

The Tur Syndrome Re-Incarnating as ARDS after Saline Use as Irrigating Fluid in Endoscopic Surgery

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Abstract

Objective: To demonstrate the TUR syndrome characterized with hyponatremia (HN) will no longer be seen after using saline as irrigating fluid in urology, but it has re-incarnated as the acute respiratory distress syndrome (ARDS) presenting with the same clinical picture of the multiple organ dysfunction syndromes (MODS).

Material and Methods: A focused objective and relevant narrative review of other eminent authors' work and mine are used here.

Results: The TUR syndrome characterized with HN will no longer occur in urology after the use of saline as irrigating fluid in endoscopic surgery. It has reincarnated as ARDS presenting with the same MODS clinical picture. It is induced by VO caused by iv fluid infusions. This induces cardiovascular shock (VOS) that causes ARDS. The latter is already common in clinical practice due to the excessive use of iv fluids in the management of shock, acutely ill patients, and prolonged major surgery as an iatrogenic complication of fluid therapy. The wrong Starling's law dictates the current faulty rules on fluid management of shock that mislead physicians into giving too much fluid. The correct replacement is the hydrodynamics of the porous orifice (G) tube which should be the new scientific basis for fluid therapy in shock management. The currently available hypertonic sodium therapy of 5% NaCl and/or 8.4% NaCO₃ is a lifesaving therapy for HN, the TUR syndrome, and ARDS.

Conclusion: The TUR syndrome may seem to have been eradicated in urology with the use of saline as irrigating fluid in endoscopic surgery. However, it has reincarnated as ARDS with the same clinical picture of MODS. It is an iatrogenic complication of fluid therapy dictated by the wrong Starling's law for which the hydrodynamic of the G tube is the correct replacement that should be the new scientific basis for a new policy on fluid management of shock.

Key words: TUR syndrome; Endoscopic surgery; ARDS; Shock; Fluid therapy; Starling's law; Capillary-ISF transfer

Keywords: Proteomics; DNA; Genome; Anti-microbial

ABBREVIATIONS

TUR: Transurethral resection, PM: Post-mortem, DGH: District General Hospital; SHO: Senior House Officer, HN: Hyponatraemia, ARDS: Acute respiratory distress syndrome, MODS: Multiple organ dysfunction syndrome, VO: Volumetric overload, VOS: Volumetric overload

shock, TURP: Transurethral resection of the prostate, HST: Hypertonic sodium therapy, IV: Intravenous, ISF: Interstitial fluid, AKI: Acute kidney injury, EGDT: Early goal directed therapy, BFT: Bolus fluid therapy, ICU: Intensive care unit, RSP: Revised starling's principle, CVP: Central venous pressure, L: Liter

INTRUDUCTION

My beginning with the transurethral resection of the prostate (TUR) syndrome started in 1981 after I attended post-mortem (PM) examinations on 3 patients who died after the TURP surgery. I was only an SHO in urology working for the late Mr. KC Perry and JP Ward at DGH in Eastbourne. At the PM examination, it was clear and obvious to me that these patients died of internal drowning as a result of massive volumetric overload (VO) of fluids used for resuscitation of a cardiovascular shock they suffered, and the fluid was retained in their bodies. When did I ask the pathologist why doesn't he mention that retained VO in his report? He replied: "because it offends treating physicians"? The word offends hit me right hard on my head like a hammer. My next question to myself was if it offends them why do physicians do it? This had led me to immediately replace the term fluid overload with the new and original Volumetric Overload (VO) after adding the cardiovascular hypotension Shock to it to become (VOS) that was introduced to avoid the word offends but it has proved to be a new scientific medical discovery.

Another few questions such as: "What is misleading physicians into giving too much fluid during the resuscitation of shock? What shock is it? I communicated with Richard Harrison III (who may be late now) who is the originator of the hyponatremic shock of the TUR syndrome and the use of 5% NaCl therapy in clinical practice for years during his retirement [1]. I reported later the true pioneer originators of this shock and the hypertonic sodium therapy (HST) were Danowski et al who induced it experimentally in dogs by massive 5%Glucose infusion [2]. Harrison advised me to "put the poison in the honey" that I could not accept. After the PM examination, I suspected and incriminated Starling's law being the scientific basis of fluid therapy in shock that dictates the wrong rules on fluid therapy for shock management documented in articles and books [3-7], for which the hydrodynamics of the porous orifice (G) tube is the correct replacement (Figures 1a and 1b) [8,9]. I felt so strongly about it that I wrote a letter to the late great professor of physiology Eric Neil and author of Sampson Wright Textbook of Physiology later in 1983 [10,11]. He nicely replied in the handwritten letter as he was in retirement asking: Why and how may Starling's law cause the death of patients? The answer is there now after 40 years of hard scientific research and investigations [12].

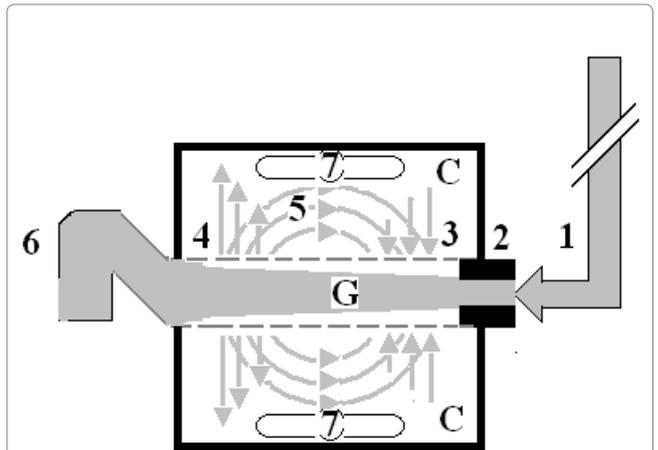


Figure 1: A diagrammatic representation of the hydrodynamic of G tube based on G tubes and chamber C. This 37-years old diagrammatic representation of the hydrodynamic of G tube in chamber C is based on several photographs. The G tube is the plastic tube with narrow inlet and pores in its wall built on a scale to capillary ultra-structure of pre-capillary 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 run 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. 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.

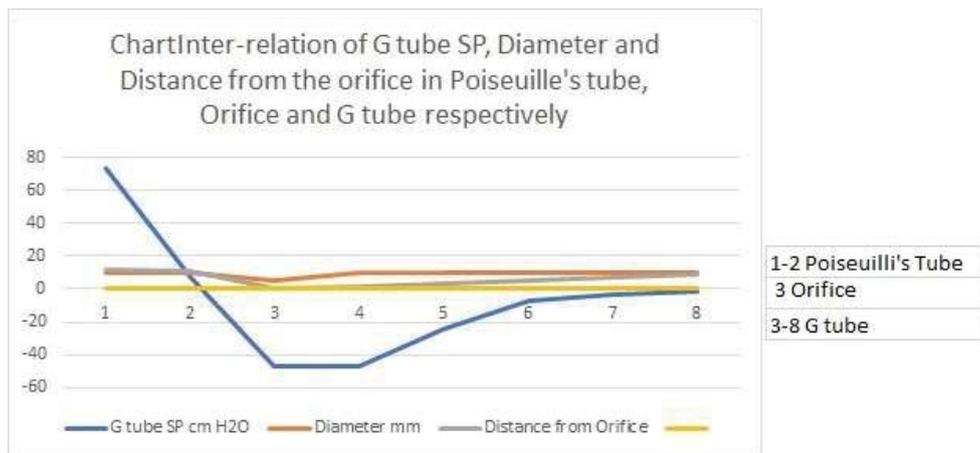


Figure 1b: The relationship between SP to the Diameter and length of the G tube which demonstrate a negative SP starting at the orifice (Point 2) (akin to precapillary sphincter) and extends as high negative pressure gradient over the proximal part of the G tube (Point 2-6) to cross 0 line at point 8 and then turn positive of 7 cm water at Point 9. This SP gradient from orifice at Point 2 to G tube lumen {Points 2-6} is negative to become positive DP at point 9 of 7 cm H2O water along the G tube. The wide section diameter of G tube is 7 mm all along the entire tube. The orifice is 5 mm while the distance from orifice to exit represent the tube' length in which the Fluid jet diameter change with increasing gradient (Figure 1a). Neither Poiseuille's law nor Bernoulli's equation can predict SP neither at orifice of Venturi's effect nor at the G tube proximal part know as Bernoulli's effect. Thus, the RBCs speed or CBS depend on the dynamic fluid jet diameter not the G tube diameter. Hence the equation in (Figure 2g) (Figure 28) and graph are wrong giving low RBCs speed or CBS over the capillary length but is correct only at point of the G tube where the jet diameter equals the tube diameter.

What is the TUR Syndrome? And what is causing the "Understanding Gap"?

Our prospective cohort study on the TUR syndrome was conducted in 1987-1988, a letter to the editor of BJU was reported in 1988 [13], MD Thesis was accepted November 1988 [14], and the article was reported in 1990 [15]. The TURP syndrome is a condition induced by gaining a large volume of sodium-free fluid overloading the cardiovascular system and spilling over into the interstitial fluid (ISF) space of vital organs and subcutaneous. The fluid of 1.5% Glycine used as irrigating fluid gets absorbed, or rather infused through peri-prostatic veins, during the TURP surgery as well as all endoscopic surgeries performed under sodium-free fluid irrigation of any type such as Mannitol, Sorbitol, Glucose, and Crystal. Also, intravenous (iv) infusion of 5% Glucose considerably and significantly contributes to it- as well as saline. What is more, excessive infusion of saline or any sodium-based fluid such as Saline, Hartman, Ringer, plasma, and plasma substitutes, and blood worsens it transferring the shock being treated from VOS 1 into VOS 2 [16] and causing ARDS 1 and 2 [17,18] with apparent correction of HN and has high morbidity and mortality later.

The TUR syndrome has a characteristic severe drop of serum sodium level causing acute dilutional hyponatremia (HN) induced by VO 1 (Figures 2 and 3) with severe clinical symptoms affecting all vital organs causing the multiple organ dysfunction syndromes (MODS) (Table 1) or ARDS [17,18] with the recognizable clinical picture but one system may predominate such as acute kidney injury (AKI). The HN of <120 mmol/l has 2 paradoxes and 2 nadirs that have eluded authorities and physicians on HN, and that has made the TUR syndrome most elusive and invisible making it though obviously, it has remained invisible even to authorities on HN. Professors and consultant urologists who are such swift good resection experts have testified that the TUR syndrome does not exist as no fluid absorption occurs, with a negative prospective study of 100 patients [19]. Of course, no such hyponatremia occurs when the irrigating fluid is saline whatever the volume absorbed and infused. Another important reason that prevents massive 1.5% glycine absorption and the TUR syndrome is for the Urologist not to breach the prostate capsule and not to open the venous sinuses where the irrigating fluid is directly injected intravenously (iv) into the periprostatic veins. There was also another good swift urologist who reported >1000 consecutive TURP surgeries without seeing the TUR syndrome. The risk of VO during



Figure 2: 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.

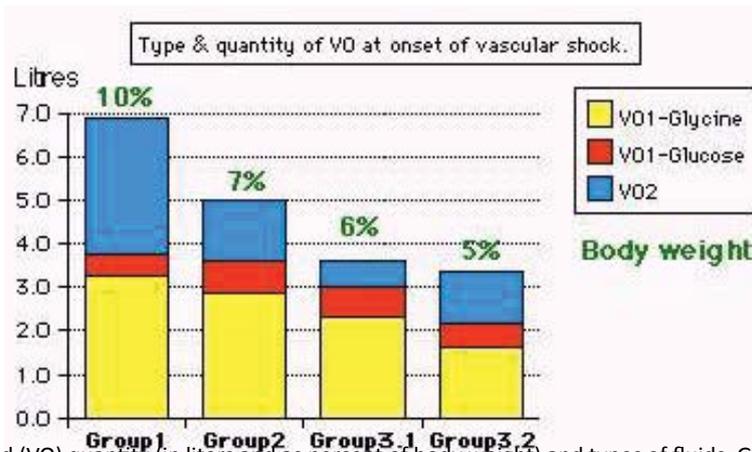


Figure 3: Volumetric overload (VO) quantity (in liters and as percent of body weight) and types of fluids. Group 1 was the 3 patients who died in the case series as they were misdiagnosed as one of the previously known shocks and treated with further volume expansion. Group 2 were 10 patients from the 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.

endoscopic surgery will continue to occur as long as there are registrars in training and even with the experienced consultants who occasionally and inadvertently breach the prostatic capsule and open the venous sinuses.

However, the TUR syndrome due to 1.5% Glycine VO with its characteristic HN has an undoubted reality [13-15] and [20-22]. Our study reported a 10% incidence of the

TUR syndrome with one near-death case that was saved [14] and a similar study done a year earlier in the same department reported a 7% incidence of morbidity with 1% mortality [22]. Before the TUR syndrome disappears into oblivion and is totally replaced by ARDS a most comprehensive literature review on the subject was reported in 2018 after the wide use of saline as irrigating

Table 1: The manifestations of VOS 1 of the TURP syndrome for comparison with ARDS manifestations induced by VOS 2. The manifestations are the same but one vital organ-system may predominate.

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

SBB¹: Sudden Bilateral Blindness

COC²: Clouding of Consciousness

MBCI³: Paralysis mimicking bizarre cerebral infarctions, but is recoverable on instant use of HST of 5% NaCl and/or NaCO₃, and so is coma and AKI

FAM⁴: Frothing Around the Mouth

APO⁵: Acute Pulmonary Oedema.

RA⁶: Respiratory Arrest.

CPA⁷: Cardiopulmonary Arrest; ARDS⁵: Occurs on ICU later.

Anuria⁸: That is unresponsive to diuretics but responds to HST of 5% Ncl and/or 8.4% NaCO₃; AKI⁹: Acute Kidney Injury. Also occurs the excessive bleeding at

AKI⁹: Acute Kidney Injury

DGR¹⁰: Delayed Gut Recovery; CV Shock*:

Excessive bleeding may occur at the surgical site and leucocytosis occurred in the absence of sepsis and septic shock.

fluid in the TURP surgery [23]. Here a distinction between a physiological VO of <2 L infused in less than one hour that is extensively studied by Hahn in volunteers and patients is known as Volume Kinetic (VK) (20) and the pathological VO of 3.5-5 L gained in < 1 h that causes the TUR syndrome [15] is highlighted. This has been a cause of a serious misunderstanding gap in the pathogenesis of the TUR syndrome. The physiological response of VK is remarkably different from the pathological response of VO which is paradoxical: VK elevates blood pressure and induces diuresis while VO causes hypotension with bradycardia and causes acute renal failure.

The TURP syndrome starts by presenting with cardiovascular hypotension shock to anesthetists and surgeons in theatre [24,25] and at times by cardiac or cardiopulmonary arrest [26] and sudden death. By the next morning the surviving patients present with coma, convulsion, and bizarre paralysis to physicians, neurologists, and ICU specialists [15]. It has the characteristic serum hypo-osmolality. But other solute contents dilutions seem to be apparently spontaneously improving due to water shift into cells (Table 2, Figures 1 and 2). The HN of <120 mmol/l causes cardiovascular hypotension shock. Volumetric overload (VO) is the most highly significant factor causing its path-etiology

with a (p=0.0007). Osmolality was also significantly low (p=0.02) while all other serum solute changes including the most remarkable drop in serum sodium and huge elevation in serum glycine did not reach statistical significance in the multiple regression analysis, yet it did alone when pre-and post-operative levels are compared!? (Table 2 and 3). This cardiovascular shock of VOS is easily confused with and mistaken for hemorrhagic or septicemia shock and is wrongly treated with further massive volume expansion that usually kills the patient as happened in the 3 patients mentioned above!?

The Toxic Theory of the TUR Syndrome and Septic Theory of ARDS

Sepsis and septic shock in the pathogenesis of ARDS is as innocent as the wolf in the Josef story [18], so is glycine in the aetiology of the TUR syndrome [15], particularly as correctly mentioned that the TUR syndrome occurs with Mannitol, Sorbitol, and Glucose. Professor Alan Arieff has clearly reported the morbidity and mortality of hyponatremia (HN) of the TUR syndrome induced by 1.5% Glycine as well as the excessive 5% Glucose infused intravenously during prolonged surgery in healthy women [27]. That does not mean that I deny the toxicity of glycine and

Table 2: It shows the mean summary of data, therapy and outcome comparing the 3 groups of 23 case series patients who's (whose) VO is shown in (Figure 3). Groip-1 was the 3 patients who died and had post-mortem examination, Group-2 were a series of severe TURP syndrome cases successfully treated with hypertonic sodium therapy (HST), and Group-3 were 10 patients encountered in the prospective study who were randomized between HST (3.1) and conservative treatment (CT) (3.2). The significant changes of serum solute contents are shown in bold font with the corresponding p-value. Most of the patients showed manifestation of ARDS of which the cerebral manifestation predominated, being on initial presentation (Regional Anaesthesia) and representation of VOS 1 (General Anaesthesia). However, most patients were given large volume of saline that elevated serum sodium to near normal while clinical picture became worse. They suffered VOS 2 that caused ARDS. The VO of patients to whom these data belong is shown.

1	Gr1	Gr2	Gr3	Gr3.1	Gr3.2	Normal Units	
2	Number of patients 3	10	10	5	5	mean	
3	Age 71	70	75	72	78	72 Years	
4	Body weight (BW) 69	70	68	71	65	69 Kg	
5	Postoperative serum solute concentration					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	4.9	5	4.46 "
10	Co ₂ (P=.002)	23	23	25.5	24	26.4	27.3 "
11	Glucose	13.2	17.3	16.4	15.9	16.9	6.2 "
12	Urea (P=.0726)	26.5	9	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	123.8 "
18	WCC (P<.005)	18.9	16.2	7.5	7.8	7.2	8 per HPF
19	Glycine			10499			293 µmol/l
20	Therapy	CT	HST	Randomized:	HST	CT©	
21	Outcome	Death	Full Recovery		Full Recovery	Morbidity	

Table 3: 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 hypo-osmolality are the only significant factors.

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	0.014	-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

the seriousness of sepsis. I am just saying they are misleading like a mirage to someone thirsty and lost in the desert. While thinking about it please, try to attend the PM examination of some patients who died from the TUR syndrome and ARDS. Every anesthetist should examine their own practice when he embarks on Bolus

Fluid Therapy (BFT) during anesthetic induction and watch out how much fluid is given during prolonged major surgery. Review the scientific basis of fluid therapy in the management of septic and all other types of shock on which bases the current practice is implemented.

Fluid Therapy Regimen and Iatrogenic Complications

The TUR syndrome occurs because of a combination of fluid absorption and direct iv infusion of the irrigating fluid when the prostatic capsule is breached, and venous sinuses are open. In clinical practice, all ARDS cases occur as a result of iv infusion of fluids. In our study, 7 cases of capsule breaching occurred among the 10 TUR syndrome cases as observed by the surgeon. The iv infusion occurs with both the liberal regimen of Early Goal-Directed Therapy (EGDT) and Bolus fluid therapy (BFT) of the conservative regimen. Hahn is a professor and consultant of anesthesia and intensive care. He is also a leader and world authority on fluid therapy and the editor of a book on the same subject. I would and have recommended him as the head of a committee to write the new guidelines on fluid therapy in shock management. He has my new book that will help him for >8 months now, please read it if you've not done so already. Like all anesthetists, Intensive care therapists, surgeons, and physicians of the whole world who remain to practice the liberal fluid therapy regimen also well known as EGDT in the management of shock, don't you? Go to any ICU near you and observe the swollen-up ARDS patients mostly with trunk edema comparing their body weight on hospital admission with their current weight while suffering from ARDS. Try to attend the PM examination of the TURP patients and ARDS patients. Allow me to reproduce this section from my article later that is most recommended reading to all physicians interested in the subject of fluid therapy, the TUR syndrome, HN, VOS, and ARDS [18].

The Role of Starling's Law

Starling's law [28,29] dictates the current faulty rules on fluid therapy in the management of shock. It thus misleads physicians into giving too much fluid during shock resuscitation [30]. More than 21 reasons were reported to show that Starling's law is wrong [31], none of it can be denied or refuted. The correct replacement is hydrodynamic of the porous orifice (G) tube [8,9] (Figures 1a and 1b) that was built on capillary ultrastructure anatomy of having precapillary sphincter [32] and a porous wall [33] that allow the passage of plasma proteins-hence nullify the oncotic pressure. It follows that the extended Starling Principle is wrong and a misnomer [34,35] and all the equations are also wrong.

Two Types of VO Inducing VOS and Causing ARDS of Type 1 and 2

There are two types of VO: Type 1 induced by sodium-free fluid and Type 2 induced by sodium-based fluid. These in turn induce VOS 1 and VOS 2 which cause ARDS 1 and ARDS 2, respectively. The clinical picture is the same for both types (Table 1). Type 1 is characterized with HN of the TUR syndrome with which the cerebral neurological manifestations of coma, convulsions, and bizarre paralysis predominate while type 2 may have moderate hypoproteinemia if induced by crystalloids and none when plasma, plasma substitutes, and blood are used. Type 2 may complicate Type 1 or may occur do Novo. Manifestations of the multiple organ dysfunction syndromes (MODS) are the same and appear in every case, but one system may predominate. When Hahn sent me his article on the Revised Starling Principle calling for revalidation [34] I immediately responded with an article: Revised Starling's Principle (RSP): a misnomer as Starling's law is proved wrong. I considered research on validating RSP as a total waste of money, time, and effort.

Proof by Eminent Authors on the VO Role in the Aetiology of the TUR Syndrome and ARDS

Professor Robert Hahn from Sweden has done lots of research infusing various types of fluid used in clinical practice to normal adult volunteers and patients, as well as animal research and clinical studies and reported >340 articles on the TURP syndrome alone (PubMed 2017) and 532 articles in total (PubMed search 2021): Here is what Robert Hahn said: in the abstract of an article reported in 2017 [36]:

"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 are 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."

Thank you, Professor Hahn, for a most impressive work indeed. New guidelines based on currently available evidence on fluid therapy for resuscitation of sepsis, septic shock, trauma patients, critically ill patients, ARDS,

and patients undergoing prolonged major surgery are badly needed. Professor Hahn is an expert witness on fluid therapy.

Why does not Hahn believe his own results? Why doesn't he make the most obvious conclusion based on what he said in the abstract above? What and how much more evidence and years that he needs to believe that the pathological VO of massive fluid infusions induces cardiovascular shock that is VOS of both types and causes ARDS? If my articles referenced here and the books [3-7] particularly the one Hahn has now for 8 months and being held in the press awaiting his introduction, then allow me most sincerely and humbly to give you a helping hand to lift you up to where I stand and clearly see the picture on the real issues discussed here.

Hahn does not need to do any more research studies. Just report a re-analysis of data from previously reported articles he has done and reported before, based on his previously published articles on the TUR syndrome and saline-based fluid infusions. Please, re-examine and re-analyze your own research work in a manner and method identical to your article reported here [20]. Please, Hahn, don't bother with equations that are hard to understand and are meaningless and perhaps misleading or even wrong. Do not use fancy sophisticated graphs that do not impress me. I would love, most sincerely and humbly, to give you a hand to get you out of the huge maze you have been lost inside it for >3 decades. All you need to do my friend now is to liberate yourself from the illusive and misleading concepts of the toxic/septic hypotheses of glycine and sepsis!? One must unlearn old bad habits to be able to receive and acquire the new correct ones.

Evidence for the VO Theory Causing VOS and ARDS

"The prevalence of "liberal fluid infusion" in the resuscitation of all types of shocks not only septic shock in clinical practice all over the world is attributed to an impactful article by Rivers et al, reported at The N Engl J Med 2001 [37]. Dr. Rivers' investigation reported EGDT in the treatment of severe sepsis and septic shock. In this single-center study published more than 20 years ago involving patients presenting to the emergency department with severe sepsis and septic shock, the conclusion was: "mortality was markedly lower among those who were treated according to a 6-hour protocol of EGDT, in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to

reach central hemodynamic targets, than among those receiving usual care" Usual care means conservative fluid regime. There is something grossly wrong with this conclusion, but I cannot tell what is it? Not yet. Let us see what other author investigators have said first. The EGDT of liberal fluid infusion has been termed "aggressive" by some authors. However, it has been adopted all over the world not only for the therapy of septic shock but also whenever fluid therapy is required for the management of all types of shocks.

"In another article by Dr. Rivers 11 years later in 2012 [38] he compared the liberal to the conservative approach concluding in his last statement: "In contrast to what is true in politics, in fluid management of acute lung injury, it is OK to be both liberal and conservative." So, Dr. Rivers says it is OK to have it both ways: "one for the EBB and one for the flow"! Sorry, sir, I disagree. It is not OK. It is not politics either. No, you cannot have it both ways. The right way is only one. The issue here is how much fluid should be infused during the ebb phase of shock and does it have a maximum limit? Replace the loss but do not overdo it. Since the cardiovascular system (CVS)' maximum capacity of an adult is 7 L and the normal blood volume is 5 L, the maximum infused volume of fluid should be limited by the maximum capacitance of the CVS. What do you expect when you try to fit 10-15 L of fluid into a 7 L capacity container? Simple physics and common sense indicate that it must spill over if it is an open system or burst if closed! The cardiovascular system is no exception. Dr. Rivers should re-examine his own data and tell us where and why he went so grossly wrong." The EGDT has spread like fire in a haystack, and it remains operative in current clinical practice all over the world that is why ARDS is so common yet remains under-recognized and underestimated affecting and killing hundreds of thousands of patients per year."

Other authors have confirmed the significant role of VO of crystalloids in causing the morbidity and mortality of ARDS both in adults and children of trauma patients [39,40]. All authors have stopped short of recognizing VOS as a Cause of ARDS or MODS morbidity and mortality.

Quoting also from this article [18] I mention here the remarkable multicenter study by Rowan et al. [41] Like Hahn they reported results that demonstrate the massive VO retained in the body of surviving ARDS patients. After sending 3 emails to Rowan commending the authors on their results and asking about the dead patients retained fluid VO, none of the 40+ authors replied.

“The PRISM Investigators reported its Trial by Rowan et al at NEJM 2017 [41] concluded: “In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics.” Thank you, Dr. Rowan and colleagues, for the excellent research and report. This is good evidence-based medicine, but more is needed, from you, and you have the data to provide it. Based on this conclusion that agrees with other multicenter trials I wonder is time to say goodbye to Dr. Rivers? The aggressive and deleterious liberal approach of EGDT is no longer wanted. It should be abandoned immediately. Even when the nasty liberal approach goes away, hopefully soon, it remains bad enough with the conservative regime as it is now that must be sorted out! I wonder what Dr. Rivers has to say about this, particularly as authors of 3 other huge prospective multicenter trials of The ProCESS/ARISE/ProMISe reported a similar conclusion by Huang et al. [42].

So, Rowan gave the results of the cumulative VO was -136 ml in the conservative-strategy group, as compared with 6992 ml in the liberal-strategy group ($P < 0.001$). For patients who were in shock at baseline, the cumulative seven-day VO was 2904 ml in the conservative-strategy group and 10,138 ml in the liberal strategy group ($P < 0.001$). For patients who were not in shock at baseline, the cumulative VO was -1576 ml in the conservative-strategy group and 5287 ml in the liberal-strategy group ($P < 0.001$)”.

“First, the negative sign (-) indicating negative fluid balance has appeared in the data above and is very important. It characterizes the non-symptomatic patients among the conservative-strategy group. These patients should be used as the controls for the statistical analysis of the data. I have been waiting for 40 years to see these VO results. I am still waiting to see VO data with statistical significance in mortality patients. I plead with and urge the respected authors of major randomized Trials of FACCT, PRISM, ProCESS, ARISE, and ProMISe to come forward with these data, please...

The Clinical Picture of (VOS, The TUR Syndrome, ARDS, and MODS)

The clinical picture of ARDS is that of the multiple organ dysfunction syndromes (MODS) (Table 1) reported previously by Khadarow and Marshal in 2002 [43]. Another remarkable article was reported by Schrier

in 2010 [44]. Demonstrating the link of the TUR syndrome with ARDS by having an identical clinical picture with minor variations was reported by Ghanem as complications of VO covering the cardiovascular/hematological that appear first under general Anaesthesia with bradycardia [45], the cerebral/neurological with coma appear first under spinal/epidural Anaesthesia and convulsions and bizarre paralysis predominate in the TUR syndrome, not in ARDS [46], the respiratory of ARDS and hepatic/gastrointestinal manifestations [47] and AKI predominate later were documented recently in individual-specific reports. Excessive bleeding and leukocytosis in the absence of sepsis also occur.

Therapy of VOS, the TUR Syndrome, and ARDS [17]

Prevention

Based on the above discussion, ARDS is an iatrogenic complication of fluid therapy in hospitals, never in the community, that is overlooked and underestimated. Being iatrogenic; means it is preventable. In order to prevent VOS and ARDS a limit to the maximum amount of fluid used during shock resuscitation or major surgery must be agreed upon. Professor Hahn [36] found that infusing 2 L of saline to human volunteers produces symptoms. Infusing > 3 L is pathological. More than 5 L is associated with deleterious morbidity [38,39]. So, the maximum volume of fluids that can be infused safely to an adult patient is 3 L which is the daily fluid requirement, and no more fluid of any kind is given for 24 hours except replacing the actual loss that does not include urine loss. The patient should be put on a weighing scale every day from hospital admission till discharge or death. Any retained volume of fluid above his body weight on admission is pathological. On using CVP for monitoring fluid therapy, please refrain from persisting to elevate CVP to levels above 12 and up to 18-22 cm saline [48]. This is a major cause for inducing VO and VOS and ARDS during shock resuscitation, particularly septic shock [37]. Lookup any physiology textbook to find out that the normal CVP is 0 and it swings between -7 and +7 cm saline which is the level that should be aimed at in monitoring fluid replacement in shock of sepsis, trauma, and bleeding, acutely ill and during major surgery. Elevating CVP is not synonymous with elevating arterial pressure.

If hypotension develops later during ICU stay, inotropic drugs, hydrocortisone 200 mg, and HST should be used.

The latter restores the pre-capillary sphincter tone (peripheral resistance) so that the capillary works as a normal G tube again [9], but no isotonic crystalloids or colloids infusions of above the daily fluid requirement should be given. If persistence with the current liberal regimen of Early Goal-Directed Therapy (EGDT) and conservative Bolus Fluid Therapy regime continues, then more reports on ARDS will continue. Future authors will be hopefully taking into consideration the mentioned above data concerning VO/Time, or the retained fluid VO at the time of inducing ARDS or death on reporting new trials or case reports.

Treatment of ARDS [6]

Hypertonic sodium therapy (HST) of 5%NaCl and/or 8.4%NaCo₃ has truly proved lifesaving therapy for the TUR syndrome and acute dilution HN [17,18] as well as Secondary VOS 2 that complicates fluid therapy of VOS 1 causing ARDS. It works by inducing massive diuresis; being a potent suppressor of antidiuretic hormone. My experience in using it for treating established ARDS with sepsis and primary VOS 2 that causes ARDS is limited. However, evidence on HST suggests it will prove successful if given early, promptly, and adequately to ARDS patients while refraining from any further isotonic crystalloid or colloid fluid infusions using saline, Hydroxyethyl starch, and/or plasma therapy- just give the normal daily fluid requirement and no more. After giving HST over one hour using the CVP catheter already inserted, the patient recovers from AKI and produces through a urinary catheter massive amount of urine of 4-5 L as you watch. This urine output should not be replaced. Just observe the patient recovering from his AKI, coma, and ARDS and ask for a drink. This is done in addition to the cardiovascular, respiratory, and renal support in ICU. For patients with AKI on dialysis, the treating nephrologist should aim at and set the machine for inducing negative fluid balance.

The HST of 5% NaCl and/or 8.4% NaCo₃ is given in 200 ml doses over 10 minutes and repeated. I did not have to use more than 1000 ml during the successful treatment of 16 patients. Any other hypertonic sodium concentration is not recommended- I know Hahn tried 1.8%NaCl and it does not work. A dose of an intravenous diuretic may be given but it does not work in a double or triple the normal dose. A dose of 200 mg of hydrocortisone is most useful. Antibiotic prophylactic therapy is given inappropriate and adequate doses to prevent sepsis and septic shock. No further fluid infusions of any kind of crystalloids,

colloids, and blood are given. The urinary loss should not be replaced as this represents a surplus in the body and must be discarded otherwise defeats the objective of treatment.

Addendum: Relevant Articles on the History of the TUR Syndrome and ARDS

This addendum is dedicated to important landmark articles on the history of the TUR syndrome and ARDS that could not be fitted directly on the above-focused narrative review on how the TUR syndrome has been reincarnated into ARDS. It is optional reading for the interested reader, but it completes this review. The first part is dedicated to eminent authors on the TUR syndrome and ARDS whether directly or indirectly. The second part is a section on self-references by the author that report important issues that highlight aspects of the presentation.

A. Other Eminent Authors

Creevy was the first author to report the TUR syndrome as acute water Intoxication [49]. Ashbaugh et al were the first to report ARDS in the Lancet in 1967 [50]. Lessels et al reported in a letter to the editor as the only article on death during prostatectomy [51]. Hendry was first to report that the osmotic pressure of various body fluids is the same as plasma [52]. Guyton and Coleman reported the negative pressure of the subcutaneous space of -7 cm water, a fact that cannot be explained by Starling's law [53]. Calnan et al reported the negative pressure in lymphatic vessels [54]. Renkin was the first to call for reconsideration of Starling's law [55]. The Coshran injuries Group, Finfer, Vincent, and futier et al demonstrated that oncotic pressure does not work and the argument on albumin versus saline is obsolete [56-59].

B. Self-references

Articles 60 and 61 have educational and entertainment value. Articles 62 and 63 show the relevance of my work on ARDS to Covid-19 pandemic ARDS. Article 64- 66 corrects other received misconceptions on capillary physiology to augment the discovery of the G tube hydrodynamics and its impact on the capillary-ISF transfer. Articles 67 and 68 reports the two clinical studies on which the above article is based. Article 68 corrects some errors and misconceptions on fluid therapy. Article 70 is on preventing renal failure in critically ill patients. Article 71 reports my Experience

with cystoprostatectomy with “prostatic capsule sparing” for orthotopic bladder replacement. Article 72 is on Features and Complications of Nephroptosis Causing the Loin Pain and Haematuria Syndrome. Article 73 reports “New Discoveries in Medicine and Physiology Originated in Urology”. Article 74 is on an Update on Ghanem’s new scientific discoveries in physics, Physiology, and Medicine, Article 75 is on Goodbye Starling’s law, hello G tube [60-76].

CONCLUSION

The TUR syndrome as defined and characterized with acute dilutional hyponatremia will no longer be seen in urology after the use of saline as irrigating solution in endoscopic surgery. However, the ARDS will replace it with the identical clinical picture of MODS that continues to occur with high morbidity and mortality that is underrecognized and underestimated. The ARDS is common in clinical practice and is induced by excessive sodium-based fluid infusion and is likely to occur in urology due to the added risk of irrigating fluid absorption and infusion through periprostatic veins. Neither the toxic theory nor the septic theory plays a significant assumed role in the pathogenesis of the TUR syndrome and ARDS. Both are iatrogenic complications of fluid therapy, induced by VO of > 3 L in <1 h time and is severe at 7-10 L of retained fluid VO in surviving ARDS patients while mortality occurs with 12 L, and both have preventative and curative therapy of HST of 5% NaCl and/or 8.4% NaCo₃. The TUR syndrome as defined and characterized with acute dilutional hyponatremia will no longer be seen in urology after the use of saline as irrigating solution in endoscopic surgery. However, the ARDS will replace it with the identical clinical picture of MODS that continues to occur with high morbidity and mortality that is underrecognized and underestimated. The ARDS is common in clinical practice and is induced by excessive sodium-based fluid infusion and is likely to occur in urology due to the added risk of irrigating fluid absorption and infusion through periprostatic veins. Neither the toxic theory nor the septic theory plays a significant assumed role in the pathogenesis of the TUR syndrome and ARDS. Both are iatrogenic complications of fluid therapy, induced by VO of > 3 L in <1 h time and is severe at 7-10 L of retained fluid VO in surviving ARDS patients while mortality occurs with 12 L, and both have preventative and curative therapy of HST of 5% NaCl and/or 8.4% NaCo₃.

CONFLICT OF INTEREST

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