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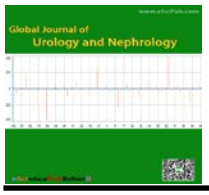

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The transurethral resection of the Prostate (TURP) syndrome and acute dilutional hyponatraemia (HN): A comprehensive literature review from first incidence in 1947 to disappearance in 2018

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ABSTRACT

Introduction and objective: To report on the literature review on the TURP syndrome from its first report in 1947 to disappearance from urology in 2018

Material and methods: The literature on the TURP syndrome from 1947 to 2018 was reviewed. We summarise the evidence on its incidence, prevalence, patho-aetiology, clinical picture and management. With the introduction of normal saline as irrigating fluid for the TURP procedure, the TURP syndrome as characterised with hyponatraemia (HN) has been eradicated. We introduce the concept of volumetric overload shocks (VOS) to be prepared when another syndrome induced by saline overload strikes.

Results: The TURP syndrome is induced by massive absorption of the sodium-free irrigating fluid and is characterized with acute dilutional HN- hence it is eradicated with use of saline as irrigant. It presents with shock and multiple vital organ dysfunction and was easily mistaken for one of the recognised shocks calling for further volume expansion with isotonic solutions with disastrous consequences. Identifying the concept of VOS does not only help in the management of the TURP syndrome but also with recognizing the syndrome induced by saline overload. Hypertonic sodium therapy has proved effective in treatment.

Conclusion: The review demonstrates that VOS in clinical practice is of two types; Type 1 (VOS1) induced by sodium-free fluid and type 2 (VOS2) induced by sodium-based fluids- the later has no serum marker of HN. Both conditions present with multi-system organ dysfunction but one system may predominate. VOS2 presents as the adult respiratory distress syndrome.

Keywords: Hyponatraemia; shock; the transurethral prostatectomy syndrome (TURS); the adult respiratory distress syndrome (ARDS), Starling's law, Capillary hydrodynamics

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About this review

This review summarises the documented literature on the transurethral resection of the Prostate (TURP) syndrome and acute dilutional hyponatraemia (HN) since its description in 1947. It covers its incidence, predisposing factors, hypothesis for pathogenesis, the reported clinical and biochemical features and methods of investigation. It outlines its incompletely understood aspects and controversial issues on its diagnosis and management. It also covers the most recent advances in its patho-etiology and treatment.

Introduction

The TURP procedure has long been recognised as the safest method of prostatectomy (Mitchel 1970), and is currently the operation of choice for prostatic enlargement. However, like any other operation, it has its complications both general and specific. Specific complications may be immediate such as severe bleeding and the TURP syndrome or delayed such as urethral stricture formation.

The TURP syndrome is one of its acute complications with an average postoperative mortality of 1.59% (Whitefield and Hendry 1985). Other authors have calculated that it accounts for a morbidity of 17-24% and a mortality of 1-2% (Chilton et al 1978, Sellevold et al 1983). Based on a prospective study an incidence of 7% with a mortality of 1% was reported (Rhymer et al 1985). Since 10% of males above the age of 40 years will, sooner or later, become candidate for prostatectomy (Editorial Br Mede Jour 1980), the total number of patients at risk from this complication is considerable (Sellevold et al 1983).

What is the TURP syndrome?

The TURP syndrome has no clear definition that allows clear clinical diagnosis. It is described as the reaction seen when a patient undergoing the TURP procedure absorbs a large volume of the irrigating electrolytes-free fluid causing HN of < 120 mmol/l (Sellevold et al 1983, Rhymer et al 1985, Whitfield and Hendry 1985, Ghanem and Ward 1990). It occurs during or soon after the operation and may have a mortality of >50% of affected patients (Osborn et al 1980, Allen Et al 1981).

Controversial Issues

The definition, aetiology, pathogenesis, diagnosis, management and the mere existence of the TURP syndrome remain controversial issues among urologists. However the documented evidence shows that the TURP syndrome is undoubted reality (Rhymer et al 1985, Whitefield and Hendry 1985, Ghanem and Ward 1990). It is believed that the syndrome is caused by either HN or hypervolaemia or water intoxication or a combination of these factors resulting from the systemic absorption of the irrigating fluid such as 1.5% glycine (Roa 1987). The cause of coma is attributed by some authors to ammonia intoxication (Roesch et al 1983, Ryder et al 1984, Shepard et al 1986, Hoekstra et al 1983). Based on prospective study (Hahn et al 1998 and Zhang 1996, Hahn RG 1996) concluded that the toxicity in the TURP syndrome is caused by glycine. Professor Hahn et al reported 480 articles of which >340 articles are on TURP syndrome [PubMed search December 2016] investigating the fluid and electrolytes dynamics (1987, 1990, 1993, 1994, 1997), effect of over-hydration on cardiac muscle (1996) and other tissues (1996), effect on renal function (1996) and compared Glycine to Mannitol (1998). Professor Hahn favoured the toxicity of Glycine as the patho-etiological cause of TURP syndrome.

Recently it has been reported that the syndrome may complicate any endoscopic procedure (Rao 1987) as well as percutaneous nephrolithotomy (Whitefieeeld and Mills 1985). Less recognized observation is that the syndrome is not unique to urology: similar but differently labelled syndromes may affect surgical, medical and obstetric patients (Ghanem 1985) commonly reported as HN (Arief et al 1976, Arief 1986, 1992, 1993, Ayus

and Arieff 1997, Ayus et al 1987). Its unique clinical presentation affords an excellent clinical model for studying the pathological effects of excessive fluid overload and its biochemical, osmotic and clinical sequalae.

Historical Background

Creevy (1947) first described the TURP syndrome as acute water intoxication that lead to intravascular haemolysis, jaundice and acute tubular necrosis and death from renal failure at the time when water was used as the irrigating solution during the TURP procedure (Creevy 1947, 1951, Creevy and Webb 1947, Mclaughlin 1947, Goodwin 1951). Creevy credited both Foley and Mclaughlin for similar and independent observations. Foley observed red urine, due to intravascular haemolysis, spurting from the ureteric orifices during the TURP procedure (Creevy 1947).

Non-haemolytic irrigating solutions were then introduced. Creevy used glucose and Nespit experimented with glycine. Nesbit outlined the criteria for a suitable irrigant as non-electrolyte, non-haemolytic, non-toxic, transparent and cheap (Nesbit and Glickman 1948). Glycine was preferred to glucose because of the hyperglycaemia that may complicate the use of glucose solutions (Nesbit and Glickman 1948). Urea, Mannitol and cytal (mainly composed of sorbitol and mannitol) and other irrigating fluids were introduced later (Marmer and Allen1970, Norris et al 1973).

The introduction of non-haemolytic solutions was considered the most important advance of transurethral surgery (Emmett et al 1969). Such solutions are non-haemolytic to red blood cells but may be either hypo- or iso-osmotic to the plasma. Plasma osmolality measures 280-300 mosm/l while that of 1.5% glycine is reported to be 220 but actually measures 195 mosm/l by freezing point depression.

Non-haemolytic solutions have reduced the morbidity and mortality of the TURP syndrome, as compared to water intoxication, by half from 50% and 4% respectively (Creevy 1951, Goodwin et al 1947). Red cell haemolysis and its consequences such as haemoglobunaemia, tubular necrosis, renal failure and jaundice have become no longer features of the TURP syndrome (Hagstrom 1955), but a complex clinical syndrome has continued to occur (Berg et al 1962).

Aetiology

Although the cause of the TURP syndrome remains controversial, it has become clear that it is associated with the systemic absorption of a large volume of the sodium-free irrigating fluid (Raw 1987). Fluid absorption may occur through the peri-prostatic venous plexus of veins directly into the circulation (Griffin et al 1955, Maluf et al 1956, Whitefield and Hendry 1985), through the retroperitoneal space when prostatic capsule is perforated or through the peritoneal membrane in cases of intra-peritoneal perforations (Thomas and Hale 1984).

Predisposing factors

Local

- The absorbed fluid volume: A volume of 4-7 litres of the irrigating fluid has frequently been reported to precipitate a fatal TURP syndrome (Bird et al 1982, Logie et al 1980). The volume in a non-complicated TURP procedure ranges between 0-1200 and averaged 300 ml (Sellevold et al 1983).The correlation between the volume of absorbed irrigant and it chemical, osmotic and clinical sequalae was reported by (Hahn et al 1987, 1990, 1996 and Ghanem and Ward 1990). Hahn (1996) found that one litre of glycine induces reduction of serum sodium concentration of 7 mmol/l. Ghanem reported that a volume of 3.5-5 litres induces a serious TURP syndrome.
- The intravesical pressure is proportional to the volume of absorbed irrigant (Rao et al 1983). In the intermittent irrigation method, this depends on the pressure of irrigating fluid in prostate fossa as measured by the height of the irrigating reservoir above the

patient. It has been recommended to limit the height of reservoir to 80 cm water head. Using the continuous suction resectoscope was thought to avoid bladder distension and minimize fluid absorption but some recent reports question this. Rao (1983) found that the intravesical pressure under continuous irrigation and suction resectoscope to be 35-40 cm water. Such pressure is well above the pressure in prostatic veins and fluid absorption may occur.

- Duration of resection: It has been reported that the longer resection time the greater the absorbed volume of the irrigating fluid and the higher the chance of developing the TURP syndrome (Rhymer et al 1985). A one hour resection time has been recommended as the maximum safer time for the procedure particularly in less experienced hands. However there are exceptions when the TURP syndrome occurred after a resection time as short as 15 minutes and a resected tissue weight as small as 10 grams.
- Experience of the resectionist: Experience, or rather the lack of it, is an important factor that may predispose to the TURP syndrome yet the most difficult to assess. The TURP procedure is highly technical operation that requires prolonged training which is obtained when the young surgeon does the operation on his own. It has been said that a resectionist has to perform 100 operations before he becomes fully oriented with the endoscopic anatomy, master the resection and haemostatic techniques and acquire the skills that enable him to recognize capsule perforation early.

The TURP syndrome tends to occur when least expected. Awareness of the condition and early recognition of perforations may lead to abandoning the TUR procedure to avoid excessive fluid absorption or giving the correct treatment thus saving the patients from a fatal reaction.

Systemic

1) The TURP syndrome occurs when the volume of the absorbed and intravenously infused fluids far exceeds the patient's maximum renal excretory ability for water. Excess antidiuretic hormone (ADH) secretion as result of drugs, anaesthesia and surgical trauma further impairs water clearance (Beirne et al 1965, Bear and Neal 1983).
2) The clinical diagnosis of the TURP syndrome is difficult to differentiate from shock, cerebrovascular accidents and myocardial or respiratory infarction which lead to extensive investigations and delay in treatment (Harrison III et al 1956, Bird et al 1982).
3) The treatment of acute HN and water intoxication has remains controversial among physicians. The conservative approach aiming at slow correction of serum sodium with isotonic saline has remained predominant till now ((Arieff 1986, Stern et al 1986, Narins 1986, Swales 1987, Halberthal 1996). It is considered that the rapid correction of serum sodium using hypertonic saline is dangerous as it may cause brain damage such as central pontine myelinolysis. Such evidence, however, is derived from a subgroup of chronic hyponatraemic patients who suffer from alcoholic malnutrition. Although conservative treatment may be adequate in the management of chronic HN, the situation of acute dilutional HN seen in the TURP syndrome and induced by excessive fluid gain is different.
4) The cardiovascular paradox of hypotension and law central venous (CVP) pressure seen in the TURP syndrome despite volumetric overload (Sellevold et al 1983) may be attributed to hypovolaemic, haemorrhagice or septicemic shocks (Spencet Hoyt 1958). This may call for further volume expansion of the cardiovascular system with blood, colloids

and isotonic saline fluids with grave consequences. Failure of vital organs such as the brain, heart, lung and kidneys may occur as result of volumetric overload (Ghanem 1985, 1987, 1988, 1990, 2016, 2017).

Pathogenesis

The bizarre presentation of the TURP syndrome with multi-organ dysfunction such as coma, shock, myocardial infarction, respiratory distress, liver and renal failure explains some of the confusion regarding its pathogenesis. Since the introduction of non-haemolytic irrigating fluids, acute water intoxication has become no longer an adequate explanation particularly as intra vascular haemolysis is not a feature (Sullevold et al 1983). Hence water intoxication, HN (Harrison III et al 1956, Rhymer et al 1985) and hypervolaemia (Griffinn et al 1955, Osborn et al 1980) has been used interchangeably to explain the pathogenesis of the TURP syndrome.

However, as no clear patho-physiological explanation was proposed further theories for explaining the picture of the syndrome were introduced. Ammonia intoxication (Roesch et al 1983, Hoekstra et al 1983, Shepard et al 1987), acid phosphatase intoxication (O'Donnell 1983) and hypocalcaemia (Rhymer et al 1985) were proposed to explain its complex pathogenesis. "Is the TURP syndrome myth or reality?" was a question posed in a prospective study to which the conclusion was "myth" (Bertrand et al 1983). This in a way summarizes the prevailing understanding of this syndrome. The evidence for and against each of these hypotheses is x

amined in order to identify the true pathogenesis of the TURP syndrome.

Current Hypotheses:

1) Acid phosphatase Toxicity:

This is the least accepted theory which suggests that the post operative increase in serum acid phosphatise in some patients suffering from the TURP syndrome who had benign prostatic enlargement and normal preoperative level may be responsible for the toxic manifestation of the TURP syndrome (O'Donnell 1983). However, levels >1000 IU/L are known to occur with prostatic carcinoma without causing toxic manifestations. No other reports have confirmed acid phosphatise elevation in association with the TURP syndrome.

2) Ammonia Toxicity

Hoekestra et al (1983) proposed ammonia toxicity to explain the cerebral features, particularly coma, seen in the TURP syndrome. Other authors have detected an abnormal level of serum ammonia in some patients suffering a severe Syndrome (Roesch et al 1983, Ryder et al 1984, Shepard et al 1986). Predictably serum glycine may increase following excessive absorption of the glycine irrgant. Hence it was assumed that ammonia was produced from the absorbed glycine and is responsible for the cerebral toxic manifestations of the TURP syndrome. It cannot be argued that ammonia causes cerebral toxic signs such as coma. However, the origin and cause of increased serum ammonia in some patients suffering from the TURP syndrome is not confirmed. Ammonia may be of endogenous origin rather than the absorbed glycine, and may be a metabolic product seen in some cases of the TURP syndrome for the following reasons:-

A Hyperglycinaemia itself may be asymptomatic and does not necessarily lead to hyper ammonaemia particularly when liver function is normal

B Glycine is normally metabolized into oxalate by the liver (Raw 1987). Ammonia is produced by glycine deamination as by product that is quickly converted into urea. The increase in serum ammonia may occur only as a result of liver and muscles dysfunction. Landis and Steinhardt (1983) stressed this fact on their editorial comment on the article by Hoekstra and colleagues who proposed the hypothesis of ammonia. They sated: "hepatic and muscle dysfunction are the most common cause of hyperammonaemia".

3) The TURP syndrome has been reported following the absorption of glycine-free fluids such as mannitol (Logie et al 1980), glucose (Allen et al 1981) and cytal (Norris et al 1973) which do not yield ammonia. The cerebral features of acute HN induced by inappropriate fluid replacement using 5% glucose is identical to that of the TURP syndrome. In this condition neither ammonia nor glycine are involved.

Hence, it is not known whether serum hyperammonaemia causes the TURP syndrome or is merely one of several metabolic by products that arise as result of excessive fluid overload leading to the multiple vital organs dysfunction. Furthermore, the therapeutic value of this pathological mechanism in treating patients suffering from the TURP syndrome is yet to be proved.

3) **Fluid overload**

Currently there is general agreement that the TURP syndrome is precipitated by the excessive absorption of the irrigating 1.5% glycine that may complicate any endoscopic procedure (Raw 1987). Fluid overload underlies the mechanism of acute water intoxication, HN and hypervolaemia which have long been used interchangeably to explain the patho-etiology of the TURP syndrome. Although correct on principle, each of these mechanisms has failed individually to satisfactorily explain the complicated pathological mechanism and the bizarre clinical picture of the TURP syndrome. This has given rise to the above toxic theories and caused much confusion as regards the diagnosis and management.

Sodium-free fluid overload, either absorbed or infused, causes dilutional HN among other biochemical abnormalities. Also fluid overload implies water intoxication and hypervolaemia. The picture of the TURP syndrome deviates from the classical picture of acute water intoxication. The pathological effects of hypervolaemia are by no means clear or fully understood. The questions of:"how much fluid, of what type when and how would it induce the bizarre picture of the TURP syndrome?" are the aim of this review. Further discussion will follow after outlining the clinical picture.

Clinical Picture

The clinical picture of the TURP syndrome reflects multi-system dysfunction. Vital organs are affected singly or in combinations (Marks and Orkin 1962, Bird 1982). The central nervous system (Hinderson and Midleton 1980), cardiovascular system (Osbon et al 1980, Charlton 1980) and respiratory system (Jackobson 1965) are affected. Annuria which is resistant to diuretics is a feature (Oester and Masden 1969, Bird et al 1982). Coagulation disorders (Colapinto et al 1973) and hepatic dysfunction may also occur (Wakim 1971).

The cerebral features:

Manifestations of the cerebral nervous system are recognized early in the conscious patient who received regional anaesthesia (Still and Model 1973). Mild signs such as confusion, disorientation, restlessness, apprehension, burning all over the body, irritability, lethargy, headache, muscle twitching, nausea and vomiting are commonly observed early features. Visual disturbance and transient blindness have also been reported (Cicarelli et al 1961, Norris et al 1973, Kay et al 1985, Sadaba et al 2006).

The patient may progress to severe signs such as convulsion, coma with fixed dilated pupils and bizarre types of paralysis which mimic cerebro-vascular infarctions. Coma and paralysis may be the presenting signs in patients who had general anaesthesia from which he fails to recover. Intensive investigations may be embarked upon causing delay in treatment. Not uncommonly the diagnosis may be missed leading to permanent brain damage or death (Arieff 1986).

The cardiovascular features:

Cardiovascular manifestations include a transient phase of hypertension and bradycardia which is followed by hypotension and bradycardia (Logie et al 1980). Hypotension may be also associated

tachycardia – a confusing situation that mimics hypovolaemic shock and may lead to misguided attempt to give more isotonic fluids and blood transfusions (Whitefield and Hendry 1985).

Other types of cardiac dysrhysthmia may occur. Electrocadriographic (ECG) changes may suggest ischaemia or infarction. They include wide QRS complex of increased amplitude, depressed S-T segment, T wave inversion and dysthrethmias (Sellevold et al, Berg et al 1962). Elevated cardiac enzymes have been reported, in the absence of vascular ischemia, during a routine TURP procedure and it has been reported in the TURP syndrome (Charlton 1980, Strom 1984, Evans et al 1992). Interestingly the same findings were found in dogs overloaded with cytal (Berg et al 1962).

An early increase and later decrease in CVP, pulmonary capillary wedge pressure and cardiac output occurs (Sellevold et al 1983). Cardiac arrest may occur unexpectedly (Charlton 1980).

Transient hypertension and bradycardia appear first in the anaesthetised patient. When these changes are overlooked during the procedure, delayed recovery from the anaesthetic may progress directly to convulsion, coma, respiratory or cardiac arrest (Henderson and Midleton 1980, Jackobson 1965).

The respiratory features:

Respiratory manifestations of the TURP syndrome are those of pulmonary oedema and the adult respiratory distress syndrome (ARDS) (Sellevold et al 1983). The increase in lung water has been confirmed by the decrease in electrical thoracic and cardiac impedance (Casthely et al 1981). Basal pulmonary crepitation, coarse bubbling, frothing around the mouth, cyanosis and decreased arterial oxygen, in spite of good oxygenation, may progress to respiratory arrest or prolonged respiratory insufficiency (Jackobson 1965, Castheley 1981).

The renal Features:

Annuria is a feature of acute renal failure which occurs in the TURP syndrome and is resistant to diuretics (Bird et al 1982, Ghanem et al 1987). However, annuria may be masked by the use of catheter irrigation. Serum urea and creatinine are increased later (Harrison III et al 1956).

Other systemic features:

Massive peritoneal and pleural effusions have been reported in the TURP syndrome (Rhymer et al 1985, Lessels et al 1982). Abdominal pain in the absence of bladder perforations may occur, as may small and large bowel ileus (Norris et al 1973). Venous bleeding from the prostatic veins may occur towards the end of the procedure and may be difficult to control. In this type of bleeding no coagulation abnormalities are detected (Norris et al 1973). It is due to the early venous engorgement as a result of hypervolaemia (Whitefield and Hendry 1985). Other bleeding syndromes due to coagulation abnormalities or disseminated intravascular coagulation may occur later (Friedman et al 1969, Editorial JAMA 1969).

BIOCHEMICL ABNORMALITIES

Serum Electrolytes

The most consistent biochemical alteration of the TURP syndrome is acute HN (Harrison III et al 1956, Rhymer et al 1985). A drop in serum sodium of >20 mmol/l or a level <120 mmol/l characterizes the TURP syndrome (Desmond 1970, Still and Modell 1973). It is believed that HN results from the dilutional effect of the absorbed fluid, rather than sodium loss in urine (Harrison III et al 1956, Ceccarelli 1961). Minimal amount of sodium may be lost in urine during the TURP procedure. In other words the HN of the TURP syndrome is dilutional and total body sodium is normal.

The concentration of other plasma constituents are reduced (Ghanem and Ward 1990) such as calcium, chloride, magnesium, phosphorus, bicarbonates, total proteins and albumin are also reduced as is haematocrit and

haemoglobin (Colapinto et al 1973, Norris et al 1973, Wakim 1971, Desmond 1970). Alteration of pH, pO^2, and pCo^2 may follow the lines of ARDS and shock particularly at later stage despite assisted ventilation. Serum potassium and glucose may remain unchanged or increase (Wakim 1971). The serum urea concentration is invariably elevated in cases of the TURP syndrome.

Serum osmolality

There are little reports on the changes of omolality in the TURP syndrome. The documented evidence is so variable that it appears contradictory. Osmolality changes during the TURP procedure we prospectively studied by Sellivold et al (1983) but neither osmolality change nor cases of the TURP syndrome occurred. Several authors have reported that serum osmolality may show little change. Osmolality may remain unaffected following massive fluid absorption despite remarkable fall in serum sodium and electrolytes (Desmond 1970, Norris et al 1973, Sellevold et al 1983). Other authors have reported an increase in serum osmolality when the absorbed fluid is made of osmotically active substances such as mannitol or glucose.

Desmond (1970) and Norris et al (1973) observed that a drop in serum osmolality following glycine absorption correlates well with the severity and fatality of the TURP syndrome. Wright and Gann (1962) showed that a reduction in serum sodium to 120 mmol/l is asymptomatic when osmolality is maintained. Kirschenbaum (1979) reported a patient in whom sodium fell to 99 mmol/l following the absorption of 3% mannitol during the TURP procedure , who remained asymptomatic and recovered fully. The author attributed his recovery to the fact that his serum osmolality was normal despite his severe HN.

Ghanem (1985, 1987, 1988), and Ghanem and Ward (1990) reported that hypo-osmolality occur after 24 h in patients who survive the TURP syndrome and correlates well with the severity of cerebral morbidity.

Investigations

Determining the volume of absorbed 1.5% glycine:

Several authors have used indirect techniques to evaluate the volume of absorbed glycine. Volumetric, radio-isotopic and and isogravimetric methods have been used (Griffin 1955, Taylor 1958, Oester and Masden 1969). Hahn used alcohol exhalation method to monitor absorption (1990, 1993). The volume of absorbed fluid that precipitates severe case of the TURP syndrome is 3-5 litres. Hence the simplest method of measuring fluid absorbed either by the change in body weight or measuring the deficit of glycine irrigant after the operation (Ghanem and Ward 1990).

Difficulties in investigating the TURP syndrome:

Despite extensive investigations over the last 70 years, the TURP syndrome's pathogenesis remains uncertain and no real progress has occurred to enhance our standing of its aetiology, pathogenesis and management (Emmitt et al 1969, O'Donnel 1983). This is perhaps due to the following difficulties encountered in investigating the TURP syndrome:-

1. Technical difficulties in keeping accurate fluid balance during and after the TURP procedure due to the use and the unavoidable spillage, of a large volume of the irrigating fluid.
2. Difficulties in estimating blood loss and urine excretion. Blood loss is subjectively assessed by the surgeon that may be quite misleading (Whitefield and Hendry 1985, Ghanem and Ward 1990).
3. Difficulty in clinically differentiating the TURP syndrome from other types of recognized shocks such as haemorrhagic, cardiogenic, hypovolaemic and septic (Bird et al 1982, Ghanem 2016, 2017, 2018).
4. Lack of predetermined criteria to identify susceptible patients (Norris et al 1973). An elderly and frail patient may escape the

condition if little irrigating fluid is absorbed, while a young and fit patient may suddenly and unexpectedly succumb to it when a large fluid volume is gained.

5. The majority of patients undergoing the TURP procedure absorb small volume of fluid ranging between 0-1200 ml with an average of 300 ml (Sellevold et al 1983). Pooling the minority who gain large volume with the majority who absorb little volume may give misleading statistical conclusions in prospective clinical trials.
6. The human body is blessed with such degree of tolerance and resilience mediated through powerful haemostatic mechanisms that may adequately handle a large volume overload. Yet there is limitation. It is also so dynamic that available statistical techniques are unable to detect the offending cause.
7. In contrast to the extensive currently known knowledge on the pathological effects of hypovolaemia and dehydration little is known about hypervolaemia, overhydration and hypo-osmotic changes that may occur when the oral route is by-passed and can be detrimental in patients on border line decomposition. This fact is compounded by difficulties in investigating and understanding physiological forces that regulate fluid transfer and osmotic shift across the capillary and cell membrane (Ghanem 1985, 1987, 2001, 2016). It is my contention that critical evaluation of the physiological law, namely Starling's law for the capillary interstitial fluid transfer, that underlies the principles for fluid and electrolytes management in surgical patients, is required.

MANAGEMENT

The management of the TURP syndrome just like acute HN induced by inappropriate fluid replacement is difficult and problematic. Despite agreement that the TURP syndrome is precipitated by the absorption of irrigating glycine making a correct and timely diagnosis is difficult. When the exact diagnosis is agreed upon there is disagreement on how best it should be treated due to the lack of exact diagnosis. Ghanem (2016, 2017, 2018) has changed all that by defining the role of volumetric overload shocks in the pathoaetiology of the TURP syndrome and acute HN and affirming that 5% NaCl is a highly successful treatment for it.

Preventative measures

Local:

Attention has been given to local measures in order to prevent or minimize irrigating fluid absorption during the TURP procedure. These include:-

1) Maintaining a low irrigating pressure either by using a continuous suction resectoscope, lowering the height of irrigant reservoir to 60 cm above the bladder (Madsen and Naber 1973, Reuter and Reuter 1978) and avoiding of bladder over distension (Whitefield and Hendry 1985).
2) Limiting the operative time to 1 hour while employing a good swift and careful operative resection technique by an experienced surgeon (Iverson Hanson et al 1978).
3) Early recognition of prostatic capsule or bladder perforation and abandoning the procedure in order to minimize fluid absorption (Marmer and Allen 1970).
4) Avoidance of opening venous sinuses by leaving a rim of prostatic tissue lining the capsule. Prompt control of haemorrhage by catheter tapenade (Whitefield and Hendry 1985).

Employing these local preventative measures should have, theoretically, eradicated the TURP syndrome. Practically, the TURP syndrome still strikes when least expected. Although local measures have made the TURP syndrome even more rare in the hands of some surgeons, it has not been totally eliminated (Wakim 1971). Evidence have accumulated to show that the TURP syndrome may occur when the operative time is as short as 15 minutes, and when the resected weight of prostate is less than 10

grams (Norris et al 1973). Also it has been reported that the volume of fluid absorption is neither related to the type of irrigation system used (Continuous or intermittent) nor to the age of the patient nor his preoperative state of physical fitness (Rhymer 1985).

Systemic

The evidence indicates that in addition to the local factors other systemic factors play a role in precipitating the TURP syndrome. The volume of intravenously infused fluids augments the volume of fluid absorbed. The combined volume overload contributed by absorbed glycine and intravenously infused fluid may overwhelm the body's haemostatic mechanism and cause the TURP syndrome (Ghanem and Ward 1990).

Gale and Notley (1985) believe that the TURP syndrome may be avoided by dehydrating the patient, avoiding intravenous drip and postoperative irrigation all together in order to minimize fluid overload and dilutional HN. However, other authors recommend a large bolus of intravenous fluid infusion using glucose 5% during the TURP procedure in order to promote dieresis and prevent clot retention postoperatively. This is a generally adopted policy in the management of patients undergoing the TURP procedure.

Treatment:

Like acute HN the treatment of the TURP syndrome is highly controversial. There are two almost opposing schools.

The conservative approach has been predominant until 1988. It is based on fluid restriction and giving diuretics in high doses. Slow correction of serum sodium using isotonic saline solutions and/or masterly inactivity may be adopted (Swales 1986). The leaders of this conservative approach also believe that giving hypertonic sodium and rapidly correcting HN is contraindicated as it causes cerebral complications (Arief 1976, Stern et al 1986, Swales 1987). Diuretics however may be totally ineffective (Bird et al 1982) and despite symptomatic and supportive treatment on ICU the outcome is totally appalling as it may cause death or severe brain damage (Arieff 1986).

The conservative approach is based on experience with chronic and drug induced HN which may differ from that seen in the TURP syndrome. Also the evidence that hypertonic sodium may cause cerebral complications is derived from a small group of HN patients who suffer alcoholic malnutrition.

The second group recommend the use of hypertonic sodium therapy (HST) and claim excellent results. This has been so far the school of minority. They consider acute HN to be dire emergency that require immediate and rapid correction by infusing HST (Harrison III et al 1956, Worthley and Thomas 1985, Ayos et al 1987, Ghanem 1987, 1990, 2017, 2018). There have been several case reports on the use of HST in the management of acute HN in a concentration of 1.8%, 3%, 5% and up to 30% (Worthley and Thomas 1985).

Harrison III et al (1956) pioneered the use of 5% NaCl in the treatment of the TURP syndrome. Norris et al (1973) advised against the use of HST in the treatment of the TURP syndrome. They used 3% NaCl in treating 2 patients in whom serum sodium dropped to 93 and 90 mmol/l. They also ignored their own advice of avoiding further volume overload and infused their patients with large volume of blood and isotonic fluids prior to the use of HST. These two patients were thought to suffer hypovolaemic shock despite massive volume overload. This paradox was highlighted by Ghanem (2016, 2017, 2018) in recognizing volumetric overload shock (VOS).

Based on a prospective study incorporating 33 patients who suffered the TURP syndrome and inappropriate fluid replacement, rapid correction of serum HN using HST of 5% NaCl was found safe and effective (Ayos et al 1987). This was the first available prospective study on this subject which is a remarkable and welcome support by a medical team headed by Professor Arief who is one of the world leaders

on the subject of HN. He switched from the conservative to HST within a space of 1 year (Arieff 1986, Ayus et al 1987). Hypertonic sodium therapy of 5% NaCl is now considered the treatment of choice for the TURP syndrome and acute dilutional HN.

The role of water intoxication, HN and hypervolaemia in the pathogenesis of the TURP syndrome: Recognizing volumetric overload shocks.

About this review part:

Glycine absorption is responsible for aetiology of the TURP syndrome in which shock, generalized cellular intoxication, and vital organ dysfunction are the salient features. Water intoxication, HN and hypervolaemia are considered the most accepted pathological mechanisms. How do they operate and how can it intoxicate cells is presented here.

Although these 3 mechanisms are intimately interrelated, an attempt is made to identify their accurate meaning and the individual part it play in inducing cellular toxicity. Although the clinical picture of acute water intoxication and acute HN is well known, the presentation of the TURP syndrome deviates from it to such an extent that either a toxic mechanism or a known type of shock such as haemorrhagic, hypovolaemic and septicaemic shock may be incorrectly incriminated.

Other clinical syndromes precipitated by a similar mechanism are pointed out. The serum marker of HN induced by sodium-free fluid overload may prove helpful in identifying volumetric overload induced by saline that lack such marker. Two new types of volumetric overload shocks have been recognized and are summarised here.

Introduction

The dangers of fluid overload are well known, yet the line between normal and overhydration particularly in a surgical patient is far from clear. Overhydration may be an easy to make diagnosis retrospectively when its pathological and clinical picture such as pulmonary oedema and heart failure become evident. However the transition from normal to hyper-volumetric state in an anaesthetised patient may occur without observing any changes in well monitored cardiovascular-respiratory parameters. Volumetric overload with sodium-free fluids has HN as biochemical marker but isotonic saline overload lacks such marker. The question whether these types of volumetric overload are capable of causing cellular toxicity and vascular shocks is presented here.

From a clinical point of view, once the normal gastro-intestinal tract is bypassed, we subject the patient to an over or under supply of fluid volume, electrolytes, osmotic load and caloric intake. We depend on the wisdom of the body to correct our mistakes by the means of kidney compensating mechanism, but this may be the “coup de grace” to the critically ill patient. In contrast to current abundant knowledge on the pathological effect of hypovolaemia and dehydration, the pathological effects of volumetric overload and over hydration are vague and confused. The TURP syndrome offers a unique clinical example to study volumetric overload.

Water intoxication:

The classical description of acute water intoxication was reported by Rowntree (1923). It is characterized by intravascular haemolysis and haemoglobinaemia (Creevy, 1947 Berg et al 1962). An initial increase of arterial pressure is followed by convulsion, coma, cyanosis and frothing around the mouth. Respiratory and cardiac arrest lead to instant death. Such picture was seen in early cases of the TURP syndrome when water was used as an irrigant (Creevy 1947, McLaughlin 1947) but is rarely seen in current clinical practice.

Water intoxication was induced in 20 dogs by intravenous infusion of water which reduced serum sodium to 115 mmol/l. This caused marked haemoglobinaemia in all animals, of whom eight dogs died and 12 survived (Berg et al 1962). In another group of dogs a similar volume of cytal induced HN of <100 mmol/l. All

dogs survived and there was neither haemoglobinaemia nor a drop in serum osdmolality. The authors attributed morbidity and mortality to the drop in serum osmolality rather than haemoglobulinaemia or HN. Wright and Gann 1962) reached a similar conclusion based on a clinical study.

It is clear that water causes cellular toxicity because of the hypoosmolality it induces. The use of isotonic fluids allowed a greater volume to be tolerated, and have also modified the clinical picture of the TURP syndrome.

Hyponatraemia (HN):

Definition and types

Hyponatraemia is defined as reduction in serum sodium concentration below 130 mmol/l (Chung et al 1986). It may be acute or chronic and may or may not be symptomatic. Hyponatraemia may be due to sodium loss in urine by drugs such as diuretics or dilutional due to fluid overload. Chronic HN is usually associated with the syndrome of inappropriate anti-diuretic hormone and sick cell syndrome (Arieff 1976, Sterns 1986).

Incidence and prevalence

Hyponatraemia in which serum sodium is <130 mmol/l is one of the most commonly encountered biochemical abnormality in clinical practice (Devane et al 1983). Most cases are asymptomatic. Batuman et al (1984) found that HN affects 33% of patients receiving parentral nutrition (range 114-129 mmol/l). In a prospective study involving surgical patients, Chung et al (1986) found post-operative HN to affect 23.1% cardiovascular, 18.9% Gastrointestinal and billiary and 92% renal transplantation patients. Anderson et al (1985) found that 1-2.5% of hospitalized patients had HN and was associated with a 60-fold increase in fatality.

The morbidity and mortality of acute HN is dependent on the level to which serum sodium drops and the rate of this fall. An acute reduction in serum sodium concentration of >20 mmol/l or to a level below 120 mmol/l is usually symptomatic, but may be asymptomatic if time is allowed for adaptation (Swales 1986) or osmolality is maintained

Hyponatraemia of the TURP syndrome

Hyponatraemia of the TURP syndrome is dilutional due to excessive absorption of the irrigant solution 1.5% Glycine. Cytal and mannitol induce the TURP syndrome and excessive glucose infusion may contribute to it. Urine sodium loss during TURP prostatectomy was measured by Ciccarelli and Mantel (1971) and has no significant contribution. In other words there is no deficit in the total body sodium.

Hyponatraemic shock

The concept of HN shock as a cause of the TURP syndrome was introduced by Harrison III et al (1956) and was reported earlier in Dogs (Danowski et al 1946). As biochemical marker HN has been accepted as diagnostic feature. However, a severe reduction in serum sodium concentration may be asymptomatic unless associated by a drop in osmolality (Ghanem and Ward 1990).

The above issue was investigated in animals (Berg et al 1962, Wakim 1971, Melton and Nattie 1983) and humans (Wright and Gann 1962, Norris 1973, Sellevold et al 1983, respectively. Glucose, glycine, cytal, mannitol and distilled water were used in inducing HN. Fluids were infused intravenously (Berg et al 1962, Wright and Gann 1962) or installed intra-peritonially (Melton and Nattie 1983). A drop in serum sodium concentration to 120 mmol/l could be induced in human volunteers using 5% glucose solution, following which patients remained asymptomatic. Asymptomatic HN caused no alteration in serum osmolality and was self-correcting (Wright and Gann 1962). These authors concluded that: “The concept of HN as a cause of shock following the TURP syndrome is not tenable”.

Melton and Nattie (1983) studied and compared the effects of induced hypo-osmotic and iso-osmotic HN on the brain cells and

cerebrospinal fluid in rats. One group was injected intra-peritoneally with water and the second group with isotonic mannitol, achieving the same degree of HN (103-109 mmol/l) in both groups. During hypo-osmotic HN serum osmolality and sodium concentration as well as those of cerebro-spinal fluid decreased as expected: the brain cells showed passive swelling. Rats suffering iso-osmotic HN had normal total brain water without cellular swelling, despite significant reduction of electrolyte contents of the cells. A remarkable case was reported by Kerschenbaum (1979) in which serum sodium dropped from 133 to 99 mmol/l after TURP using 3% mannitol as irrigant in which serum osmolality was normal and the patient recovered.

Hypervolaemia:

Definition

Hypervolaemia means an increase in the intra-vascular fluid volume. Odema refers to an increase of the interstitial fluid volume and cellular oedema refers to an increase in cellular volume. The term fluid overload is vague and suggests one or more of the above to describe a “hypervolumetric state” of which hypervolaemia is presumed to be a component.

Intravascular volume and pressures following fluid overload.

In cases suffering from the TURP syndrome, an initial rise in arterial blood pressure (BP) and central venous pressure (CVP) may occur but is transient features. Both BP and CVP drop later in spite of the massive volumetric overload (Sellevold et al 1983, Mommsen et al 1977). The actual intravascular volume in patients suffering from the TURP syndrome has not been measured. Blood loss during the TURP procedure averages 300 ml with a maximum of 1.3 litres (Redick and Walton 1973, Henderson and Midleton 1980, Ghanem and Ward 1990).

The initial hypertension and bradycardia are not consistent and may pass unnoticed. The Hypotension and low CVP occurring later in spite of volumetric overload are usually attributed to blood loss or septic shock, although is far out of proportion to the actual blood loss which is usually replaced. This clinical state of shock may misleadingly call for further fluid and blood infusions with disastrous bearing on the outcome of the TURP syndrome (Whitefield and Hendry 1985).

Berg et al (1967) measured the arterial and venous pressures and the blood volume changes in dogs overloaded with cytal. There was an initial rise followed by a fall in both pressures and blood volume. Neither septic nor haemorrhagic shock occurred in these experiments.

Clinical and experimental studies correlating the effect of fluid overload in terms of volume and tonicity to the resultant serum osmotic, volumetric and cardiovascular changes and their clinical sequalae were lacking until Ghanem and Ward reported their prospective study (1990).

Body fluid compartments:

A 70 kg man has a plasma volume of 3.5 litres (5% Body weight), an interstitial fluid volume of 11.5 litres (15%) and cellular fluid volume of 25 litres (40%). The vascular and interstitial fluid volumes are referred to as extra-cellular fluid (ECF) (Gamble 1949). Water movement across the cell membrane is controlled by osmotic forces which are affected principally by sodium and potassium ion distribution. All of these compartments are in iso-osmotic equilibrium.

The fluid volume absorbed during the TURP procedure

The volume of fluid absorbed during routine TURP procedure ranges between 0-1.3 litres with an average 0.3 litre (Sellevold et al). Such volume is probably insignificant. A volume of 4-7.5 litres of sodium-free fluid has frequently been reported to precipitate the TURP syndrome (Norris et al 1973, Logie et al (1980). An equivalent volume of fluid overload, mostly 5% dextrose, has been reported to precipitate an identical syndrome in surgical patients (Arieff 1986). Other similar syndromes

precipitated by excessive 5% glucose infusions are not uncommon in medical, surgical and obstetric patients (Ghanem1987).

Sodium-free fluid overload may be induced by mannitol, glucose, cytal and glycine solutions and induce proportional degree of HN (Norris et al 1973). From a volumetric point of view, 5 litres cannot be added and accommodated within limited intravascular space and shift to dilute ECF. Water may also shift to the intracellular space in order to restore osmotic balance between ECF and intracellular fluid (Swales 1986).

The TURP syndrome in which cardiac arrest occur during or immediately after the operation has been reported with massive absorption of glycine (Jackobson 1965, Charlton 1980, Osborn 1980) and with 3% mannitol (Still and Modell 1973, Maluf et al 1956, Allen et al 1981, Hutlen et al 1983) . The volume of absorbed fluid is usually unknown at the time of diagnosis. In the face of circulatory shock further intravenous infusions are given with disastrous results.

Saline overload

The pathological effect of saline overload is harder to detect as it lacks serological markers, though its pathological effects are described in animals (deWarner et al 1961). The clinical diagnosis of pulmonary oedema and heart failure are usually made retrospectively and subjectively. The clinical and cardiovascular pressure parameters on which basis fluid infusion is guided rarely give an early warning of overload particularly in an anaesthetised patient.

Furthermore the volume of saline that can be tolerated is 2-3 times greater than the volume of sodium-free fluid. When syndromes such as pulmonary oedema, adult respiratory distress syndrome (ARDS) and multiple organ failure complicate major surgery, although volume overload is usually reported association is rarely considered as a possible cause. Fluid overload of up to 10 litres has been reported with such syndromes (Ashbaugh et al 1967, Apple and Showmaker 1981, Tranbaugh and Lewis 1982).

In such situation, the intravascular pressure parameters such as CVP become useless in deciding whether to keep the patient on the “dry or wet” side (Apple and Shoemaker 1981). In my view, the problem here lies with Starling’s law for the capillary exchange; according to which further volume expansion is advised in order to keep vascular pressure up and maintain tissue perfusion. On the other hand it is clinically obvious that fluid overload already exists and further infusions should be withheld. This physiological law which dictates the principles underlying the decision on fluid and electrolytes management does require re-evaluation (Ghanem1987). Clinical and experimental evidence to prove that Starling’s law is wrong while providing an alternative for it is now available (Ghanem 2001, 2016, 2017, Pindoria 2017).

Similar syndromes

Recognized clinical syndromes that contribute, singly or in combination, to the TURP syndrome and have been described as parts of its clinical picture include: 1) Brain oedema that causes coma, convulsions and paralysis mimicking cerebro-vascular accidents (Still and Model 1973, Hinderson and Midleton 1980). 2) Pulmonary oedema (Jackobson 1965, Norris et al 1973, Sellevold et al 1983) and ARDS (Appel and Showmaker 1981). 3) Cardiac dysrhysthmia, arrest and failure (Charlton 1980, Evans et al 1992). 4) Acute renal failure (Allen et al 1981, Jackobson 1965). 5) Paralytic ileus . 6) Electrolytes and water disturbance (Mommsen et al 1977, Beirne et al 1965). 7) Disseminated intravascular coagulation (Friedman et al 1969, Editorial JAMA (1969). 8) Liver oedema and failure (Wakim 1971). 9) Shock syndromes such as septicaemic, hypovolaemia and cardiogenic shocks (Bertrand et al 1981, Spencer Hoyt et al 1958, Charlton 1980). Identical syndrome named hypoalbuminaemic hyponatraemia was

reported (Dandonna et al 1985). Clinically the presentation of the TURP syndrome is identical to any type of shock (Mofat et al 1985). An association of the acute HN and one or more of the above clinical features characterizes the TURP syndrome.

Several other syndromes, which like the TURP syndrome, are characterized by HN induced by fluid overload. They include: Hypo-albuminaemic hyponatraemic syndrome (Dandonna et al 1985). The dextrose – vasopressin syndrome is known in obstetric patients (Heytens and Camu 1984), dialysis disequilibrium syndrome (Wakim 1971). The condition that affected 15 women after surgery (Arieff 1986), and the condition that complicates parentral nutrition (Watters et al 1984) are reported. The TURS has been reported in women undergoing trans-cervical endometrial surgery (Arief 1993, Ister et al 1994).

Syndromes that are associated with volume overload but lack HN as a marker include: Shock lung, ARDS (Ashbaugh et al 1967, Apple and Shoemaker 1981), Excessive or multiple transfusion syndrome, multiple organ Failure and several other postsurgical syndromes (Pichlmayr and Kock 1980). Volume overload is common but is rarely incriminated. These syndromes affect hospitalized patients only and are iatrogenic.

Volumetric overload shocks (VOS):

Currently with the shift to use normal saline as irrigating solution, the TURP syndrome characterized with acute dilutional HN has vanished from urology. Be prepared to face the new version of a syndrome that mimics ARDS. Hence it is important to familiarise yourself with VOS.

Volumetric Overload Shock (VOS) is a condition caused by massive fluid infusions in a short time (Ghanem 2016, 2017, 2017) and is of two types; Type one (VOS1) and Type two (VOS2). VOS1 is induced by sodium-free fluid gain of 3.5-5 litres in one hour such as Glycine, Glucose, Mannitol and Sorbitol. It is known as the TURP syndrome or hyponatraemic shock (Harrison III et al 1956) that was previously induced in dogs (Danowski et al 1946). VOS2 is induced by massive infusion of sodium-based fluids such as normal saline, Ringer, Hartmann, plasma, plasma substitutes and blood transfusions that may complicate the therapy of VOS1. VOS2 also complicates fluid therapy in critically ill patients suffering from other known shocks such as hypovolaemic, haemorrhagic and septic shocks and present with ARDS (Ashbaugh et al 1967, Boutcher and Foster 1984, Apple and Shoemaker 1981). VOS2 is induced by the gain of 12-14 litres of sodium-based fluids when reported in ARDS. The occurrence of massive interstitial tissue oedema with congestion of vital organs, pleural and peritoneal effusions, in the presence of hypotension shock, casted doubt on Starling's law! These issues were investigated at the clinical and physiological/physical fronts (Ghanem 2016, 2017, Pindoria et al 2017).

Two clinical studies aiming to understand the TURP syndrome and recognising VOS were done. A prospective clinical study on 100 consecutive TURP patients of whom the condition of TURP syndrome affected 10 patients with severe hypotension and bradycardia and severe acute dilution HN of <120 mmol/l. Volumetric overload was the only significant factor in causing the condition. The second clinical study involved a case series of 23 cases of the TURP syndrome manifesting as VOS1. Volumetric overload quantity and type is shown in *(Figure 1)*. The first 3 cases died as they were diagnosed and treated erroneously as one of the recognised shocks and treated with further volume expansion. The remaining 20 patients were correctly diagnosed as VOS1 and treated with hypertonic sodium therapy (HST) of 5% Sodium Chloride or 8.4% Sodium Bicarbonate. Each patient passed 4-5 litres of urine followed by recovery from shock and coma. This treatment was successful in curing all patients bringing them back from dead (Ghanem et al 2016, 2017, 2017).

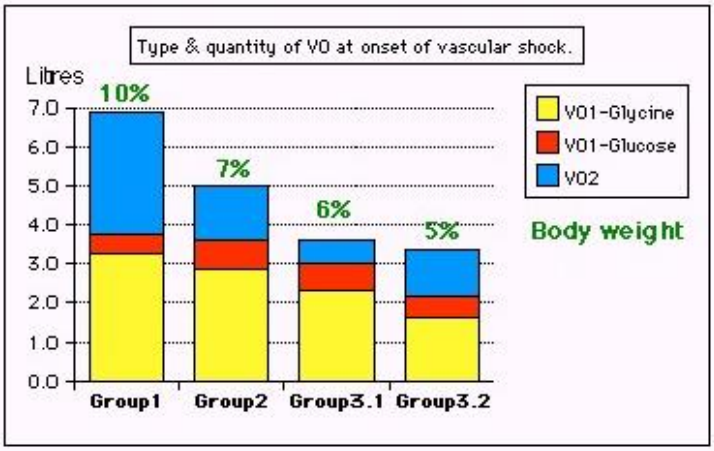

Figure 1 shows volumetric overload (VO) quantity (in litres and as percent of body weight) and types of fluids. Group 1 was the 3 patients who died in the case series as they were misdiagnosed as one of the previously known shocks and treated with further volume expansion. Group 2 were 10 patients from 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 expansion using isotonic saline. . (Reproduced with permission from Ghanem [2017])

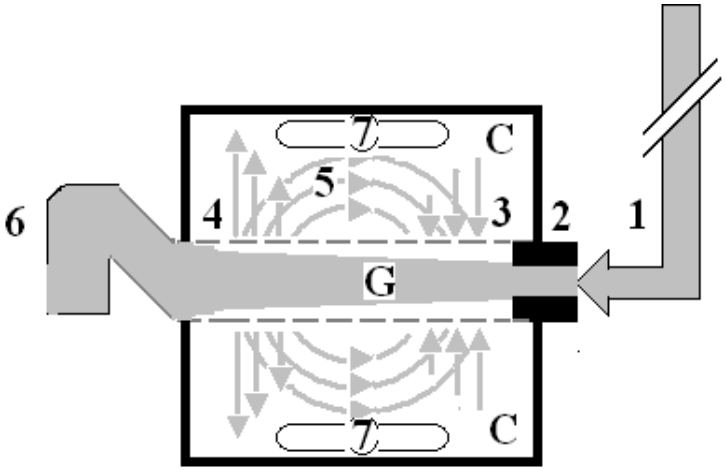

Figure 2 shows Diagram of the porous orifice (G) tube enclosed in chamber (C) based on several photographs demonstrating the magnetic field-like G-C circulation phenomenon. The proximal inflow (arterial) pressure (1) pushes fluid through the orifice (2) creating fluid jet in the lumen of the G tube. The fluid jet creates negative side pressure gradient causing suction maximal over the proximal half of the G tube near the inlet (3) that sucks fluid into lumen. The side pressure gradient turns positive pushing fluid out of lumen over the distal half maximally near the outlet (4). Thus the fluid around G tube inside C moves in magnetic field-like fluid circulation (5) taking an opposite direction to lumen flow of G. tube. The inflow (arterial) pressure (1) and orifice (2) induce the negative side pressure energy creating the dynamic G-C circulation phenomenon that is rapid, autonomous and efficient in moving fluid out from the G tube lumen at (4), irrigating C at (5), then sucking it back again at (3), maintaining net negative energy pressure (7) inside C. The distal outflow (venous) pressure (6) enhances outflow at (4) and its elevation may turn the negative energy pressure (7) inside C into positive, increasing volume and pressure inside C chamber. (Reproduced with permission from Ghanem [2017])

The physical investigation involved studies of the hydrodynamics of the porous orifice (G) tube comparing it to that of Poiseuille's tube. Thousands of experimental measurements of pressures at various parts of a circulatory system incorporating the G tube in a chamber to mimic the capillary-interstitial fluid compartment (Ghanem 2001, 2017). The effect of changing the proximal (arterial), the distal (venous) pressures and the diameter of the inlet on side pressure of the G tube and chamber pressure as well as the dynamic magnetic field like fluid circulation around the G tube. It is quite remarkable how this circulatory model mimic the circulatory system in heath and disease. This dynamic magnetic field like fluid circulation around the G tube and surrounding it in C chamber provides adequate replacement for Starling's law. The physiological equivalent of this physical study was done on the hind limbs of sheep (Ghanem 2017). It demonstrated that arterial pressure causes suction not filtration due to the effect of pre-capillary sphincter. It is the only possible explanation why the interstitial tissue pressure is negative of -7 cm water (Guyton and Coleman 1968). Venous pressure augmented filtration and oedema or dropsy formation.

Shock is a disturbance at the capillary cellular level impairing the capillary-interstitial fluid transfer; hindering delivery of oxygen and removal of waste products. The process is also governed by Starling's law (1886). In this law the arterial pressure is considered the force causing capillary filtration! If this is true, how come that arterial hypertension though very common never causes oedema? Starling based his hypothesis on Poiseuille work on strait uniform brass tubes. Latter evidence however demonstrated that the capillary is a porous narrow orifice (G) tube as it has a pre-capillary sphincter (Rhoden 1967) and pores that allow the passage of plasma proteins (Karnoveski 1967). As the capillary pores allow the passage of plasma molecules, nullifying the osmotic pressure of plasma proteins i.e. oncotic pressure does not exist, a call for reconsideration of Starling's hypothesis was previously made but there was no alternative at that time (Renkin 1986). This replacement came to light when the hydrodynamics of the G tube were discovered.

The hydrodynamics of the G tube (Ghanem 2001, 2016, 2017) (Figure 2) demonstrated that the proximal (arterial) pressure induces a negative side pressure gradient on the wall of the G tube causing suction most prominent over the proximal half and turns into positive pressure over the distal half. Incorporating the G tube in a chamber (C), representing the interstitial space surrounding a capillary, demonstrated a rapid dynamic magnetic field-like fluid circulation between the C and G tube lumen. This is a mixing engine between C and G effecting rapid irrigation under negative pressure i.e. without flooding or oedema or dropsy formation. Incorporating the G tube and C in a circulatory model driven by electric pump inducing proximal pressure similar to arterial pressure; causing suction from C into the lumen of G tube. The distal (venous) pressure augments filtration. This proves that the arterial pressure causes suction not filtration at the capillary interstitial fluid circulation, and hence Starling's law is wrong. The reported hydrodynamics of the G tube provides an adequate mechanism for the capillary interstitial fluid circulation.

Conflict of interest: None declared.

Abbreviations:

VOS: Volumetric overload shocks

VOS1: Volumetric overload shock, Type 1

VOS2: Volumetric overload shock, Type2

TURP: The transurethral res4ection of the prostate

ARDS: The adult respiratory distress syndrome

HN: Hyponatraemia

HST: Hypertonic sodium therapy

G Tube: The Porous orifice tube

CVP central venouspressure

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