Research Article

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Supplementary Information (SI) 1

The reviewer wrote the following criticisms that have been proved most constructive and useful allowing editing of the article as reported subsequently in 2 articles [13,14]. These email letters were sent to the anonymous reviewer via anonymous Editor. Because I believed the reviewer's input through his/her comments, remarks and criticisms had a remarkable impact on improving the article bringing it to new heights qualifies him/her to join me as co-author. The last 3rd email sent on 7 February 2020 is quoted here.

"Sir,

I am writing to you again to express my sincere thanks to you and your reviewer for his most helpful criticisms of my article. I have taken it all into consideration and have amended the article accordingly. I thought of writing to you first as I wish to acknowledge the reviewer's help in the article. In fact, I would be delighted and honoured if he/she would accept my invitation to co-author the article with me. His input is more than adequate to qualify him/her for that. If he agrees, I will consider him as my best knowledgeable friend on the subject that I have known so far. If he declined my invitation, I wish to get his consent to make a thank you acknowledgment in the article. If he wishes to remain anonymous, would you ask him to agree to use his criticism and my reply to it in an appendix to future article?

Please respond to this email as soon as possible. Kind regards."

No Reply.

The reviewer's comments are:

"Comments to the Author (were written on the old version of the articles [13,14]):

Reviewer:

1. Comments to the Author

I have major concerns with this paper, even though the ideas behind it are interesting. This paper has an unusual format as it complies different levels of investigations, it has not a clear objective and it quoted references coming from a single author, the one of the present papers himself. This is not fair.

The author claims that he based his present paper on a literature search, but it is not the case. Apart from the initial report by Ashbaugh et al on the original description of ARDS, none of the major references on ARDS released over the years are quoted, like the trials conducted by ARDS network (the FACCT trial NEJM 2006 is relevant for present purpose), the Lung Safe Study, and these are only a few examples.

The warning on the risk of excess in fluid resuscitation is well recognized by the intensivists and is not overlooked. You may look at the ESICM recommendations of the Acute Kidney Injury section published in ICM June 2017 for instance. From the classic experiment by Norman Staub, we already know that once the alveolar-to-capillary membrane is injured the critical left atrial pressure above which an increase in fluid flux across the membrane and the rate of lymph flux goes up is lower than it would be in an intact membrane.

A landmark paper has not been quoted by the author, the one by River et al (NEJM 2001). In this paper the authors launched the concept of early goal directed therapy (EGDT) and found a beneficial in-patient outcome by following targets for fluid resuscitation based on mean arterial pressure, central venous pressure, hourly diuresis, and oxygen saturation in the superior vena cava which was monitored as used as a target (more than 70%) in the experimental group and not used in the control group. With this protocol patients received indeed a large amount of fluid, 13 liters over 3 days, in each group. The mortality was reduced in the experimental group which was given more fluid over the first 6 hours.

This result was not confirmed in 3 further large trials (Arise, Process, and Promise) published in the NEJM. Angus made an individual patient meta-analysis (NEJM 2017) and found no significant effect of early goal directed therapy. A study done in Africa tested over 3000 children with severe infection 3 strategies: no fluid bolus therapy (FBT), albumin bolus and saline bolus as fluid resuscitation (NEJM 2011 Maitland et al). The mortality was lower without any bolus. All these fundamental studies are not quoted and underlined the fact that indeed the concern of fluid resuscitation with its benefit and risk are well known by the intensivists. Not discussed is the role of the nature (Type) of the solutes beyond their total amount given. There is an astonishing amount of literature about that with a big controversy between crystalloids and colloids that generated dozens of original studies, meta-analysis, and reviews. None is quoted.

The Starling law of fluid flux across capillaries in humans has been largely questioned, and new concepts introduced recently. See for instance Alphonsus Anesthesia 2014, Woodcock BJA 2012, Jacob Current Opinion in Crit Care 2013 and many others. None of them are quoted in present paper. Another major concern I have is an ethical one regarding the clinical study. The author does not mention anything about the protocol, its registration to an official platform like clinicaltrials.gov (it is a clinical trial), whether it has been approved by an ethical committee, whether the patients or their next of kin gave informed consent to participate. The reading

of this part gives the impression that this trial has been done without any agreement to participate from the patients or the next of kin. The power of the study is not indicated. Allocating only 5 subjects per group makes a priori no sense. The statistical analysis is not detailed. Regarding the experiment with the (G) tube, which is interesting, it is given without any detail that would make the reviewer more comfortable to understand the point. The overall impression is that the author would like to make a sort of summary of what he did previously in this field. The appropriate way would be to write down a comprehensive review article and going through the overall literature.".

Minor comments

In the Abstract, Abbreviations are not defined: VOS, ARDS, TURP; In the sentence "among whom 10 developed TURP syndrome" you mean developed ARDS? The same goes for the next sentence."

Corresponding Author's reply:

Thank you very much indeed again, sir, for your comments and criticism of a previous version of the article reported later as [13,14]. You would be pleased to know that we have taken all your comments and criticisms into consideration and responded to it positively. Thanks to you it has brought the article into new heights that have made 2 new articles out of one that are suitably acceptable by the editor and reviewers of other journals [13,14]. The changes that have been made and added to the old version of the article are as follows: An up-to-date literature search on ARDS and fluid therapy using PubMed was done and used in the new discussions [13,14]. The issue on heterogeneity of the report evidence is discussed and justified. Why quote me so often? Simply because we could not find any other references that say the same on a discussed issue. The self-references are not listed in PubMed and we wish fellow authors, researchers, and physician to know about it. We sincerely tried to be fair as much as we could as discussed in the article.

2. All the references you mentioned above, and more, have been brought from PubMed and NEJM web site and other journals as necessary were downloaded into the Laptop for later reading and critical analytical review of the literature as shown above in the discussion section under the title: " Updated analytical review of the literature"; quoting the newly updated references [38-55]. Only one reference you brought into our attention that was most enjoyable to read, the lecture by Norman Staub, Am J Physiol Lung Cell Mol Physiol. 2002; 283: L683–L687 is held for a later second reading and future use as reference. The letter by Woodcock BJA 2012 on (No more colloid trials!) is very interesting, as was Jacob Current Opinion in Crit Care 2013 that concerns the albumin versus saline argument which is not discussed in our article for reasons explained in the discussion above. Jacob is referred to in Reference [3] and Alphonsus in Anesthesia 2014 is listed as reference [42]. All the multi-center trials on ARDS have been mentioned.

3. We agree with you. This point has been adequately discussed in the new articles [13,14].

4. Fully discussed in the new articles. We disagree on your last sentence. Again, see the new articles.

5. The results of major Trials on ARDS have been discussed above.

6. We also discus FBT and agree on what you say. We have gone beyond that to identify the role of FBT in inducing ARDS in new discussion. Albumin v saline, no more of that thank you. Your last sentence? not quite so yet, see new discussion!

7. Mentioned to be dismissed!

Starling is major issue discussed in the new articles.

All have been used and quoted. Thank you. Regarding the protocol, its registration to an official platform like clinicaltrials.gov (it is a clinical trial), whether it has been approved by an ethical committee? The internet did not reach personal computers in1984 when I bought my Apple® Macintosh® then before the study was done 19851986. There was no internet or clinicaltrials.gov. at the time. The 35-years old Apple® Macintosh® which remains under my bed does not have internet connection and cannot communicate now. The informed consent was obtained. Please see the new sections on Ethics and Statistics of the article [13]. It discusses all your concerns– 12. These issues we agree about and have been mentioned in detail in article [13,14].

The power of the study is not indicated. Please see the newly added section on statistics and limitation of the study [13]. Of the 3 statisticians consulted at the time of the study none asked for this at the time; one was seen before and one 10. Please see the new section: Limitation of the study. As you see from the newly added section on ethics and statistics your suggestions have been implemented. The study was approved by the Medical Ethical Committee of Eastbourne Health Authority, UK. The authority awarded Mr. JP Ward, FRCS my co-author on the article [4], and I, The Princes Alice Memorial Award 1988. A new section on ethics and consent for the prospective cohort study is added under the result section of this article. Also added is a detailed section on statistics. I saw 3 statisticians; one before the start of the trail from London, U.K. to see me. The second was seen after the study and the third was BUJ Int. Journal' statistician. None of them raised this issue on the statistical power. If it is something that is essential and retrievable from the trial data, it may justify a visit to the 35-years old Macintosh under the bed.

Allocating only 5 subjects per group makes a priori no sense. The Stat View® statistical package program on the 35-years old Apple® Macintosh® detected a significant statistical difference between the conservative and HST groups randomized 5 patients for each group. The newly added figures and tables that illustrate and compare the

therapy of the two groups of 5 patients each, were randomized on 1:1 basis. The statistical analysis is not detailed. Please see the newly added section Statistics under results [13]. Please also see the newly added (Tables 2 &3) presenting the multisystem and organ dysfunction that account for the clinical picture of MODS and of the TURP patients. The biochemical abnormalities immediately after surgery and 24 hour later that characterize TURP syndrome but not ARDS is shown in the newly added figures. The immediate postoperative figures and data demonstrate HN that characterize the TURP syndrome. The 24 hours changes show the renal and hepatic dysfunctions of the condition as well as the hematological and increase in white cell count in the absence of sepsis plus the new discussion on MODS in ARDS.

Regarding the G tube I gave the conclusion and diagram that demonstrate the proximal, akin to arterial, pressure causes suction not filtration as proposed by Starling. I added some text in the discussion to illustrate how we believe this is relevant to the CVS hemodynamic induced by the precapillary sphincter. The physics and physiological references on evidence are quoted for further reading [the new presented article here] to feel more comfortable about it. Other articles, [7-11] further address this issue. I agree. However, after implementing all your concerns I ended up with ridiculously too long article even without a comprehensive review! That must be another article on the comprehensive review that is something I may do in future perhaps in collaboration with you.

Please see the new abstract no more undefined abbreviations. See also the discussion that reveals a new link of the TURP Syndrome with ARDS. Please see the discussed analytical review achieves the objectives of this article as it shows in its title, key points and abstract of: VOS causes ARDS [13,14]. These changes made to the article ridiculously too long but do demonstrate that we have been fair to everyone, of the previous researchers as much as we can and as much as we would like others of Editor, reviewers, and peers to be fair to us. I KEPT YOUR NAME ANONYMOUS FOR NOW, though I have one guess on who you are I am not revealing it. You are now reading my articles as I am reading your contributions and I believe that we could make a powerful team collaborating on future co-authoring of articles of mutual interest, starting with an updated review perhaps on VOS and ARDS.

I look forward to knowing who you for sure soon. Finally, your input sets a standard for fellow peer reviewers to follow and is most appreciated.

Kind regards.

Dr, Ahmed N. Ghanem, MD (Urol.), FRCS Ed.

Supplementary Information (SI) 2

Hydrodynamic of the G tube

I investigated the hydrodynamics of the porous orifice (G) tube built on a scale to the capillary ultrastructure with its precapillary sphincter [18] and wide intercellular cleft pores [19] that allow the passage of plasma proteins. The hydrodynamics of Poiseuille's tube were also investigated and contrasted to the hydrodynamics of the G tube. The side pressure (SP) in Poiseuille's tube exerted on its wall is an all positive pressure gradient causing filtration all along the tube, maximum near the inlet and minimum near the exit as already well known (Figure 1) but reported here for comparison with G tube dynamics (Figure 2). In contrast, the SP of the G tube creates negative side pressure gradient along the G tube that is maximum negative near the inlet and turns gradually positive to become maximum positive near the exit (Figure 2).

A full set of G tubes and G-C apparatus is shown in (Figure 3). Thus, in the G tube suction or absorption of fluid occur through side holes maximum near the inlet (Figure 4) while filtration occur through holes higher near the exit (Figure 2&5). This creates autonomous rapid dynamic magnetic field-like fluid circulation between fluid around the G tube in a surrounding chamber (C) and fluid inside the lumen of the G tube (Figure 2&5). The negative SP of the G tube creates net negative pressure in the surrounding chamber (C) around the G tube (Figures 5-7), akin to the pressure in the interstitial fluid (ISF) space that is also negative of -7 cm water [20].

The direction of flow in chamber C is in the opposite direction to the flow inside the G tube and has a magnetic field-like pattern of flow (Figures 2&5). It is clear from the above that Starling did not know the following facts when he proposed his hypothesis for the capillary-ISF transfer and the formation of oedema at the Lancet in 1886 [21] and 10 years later at J Physiol. in 1896 [22]:

The hydrostatic pressure that is of a stagnant fluid is different from the dynamic pressure of fluid in motion. The lumen pressure of moving fluid inside any tube such as Poiseuille's and G tube has 2 dynamic pressure components at any one point- unlike the hydrostatic pressure of a stagnant fluid which has only one value. The 2 dynamic pressure components are:

Flow pressure (FP) in the direction of flow that is high positive in both Poiseuille's and G tubes and is responsible for the flow. FP has a descending gradient along the tube.

Side pressure (SP) exerted on the tube's wall that is positive but lower than FP in Poiseuille's tub**e**.**

**This SP is negative pressure gradient in the G tube that is maximum negative near the inlet and turns positive maximum near the exit. A full set of G tubes and a G-C apparatus, curtesy of designer engineer Mr Peter Holder of Eastbourne UK, are shown in (Figure 3).

The negative SP of G tube is demonstrated in (Figures 4&5). This SP creates net negative pressure in a chamber C surrounding the G tube as shown in (Figures 5-7). Also, Starling when he proposed his hypothesis of fluid filtration by the hydrostatic pressure of the capillary and absorption by the oncotic pressure of plasma proteins did not know about the precapillary sphincter [18] and the wide pores of normal capillaries that is made of intercellular clefts [19] that allow the passage of plasma proteins- hence oncotic pressure does not exist in vivo. These capillary ultra-structures were discovered >80 years after Starling's report. Both discoveries were reported in 1967 >80 YEARS after Starling's hypothesis reported in 1886 and 1896 [21,22]. The G tube was purposefully built on these ultra-structures of the capillary tube to investigate and contrast with Poiseuille's tube. The investigations ware done and concluded during 1981-1983 at Eastbourne, in the U.K. A full set of G tubes and a G-C apparatus, curtesy of designer engineer Mr. Peter Holder of Eastbourne UK, are shown in (Figure 3). Factors which induce and affect SP and CP are the orifice diameter (Figures 8 & 9), the proximal pressure [PP] (Figure 10) and the distal pressure (DP) (Figure 11).

The relation of orifice diameter to SP and CP is an inverted bell-shaped (Figure 9) with maximum negativity at an orifice of 5 mm of the G tube's diameter of 7 mm (i.e., a ratio of 0.7) that is the equivalent of 0.5 of cross section area when maximum suction occurs, and a most efficient and speedy G-C circulation operates. An increase in PP augments suction and increases the negativity of SP and CP and the speed and efficiency of the G-C circulation (Figure 10). Please note that the negative SP and CP occur at low PP as low as 24 cm water (Figure 10&16). This pressure is lower than that of the capillary pressure measured by Landis [20] at the arterial end of the capillary of 32 mmHg. An increase in DP increases volume in chamber C and reverted CP from negative to positive (Figure 11).

The increased volume in C is akin to ISF oedema formation. An increase in DP has similar effect to a drop or decrease in PP, not an increase. The direction of fluid flow in chamber C is in the opposite direction to flow inside the G tube (Figure 5&12).

Hydrodynamic of the G tube in a circulatory model

The hydrodynamic of the G-C apparatus connected to a circulatory system is shown in (Figures 13&14) and contrasted to the circulatory hydrodynamic of Poiseuille's tube (Figure 15). A negative SP gradient of the G tube reflected on chamber C pressure causing net negative chamber pressure (CP) in C (Figures 5-7). The direction of fluid flow in chamber C is in the opposite direction to flow inside the G tube and circulatory model (Figure 12). The negative SP gradient of the G tube connected to a circulatory model (Figures 16). is the same as G tube isolated as shown in (Figure 2). It has maximum negative pressure near the inlet where suction or

absorption occurs (Figure 4), and maximum positive pressure near the exit of the G tube where filtration occurs (Figure 2,5,16).

Adding tea leaves of fine size that crosses the wall holes of the G tube, and coarse size that does not, shows that both types of tea leaf particles are concentrated at the centre of the G tube's jet in a G-C apparatus in circulatory model maintaining higher concentrations inside the circulatory system than in the surrounding chamber C (Figure 5). On passing through the G tube, the tea leaves concentrate inside the cone shaped fluid jet leaving a free zone lining the G tube's wall mimicking the plasma protein molecules, platelets, and red blood cells (RBCs) speed in the capillaries of the cardiovascular circulatory system. Fine leaves enter chamber C in a small amount through holes near the distal end of the G tube, governed only by fluid flow kinetics in the G tube as in the capillary. This is represented by the cone shaped fluid jet inside the G tube shown in the diagram in (Figure 5). This mimics the protein-free and erythrocytes-free layer zone next to the glycocalyx membrane that lines the capillary endothelium. Any excess fluid, big particles, and fat globules in the ISF space is off course drained by the lymphatics or manually cleaned up in the G-C apparatus.

It was also observed, though not measured, that the speed of tea leaves passing through the G tube is FASTER than that in the proximal tube of the circulatory system shown in (Figures 13&14). Please keep that in mind on discussing the capillary blood speed (CBS) or the red blood cells (RBCs) speed in the capillary as compared to the aorta later. In Poiseuille's tube SP is positive all along the tube that is maximal near the inlet (proximal pressure is akin to arterial pressure) and lower near the exit that is distal pressure (akin to venous pressure) inducing net positive pressure inside the surrounding chamber C as shown in the middle two manometers in the middle of (Figure 15). The direction of flow in chamber C around Poiseuille's tube is down the pressure gradient that is the same direction as fluid flow inside the tube and the circulatory system.

The dynamic FP and SP of both the G tube and Poiseuille's tube were measured as shown in (Figure 17) and represented graphically in (Figure 18). These figures' data affirm that the lumen pressure of a dynamic fluid has two pressure components inside both the G tube and Poiseuille's tube: FP and SP. Measuring the FP in a tube by a cannula facing upstream that totally obstruct the tube's lumen represent the high positive hydrostatic pressure, called the MEASURED hydrostatic pressure (MHP) like that measured by Landis at the arterial end of the capillary [23]. It represents FP but does not show SP at all. So, the measured hydrostatic pressure (MHP) does not show the negative SP at all neither in the G tube nor in Poiseuille's tube. This is important for the coming discussion on defining and precising the meaning of P and ΔP used in the equations of Poiseuille's law and Bernoulli's equation.

Factors which induce and affect SP and CP are the orifice diameter (Figures 8 and 9), the proximal pressure (PP) (Figure 10) and the distal pressure (DP) (Figure 11). The relation of orifice diameter to SP and CP is an inverted bell-shaped with maximum negativity at an orifice of 5mm that is 0.7 of the G tube's diameter of 7 mm that is the equivalent of 0.5 of cross section area when maximum suction occurs, and a most efficient and speedy G-C circulation operates- this is akin to the resting tone and diameter of the precapillary sphincter. An increase in PP augments suction and increases the negativity of SP and CP and the speed and efficiency of the G-C circulation (Figure 10). An increase in DP increases volume in chamber C and reverted CP from negative to positive (Figure 11). The increased fluid volume in C is akin to ISF oedema formation. An increase in DP has similar effect to a drop or decrease in PP, not an increase. This is important issue based on which the report by Pappenheimer and Soto-Rivera [24] is criticized later. The direction of fluid flow in chamber C is in the opposite direction to flow inside the G tube (Figure 5&12). The G tube inside G-C apparatus in a circulatory model (Figure 16) acts the same as when isolated (Figure 2).