result, the interstitial colloid pressure was reduced in the swollen arms, as also was the interstitial protein concentration. Although inexplicable, this result matches other data reported in literature[8].

## IV.c - Incomplete venular absorption and the traditional Starling principle

The first observations about the incomplete absorption at the venular end of capillaries were performed by Zweifach and Intaglietta[9]. They reported *We have not to date … encountered vessels that consistently showed inward filtration*.

The phenomenon was confirmed by other independent experiments, for instance, Bates[7], posing the practical question of finding the available draining pathways for the ultra-filtrate. Thus, the fluid exchange symmetry was already questioned before the revised Starling principle was formulated.

Michel and Phillips[10] tested the capillary behaviour under quick changes of the capillary pressure (transient condition) or, on the contrary, maintaining the pressure unaltered at least for 2 minutes (steady-state). During the first condition a venous absorption became evident, while during the latter no absorption occurred at all.

The transiently capillary absorption is therefore one of the possible solutions, the other one being of course the large intervention of the lymphatic system.

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