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Editorial

Cardiovascular and Hematological Manifestations of the Acute Respiratory Distress Syndrome (ARDS) Caused by the Newly Discovered Volumetric Overload Shocks (VOS). Is it Relevant to Covid-19 Pandemic ARDS?

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VOS: Volumetric Overload Shocks; ARDS: The Acute Respiratory Distress Syndrome; MODS: The Multiple Organ Dysfunction Syndromes; CVS: Cardiovascular System; VO: Volumetric Overload; L: Liter

Substantial physics and physiological evidence with clinical relevance and significance currently exists that affirm Starling's law wrong (Figure 1) [1-4], particularly now as the definitive affirmative proof is being reported [5]. Evidence that volumetric overload shocks (VOS) [6-9] cause the acute respiratory distress syndrome (ARDS) is also available [10,11]. These VOS are complications of fluid therapy in hospital practice, particularly in surgical patients due to many errors and misconceptions on fluid therapy [12] that mislead physicians into giving too much fluid during the resuscitation of shock, acutely ill patients, and prolonged major surgery [13]. The clinical manifestations of VOS causing ARDS is that of the multiple organ dysfunction syndromes (MODS) shown in table 1, among it are the cardiovascular system (CVS)and hematological manifestations of ARDS [14-16]. These include cardiac dysrhythmia particularly and characteristically bradycardia with signs of shock prevailing. This shock is always mistaken for one of the recognized shocks of septic or haemorrhagic and treated wrongly with further volume expansion using colloids/crystalloids and/or blood transfusion!

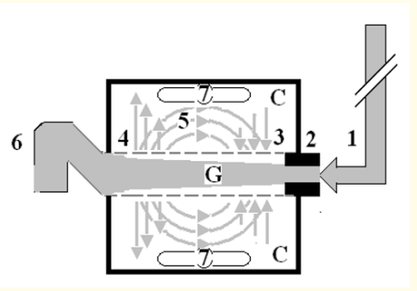

Figure 1: *Shows a diagrammatic representation of the hydrodynamic of G tube based on G tubes and chamber C. This 37-years old diagrammatic representation of the hydrodynamic of G tube in chamber C is based on several photographs. The G tube is the plastic tube with narrow inlet and pores in its wall built on a scale to capillary ultra-structure 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 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 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 centre 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 (Woodcock and Woodcock 2012) [3]. 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.*

Cerebral	Cardiovascular	Respiratory	Renal	Hepatic & GIT
Numbness	Hypotension	Cyanosis.	Oliguria	Dysfunction:
Tingling	Bradycardia	FAM[4]	Annuria[8]	Bilirubin ↑
SBB[1]	Dysrhythmia	APO[5]	Renal failure or	SGOT ↑
COC[2]	CV Shock*	RA[6]	AKI[9]	Alkaline Phosph.
Convulsions	Cardiac Arrest	Arrest	Urea ↑	GIT symptoms.
Coma	Sudden Death	CPA[7]	Creatinine ↑	DGR[10]
PMBCI[3]		Shock lung		Paralytic ileus
		ARDS[$]		Nausea and Vomiting.

Table 1: *Shows the manifestations of VOS 1 of the TURP syndrome for comparison with ARDS manifestations induced by VOS2. The manifestations are the same but one vital organ-system may predominate.*

Abbreviation

SBB[1]: Sudden Bilateral Blindness; COC[2]: Clouding of Consciousness; MBCI[3]: Paralysis mimicking bizarre cerebral infarctions, but is recoverable on instant use of HST of 5%NaCl and/or $NaCO_3$, and so is coma and AKI; FAM[4]: Frothing Around the Mouth; APO[5]: Acute Pulmonary Oedema; RA[6]: Respiratory Arrest; CPA[7]: Cardiopulmonary Arrest; ARDS[$]: Occurs on ICU later; Annuria[8]: That is unresponsive to diuretics but responds to HST of 5%Ncl and/or 8.4%$NaCO_3$; AKI[8]: Acute Kidney Injury. Also occurs the excessive bleeding at; AKI[9]: Acute Kidney Injury; DGR[10]: Delayed Gut Recovery; CV Shock: Excessive bleeding may occur at the surgical site and leukocytosis occurred in the absence of sepsis and septic shock.*

Indeed, although both CVS and hematological manifestations are always observed and reported in ARDS as MODS, it has not been previously and primarily reported as standalone article until recently only with Covid-19 induced ARDS [17-21], mostly on hematological manifestations only. These CVS and hematological manifestations commonly seen in regular clinical practice are, however, incorrectly attributed to the over incriminated sepsis and septic shock. Recent evidence demonstrates that sepsis may be as innocent as the Wolf in Josef's story in the patho-aetiology of ARDS [10]. Volumetric overload (VO) over time (T), or the retained VO at the time of onset of ARDS morbidity and mortality has never been incriminated by previous authors until recently. Although, recent reports of multicenter prospective studies such as PRISM [15] and ProCESS/ARISE/ProMISe [16] have documented VO as retained fluid of 3-10 liters (L) in the result section associated with morbidity of ARDS surviving patients but not incriminated as its patho-aetiology.

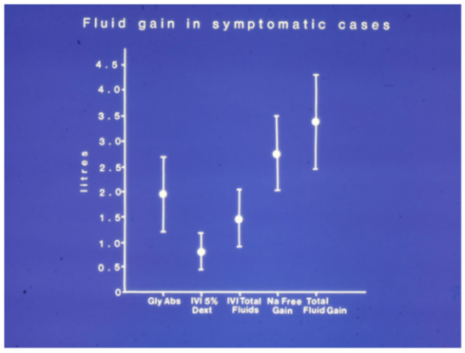

Figure 2: *Shows the means and standard deviations of volumetric overload in 10 symptomatic patients presenting with shock and hyponatraemia among 100 consecutive patients during a prospective study on transurethral resection of the prostate. The fluids were of Glycine absorbed (Gly abs), intravenously infused 5% Dextrose (IVI Dext) Total IVI fluids, Total Sodium-free fluid gained (Na Free Gain) and total fluid gain in litres.*

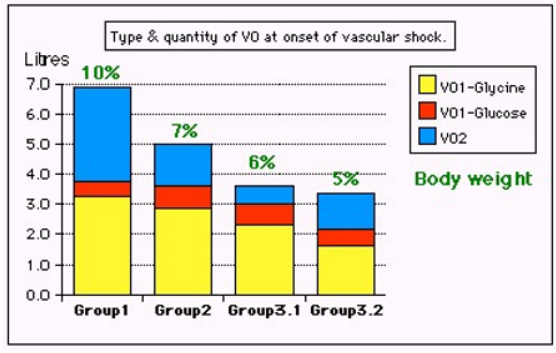

Figure 3: *Shows volumetric overload (VO) quantity (in litres and as percent of body weight) and types of fluids. Group 1 was the 3 patients who died in the case series as they were misdiagnosed as one of the previously known shocks and treated with further volume expansion. Group 2 were 10 patients from the series who were correctly diagnosed as volumetric overload shock and treated with hypertonic sodium therapy (HST). Group 3 were 10 patients who were seen in the prospective study and subdivided into 2 groups; Group 3.1 of 5 patients treated with HST and Group 3.2 of 5 patients who were treated with guarded volume.*

	A	B	C	D	E	F	G	H
1		**Gr 1**	**Gr 2**	**Gr 3**	**Gr 3.1**	**Gr 3.2**	**Normal**	**Units**
2	**Number of patients**	3	10	10	5	5	**Mean**	
3	**Age**	71	70	75	72	78	72	Year
4	**Body weight (BW)**	69	70	68	71	65	69	kg
5	**Postoperative serum solute concentrations:-**						**Preoperative**	
6	Osmolality	**271**	**234**	**276**	**282**	**271**	292	mosm/l
7	Na+	**110**	**108**	**120**	**119**	**121**	139	mmol/l
8	Ca++	**1.69**	**1.79**	**1.85**	**1.84**	**1.86**	2.22	"
9	K+ (P<.05)	5.6	4.8	5.0	4.9	5.0	4.46	"
10	Co2 (P=.002)	**23.0**	**23.0**	**25.5**	**24.0**	**26.4**	27.30	"
11	Glucose	**13.2**	**17.3**	**16.4**	**15.9**	**16.9**	6.20	"
12	Urea (P=.0726)	**26.5**	9.0	6.6	6.8	6.4	6.7	"
13	Bilirubin (P<.05)	**19**	**16**	8	6	9	7	"
14	AST	**124**	32	20	18	21	20	"
15	Protein	**43**	**52**	**48**	**44**	**52**	62	g/l
16	Albumin	**23**	**30**	**30**	**28**	**32**	39	"
17	Hb (P=.0018)	**119.3**	**127.9**	**114.5**	**105.2**	**123.8**	138.8	"
18	WCC (P<.005)	**18.9**	**16.2**	7.5	7.8	7.2	8.0	per HPF
19	Glycine			**10499**			293	µmol/l
20	Therapy	CT	HST	Random:	HST	CT@		
21	**Outcome**	Death	Full Rec.		Full Rec.	Morb.@		

Figure 4: *Shows the data of the 23-patients of the case series study [11]; the second clinical study on which this article is based. The significant changes of serum solute contents are shown in bald font with the corresponding p- value. Most of the patients showed manifestation of ARDS (Table 1) of which the cerebral manifestation predominated, being on initial presentation (Regional Anesthesia) and representation of VOS 1 (General Anesthesia). However, most patients were given large volume of saline that elevated serum sodium to near normal while clinical picture became worse. They suffered VOS2 that caused ARDS. The VO of patients to whom these data belongs are shown. Please note the elevation of urea and unurea of Group 1 who died indicated AKI. Elevations oh Bilirubin and AST indicated hepatic dysfunctions. White cell count (WCC) elevation indicated inflammatory response of VOS 2 in ARDS or SIRS in the absence of sepsis.*

Parameter	Value	Std. Err	Std. Value	T Value	P
Intercept			0.773		
Fluid Gain (l)	0.847	0.228	1.044	3.721	0.0007
Osmolality	0.033	00.014	-0.375	2.42	0.0212
Na+ (C_B)	0.095	0.049	0.616	1.95	0.0597
Alb (C_B)	0.062	0.087	0.239	0.713	0.4809
Hb (C_B)	-0.282	0.246	-0.368	1.149	0.2587
Glycine (C_B)	-4.973E-5	5.975E-5	-0.242	0.832	0.4112

Table 2: *Shows the multiple regression analysis of total per-operative fluid gain, drop in measured serum osmolality (OsmM), sodium, albumin, Hb and increase in serum glycine occurring immediately post-operatively in relation to signs of the TURP syndrome. Volumetric gain and hypoosmolality are the only significant factors.*

Furthermore, these hugely expensive multicenter prospective studies did not mention the VO associated with and causing the mortality. All the self-references mentioned here affirm VO/T as the pathological insult that induces VOS causing cardiovascular manifestations of ARDS and acute kidney injury (AKI) as parts of MODS and is highly significant (p = 0.0007) (Figure 2 and table 2). This concept of VO/T was first reported in MD Thesis in 1988 [22], in an original article based on prospective cohort study done mid-eighties and reported in 1990 [23], another in 2001 [1] and extensively reported in over 100 articles between 2016 and 2021 [1-13]. For VOS 1 the mortality occurred with VO of 7L or 10% Body weight (BW) (Figure 3 and 4). For VOS 2 the first report on ARDS by Ashbough., *et al.* [24] documented 12 - 14L of retained fluids in mortality cases but again VO was not incriminated in ARDS patho-aetiology.

Recent substantial evidence by other eminent researchers reported the retained VO in ARDS patients but stopped short of incriminating it as cause of ARDS. Professor Hahn [25] wrote: "Adverse effects of crystalloid fluids are related to their preferential distribution to the interstitium of the subcutis, the gut, and the lungs. The gastrointestinal recovery time is prolonged by 2 days when more than 2 liters is administered. Infusion of 6 - 7 liters during open abdominal surgery results in poor wound healing, pulmonary oedema and pneumonia. There is also a risk of fatal postoperative pulmonary oedema that might develop several days after the surgery. Even larger amounts cause organ dysfunction by breaking up the interstitial matrix and allowing the formation of lacunae of fluid in the skin and central organs, such as the heart". Other authors have confirmed the significant role of VO in causing the morbidity and mortality of ARDS" [26,27].

Having observed the link of the TURP syndrome with ARDS, the concept of VO was conceived. The TURP syndrome was 1st reported by Creevey [28]. Harrison III., *et al*. were the 1st authors to report it as hyponatraemic shock induced by 1.5% Glycine absorption during the TURP surgery [29]. This hyponatraemic shock was first ever reported experimentally in dogs by Danowski TS, Winkler AW, Elkington JR in 1946 [30]. Professor Arieff., *et al*. reported hyponatraemia induced by both 1.5% Glycine absorption and 5% Glucose infusion in women [31]. Ghanem reported VOS in the TURP syndrome in 1988 in MD Thesis [22], in an article on prospective cohort study of 100 patients in 1990 [23] and extensively and precisely between 2016 - 2021. All the discoveries in physics, physiology, and medicine originated in urology [32], reported in > 100 original articles and 8 published books of which 3 are relevant here and available from the publishers and amazon.com [33-37]. All my recent articles related to VOS project are not referenced in PubMed because they were published in open access journals but are fully listed in Google Scholar and probably other search engines.

My first encounter with the TURP syndrome was in 1981 when I attended a postmortem examination of 3 patients killed by the TURP syndrome while working as senior house officer in Urology Department at District General Hospital, Eastbourne, UK. They were internally drowned with fluids. When I asked the pathologist: "Why don't you mention this fluid overload in your report?". His reply was: "Because it offends the treating physician." This was the time I made a pledge to investigate the role of VO in the patho-aetiology of the TURP syndrome and ARDS later.

The journey took me 40 years to resolve the puzzles of the TURP syndrome, hyponatraemia and ARDS, during which I made 14 discoveries in physics, physiology, and medicine and all are now documented in books [33-37]. In addition to the most careful and precise clinical observations, my other methods of scientific research are simple but most effective included: Careful reading of relevant literature taking time to comprehend and later write a critical analytical criticism review. Being independent investigator with no external funds whatsoever has allowed me the freedom of time to dive deep into physiology and physics and fly high to the highest standard of clinical research crossing all boundaries and my limit is the sky.

For the interested reader to appreciate the concept of VO/Time inducing VOS [6-9] that cause ARDS [10,11], he/she needs to understand and feel comfortable with the hydrodynamic of the porous orifice (G) tube (Figure 1) [1]. The errors and misconceptions caused by the faulty rules on fluid therapy dictated by the wrong Starling's law should be recognized [12]. These errors mislead physicians [13] into giving too much fluid during the resuscitation of shock, acutely ill patients and during prolonged major surgery causing VO presenting with cardiovascular shock or arrest in theatre or during the resuscitation of another well-known shocks. These VOS cause ARDS presenting first with the manifestations of CVS and hematological such as excessive bleeding at the surgery site due to dilutional coagulation disorders as well as leukocytosis in the absence of sepsis (Table 1). It also causes neurological and cerebral coma, AKI, hepatic dysfunction, and GIT manifestations as parts of MODS. These are the new discoveries in physiology and medicine originated in urology [32].

Dr, Starling [38] based his hypothesis on Poiseuille's work on strait bras tube of uniform diameter [39] in which the hydrostatic pressure causes filtration, and the oncotic pressure force of plasma albumin was assumed to cause re-absorption [40]. Recent evidence demonstrates Starling's law is wrong on both of its hydrostatic and oncotic pressure forces and provides the correct replacement of hydrodynamic of the G tube (Figure 1) [1-5]. The capillary has a pre-capillary sphincter [41] and wide intercellular slit pores [42] that allow the passage of molecules larger than plasma proteins. This makes the capillary a porous orifice (G) tube with different hydrodynamic from Poiseuille's tube [1,5]. The side pressure of G tube causes suction not filtration- highest at the arterial end. The wide capillary pores nullify the oncotic force *in vivo* based on biochemical [43] and clinical research using albumin versus saline [44-46] and hydroxyethyl starch versus saline for fluid resuscitation [47].

The osmotic chemical composition of various body fluids is identical to plasma proteins [43]. The interstitial fluid (ISF) space has a negative pressure of -7 cm water [48], so is lymph [49]. Clinical evidence on plasma albumin versus Saline shows no significant difference [44-46], meaning that albumin does not work [44]. This evidence affirms that the oncotic force does not exist *in vivo* that partly prove Starling's law wrong. Inadequacy in explaining the capillary-ISF transfer, has previously called for reconsideration of Starling's hypothesis [50].

New physics and physiological research results [1-5] demonstrate that side pressure does not cause filtration across the wall of the G tube, it causes suction. In G tube the negative side pressure gradient on its wall causing suction maximum near the inlet and turns positive maximum near the exit causing filtration. This creates a circulation between fluid in the lumen of G tube and surrounding fluid chamber (C) that runs in the opposite direction creating autonomous dynamic rapid magnetic field-like circulation (Figure 1) [1-5]. The physiological study completed the evidence that Starling's law is wrong demonstrating that the capillary works as G tube not Poiseuille's tube.

Oedema occurred with both albumin and saline infusions when the fluid is run through the vein but not the artery. Both absorption and filtration are autonomous functions of G tube thus fit to replace Starling's law. The clinical significance is that Starling's law dictates the faulty rules on fluid therapy causing many errors and misconceptions [12] that mislead physicians into giving too much fluid infusions of colloids and crystalloids for the resuscitation of shock [13] which both cause oedema of ISF space and vital organs as well as hypervolaemia with hypotension and characteristically bradycardia [1-11]. This shock is always mistaken for septic or hemorrhagic shock and is wrongly treated with further huge volume expansion, occurring with both liberal EGDT fluid therapy [51,52] and conservative approach of bolus fluid therapy [53]. In the later article, the revised Starling equation and the glycocalyx model of trans-vascular fluid exchange for

an improved paradigm for prescribing intravenous fluid therapy was reported. This is known as the Revised Starling's Principle (RSP) [54] that has also proved to be a misnomer and wrong [55].

The CVS manifestations are the first to appear in patients who undergo prolonged major surgery under general anesthesia to whom too much fluid was infused. In patients who received regional anesthesia, the cerebral-neurological manifestations appear first. It took me exceptionally long years to recognize and appreciate the earliest CVS manifestations of VOS that cause ARDS later. Now it is exactly 40 years that resulted in achieving 14 scientific discoveries in physics, physiology, and medicine with publication of > 100 articles and 8 books 4 published and 4 in the press, only 3 are relevant and referenced here [27,33]. Careful, precise clinical observations affirmed that VOS present first with severe hypotension and characteristic BRADYCARDIA while the patient is hypervolaemic and over hydrated. This should segregate, and characterize VOS from septic and haemorrhagic shocks that have tachycardia.

However, any type of dysrhythmia may occur up to sudden cardiac or cardiopulmonary arrest that may be wrongly attributed to other causes. As example of this is the case recently reported in NEJM occurring during Cesarian section that was wrongly attributed to amniotic fluid embolism [56]. But I believe that VO by excessive intravenously infused fluid is the real culprit here [57]. These observations may particularly interest anaesthetists and surgeons and warn them against any further volume expansion for treating VOS. They should try something else such as giving the hypertonic sodium therapy (HST) of 5%NaCl and/or 8.4%NaCo3 that induce massive diuresis when diuretics fail to work. The massive amount of diuresis of up to 5 litres of urine that occur immediately after this HST infusion testify to the aetiological VO that it should not be replaced either. It is a most effective magical lifesaving therapy for hyponatraemia, VOS and ARDS [7,8,10,28,29].

Volumetric overload inducing VOS is of 2 types; VOS 1 is induced by sodium-free fluids of 3.5 - 5L for which the transurethral resection of the prostate (TURP) syndrome [20], acute dilutional hyponatraemic shock are examples which are now linked to ARDS or MODS [10,11] and acute kidney injury (AKI) [58,59]. Volumetric overload is induced by persistence to elevate central venous pressure (CVP) to high level of 18-22 cm H_2O [60] as based on the faulty Starling's law. Three books that precisely explain how and why have been published [33-37] and new articles are now reported that demonstrate VOS cause ARDS [10,11]: The plenary evidence on patho-aetiology and therapy [10] and constructing the BRIDGE between physics, physiology, biochemistry, and clinical medicine [11]. For readers who are interested but too busy to read the details in the books, this brief article on the new scientific discoveries in physics, physiology, and medicine may interest them [61].

There are 21 valid reasons affirming Starling's law is wrong that cannot be denied or refuted [62]. In addition to that, the study that transferred Starling' hypothesis into a law was faulty due to serious experimental error: The authors thought that elevating the hydrostatic capillary pressure may be obtained by increasing the venous or arterial pressures alike, which is wrong. Increasing venous pressure causes oedema but increasing arterial pressure does not.

It is also time to bring about the new successful lifesaving therapy of hyponatraemia and ARDS that prevents and cures all the manifestations of MODS that include the Cerebral coma, Cardiovascular, Hematological, Respiratory, Renal and Gastro-Intestinal and Hepatic manifestations (Table 1). It is also time for new guideline regulations on fluid therapy for shock, the acutely ill patients and during prolonged major surgery [35-37]. So, it is time for a farewell saying: "Goodbye Starling's law and hello G tube" [63]. The question whether this reported article above is related to Covid-19 pandemic ARDS remains un-answered. An answer is eagerly and urgently awaited with anticipation. This recently reported article [64] paves the way for a satisfactory answer. Up to the time of writing this report on January 25th, 2021, VOS remains unrecognized and underestimated cause of ARDS. I believe there is a link with ARDS induced by Covid-19.

Conflict of Interest

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