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REVISED STARLING'S PRINCIPLE (RSP): A MISNOMER AS STARLING'S LAW IS PROVED WRONG.

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Substantial evidence based on results of new physics experiments and physiological research affirm Starling's law wrong. Here we demonstrate that the Revised Starling's Principle (RSP) is also misleading. The article is a futile attempt to revive Starling's law after it has long been dead and buried. A most recent article seriously criticized RSP. We hope the excuse for the authors is unawareness of new contributions rather than a desperate attempt to defend the indefensible. Nether Starling nor the authors who made the hypothesis a law were aware of the discovery of the precapillary sphincter that demonstrates capillary pressure induce suction not filtration as demonstrated in the G tube, and the wide intercellular slit pores of the capillary wall that allow the passage of plasma proteins, thus nullifying oncotic pressure in vivo.
In addition to previously reported 21 reasons affirming Starling's law is wrong we add two more that concern the main reports that transformed Starling's hypothesis into a law. Physiologists and physicists are concerned about formulae and calculations while physicians are more concerned about the lives and safety of their patients. Hence physicians understand the importance of discarding Starling's law; being wrong is responsible for the induction of the new volume kinetic shocks and the causation of the acute respiratory distress syndrome that kills hundreds of thousands of patients every year. Now, there is a replacement for it: The hydrodynamic phenomenon of the porous orifice (G) tube. It is time to say goodbye Starling's law, hello G tube.

Substantial evidence based on the results of new physics experiments [1-3] and physiological research [4] affirm that Starling's law is wrong. Here we demonstrate that the Revised Starling's Principle (RSP) is also misleading [5,6]. When I read this article [1] sent by Professor Robert in February 2020, one understood that the authors express discontent with faulty Starling's law, particularly as the Editor of the British Journal of Anaesthesia commented: "Starling's principle does not hold in a clinical setting." On reading this article on RSP later, one realized that the term does not mean what it says. Like others, among whom the authors [6] referenced Professor Robert Hahn [7], we initially thought the term RSP means discontent with a faulty Starling's law as it implies.

However, to our surprise and dismay, the twisted meaning was realized after reading this article [6] for the first time on July 25th. The article is a futile attempt to revive Starling's law [8,9] after it has long been dead and buried [1-4]. A most recent article by Hahn et al [10] seriously criticized RSP and justifiably and acceptably rejected it. The only disagreement we have with Hahn et al., is the need to clinically validate RSP. It will prove total waste of energy, efforts, time and money. We hope the excuse for the authors [6] is unawareness of Ghanem's contributions on the subject rather than a desperate attempt to defend the indefensible. All articles are reported in Open Access Journals not indexed in PubMed but all are listed in Google Scholar with citations.

In fairness to Professor Starling, who was a great physiologist, the authors [6] are correct in Stating that when Starling reported his hypothesis on the capillary interstitial fluid (ISF) transfer and edema formation first in The Lancet [8] and 10 years later in J Physiol. [9], he neither wrote any equations nor proposed a law. The transformation came 2-4 decades later after Landis in 1927 [11] and Pappenheimer and Soto-Rivera in 1948 [12] reported their investigations on Starling's forces. After that Starling's hypothesis became law and equations were introduced for it.

The above authors were unaware of the capillary ultrastructure and correct physiology brought about by the brilliant discovery of the precapillary sphincter [13] and the wide intercellular slit pores of the capillary wall [14] that allow the passage of plasma proteins, thus nullifying oncotic pressure in vivo. Both discoveries were reported in 1967. Of course, none of the mentioned authors, as well as most contemporary physicists and physiologists, was aware of the discovery of hydrodynamics of the porous orifice (G) tube and its magnetic field-like phenomenon (Figure 1) as the correct replacement for Starling's law. Despite reporting the physics evidence as a preliminary report in 2001 [2], emphasized in 2017 [3] and concluded in 2020 [1], and the physiological evidence was reported in 2017 [4], the results are not yet recognized, fully understood or comprehended. Most of the contemporary physiologists and physicists remain also unappreciative of the difference between the hydrostatic and hydrodynamic pressures. Thus, not only Starling's hypothesis [8,9] was wrong but also the law on both forces and equations is wrong. What is built on wrongdoing must also be wrong! Here are the other reasons for saying so to add to the 21 reasons affirming Starling's law is wrong previously reported [15]. This evidence is overwhelmingly convincing and none of the given reasons can be denied or refuted.

Starling's hypothesis [8,9] was transferred into a law 2 decades after the report by Landis in 1927 [11]. Landis measured the hydrostatic pressure of the capillary lumen at both arterial and venous ends by a cannula facing upstream that occluded the capillary lumen. This method does not reflect the dynamic pressures of the capillary tube of flow pressure (FP) and side pressure (SP) demonstrated in both the G tube and Poiseuille's tube physics experiments [1-3] and physiological research [4]. The hydrodynamic of G tube has been investigated, contrasted to Poiseuille's tube and its physiological relevance and clinical significance are demonstrated [1]. The G Tube has a different hydrodynamic from Poiseuille's tube.

The G tube has a negative SP gradient that is maximum negative near the inlet and turns gradually positive to become maximum near the exit. Thus, the G tube suction or absorption of fluid occurs through side holes near the inlet while filtration occurs through holes near the exit. This creates an autonomous rapid dynamic magnetic field like fluid circulation in a surrounding chamber (C) between fluid around the G tube and fluid inside its lumen. The negative SP of the G tube creates net negative pressure in the chamber (C). The flow in chamber C is in the opposite direction to the flow of fluid in the G tube lumen as shown in the diagram based on many photographs (Figure 1).

The G tube's magnetic field like the fluid circulation phenomenon between the fluid inside its lumen and that surrounding it in chamber C works in both macro and microtubes alike. It works in capillaries as based on the physiological evidence [4] as well as modern videos on the speed of flow in the capillary circulation (The video is available on Thomas Woodcock's Blog [5] and reported by HN Mayrovits). The speed of blood flow in the capillary shown in this video is fast enough to induce the magnetic phenomenon of the G tube in a capillary. The low proximal pressure is certainly adequate for inducing the G tube phenomenon in the capillaries. The speed of flow in the capillary shown in this video is "very fast", and certainly cannot be described as "very slow" as generally believed and taught in current classical teaching on the capillary circulation. The fluid transfer of the G-C model occurs according to the precise circulation of fluid between the G tube lumen and surrounding chamber C, not diffusion. We believe this G-C circulation represents the capillary-ISF circulation, which is not diffusion.

Here are 2 more reasons why we believe Starling's law is wrong. Results of new physics experiments on both the G tube and Poiseuille's tube demonstrate that if the measuring cannula facing upstream occludes the lumen of the tube, it transfers the two dynamic pressure components of FP and SP into one high positive hydrostatic pressure only that does not reveal anything about the side pressure exerted on the tube's wall. This is what Landis [11] did when he measured the capillary lumen pressure at the arterial and venous ends. He measured the **MEAN** hydrostatic pressure that reflected the flow pressure but does not show anything about the dynamic negative side pressure. The occluding measuring cannula, out of necessity on reaching a balance of pressure measurement, stops the flow thus the 2 dynamic pressures of FP and SP are transferred into only one positive hydrostatic pressure, and the negative SP disappeared.

The values Landis obtained for this **MEAN** hydrostatic pressure at the arterial and venous ends of the capillary were 32 and 12 mmHg, respectively. The pressure gradient from the proximal to the distal end of the G tube (Figure 2) is less than that reported by Landis in the capillary. Hence the speed of blood flow through the capillary follows a gradient along the tube that is higher at the proximal part than at the distal part. Applying Poiseuille's law or Bernoulli's equations only represents the MEAN hydrostatic pressure and speed of flow over both the proximal and distal parts of the tube. The side pressure (SP) exerted on the tube' wall is lower or negative over the proximal part and becomes high positive over the distal part of both Poiseuille and G tubes.

The report by Pappenheimer and Soto-Rivera [12] was the main reason for the transformation of Starling's hypothesis into a law. These authors thought that elevating the capillary pressure may be achieved by elevating the venous pressure or arterial pressure alike, matching mmHg for mmHg, and they reported this to be in support of Starling's hypothesis. However, this also has proved wrong, as demonstrated in the G tube and Poiseuille's tube experiments, as well as evidence from clinical practice: Elevating distal pressure (DP) akin to venous pressure, augments filtration as shown in graph (Figure 3) and in clinical practice causes edema formation while elevating proximal pressure (PP) akin to arterial pressure does not, it enhances suction or absorption maximum near the inlet of the G tube as shown in the graph in (Figure 4) [1-4].

In support of the above fact is: High venous pressure, or obstruction, is the main cause of the most common clinical edema but arterial hypertension though quite common it never causes edema. Of course, neither Starling nor any of the authors who transferred his hypothesis into law were aware of the brilliant discovery of the precapillary sphincter [13] and wide porous wall of the capillary [14] that were discovered later in 1967. It is worth mentioning the relation of G tube orifice diameter to side pressure (SP) of the G tube and the surrounding chamber C pressure (CP) that is shown in (Figure 5), This is relevant to the negative ISF pressure measured by Guyton and Coleman subcutaneously to be of -7 cm water [16] that can only be explained by the hydrodynamics of the capillary working as G tube (Figure 1 & 5). Starling's forces cannot account for this negative pressure of ISF space and lymph vessels at all [1].

Physiologists and physicists may be reluctant to support the truth brought about by the discovery of the hydrodynamics of the G tube denying its applicability to the capillary hydrodynamics, being most concerned about formulas and calculations. Physicians, however, particularly Anaesthetists, Surgeon, and Intensivists are most concerned about the lives and safety of their shocked, acutely ill patients and patients undergoing major surgery. Physicians who must rely on Starling's law for giving intravenous fluid therapy in clinical practice do realize the seriousness of this affair. These Physicians know how Starling's law does not hold in these clinical settings: Being wrong has induced errors and misconceptions on fluid therapy [17]. These errors mislead physicians into giving too much fluid during the resuscitation of shock, acutely ill patients, and prolonged major surgery [18]. It thus induces the volumetric overload shocks (VOS) [19] also known as volume kinetic (VK) shocks [20] that cause acute respiratory distress syndrome (ARDS) [21]. The faulty Starling's law is the primary culprit responsible for the death of hundreds of thousands of ARDS patients every year all over the World [22,23]. The truth should be allowed to prevail and shine. All should welcome the discoveries in physics, physiology, and medicine [1-4,17-23]. The physics, physiological and clinical evidence is so overwhelming that it justifies saying: "Goodbye Starling's law, hello G tube" [24].

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Addendum

1. Letter to the Editor of Nature

Sir,

We commend and congratulate the authors on their brilliant article [1] on the role of the precapillary sphincter and its primary important role in regulating blood flow and pressure into the cerebral cortex as well as every other tissue in the body. Their tremendous effort in conducting this awesome research work is most appreciated. However, we fear that some of their derived physiological functions on capillary blood flow and pressure are incorrect due to a fault that is not their own. This has led to some incorrect results, graphs, and conclusions highlighted by using the word "perfusion" in the title of their article. This is a common and prevailing physiological belief found in all current textbooks and physiological teaching on the capillary-Interstitial fluid (ISF) transfer.

The word perfusion is based on the currently accepted physiological law of Starling that is generally believed to regulate the capillary-ISF transfer through perfusion influenced by its forces. The two main forces of Starling's law believed to induce this perfusion state are the hydrostatic pressure of the capillary causing filtration, and the osmotic (oncotic) pressure of plasma protein (albumin) causing absorption. Here we demonstrate that Starling's law is wrong on both forces and the correct replacement for it is the hydrodynamics of the porous orifice (G) tube preliminary reported in 2001, emphasized 2017, and concluded in 2020. (Please see attached report for figures and references.)

The G tube was built on a scale to the capillary ultrastructure anatomy of the precapillary sphincter and the wide intercellular pores that allow the passage of plasma proteins, hence nullify the oncotic pressure in vivo. Investigating the hydrodynamics of the G tube demonstrated that the hydrostatic pressure is different from the 2 hydrodynamic pressures of flow pressure (FP) and side pressure (SP) exerted on the wall. The hydrodynamics of the G tube is different from Poiseuille's tube.

The G tube has a negative SP gradient that is maximum negative near the inlet and turns gradually positive to become maximum near the exit. Thus, the G tube suction or absorption of fluid occurs through side holes near the inlet while filtration occurs through holes near the exit. This creates an autonomous rapid dynamic magnetic field like fluid circulation in a surrounding chamber (C) between fluid around the G tube and fluid inside its lumen. The negative SP of the G tube creates net negative pressure in the chamber (C). The flow in chamber C is in the opposite direction to the flow of fluid in the G tube lumen. The magnetic field like fluid circulation regulates the capillary-ISF transfer.

We trust that the authors have adequate data and the capability to correct the erroneous conclusions and title based on the enclosed article and report back a correction here in Nature.

2. Report on: Does the hemodynamics of the capillary with its precapillary sphincter work as the porous orifice (G) tube?

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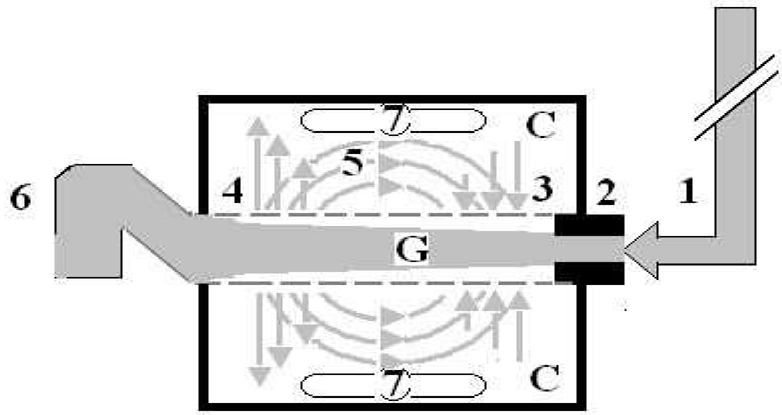

Figure 1 shows a diagrammatic representation of the hydrodynamic of G tube based on G tubes and chamber C. This 38-years old diagrammatic representation of the hydrodynamic of G tube in chamber C is based on a few photographs. The G tube is a plastic tube with narrow inlet and pores in its wall built on a scale to capillary ultra-structure of the precapillary sphincter and wide intercellular slit pores, and the chamber C around it is another bigger plastic tube to form the G-C apparatus. The chamber C represents the ISF space. The diagram represents a capillary-ISF unit that should replace Starling's law in every future physiology, medical and surgical textbooks, and added to chapters on hydrodynamics in physics textbooks. The numbers should read as follows:

1. The inflow pressure pushes fluid through the orifice
2. Creating fluid jet in the lumen of the G tube**.
3. The fluid jet creates a negative side pressure gradient causing suction maximal over the proximal part of the G tube near the inlet that sucks fluid into the lumen.
4. The side pressure gradient turns positive pushing fluid out of the lumen over the distal part maximally near the outlet.
5. Thus, the fluid around G tube inside C moves in magnetic field-like circulation (5) taking the opposite direction to lumen flow of G tube.
6. The inflow pressure 1 and orifice 2 induce the negative side pressure creating the dynamic G-C circulation phenomenon that is rapid, autonomous, and efficient in moving fluid and particles out from the G tube lumen at 4, irrigating C at 5, then sucking it back again at 7. Maintaining net negative energy pressure inside chamber C.

**Note the shape of the fluid jet inside the G tube (Cone shaped), having a diameter of the inlet on the right-hand side and the diameter of the exit at the left-hand side (G tube diameter). I lost the photo on which the fluid jet was drawn, using tea leaves of fine and coarse sizes that run in the center of the G tube leaving the outer zone near the wall of the G tube clear. This may explain the finding in a real capillary of the protein-free (and erythrocyte-free) sub-endothelial zone in the Glycocalyx paradigm (Woodcock and Woodcock 2012) [1]. I also noted that fine leaves exit the distal pores in a small amount maintaining a higher concentration in the circulatory system- akin to the higher concentration of plasma proteins in the circulatory system than in the ISF space.

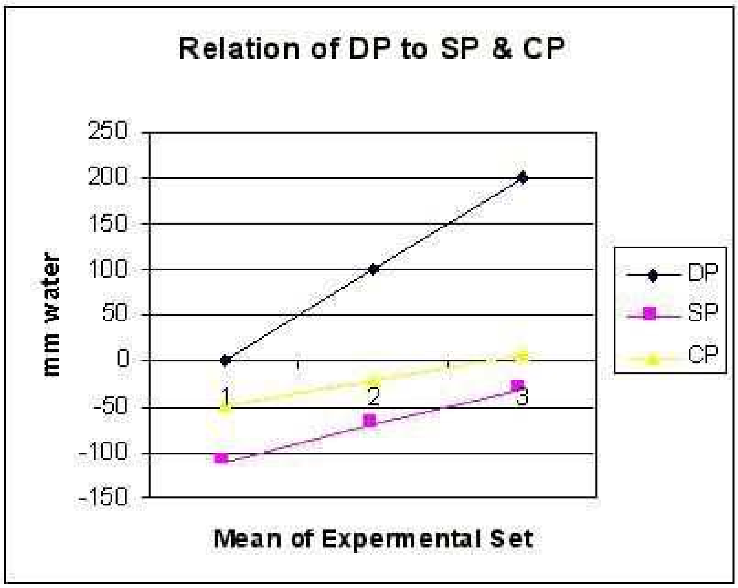

Figure 2 shows the relation of distal pressure (DP) akin to venous pressure on side pressure (SP) of the G tube and chamber pressure (CP)- akin to ISF space pressure. Both SP and CP revert to positive pressure when DP (venous Pressure) is elevated to 20 cm water akin to edema formation. Elevated DP and reduced PP (not elevation) have similar effects on SP and CP.

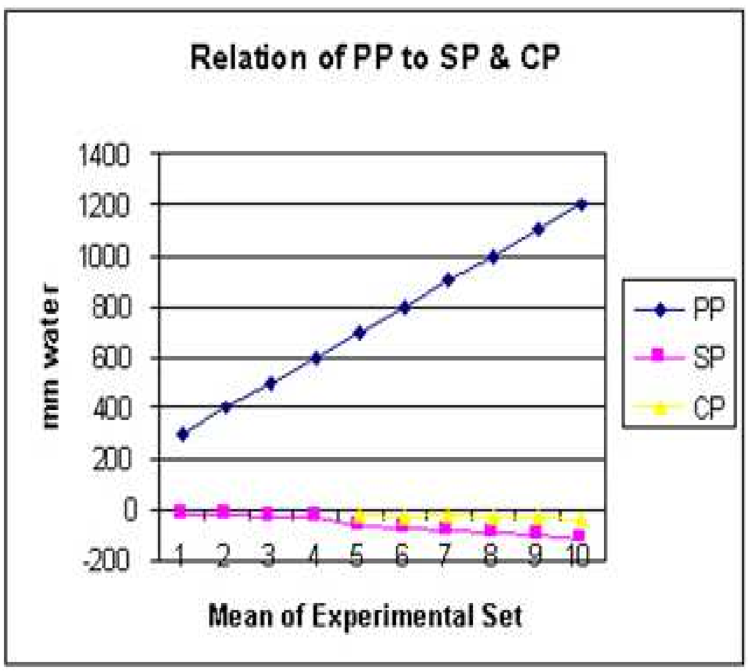

Figure 3 demonstrates the relation of proximal pressure (PP)- akin to arterial pressure on SP and CP. Elevation of PP increases the negativity of SP and CP with the most efficient G-C circulation allowing good rapid irrigation of C without oedema formation.

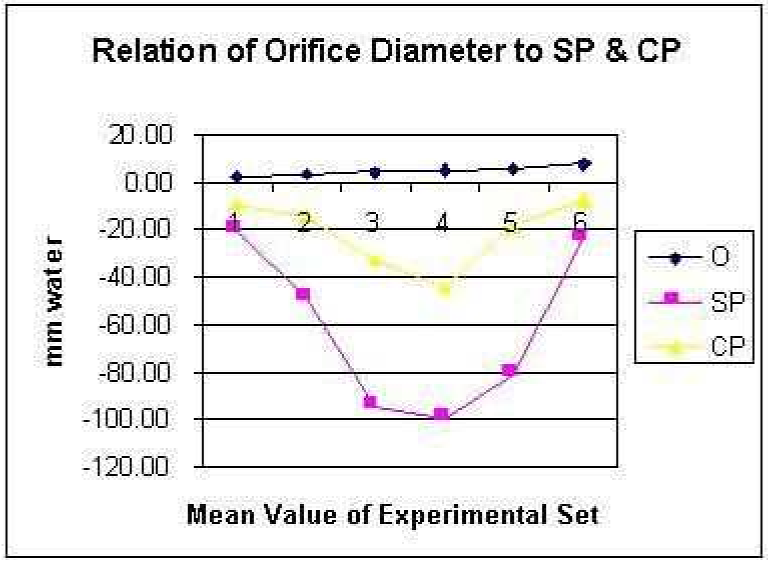

Figure 4 demonstrates the relation of orifice diameter of G tube to the dynamic negative side pressure (SP) of G tube- akin to capillary side pressure exerted on its wall, and the chamber pressure (CP)- akin to the pressure in the ISF space. It is inverted bell-shaped with maximum negativity at 0.7 the diameter of G tube, the equivalent of 0.5 cross-section area of the G tube. At this diameter and cross-section area the magnetic fluid G-C circulation is speediest and efficient in exchanging fluid between that in the lumen of G tube-akin to capillary and a surrounding fluid in chamber C- akin to ISF fluid space.