



**Editorial**

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## Albumen does not work: what alternative hypothesis for Starling's capillary-interstitial transfer is there? The hydrodynamics of the porous orifice tube

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**Editorial**

The news article and systematic review of randomised controlled trials analysing the results of colloids versus crystalloids use in resuscitating the critically ill patients [BMJ 2004;328:852] is informative. The respected members of Cochrane Injuries Group Albumin Reviewers concluded: "There is no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia and a strong suggestion that it may increase mortality". I urge this group and all concerned not only to "urgently review the use of plasma proteins in resuscitating the critically ill patients" but also to investigate the scientific basis on which it was advocated in the first place. The documented evidence supporting these issues and implications are highlighted here.

The study reported powerful statistical evidence of increased mortality on using plasma proteins in resuscitating the critically ill patients. To my understanding this implies that the oncotic pressure effect of albumen is a fallacy. Knowing that there is already much documented evidence that the oncotic pressure does not work at all *in vivo*, one wonders if such evidence should resolve the old argument. Based on 3 decades of investigations and judging by the controversial responses on the original study, one sees no way out of this clinical dilemma unless the underlying physiological error is rectified [1].

The use of plasma proteins in resuscitation is based on its assumed oncotic pressure being the main suction force in Starling's law [2], on the capillary-interstitial fluid (ISF) transfer, thought to return fluid from ISF space back into capillary lumen across its wall. For such oncotic pressure to work it is assumed that the capillary wall is impermeable to albumin, but documented evidence demonstrates this is untrue. Thus the half century old argument on colloids versus crystalloids is based on the fallacy of oncotic pressure force attributed to plasma albumen in capillary-ISF transfer. The main filtration force of Starling's law is attributed to capillary pressure, induced by arterial pressure, also assumed to be the force pushing fluid out from capillary lumen into ISF space! This also has proved wrong [3].

It is worth mentioning here that the basis of the widely held belief and practice of overzealous "vascular volume expansion", in resuscitating shock and critically ill patient, is based on the assumed rule of capillary arterial pressure as the main filtration force. Starling based this part of his hypothesis on Poiseuille's work on long Brass tube of uniform diameter. There is new physical evidence that such pressure works differently in porous orifice tubes that mimic the capillary structure [1,3]. Thus, both forces in Starling's law have proved wrong. Verifying this issue is not only an academic exercise of physiological value but also a vital clinical issue related to the morbidity and mortality of the resuscitated critically ill and shock patients. It is well known that the morbidity that is the main cause of mortality, among most patients who survive the initial insult, is the multiple vital organ dysfunction/ failure (MVOD/F) syndromes also known as the acute respiratory distress syndrome (ARDS) that remain puzzling and unresolved.

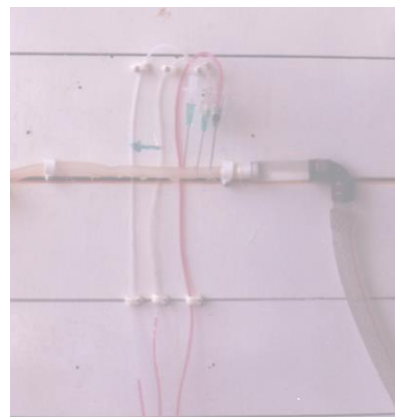
Related clinical observations-initiated verification of Starling's law 30 years ago. The documented evidence on capillary structure and function demonstrating that oncotic pressure does not exist in VIVO is summarized here and detailed elsewhere [1,3]. In 1967, Rhodin [4] showed that the capillary tube is encircled by a cuff of smooth muscle fibres at its arteriolar junction, named the pre-capillary sphincter

(3-5 micro meter), which is the narrowest part of the whole vascular system. Also in 1967, Karnovsky [5] showed that the capillary wall is made of flat cells and their intercellular junctions are slits 10 to 20 nm wide that are the pores through which fluids, nutrients and protein molecules pass freely. His photographs show the stained horse radish globules, which are much larger than plasma protein molecules, passing freely through these pores. This fact alone nullifies the oncotic pressure of albumen across the capillary membrane.

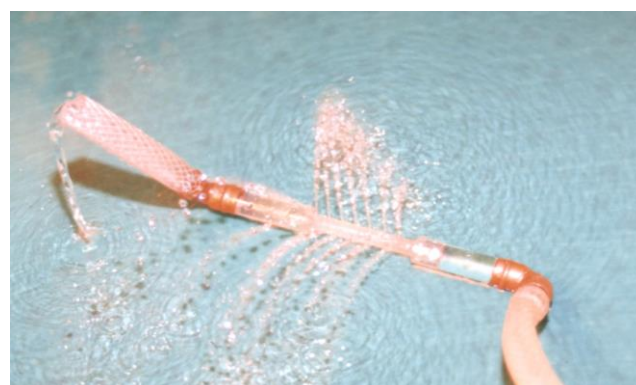
In 1962, Hendry [6] measured the oncotic pressure of various body fluids and found it identical to that of the plasma, pointing out: 'the osmotic pressure of plasma proteins is too weak and too slow a force to return fluids back into the capillary lumen'. In 1963, Guyton and Colman [7] measured ISF tissue pressure, using an implanted perforated capsule, and found that ISF space to have a negative pressure of -7 cm water. In 1972, Calnan et al [8] confirmed this finding and showed that molecules, including plasma proteins, pass freely and rapidly between the capillary blood and the implanted capsule, and vice versa. In 1982, Keele, Neil and Joels [9], summarized evidence that: "The concentration of tissue proteins in the liver, lung and muscles is 60% that of plasma proteins. In the pulmonary circulation the arterial pressure is less than the plasma oncotic pressure! Thus fluid filtration in the lungs and re-absorption in the liver and muscles lacks explanation." The oncotic pressure neither can explain the negative pressure in ISF space [7] nor the speed and efficiency with which the capillary-ISF fluid, nutrients and oxygen transfer occurs. Lymph drainage cannot explain the negative ISF pressure [7,8].

The above findings came 70 years after Starling's hypothesis that have cancelled the absorption force of the equation. After all, plasma proteins' main function, like blood glucose, must be a nutrient material for the cells, how does it reach cells? In 1983, Mattfeldt and Mall [10] reported the ultra-structure dimensions of capillaries. The 'ideal' capillary is a tube connecting an arteriole to a venule. According to Crogh's model it is a perfect, anisotropic, straight and un-branched tube with a diameter of 7-18 micro m. The pre-capillary sphincter and intercellular slits make the capillary a strait 'porous orifice tube', based on which the G tube was made on a larger scale. This knowledge on capillary ultra-structure and permeability to macromolecules, prompted Renkin [11] in (1986) to call for reconsideration of Starling's hypothesis but an alternative hypothesis did not exist yet. At this time a mechanism that paves the way to a new hypothesis on capillary-ISF circulation was evolving at my kitchen in Eastbourne, UK.

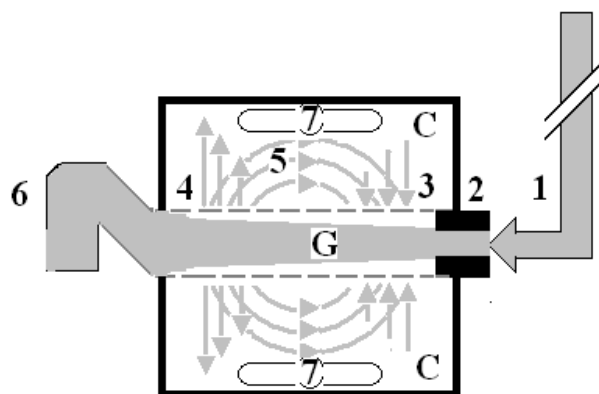
I investigated the main force in Starling's law i.e. the capillary pressure presumed to induce filtration! The hydrodynamics of a porous orifice (G) tube made on a large scale to mimic a capillary was studied. It behaved totally different from Poiseuille's tube particularly when surrounded by chamber (C) mimicking ISF space and incorporated in a circulatory model with proximal (PP) and distal pressure (DP) mimicking arterial and venous pressures, respectively. I discovered that PP akin to arterial pressure induces a fluid jet inside the G tube lumen induced by the orifice that causes suction not filtration (Figures 1-5)! The suction effect has a side pressure (SP) gradient on the wall of the G tube, maximally negative near inlet and turns positive near the exit (Figure 1,2). Increasing PP increases the suction of SP. This is consistent with the clinical fact that arterial hypertension never causes oedema. The distal pressure (DP) in the G tube augments filtration, increasing DP increases filtration occurring maximally at distal part near the exit of the G tube. The SP of the G tube creates a net negative pressure in chamber C (Figure 4). This is supported by the clinical fact that mild increase in venous pressure causes oedema. My experiments on a circulatory model with PP akin to arterial pressure and a DP akin to venous pressure demonstrated new hydrodynamic phenomenon that provides for the first time an alternative hypothesis explaining the capillary-ISF circulation (Figures 3).



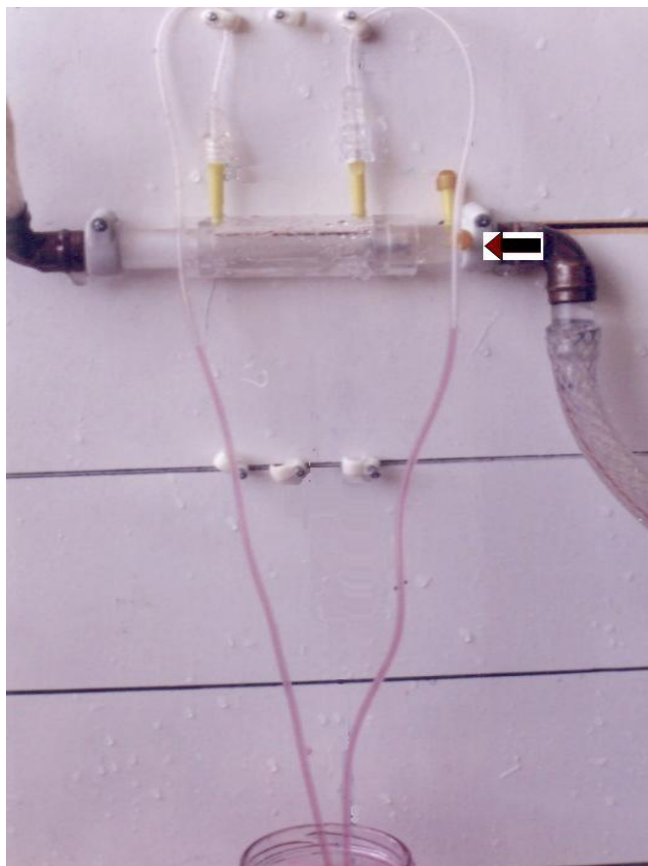
**Figure 1:** Perpendicular needles inserted into a rubber orifice tube at 10, 20 and 30 mm distance from the orifice, with bevels facing downstream, demonstrate the negative energy SP gradient along the proximal part of the tube by the sucked columns of fluids in manometer tubes from a jar 300 mm below the tube.



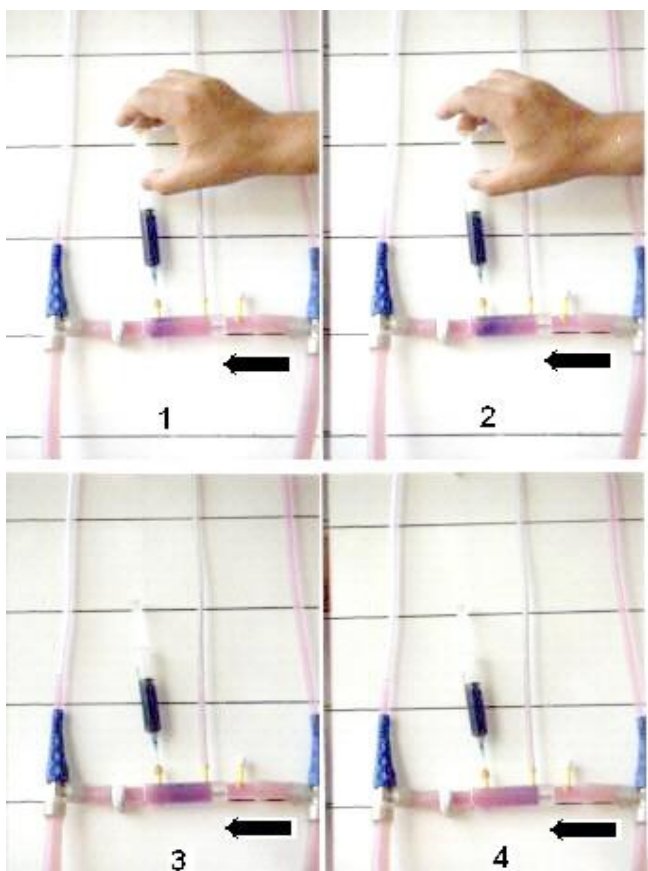
**Figure 2:** Shows fluid flowing out autonomously through distally situated side holes of a porous orifice (G) tube where SP is positive gradient. Air suction occurs through side holes of the proximal part, as shown in Figure 1, but is not seen here. The fluid around the G tube has magnetic field shape shown above the G tube and in (Figure 3).



**Figure 3:** Shows diagram of the porous orifice (G) tube enclosed in chamber (C) based on several photographs demonstrating the magnetic field-like G-C circulation phenomenon. The proximal inflow (arterial) pressure (1) pushes fluid through the orifice (2) creating fluid jet in the lumen of the G tube. The fluid jet creates negative side pressure gradient causing suction maximal over the proximal half of the G tube near the inlet (3) that sucks fluid into lumen. The side pressure gradient turns positive pushing fluid out of lumen over the distal half maximally near the outlet (4). Thus the fluid around G tube inside C moves in magnetic field-like fluid circulation (5) taking an opposite direction to lumen flow of G. tube. The inflow (arterial) pressure (1) and orifice (2) induce the negative side pressure energy creating the dynamic G-C circulation phenomenon that is rapid, autonomous and efficient in moving fluid out from the G tube lumen at (4), irrigating C at (5), then sucking it back again at (3), maintaining net negative energy pressure (7) inside C. The distal outflow (venous) pressure (6) enhances outflow at (4) and its elevation may turn the negative energy pressure (7) inside C into positive, increasing volume and pressure inside C chamber.



**Figure 4:** The net negative pressure of a closed chamber (CP) surrounding the G tube, is demonstrated by the sucked fluid in two vertical manometer tubes from a jar 300 mm below.



**Figure 5:** Shows Injecting ink into the surrounding chamber near the exit of the G tube moves in an opposite direction to the G tube flow (arrow) and gets absorbed near the inlet. Note that the ink clears up by absorption very fast after ceasing the injection.

The hydrodynamic phenomenon of fluid moving between the G tube lumen and surrounding chamber C is rapid autonomous G–C circulation of magnetic field-like shape and behaviour (Figures 2,3). The G–C circulation is so fast in mixing fluid inside the G tube and chamber C that it cleared any injected ink into chamber C as soon as the injection ceased (Figure 5). Fluid and particles move freely between the G tube lumen and chamber C, limited only by pore diameter and flow kinetics. Reproducible results were obtained in hundreds of experiments done under steady PP head and using a circulatory system model (Figure 5). The physiological and clinical relevance of results are discussed with reference to its physiological equivalents outlined in the reviewed literature as well as known pathological conditions and mentioned clinical observations [12,13]. The given data will help concerned groups to resolve problems of physiological and clinical fundamental importance that clinicians have to face in treating shock and resuscitating critically ill patients'. This will no doubt resolve the puzzles of MVOD/F syndrome and ARDS [12-14].

**Competing interests:** No competing interests

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