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The Acute Stress Reaction to Major Thoracic Surgery

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1. Introduction

The aim of this review is to examine the current literature on the physio-pathological mechanism liable for the inflammatory reaction after major surgical injury and the nature and development of the related morbidity. We describe the endocrine and metabolic changes that occur as consequences of major thoracic surgery and the clinical implications of these reactions. The understanding of the stress response mechanism and the early detection of its clinical manifestations will aid in recognizing and probably help in correcting deviations from the norm.

Major surgical procedures represent an important insult for the homeostasis and determine a systemic inflammatory response syndrome, evolved to ensure survival, characterized by changes in haemodynamic, endocrine and immune functions directed towards preservation of the blood supply to essential organs. [1]

The first description of the clinical manifestations of such responses was presented in 1942 by Cuthbertson [2] who described a biphasic immune, inflammatory and metabolic response to injury. However during the last 20 years, as knowledge has continuously accumulated, it has become clear that the physiologic response to injury is not as simple as initially described and represents a rather complex physiological phenomenon, yet even today it is not completely understood.

The data we recently published confirmed the generalized tendency to accumulate large volumes of fluids in the postoperative days after pulmonary lobectomy. Fluid retention with weight gain was evident despite a negative intra-operative fluid balance, peri-operative strict fluid restriction, early mobilization and an encouraged intake of oral fluids as part of a normal diet. [3]

As reported by several authors following lung resection, multiple factors such as thoracotomy, rapid fluid infusion, and manipulation of the lung result in an increase of the extravascular lung water. Fluids from the interstitial space transudate into the alveolar space severely impairing gas diffusion and facilitating the occurrence of pulmonary edema.

2. Overview

Generally speaking the term “inflammatory reaction” refers to events which occur in tissues in response to a pathogenic stimulus. It consists of a series of specific immunological reactions that are protective, aimed at promoting survival. In the case of specific pathogenesis (bacteria, viruses), the inflammatory response is tightly linked to immune-mediated reactions and specifically cellular activation (lymphocytes, antibodies, macrophages, mast cells). Whereas if the stimulus is non-specific (neoplastic disease, surgical stress), the systemic inflammatory response relies on the innate defence mechanisms.

Post injury stress or inflammatory response, is the name given to the hormonal and metabolic changes which follow an anesthetized (e.g. surgery) or unanesthetized (e.g. trauma) injury [4]. It includes an adaptive set of events, a predictable well orchestrated reaction, that has evolved to maximize an organism’s healing potential and it is not unique to humans but is found in all vertebrate animals [1].

In evolutionary term it seems likely that the stress response developed as a survival mechanism to allow injured animals to sustain themselves until their injuries were healed, by catabolising their own stored body fuels and retaining salt and water. However it has been argued that such response is unnecessary in current surgical and anaesthetic practice [4].

During the last century, scientific efforts to clarify aspects of non-cellular inflammatory responses have revealed some special molecules that play an important role in local and systemic alterations in the affected individual: histamine, prostanoids leukotrienes, platelet activating factor, bradykinin, nitric oxide, neuropeptides and cytokines.

The cytokines are a group of low molecular-weight proteins released in inflammatory and immune reactions which include interleukins, interferons, tumor necrosis factor, growth factors and chemokines. They are produced by activated leucocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation. [5] They have local effects of mediating and maintaining the inflammatory response to tissue injury and after major surgery the main cytokines released are interleukin-1 (IL-1), tumor necrosis factor- α (TNF α) and IL-6 [4, 5].

The activation of the cytokine cascade is accompanied by the release of soluble cytokine receptors with significant growth factor functions, and by the activation of the massive neuro-endocrine-hormonal flux involving the production and secretion of catecholamines, antidiuretic hormone, cortisol, insulin, glucagon and growth hormone. The natural final goal is the retention of water and sodium; if the body is going to conserve water and sodium as a response to the surgical trauma, that would imply that smaller quantities of these elements should suffice to maintain homeostasis [6].

Localized inflammation is a physiological protective response which is generally tightly controlled by the body at the site of injury. Loss of this local control or an overly activated response results in an exaggerated systemic response which is clinically identified as systemic inflammatory response syndrome (SIRS). Compensatory mechanisms are initiated in concert with SIRS and outcome (resolution, multiple organ dysfunction syndrome or death) depends on the balance of SIRS and such compensatory mechanisms. No direct therapies have been successful to date in influencing outcome [7].

The outcome of the inflammatory response may be altered in several conditions; in particular following major thoracic surgery preexisting diseases (such as chronic obstructive pulmonary disease, renal failure, coronary artery disease, diabetes, hypertension), type and quantity of fluid infused, lung manipulation, anesthetic agents and single lung ventilation may interact with the inflammatory response and affect the ability of an individual to mount an appropriate stress response. Some patients develop an exaggerated response that results in what is commonly referred to as systemic inflammatory response syndrome (SIRS), on the contrary after an illness that depletes the organism, outcome may result in generally compromised organ function that is known most commonly by the multiple-organ dysfunction syndrome (MODS) or, more generically, chronic critical illness.

3. The biphasic reaction

This reaction characterized by a biphasic immune, inflammatory and metabolic response was described for the first time in 1942 by Cuthbertson [2] and some decades later some detail was added by Moore [8].

In the first phase the major points are the attempt to limit the blood loss by the activation of the responses that must ensure survival following injury; i.e. peripheral vasoconstriction, the derived hypothermia, the translocation of blood and substrate from the peripheral to vital organs (heart and central nervous system) circulation, retention of salt and water and decreases of energy expenditure. The length of this phase of the response that in Cuthbertson's description lasted 24 hours, can be restricted by appropriate treatment of the trigger. The activation of these conservative mechanisms occur in anesthetized or unanesthetized injury. In the former (elective major surgery) the beginning may be represented by the dilatation of the venous capacitance system produced by the commonly used anesthetic induction agents which decreases the blood return to the heart diminishing the cardiac output [1] or by the cytokines produced by activated leucocytes, fibroblasts and endothelial cells at the site of the surgical insult. [5]

In case of unanesthetized injury the neuro-endocrine-hormonal response is activated by afferent neuronal impulses from the site of injury that travel along sensory nerve roots through the dorsal root of the spinal cord to the medulla to activate the hypothalamus [4]. In this early stage of shock, adequate fluid therapy comprise of goal-directed filling [9] to prevent evolution to multiple organ dysfunction syndrome (MODS).

The second phase of the response is termed the hypermetabolic phase and is driven and is proportional to the degree of initial injury [1]. It is characterized by the peak, on the second postoperative day, of all the mediators of inflammation, and by the activity of the reparative cells, in particular white blood cells (WBCs). The energy needs come from catabolism of both skeletal and visceral muscle with release into the circulation of protein and amino acids resulting in loss of body cell mass that primarily reflects a decrease in skeletal muscle mass. The cardiovascular system plays a critical role in this phase; the vasculature dilates to improve flow and substrate delivery. Vascular leak allows fluid and substrate to flow towards the avascular area of injury and to remove waste products. [1]

The resultant tachycardia and elevated cardiac output boosts myocardial oxygen consumption, and increase in resting energy expenditure and in total body oxygen consumption and CO₂ production.

The net effect is an increased catabolism with increased substrate availability for energy production, and sodium and water retention to maintain fluid volume and haemodynamic stability [4, 10]. Sodium and water are retained avidly in the first few days, and convalescence and recovery are heralded by a return of the capacity to excrete any salt and water overload acquired during the earlier phase [11].

Following major surgery the well known clinical manifestations of this hypermetabolic phase include tachycardia, hyperthermia (representing hypermetabolism), hyperglycemia, leukocytosis, micro-albuminuria and edema (from capillary leak). This phase continues for several days and ceases with the transition from catabolism to anabolism, resolution of vasodilatation, and edema. At this point fluids are reabsorbed and eliminated with diuresis. All these facts support the concept that parts of intra-operatively administered fluids are redistributed into the interstitial and intracellular spaces, which undergo reabsorption in the postoperative period [12].

4. The endothelial surface layer and the pathogenesis of extra vascular water

The current basic research has brought fascinating insights to the function of the endothelial vascular barrier and, in particular, to the functional changes that lead to vascular leakage.

The etiopathogenesis of extravascular water is explained very clearly by S.R. Walsh et al in an interesting manuscript "Perioperative fluid restriction reduces complications after major gastrointestinal surgery" [6]. They reported that the body's fluid and electrolyte balance is maintained within a tightly defined range and this is achieved mainly by the kidney, under the influence of antidiuretic hormone and the renin--angiotensin--aldosterone axis, which influence sodium and water excretion and retention as necessary to maintain the volume and osmolality of the extracellular fluid. The mechanism involves a daily obligatory sodium loss of about 100 mmol and a daily maintenance sodium requirements of about 1.0--1.2 mmol/kg. Daily water requirements are between 25 and 35 mL/kg. The surgical trauma causes an intense distortion of the normal physiology. Preoperative fasting, intraoperative

bleeding, and insensible losses combine to produce extracellular volume depletion. Leukocyte activation increases capillary wall permeability, allowing seepage of proteins, water, and electrolytes out of capillaries into tissues, further depleting the intravascular space. The increase in capillary permeability is sufficient to allow the passage of large albumin molecules into the interstitium at a faster rate than the lymphatic system can drain it. The resulting accumulation of albumin increases the oncotic pressure of the interstitium, serving to draw further water and sodium from the intravascular space. [6]

A new insight in the mechanism liable for the fluid's transendothelial permeability came from the comprehension of the endothelial surface layer (ESL) and the role of endothelial glycocalyx as reported by Strunden [13]. Every healthy vascular endothelium is coated by transmembrane syndecans and membrane-bound glypicans containing heparan sulphate and chondroitin sulfate side chains, which together constitute the endothelial glycocalyx [14,15]. Bound plasma proteins, solubilized glycosaminoglycans, and hyaluronan are loading the glycocalyx to the endothelial surface layer (ESL), which is subject of a periodic constitution and degradation. Under physiologic conditions, the ESL has a thickness of approximately 1 μm and binds approximately 800 ml of blood plasma, so plasma volume can be divided into a circulating and non circulating part [15,16]. Accordingly, the glycocalyx seems to act as a molecular filter, retaining proteins and increasing the oncotic pressure within the endothelial surface layer.

A number of studies identified various agents and pathologic states impairing the glycocalyx scaffolding and ESL thickness.

In a genuine pig heart model, Chappell et al. demonstrated a 30-fold increased shedding of heparan sulphate after postischemic reperfusion [17]. These data were approved by a clinical investigation, which showed increased plasma levels of syndecan-1 and heparan sulphate in patients with global or regional ischemia who underwent major vascular surgery [18].

Beside ischemia/reperfusion-injury, several circulating mediators are known to initiate glycocalyx degradation. Tumor necrosis factor-(a), cytokines proteases, and heparanase from activated mast cells are well-described actors in systemic inflammatory response syndrome leading to reduction of the ESL thickness, which triggers increased leucocyte adhesion and transendothelial permeability [17,19, 20].

Interestingly, hypervolemia represents one of the several factors able to cause glycocalyx impairment mediated by liberation of atrial natriuretic peptide as shown by Bruegger D in the recent manuscript "Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts" [21].

Therefore hypervolemia resulting from inadequately high fluid administration therefore may cause iatrogenic glycocalyx damage [13].

As shown in basic research, the dramatic consequence of a rudimentary glycocalyx, which loses much of its ability to act as a second barrier, is strongly increased transendothelial

permeability and following formation of interstitial edema [17,21]. The relevance of these experimental data were impressively underlined by Nelson et al., who found increased plasma levels of glycosaminoglycans and syndecan-1 in septic patients, whereas median glycosaminoglycan levels were higher in patients who did not survive [13, 22].

5. The pathogenesis of extra vascular lung water (EVLW) and pulmonary edema

The lungs provide valuable insight into dynamic microcirculatory changes during systemic inflammation because they are maximally exposed to the proinflammatory cascade, receiving the entire cardiac output [23]. The pulmonary artery follows the course of bronchial anatomy and carries blood to the alveoli where the gas exchange will occur. The blood pressures in the areas of the small circle are lower than in the large circle. The reason lies in the low impedance and resistance of the pulmonary vessels. In addition, the blood flowing in the pulmonary arterial bed is different in composition than the systemic blood. The laws that balance the content of lung capillaries and the surrounding environment are, however, the same underlying vascular physiology in other districts. These are defined in part by the Starling forces and by variations in capillary permeability. The alveolar ventilation and perfusion are therefore the two transport systems of the gas until the alveolus. The way in which an efficient gas exchange is produced, is subtended by the ratio ventilation / perfusion which brings together (in the ideal condition, therefore purely theoretical) the amount of blood and the volume of air which carry oxygen and carbon dioxide in different moments of shipping.

In this context, all cellular functions, the systemic endocrine regulation, intercellular communication, extracellular matrix features, the neurophysiological control systems and many other functions and properties find space.

The respiratory dynamics are achieved through countless joints, but the basic steps are 6. 1) gas exchange between alveoli and external environment, 2) gas exchange between alveoli and blood, 3) transport of gas from the lungs to the tissues, and viceversa, through blood, 4) gas exchange between blood and interstitium, 5) gas exchange between the cell and interstitium, 6] mitochondrial metabolism [24].

The respiratory unit consists of a respiratory bronchiole, the alveolar ducts and the alveoli. The walls of the alveoli are thin and placed in communication with each other through a network of interconnected capillaries [25]. The thickness of the alveolar walls is accompanied by an equally thickness of the lamina of blood flowing through them. Thanks to this contact, alveolar and blood gases can determine the respiratory exchange. The respiratory membrane therefore represents the interface between the environment and the organism but not only, it is also the site of oxygen flow and discharge of carbon dioxide. The efficiency of the respiratory membrane provides the metabolic capacity and thus cellular function is directly responsible for the availability of the organism to accomplish any aerobic metabolism.

The respiratory membrane is composed of several layers that described, from the inside of the alveolus, are: 1) liquid surfactant, 2) alveolar epithelium, 3) basement membrane, 4) the interstitial space, 5) the capillary basement membrane, 6) epithelium of the capillary. Each of these areas of the respiratory membrane is subjected to different stimulations that vary, depending on the conditions, the efficiency and the speed of the exchanges.

For the air–blood barrier, a minimum volume of interstitial water assures the maximum surface/ thickness ratio to optimise gas diffusion. In the lung the endothelium of the capillary wall is tightly glued to the epithelial wall. Most of the diffusion occurs in the so called “thin” portion that accounts for almost 50% of the barrier surface and whose thinness is as low as 0.2–0.3 μm . The thinness of the air–blood barrier reflects a functionally “dry” condition. In addition, for the extravascular space of the lung one can speak of a “minimum” volume of water. In fact, when fluid fluxes increase due to alteration in fluid dynamics, this results in an impairment of diffusion [26].

The Pathophysiology of fluid and the dynamics of extravascular lung water in the Interstitium After Lung Thoracic Surgery, has been clearly elucidated in a series of manuscripts by Miserocchi and collaborators that we here cite.

The lung’s air-blood barrier is 0.2-0.3 microns thin with a “minimum” volume of water reflecting a functionally “dry” condition that ensures a high efficiency of the gas diffusion [27]. Furthermore similarly to the pleural fluid, also lung interstitial fluid is kept at a subatmospheric pressure (also ~ -10 cmH₂O) due to the powerful draining action of lymphatics in face of a very low microvascular permeability [26].

Two important molecules, belonging to the proteoglycans (PGs) family, whose role appears crucial to control the extravascular water volume, as they act as highly hydrophilic link proteins are Perlecan, an heparansulphate PG (MW 0.1-0.5 MDa) placed in the basement membrane that controls the porosity to water and solutes. Versican (MW 0.5 MDa), a large PG bound to hyaluronan (a random coiled molecule), provides rigidity to the tissue by establishing multiple non-covalent links with other molecules of the matrix and with cells [28, 29].

Miserocchi reported that the volume of the extravascular water is strictly controlled so that the lung appears quite resistant to the development of edema. In fact, at least three mechanisms cooperate to allow only minimal variations in extravascular water volume relative to the steady state condition [26].

First, the glycosaminoglycan chains of PGs can bind excess water to form gel-like structures; this results in an increase in the steric hindrance of proteoglycans and corresponding decrease in the porosity of the basement membrane and thus also in microvascular permeability.

Second, the assembly of large matrix PGs within the extracellular matrix provides low tissue compliance and this represents an important “tissue safety factor” against the development of edema. In fact, a minor increase in extravascular water in response to increased

microvascular filtration, causes a marked increase in interstitial pressure (e.g., from ~ -10 to ~ 5 cmH₂O) [26] that buffers further filtration.

Third, arteriolar vasoconstriction represents an important reflex to avoid or actually decrease capillary pressure when filtration is increased due to an increase in microvascular permeability [31,32]

Fragmentation/degradation of PGs of the basement membrane cause an increase in microvascular permeability of the paracellular pathway as pore size can reach 50-100 nm allowing easy leakage of albumin. Finding of red blood cells in the alveolar fluid reflects major lesions of the air blood barrier. Fragmentation of matrix PGs removes the “tissue safety factor” by causing an increase in interstitial compliance. The loss of integrity of PGs reflects the sustained increase in parenchymal stresses, the weakening of the non-covalent bonds due to increased water binding, and the activation of tissue metalloproteases (32 Miserocchi et al, 2001a). The hypothesis that the activation of tissue metalloproteases leads to the loss of integrity of PGs faces to new therapeutic approaches by drugs able to control this family of proteinases [33,34,35].

The development of severe pulmonary edema is known as a tumultuous event taking place in minutes. Experimental models in animals have allowed us to attribute the sudden increase in extravascular lung water [32] to the loss of integrity of the proteoglycan components of the macromolecular structure of the lung interstitial space.

One shall consider interstitial edema as a sharp edge between tissue repair and severe disease: in fact, the transition from interstitial to severe lung edema occurs through an “accelerated” phase when the loss of integrity of the interstitial matrix proceeds beyond a critical threshold. Interestingly, the same pathophysiological mechanism can be extended to all forms of lung edema, the only difference being the time sequence of fragmentation of the families of PGs. The initial degradation process involves the large matrix PGs in cardiogenic edema, while in the lesional edema model, the initial process involves PGs of the basement membrane. In the hypoxia lung edema model, both PGs families are involved [32]. A further peculiar feature of lung edema is that it develops in a patchy way, thus revealing regional differences in the efficiency of control of extravascular water volume. These differences have been recently documented in a hypoxic edema model [30] and the hypothesis was put forward that alterations in the geometry of the microvascular-alveolar design might favor an imbalance in interstitial fluid dynamics.

6. Clinical considerations

Post operative or post traumatic fluid retention represents a frequent clinical result of the reaction to surgical stress or injury and frequently is underestimated. In clinical practice this condition is not always emphasized and assessed. Because it may show several clinical manifestations, it is not always clinically evident and may be asymptomatic. The incidence of postoperative edema is common, affecting up to 40% of patients [36], and a similar incidence is reported in patients managed in the intensive care unit after surgery [37].

Indeed edema is a frequent manifestation of fluid retention and it is not easily recognized because fluids collect in a dependent position. Furthermore, often, fluid retention, i.e. edema formation and weight gain, even if reported, are not overall considered a marker of impending complications. Even in our previous manuscripts the we did not reported any information on the presence of post operative fluids retention [38,39,40]

This condition has been thoroughly investigated only in the last two decades. Fluids i.e. water and sodium retention have several clinically important consequences. The increase of water in the interstitial space leads to tissue edema, affecting several organ systems. In the gut wall it impairs motility, prolonging gastric emptying times and predisposing the patients to postoperative ileus [41]. Peripheral edema may impair mobility, the hydrostatic pressure exerted on tissue microvasculature harm tissue perfusion and oxygenation slowing down wound healing and predisposing to wound infection, dehiscence, or anastomotic breakdown [42].

However this condition is associated with a worse prognosis. After major abdominal surgery a weight gain of 3-6 kg is typical and associated with increased morbidity including prolonged ileus, sepsis and delayed recovery time [41,42,43]. Lowell et al. showed a weight gain of more than 10% in >40% of patients admitted to the intensive care unit after major surgery and this increase of body weight, representing interstitial edema, correlated strongly with mortality [37].

After thoracic surgery and particularly after major pulmonary resections, besides the activation of the stress response to the surgical injury [4] several factors may induce pooling of water in the lung interstitium. It may be explained by the volume and the type of fluids administered during the surgical procedure, hypoxia, blood loss, the anaesthesia effects [44], one-lung ventilation [45] and lung manipulation. In this setting the incidence of post-pneumonectomy pulmonary edema may be as high as 12–15% [45]; and this condition may be very dangerous because the increase of extra-vascular lung water can severely impair gas exchange and oxygenation.

Indeed a cornerstone to prevent and treat the reaction to stress of patients in the operating room and in the immediate postoperative period is appropriate types of fluid and volume therapy. In this setting, in clinical practice sometimes an exact determination of fluid balance may be cumbersome and independent risk factors for an increased need for peri-operative fluid replacement are advanced age, diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure, so minimizing interstitial fluid accumulation in these patients is particularly important.

The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients' [46] reported that the most reliable method to estimate fluid balance in surgical patients is considered daily weighing, with fluid replacement being based on clinical observation of fluid loss. But daily fluid balance may be inaccurate due to "perspiratio insensibilis", poor quantitation of oral fluid intake and/or urine collections [3].

Fluid loss from insensible perspiration also is often overestimated in many patients, although loss of only 1 ml/kg per hour occurs even when the abdominal cavity is opened [47]. Daily weighing may be cumbersome in clinical practice, not so accurate as expected or even unfeasible in the early PODs due to the presence of chest drains and difficulties in maintaining an upright position. Furthermore this measure does not include a determination of the capillary permeability and postoperative fluid retention is reported despite fluid-restriction regime. Undoubtedly, there are other factors, not sufficiently investigated, that could cause this event [3].

Urine production and insensible perspiration are physiologically replaced by free water absorbed from the gastrointestinal system and primarily affect the extravascular space, if they are not pathologically increased. Because the physiologic replacement is limited in fasted patients, it has to be compensated artificially by infusing crystalloids. During surgery, trauma or septic shock additional fluid loss (blood loss, vascular leakage) affects mainly the intravascular compartment [48]. Consequently, the first type of fluid loss is attenuated by slow redistribution between intracellular, interstitial, and intravascular space and causes dehydration, whereas the second type of loss leads to acute hypovolemia. [21]

Preoperative hypovolemia after an overnight fasting period, as reported [49,50], cannot be explained by the considerations above and does not occur regularly in all patients [51]. Fluid reloading is unjustified, at least in cardiovascular healthy patients before low-invasive surgery [51]. Mediated by increased liberation of atrial natriuretic peptide, undifferentiated fluid loading can cause glycocalyx degradation, increase vascular permeability, promote tissue edema formation and therefore may constitute a starting point of the vicious circle of vascular leakage and organ failure [52].

Several facts support the concept that parts of intra-operatively administered fluids are redistributed into the interstitial and intracellular spaces, and undergo reabsorption in the postoperative period [12]. As shown by blood volume measurements, major surgery causes a deficit of 3-6 liters in the perioperative fluid balance. The peak even persists up to 72 hours after trauma or surgery. The common explanation for this phenomenon is a fluid shift into the so-called third space [53,54].

Physiologic fluid shifting from the vessel toward the interstitial space across an intact vascular barrier contains only small amounts of proteins. It does not cause interstitial edema as long as it can be quantitatively managed by the lymphatic system [13]

The transpulmonary thermodilution is an invasive method that allows the estimation of extravascular lung water (EVLWI) and the extent of capillary leak and fluid overload [55,56]; this technique requires a central venous catheter and a thermistor-tipped arterial thermodilution catheter (PulsioCath 5F) inserted into the femoral artery and attached to a PiCCOplus® system (Pulsion Medical Systems, Munich, Germany). Therefore this procedure is not feasible in all the surgical and intensive care units.

In clinical practice quantitative and non-invasive methods to estimate fluid retention could be very useful to monitor patients susceptible of fluid compartmentalisation after major surgery and early detection may reduce the risks associated with this condition.

In our experience we investigated, following pulmonary lobectomy, fluid retention by the methods commonly utilized to evaluate body fluids. We found a significant postoperative weight gain, the mean increase in body weight was 2.7 kg ([1.9– 3.4]; $p < 0.001$) on postoperative day 2.

Fluid balance was calculated from the day of operation up to the discharge. Bioimpedance analysis(BIA)-derived parameters resistance(R) and reactance(Xc) is a reproducible, non-invasive method, used in various clinical settings to estimate total body water (TBW). It is based on the different conductive and resistive properties when a small electric current is applied to tissues in vivo [57]. Natriuretic peptides, B-type (BNP), are vasoactive hormones involved in the regulation of blood pressure and volume homeostasis. Alterations in the natriuretic peptide system have been described in several conditions associated with abnormal regulation of body fluids and blood pressure control [58].

In our experience, the three methods used to assess fluid gain consistently showed a significant fluid retention over the course of the study. BIA is a bedside tool allowing non-invasive, early, informative and convenient assessment of fluid retention independent of intake. The time course of BIA in our study is consistent with the results reported by Itobi et al. following major abdominal surgery [36]. Besides, as reported by the Danish Study Group on Peri-operative Fluid Therapy [43], BIA is a more sensitive indicator of fluid overload than body weight and clinical examination. In our patients, preoperative BNP was within the normal range, whereas, in the postoperative observation, plasma BNP rapidly increased and remained above the normal range for the whole study period as reported by several Authors. Nojiri et al. [22]

7. Conclusion

Fluids compartmentalization in mammals and its dynamics is an evolving topic for several reasons. All subjects in biology, medical sciences and clinical practice finally come to interface H₂O balance. The basic research recently moved important steps but this trend has not been followed by applicative research yet. Such discrepancy shows the need of investigation on novel techniques to translate into the clinical practice the ever greater knowledge on body fluids. The possible application and measurement of extravascular water in different systems and organs will possibly open scientific and clinical opportunities. Some devices are already available but some less invasive, reproducible and specific instruments have to be developed. Furthermore, among all the molecules that can bring information on homeostasis, no specific one is so far recognized and further investigations are thus required.

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