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The New Scientific Foundation of Fluid Therapy in Shock Management

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1. Abstract

Intravenous fluids are commonly prescribed, but uncertainty remains about how to assess when fluids are required and how much to give [1]. Two recent guidelines have acknowledged a limited evidence base to guide fluid assessment. A recommended means to assess hypovolaemia includes assessment of fluid responsiveness. Fluid responsiveness is a rise in stroke volume following an increase in preload, achieved using a fluid challenge or a passive leg raise. However, the means of defining fluid responsiveness and its ability to identify patients who would benefit from fluid resuscitation is currently unclear.

In acute medical scenarios such as shock, the benefits are less well documented [2], although fluid therapy is highly recommended in many guidelines and reviews, for example in a recent review which stated that 'fluid therapy…is an essential part of the treatment of any form of shock' [3,4] Acute kidney injury guidelines advise that we should identify and correct hypovolaemia through 'adequate' fluid replacement [4,5] and international sepsis guidelines state that the use of IV fluid 'is a cornerstone of modern therapy' [5,6] Despite this, evidence to describe the indications, dose and rate of administration of IV fluid is lacking. The objective of fluid therapy is to restore the circulatory haemodynamic disturbances of shock, particularly at the capillary-interstitial fluid (ISF) level. Medical practitioners currently rely on their clinical acumen alone to guide prescribing practices of fluid therapy in shock management. Lurking deep inside their thought are one wrong physiological law, 2 misconceptions on capillary haemodynamic and one misconception on circulatory haemodynamic. The latter concerns the volume pressure relationship of the cardiovascular system that is incorrectly believed to have a proportional relationship in an indefinite straight line. However, during shock management once hypervolaemia occurs, an irreversible hypotension sets in. The other errors concerning The wrong Starling's law and the 2 misconceptions on capillary haemodynamic are briefly summarised.

2. Introduction

The current scientific foundation of fluid therapy: Does any evidence-based exist?

Intravenous fluids are commonly prescribed, but uncertainty remains about how to assess when fluids are required and how much to give [1]. Two recent guidelines have acknowledged a limited evidence base to guide fluid assessment. A recommended means to assess hypovolaemia includes assessment of fluid responsiveness. Fluid responsiveness is a rise in stroke volume following an increase in preload, achieved using a fluid challenge or a passive leg raise. However, the means of defining fluid responsiveness and its ability to identify patients who would benefit from fluid resus-

citation is currently unclear.

'Medicine is a science of uncertainty and an art of probability.' Sir William Osler (1849–1919).

Intravenous (IV) fluid use in some resuscitation scenarios, such as traumatic blood loss, is well evidenced. In acute medical scenarios such as shock, the benefits are less well documented [2], although fluid therapy is highly recommended in many guidelines and reviews, for example in a recent review which stated that 'fluid therapy…is an essential part of the treatment of any form of shock' [3]. Acute kidney injury guidelines advise that we should identify and correct hypovolaemia through 'adequate' fluid replacement [4], and international sepsis guidelines state that the use of IV fluid 'is a cornerstone of modern therapy' [5]. Despite this, evidence to describe the indications, dose and rate of administration of IV fluid is lacking, as is the use of IV fluid over the course of a patient's illness. Medical practitioners currently rely on their clinical acumen alone to guide prescribing practices, akin to the 'science of uncertainty and art of probability' described by Sir William Osler in the past century.

Common practice is to use the clinical features of hypovolaemia and hypervolaemia to signal when treatment should be started and stopped. Such features are well described; however, none are specific to volume status8 and many are not easy to assess. A recent systematic review of 30 studies found that clinical features (including hypotension and tachycardia) were not reliable predictors of hypovolaemia. The same is true of features of hypervolaemia, which are present in many conditions. Even if it could be diagnosed accurately, hypervolaemia due to excess fluid is an iatrogenic overdose and should not be used as a marker to stop fluid administration. In support of this, a recent trial in Zambia randomised hypotensive, septic adults to a usual care group (IV fluid determined by the treating clinician) or a sepsis protocol (aggressive IV fluid limited only by clinical signs of hypervolaemia, alongside vasopressors and blood transfusion when indicated) [6]. 11 Use of the sepsis protocol led to a significant increase in in-hospital mortality (48.1%) compared to usual care (33.0%) [7].

The Surviving Sepsis Campaign (SSC) took a prescriptive approach to fluid use in sepsis, advising a fixed dose once septic shock is identified [5]. It 'strongly' recommends 30 mL/kg of IV fluid within 3 hours in patients who meet the criteria for septic shock (hypotension or lactate ≥4 mmol/L). Despite this advice, the guideline acknowledges the evidence for their recommendation is weak, noting 'there is little available evidence from RCTs to support its [IV fluid] practice'.

The recommendation is based on the results of a single-centre, unblinded trial involving 263 septic patients [8] .26 It found a 16% mortality reduction when an 'early goal-directed therapy' (EGDT) protocol was used in place of usual care. However, three subsequent huge prospective trials, involving a combined total of 4,175 patients, found no benefit of EGDT compared to usual care [9-11]. Furthermore, a retrospective cohort study found that 67% of patients had evidence of fluid overload at 24 hours when EGDT recommendations were followed, with a corresponding 92% increased risk of mortality [12].

If initial fluid resuscitation is followed by ongoing hypotension or hyperlactataemia, the SSC guideline recommends the use of physiological variables to determine the need for additional IV fluid [5]. Recommended variables include central venous pressure (CVP), central venous oxygen saturation (ScvO2), bedside echocardiography and a dynamic assessment of fluid responsiveness. However, these variables measure different physiological processes. A rise in CVP can be a marker of fluid excess in the venous compartment. Central venous pressure and pulmonary artery occlusion pressure should be avoided.

ScvO2 is a surrogate for the balance between oxygen delivery and consumption. Echocardiography allows the measurement of cardiac contractility and can estimate venous pressures. Fluid responsiveness describes an increase in cardiac performance following a fluid bolus. There is no recommendation on which assessment tool to use or whether combining these variables may help determine fluid status. Furthermore, many of these variables would be challenging to measure in an acute medical setting.

The latest National Institute for Health and Care Excellence (NICE) guideline for the recognition, assessment and early management of sepsis adopted a more conservative use of IV fluid in sepsis [13]. 31 It advocated up to 1000 mL of IV fluid, if indicated, before senior involvement. To determine whether IV fluid was indicated, it recommended the use of the 2013 NICE guideline for IV fluid use in adults, which included guidance to identify hypovolaemia defined simply as a reduced circulating volume [13]. 14 The diagnostic ability of the parameters within this guidance is questionable. The National Early Warning Score (NEWS) is the recommended early warning score in the UK to identify acutely unwell patients. The guideline acknowledges the evidence for their recommendation is weak, noting 'there is little available evidence from RCTs to support its [IV fluid] practice'.

No consensus exists regarding the type, rate and amount of fluid that should be used. A recent systematic review of 71 studies explored how a fluid challenge has been defined with 75% of studies using 500 mL of fluid and 62% using colloids [14]. 43 More recently, 'mini-fluid challenges' of 100 mL have been shown to predict the effects of larger fluid challenges [15]. 44 The rate of fluid also varied widely between 5 and 90 minutes per bolus, with 45% of studies giving fluid over 30 minutes. We still do not know when to give fluids (or when to withhold them), how much to give or how to accurately assess the response, especially in our ageing, multimorbid and poly-medicated patients. Building an evidence base to help clinicians use IV fluid appropriately is essential. While

there is awareness of the complications of IV fluid therapy, there is a limited understanding of the incidence of these complications and their impact on outcomes. The need to improve our understanding of the harms related to IV fluid has been acknowledged by the NICE guideline and forms a key research recommendation [13,14].

Summary: The evidence to support when and how to prescribe fluids is limited. Therefore, robust, evidence-based recommendations for the use of fluid resuscitation by the acute physician are not currently possible. Instead, there are a high number of review articles and educational pieces which rely upon expert opinion and usual practice. Such paucity of data is hard to justify in our era of evidence-based practice and there is a clear need for more research to guide how fluid resuscitation should be used in the acutely ill patient.

The new scientific foundation of fluid therapy: The future research starts here and now.

The objective of fluid therapy is to restore the circulatory haemodynamic disturbances of shock, particularly at the capillary-interstitial fluid (ISF) level. Medical practitioners currently rely on their clinical acumen alone to guide prescribing practices of fluid therapy in shock management. Lurking deep inside their thought are one wrong physiological law, 2 misconceptions on capillary haemodynamic and one misconception on circulatory haemodynamic. The latter concerns the volume pressure relationship of the cardiovascular system that is incorrectly believed to have a proportional relationship in an indefinite straight line. However, during shock management once hypervolaemia occurs, an irreversible hypotension sets in. The other errors concerning The wrong Starling's law and the 2 misconceptions on capillary haemodynamic are briefly summarised here having been reported in whole book [16].

Error 1: The wrong Starling's law

Starling's law has proved wrong on both of its forces [17-23] However, it continues to dictate the current faulty rules on fluid therapy in the management of shock. It thus misleads physicians into giving too much fluid during shock resuscitation [24]. More than 21 reasons were reported to show that Starling's law is wrong [25]. The correct replacement is the hydrodynamic of the porous orifice (G) tube [17] (Figure 1 and 2) that was built on capillary ultrastructure anatomy of having precapillary sphincter [26] and a porous wall [27] that allow the passage of plasma proteins-hence nullify the oncotic pressure in Vivo. It follows that the extended Starling Principle is wrong and a misnomer [23] and all the equations are also wrong.

Substantial evidence currently exists to demonstrate that Starling's law is wrong [17-23], the revised Starling Principle is a misnomer [23] and all the formulae that goes with it are also wrong. Commonly received but erroneous concepts and laws represent fraud in modern science. Starling's law for the capillary-interstitial fluid (ISF) transfer is a famous example. Persistent to defend such erroneous concepts is a futile attempt to defend fraudulent science.

Starling reported his hypothesis in 3 articles in the Lancet in 1886 [28] and a fourth in J Physiology in 1896 [29]. He proposed that fluid exchange across the capillary wall is dependent upon the balance between two main opposing forces: The hydrostatic pressure pushing fluid out and the oncotic pressure withdrawing fluid into the capillary lumen. The capillary hydrostatic pressure is a function of the arterial pressure and is higher near the capillary inlet that pushes fluid out over the proximal part as based on Poiseuille's work on a strait, uniform brass tubes. The oncotic pressure of plasma proteins becomes higher near the capillary exit and sucks fluid in over the distal part. In fairness to professor Starling, he nether proposed a law nor equation for his hypothesis. Starling's hypothesis became a law later with equation after the report by Pappenheimer and Soto-Rivera in (1948) [30] as shown below. The discovery of the hydrodynamic of the porous orifice (G) tube has not only proved and validated that Starling's law is wrong but has also provided the correct alternative mechanism for the capillary-Interstitial fluid transfer (More on this issue below).

Error 2: A significant error in the study that transferred Starling's hypothesis into a law

Starling's hypothesis became a law later with equation after the report by Pappenheimer and Soto-Rivera in (1948) [30]. A serious experimental error by these authors is identified and reported here. 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 has proved wrong, based on evidence from clinical practice: Elevating venous pressure (distal pressure (DP)) augments capillary filtration causing oedema formation as well known in clinical practice while elevating proximal pressure (PP) akin to arterial pressure does not, it enhances suction or absorption via the negative side pressure (SP) maximum near the inlet as demonstrated in the porous orifice (G) tube (Figure 1 and 2), and chamber C around it (Figure 3 & 4).

In support of the above fact is: High venous pressure, or obstruction, is the main cause of the most common clinical oedema but arterial hypertension though quite common it never causes oedema. Of course, neither Starling nor any of the authors who transferred his hypothesis into a law were aware of the brilliant discoveries of precapillary sphincter [25] and wide porous wall of intercellular clefts [26] of the capillary that allow the passage of plasma proteins thus nullifies oncotic pressure in vivo that were discovered later in 1967. The G tube discovery demonstrates that PP akin to arterial pressure induces negative SP gradient exerted on the G tube's wall that is maximum near the inlet causing suction or absorption. In addition to this I have reported 21 reasons that prove starling's law wrong [19]. So, both Starling's forces are wrong and so is the equations.

The same wrong conception that elevating CVP to levels of 20- 22

cm H20 may elevate the arterial pressure in shock management by infusing too much fluid was prevailing in clinical practice till recently. Fortunately, such practice has stopped now since it was realized that it induces volumetric overload shocks (VOS) [9] that cause the interstitial oedema of vital organs and subcutaneously causing ARDS [31]. It is worth mentioning the relation of G tube orifice diameter to SP of the G tube and the surrounding chamber C pressure (CP) shown in (Figure 1,2). This is relevant to the negative ISF pressure measured by Guyton and Coleman subcutaneously to be of -7 cm water [32]. This negative pressure of the ISF space can only be explained by hydrodynamics of the capillary working as G tube. Starling's forces cannot account for this negative pressure of ISF space and lymph vessels at all.

Error 3: Misconceptions on Capillary Cross-Section Areas and Blood Speed

Current teaching on capillary physiology indicates that the red blood cells (RBCs) speed or the Capillary Blood Speed (CBS) is "very slow" running leisurely through capillaries to allow for the slow "perfusion" to take place as based on Starling's forces. This is based on another misconception that the sum of cross section areas of all the capillaries is very much greater than the cross-section area of the Aorta. It is hard to trace the scientific foundations of these 2 misconceptions. I have previously reported that Starling's law is wrong [4-9], the Revised Starling's Principle (RSP) is a misnomer [10], and the correct replacement is the hydrodynamics of the porous orifice (G) tube [4-9]. This creates a negative side pressure gradient exerted on the wall of the G tube. A unique autonomous rapid dynamic magnetic field-like fluid circulation occurs between fluid in G tube lumen and fluid around it in a surrounding chamber C. This induces a fast fluid transfer between lumen of the G tube and fluid surrounding it in chamber C (Figure 1-4). The same phenomenon of the G tube explains the capillary-interstitial fluid (ISF) transfer.

Here I report the new Tree Branching Law (TBL) that demonstrates that the above two well-known and received concepts concerning capillaries cross section area is "greater than the aorta" and RBCs Speed is "very slow" are in fact erroneous misconceptions. Discovery of the TBL rectifies these two misconceptions.

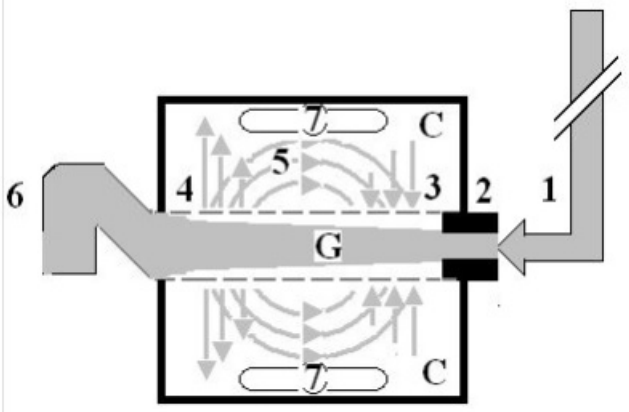

Figure 1: Shows a diagrammatic representation of the hydrodynamic of G tube based on G tubes and surrounding chamber C. This 37-years old diagrammatic representation of the hydrodynamic of G tube in chamber C is based on several photographs. The G tube is the plastic tube with narrow inlet and pores in its wall built on a scale to capillary ultrastructure anatomy of precapillary sphincter and wide inter cellular cleft pores, and the chamber C around it is another bigger plastic tube to form the G-C apparatus. The capillary is represented by the G tube and the ISF space is represented by Chamber C. 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 negative side pressure gradient causing suction maximal over the proximal part of the G tube near the inlet that sucks fluid into lumen.
4. The side pressure gradient turns positive pushing fluid out of 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 an 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 3,
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 right hand side and the diameter of the exit at 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 runs in the center of G tube leaving the outer zone near the wall of G tube clear. This may explain the finding in real capillary of the protein-free (and erythrocyte-free) sub-endothelial zone in the Glycocalyx paradigm. It was also noted that fine tea leaves exit the distal pores in small amount maintaining a higher concentration in the circulatory system than that in the C chamber- akin to plasma proteins and ISF space.

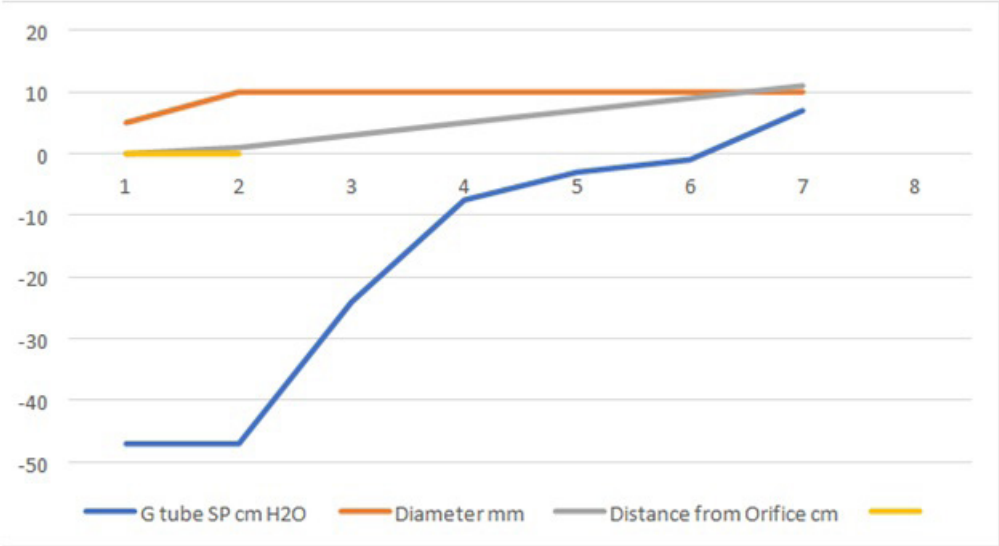

Figure 2: shows the relationship between SP to Diameter and length of the G tube which demonstrate a negative SP starting at the orifice (Point 1-2) and extends as negative gradient over the proximal part of the G tube (Points 2-6) to cross 0 line and then turn positive of 7 cm water at the tube's exit (Point 7). Data are taken from (Figure 17). This SP gradient from orifice Point 1-2 to G tube lumen {Points 2-6) is negative to become positive of 7 cm H20 at point 7 at the G tube's exit. The wide section diameter of the G tube is 7 mm at exit and 5 mm at orifice while the Length (L) from orifice to exit is 100 mm. The fluid jet has an increasing diameter gradient (Dj) (Figure 5). Neither Poiseuille's equation nor Bernoulli's equation can predict the negative SP neither at orifice nor at the proximal part of the G tube. Thus, the Fast RBCs speed or CBS depend on the orifice diameter or precapillary sphincter diameter not the G tube or capillary diameter. In the wide section of the G tube or capillary the fluid jet presented with increasing diameter inside the G tube (Figure 5). Hence the equation in (Figure 2g) (Figure 30) procures wrong result producing too slow and single RBCs speed or CFS for the whole body of the tube. The figure of 4.7 mm/s [2] applies precisely only at the distal part near the exit of the capillary- not along its entire length as a in the G tube.

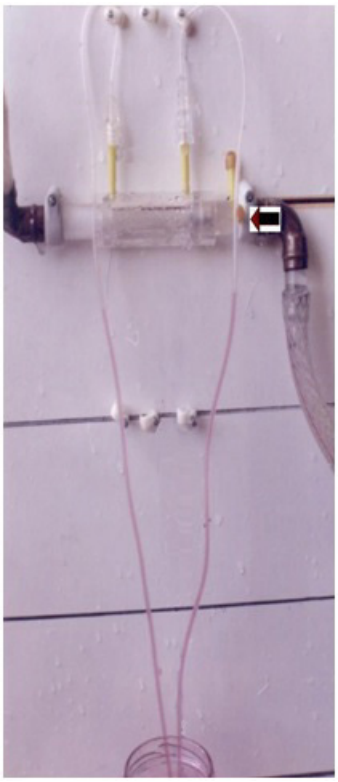

Figure 3: shows the G tube enclosed in chamber C (The G-C apparatus). The negative side pressure of G tube also creates a negative pressure in C shown here to suck the red water from a jar 300 mm below G tube into the manometers.

Figure 4: Shows the G tube enclosed in a rubber chamber (C) which is sucked in not ballooned out demonstrating the negative pressure in (C) akin to the negative pressure measured by Guyton and Colman [17] using a subcutaneous implanted chamber- a remarkable fact that cannot be explained by Starling's forces.

3. The Tree Branching Law (TBL)

3.1. Definition

The TBL states that: "The trunk of a branching tree does not, and cannot, give rise to branches that have sum of all its cross-section areas larger than its own". In other words: "The sum of all tree branches' cross-section areas is less than its own trunk."

This observational theory on green trees as well as the red vascular tree of the aorta and its arterial branches that was mentioned before [17] have now been investigated and reported [33]. The results of scientific, mathematical, and experimental evidence show that TBL is correct and are summarized here. This law rule applies up a green tree to its leaves as a branch becomes a mother trunk for its own sibling branches (Figure 5) and further down the arterial tree to the terminal arterioles and capillaries (Figure 6)

Aorta and its primary arterial branches that applies TBL down to arterioles and precapillary sphincters. The same principle from the green tree applies to the aorta and its primary arteries originating from its trunk. The aorta gives rise to 45 named arteries of various diameters, the sum of all arteries' cross-section areas is not greater than that of the aorta. In fact. it is less than the aorta (Table 1). The same principle applies further down as arteries divide into smaller arterial branches and so on down to the smallest arteriole and its own capillaries. The rule still applies to the capillaries despite having a bigger diameter than the precapillary sphincter but not bigger than the preceeding arteriole. Remmember also that not all the capillaries work at the same time, large number are functional but not all. It also continues down the aortic arteries to the level of terminal arterioles and precapillary sphincters where the capillaries originate. So, the sum of cross sections area of all the arterioles as compared to that of the aorta is less than, not more than, its trunk. The sum of cross section areas of all the capillaries are also less than the feeding arterioles and accordingly less than the aorta.

The measurements of the aorta and arteries diameters in this study are taken on the outside of the aorta and arteries wall from the photograph (Figure 6). A more acurate method is to measure the internal daimeters of the aorta and its arterial branches. The best way to achieve that is to make a rigid cast of the aorta, the 1st order arteries and the 2nd order branches using liquid cement injected into the aorta, leaving it to dry and harden, then remove the outer aorta and arteries walls, leaving the hard cast intact for measurements of diameters. This is a worthwhile project for a young researcher working on his MD dergee in cardiovascular anatomy or physiology.

The TBL is not just a scientific curousity of trivial importance but very important issue for understanding the capillary physiology. It verifies that the cross-section areas of the sum of all functional capillaries must be less than that that of the aorta. This is the scientific basis for the wrong believe that the cross section areas of the capillaries is "much greater" than the aorta- based on which the predicted CBS or RBCs speed is thought "very slow", while in reality it is proved fast [17]. The speed gradient of CBS or RBCs speed along the capillary must account for the magnetic field-like fluid circulation around the capillary as it occurs in the G tube (Figure 1).

Figure 5: Shows Monera's Household Croton Tree. It faithfully applies the TBL down to and including the terminal branches. The leaf stems, however, represent an exception to the law perhaps because it represents terminal function unit rather that the transport conduit that all branches represent.

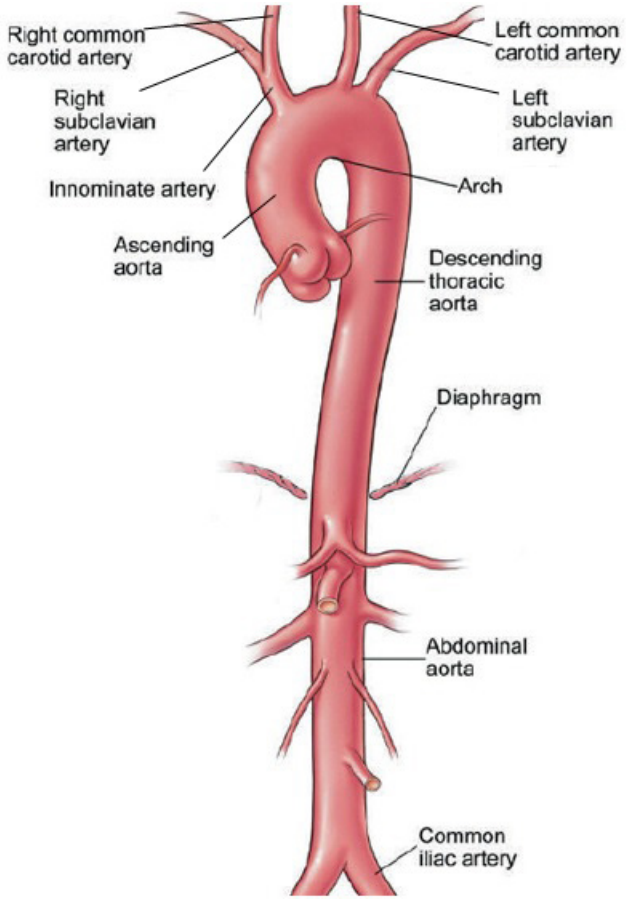

Figure 6: Shows the Aorta (Trunk) and its main first level arteries (Branches). The aorta gives rise to 45 first degree order arteries that vary in diameters but are all measurable, hence the cross-section area is calculated and compared to that of the aorta. When the precise engineering measurement data on terminal arterioles and capillaries become available it should be possible to calculate an approximate correct number of capillaries based on known capillary diameter and its number arising from the terminal arteriole. (This figure is reproduced from an article on the aorta by Cleveland clinic.).

Table 1: shows the data on the aorta and its primary branching arteries. The number in bald red compares the cross-section area of the aorta to the total number of branches' cross section area.

Showing or not	Aorta D	Branch Name	Br No	D	A mm^2	total Area
Showing	11.95	Coronary	2	1	0.78571429	1.57142857
Showing	5.975	Innominate A	1	3.96	12.3212571	12.3212571
Showing		L Common Carotid A	1	2.56	5.14925714	5.14925714
Showing		L Subclavian A	1	2.57	5.18956429	5.18956429
Showing		Coeliac A	1	4.18	13.7283143	13.7283143
Showing		Super Mesentric A	1	2.4	4.52571429	4.52571429
Not Showing		Suprarenal A	2	0.5	0.19642857	0.39285714
Showing		Renal A	2	2.9	6.60785714	13.2157143
Showing		Gonadal A	2	1	0.78571429	1.57142857
Showing		Inferior Mesentric A	1	2	3.14285714	3.14285714
Showing		R Common iliac A	1	5	19.6428571	19.6428571
Showing		L Common Iliac A	1	4.94	19.1742571	19.1742571

Not Showing		Intercostal Arteries	18	0.5	0.19642857	3.53571429
Not Showing		*Inferior Diaph A*	2	0.5	0.19642857	0.39285714
Not Showing		Lumbar Arteries	8	0.5	0.19642857	1.57142857
Showing		Sacral Artery	1	1.2	1.13142857	1.13142857
	112.202	Total	45		92.577	**105.864**

4. Conclusion

The objective of fluid therapy is to restore the circulatory haemodynamic disturbances of shock, particularly at the capillary-interstitial fluid (ISF) level. In current practice, the scientific foundation is erroneous and evidence-based policy is lacking. Medical practitioners currently rely on their clinical acumen alone to guide prescribing practices of fluid therapy in shock management. Lurking deep inside their thought are one wrong physiological law, 2 misconceptions on capillary haemodynamic and one misconception on circulatory haemodynamic. The latter concerns the volume pressure relationship of the cardiovascular system that is incorrectly believed to have a proportional relationship in an indefinite straight line. However, during shock management once hypervolaemia occurs, an irreversible hypotension sets in. The other errors concerning the wrong Starling's law and the 2 misconceptions on capillary haemodynamic are briefly summarised here having been reported in whole book.

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