Chapter 12
Personalized Medicine in Body Fluid Management

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Introduction

The human body consists mainly of water, in which many molecules (electrolytes and proteins) are dissolved.

Water within the human body ranges according to the age: in infants, it's about 75% of body weight, lowering down to approximately 60% in adults and to 45% in elderlies. It is distributed into two main compartments: intracellular space (ICS), which contains nearly 55% of body water, and extracellullar space (ECS), which is further divided into three spaces—the intravascular space (IVS), the interstitial space (ISS) and the transcellular space (TCS). Extracellular space contains approximately 45% of body water (15 L in a normal adult), although it could vary depending on many factors which affects the fluid imbalance, reducing the circulating volume (massive blood loss, severe dehydration) (Brandstrup 2006; Chappell et al. 2008).

Intravascular space contains about 15% of extracellular fluid (ECF), composing the fluid component of blood, plasma. It is separated by the vessel walls in the interstitial space, which is around 45% of ECF. Transcellular space (40% of ECF) is a functional compartment of fluids and electrolytes continually exchanging cells and plasma with ISS. All these compartments, are separated by a semi-permeable membrane made up by a phospholipidic bilayer: water and small solutes can move through this membrane from one compartment to another.

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Properties of Body Fluids

Fluids and electrolytes pass through semi-permeable biological membranes thanks to different forces: hydrostatic, osmotic and oncotic. Particles dissolved in body fluids are responsible for osmolarity and osmolality, the two main colligative properties of solutions, which only depend on the number of particles dissolved in a solution. Osmolarity is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (L) of solution (Osm/L). The osmolarity of a biologic fluid is usually expressed as mOsm/L. Ionic compounds, such as salt, can dissociate in solution into their constituent ions. Van't Hoff factor considers the degree of dissociation of ionic compounds, in an ideal solution it is equal to the number of discrete ions in a formula unit of the substance. For example, a 1 L solution containing 1 mole of NaCl is 2 Osm, because NaCl dissociates completely in sodium and chloride ions (Van't Hoff factor is 2). Non-ionic compounds, such as glucose, do not dissociate in a solution, therefore Van't Hoff factor is 1 and a 1 L solution of 1 mole of glucose is 1 Osm. Osmolality is the measure of solute concentration defined as the number of osmoles (Osm) of solute per Kg of water. While osmolarity expresses the concentration of particles (Osm) per volume of solution, osmolality refers to the mass of solvent.

Plasma osmolality is primarily regulated by Antidiuretic Hormone (ADH), produced by hypothalamus and secreted by posterior pituitary gland in response to any increase of plasma osmolality (closely related to plasma sodium concentration). One of the mechanisms of action of ADH is to increase free water reabsorption by kidney in collecting tubules, thus correcting plasma osmolality.

When two solutions with different osmolarities are separated by a semi-permeable membrane, which allows only water (not solutes) to pass freely through it, water moves from the solution with lower concentration to the one with higher concentration. Osmotic pressure is responsible for this movement of water and depends on electrolytes' concentration of the solution.

Tonicity is a measure of the effective osmotic pressure gradient between two solutions with different osmotic pressure. It depends on the relative concentration of solutes dissolved in solution and determines quantity and direction of movement of water.

Plasma tonicity is 288 ± 5 mOsm/kg H_2O; mainly depends on Na concentration, but Cl, glucose and urea can influence it as well. Plasma tonicity forces water to move in and out of the cell, hence Na concentration affects the relative volume of ICF and ECF.

Infused solution can be isotonic (same tonicity as plasma), hypotonic (lower tonicity than plasma) and hypertonic (higher tonicity than plasma). Hypotonic solutions reduce plasma osmotic pressure, causing water to move from bloodstream to the cell. Hypertonic solutions increase plasma osmotic pressure, causing water to move from the cell to plasma.

Oncotic or colloido-osmotic pressure (π) is a form of osmotic pressure due to proteins, mainly albumin, which cannot cross the semi-permeable membrane, thus

determining water to cross biological membranes from low- to high-protein concentration solutions. Thanks to oncotic pressure blood draws water from ISS into capillaries, contrasting the hydrostatic pressure.

Starling equation describes fluid filtration through capillary membrane:

$$J_v = K_f \left(\left[P_c - P_i \right] - \sigma \left[\pi_c - \pi_i \right] \right)$$

Transendothelial fluid exchange depends on six factors:

- Capillary hydrostatic pressure (P_c);
- Interstitial hydrostatic pressure (P_i);
- Capillary oncotic pressure (π_c);
- Interstitial oncotic pressure (π_i);
- Filtration coefficient (K_f), which depends on surface and permeability of the membrane;
- Reflection coefficient (σ).

Net fluid filtration is proportional to net driving force. For convention, outward force is positive, inward force is negative, so when it is positive, fluid leaves bloodstream moving to the interstitial space, when it is negative, fluid enters the capillary (absorption).

Perioperative fluid management is a central part of any surgical procedure and it starts before the operation, since the patient should be allowed and, sometimes, encouraged to drink clear fluids such as water, fruit juice without pulp, carbonated beverages, carbohydrate-rich nutritional drinks, clear tea and black coffee (Smith et al. 2011; 2017).

A meta-analysis of randomized trials reports a lower risk of aspiration (gastric volume less than 25 mL and pH greater than 2.5) when clear liquids are given 2–4 h before a procedure compared with fasting overnight. After an 8-h "fast," roughly 500–1250 mL of fluid is added naturally to the stomach (Nordgren 1963). Allowing unrestricted access to clear fluids (preferably containing carbohydrates) up to 2 h before surgery reduces the acidity of gastric contents which is likely to improve patient comfort and safety.

Fluid Losses

Loss of fluid and electrolytes occurs continuously, due to many factors. Insensible perspiration is the only loss of pure water in the body, through the skin and the respiratory system. During surgery, the amount of water loss increases, due to perspiration through the surgical wound and exposed internal organs. This is particularly true in major abdominal surgery (Lamke et al. 1977). Diuresis is another source of fluid loss, depending on many factors including blood pressure, fluid intake, stress response, surgical trauma and anesthesia.

Blood loss is variable case-by-case, but severe bleeding may occur during surgery, due to either vascular damage (e.g. arterial bleeding) or to non-vascular sources of hemostatic perioperative bleeding (bleeding disorder, hemodilution or hemostatic factor consumption, fibrinogenolytic and inflammatory pathways, and hypothermia) (Ghadimi et al. 2016).

Physiological responses to acute blood loss are both activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), which accordingly enhance ADH levels. Such responses lead to a fluid shift from the extravascular space to the intravascular one, resulting in plasma volume restoration and decrease in colloid-osmotic pressure. After a 30% blood loss, return to a normal plasma protein concentration (80% COP) occurs within 24 h. The body replaces a blood loss $\leq$ 15% (about 750 mL) in about 24 h, without administering any intravenous fluid (Lundvall and Länne 1989).

Crystalloids vs. Colloids

Starting from 1913 (Nadler et al. 1962), a wide amount of literature about fluids was published. Different solutions are commercially available, but debate remains concerning the characteristics of the ideal fluid.

Crystalloids

Crystalloid solutions are composed by low-molecular weight salt, dissolved in water that pass freely from the plasma to the interstitial space and vice versa (McIlroy and Kharasch 2003).

There are four generations of crystalloids available on the market, classified into hypertonic, isotonic and hypotonic depending on their tonicity:

- Normal Saline Solution: contain only sodium and chloride at 0.9% and high concentration (154 mmol/L). It is a hypertonic fluid (osmolality 308 mOsm/kg).
- Ringer Lactat and Ringer Acetate: compared to saline solution, they contain less sodium (130 mmol/L) and less chloride (112 mmol/L). Moreover, they contain potassium, calcium, magnesium and metabolizable ions: lactate (Ringer Lactate) and acetate (Ringer Acetate) (Agrò 2013; Agrò et al. 2018a, b)
- STEROFUNDIN (ISO): it is the latest-generation of Crystalloids and its ionic composition is very close to the one of plasma: a lower chloride content together with both acetate and malate. As a result, it is an isotonic, balanced and plasma-adapted solution, which reduces the risk of chloride excess and dilutional acidosis, with a decreased influence on lactate monitoring, lactic acidosis and base excess (Agrò 2013; Agrò et al. 2018a, b)

Olson et al. found that only 20% of administrated crystalloids are distributed within the vascular space, and of these, 30% remains there for 30 min (Olsson et al. 2004). The 80% of the infused fluids is distributed in the EVS. Thus, crystalloids can be used for short-term volume expansion, but they do not actually help in restoring fluid balance and blood pressure in case of massive or rapid loss of fluids.

In this case, massive and repeated infusions of crystalloids are required, which, on the other hand, are likely to cause interstitial edema and electrolyte imbalance.

Therefore, the use of hypertonic crystalloid solutions (HCS), containing high concentrations of sodium (3–7.5%), was initially proposed. HCS appears to have direct cardiovascular effects, improving inotropism, also leading to vasodilation and reduction of venous compliance. If administered together with colloids it has shown prolonged effectiveness in volume expansion (Coppola et al. 2014).

Wade et al. (1997) and Bunn et al. (2004) hypothesized in their meta-analyses that the combined use of HCS and dextran would be superior to isotonic fluid resuscitation. HCS causes a rapid shift of water from EVS, to IVS, without a reduction in COP.

The initial enthusiasm for the HCS in patient with refractory hypovolemic shock states has gradually diminished because of side effect danger. Among them, the most significant is albumin dilution, which could also cause tissue edema. These effects cause a reduction in colloid oncotic pressure (COP) that, in critically ill patients, is associated with a mortality rate of 50% (Morissette et al. 1975; Rackow et al. 1977).

Excessive use of crystalloids results in the development of "compartments syndrome" as well. The hemodilution also causes a decreased concentration of antithrombin III and a hypercoagulability state (Ruttmann et al. 2002; Agrò 2013; Agrò et al. 2018a, b).

Colloids

Colloids are high molecular weight molecules that do not freely pass through membranes as they are not completely soluble in water. Colloids determine the oncotic pressure and, in proportional measure, the initial volume increase in the intravascular space. The high molecular weight (MW) also determines the volumetric expansion (Mitra and Khandelwal 2009).

In another study, it was found that an isotonic colloid is distributed only within the IVS, therefore a 100% plasma volume expansion results from the clinical use of this fluid (McIlroy and Kharasch 2003). Many colloids are currently available, differing in their physicochemical properties, pharmacokinetics, clinical effects and safety.

Natural Colloids: Human Albumin (HA)

HA is the main plasma protein, responsible for 80% of normal oncotic pressure. It is made up of 585 amino acids, with a molecular mass of 69,000. For many years it has been considered the gold standard treatment for acute hypovolemia, especially following trauma, surgical hemorrhage and cardiac surgery. However, HA is not exclusively retained in the IVS; rather, about 10% of HA leaves the IVS within 2 h and moves into interstitial space, with the risk of aggravating pre-existing interstitial edema or hypoalbuminemia. In fact, HA potentially causes or worsens pulmonary edema, especially in critically patients where a rapid volume replacement may cause cardiac failure. HA also may impact coagulation and hemostasis by enhancing antithrombin III activity and inhibiting platelet function (Nadler et al. 1962; Jøorgensen and Stoffersen 1979; Rozich and Paul 1989; Roberts and Bratton 1998; Randolph et al. 2002; McIlroy and Kharasch 2003; Ertl et al. 2007; Feldschuh and Katz 2007; Goepfert et al. 2007; Mutoh et al. 2007; Bunn et al. 2008; Mitra and Khandelwal 2009; Bunn et al. 2011; Smith et al. 2011; Bunn and Trivedi 2012; Agrò 2013; Padashi et al. 2016; Agrò et al. 2018a, b; Sezari et al. 2018).

Currently, HA is strictly indicated in acute condition requiring plasma expansion and in chronic conditions characterized by low albumin plasma levels (Vincent et al. 2003):

- > 5 L or > 5 g/L of albumin in ascites fluids after paracentesis
- Therapeutic plasmapheresis: plasma exchange > 20 mL/kg
- Spontaneous bacterial peritonitis in cirrhosis.

Synthetic Colloids

According to concentration, initial volume effect and duration of the volume effect they are further classified in dextrans, gelatins and hydroxyethyl starches.

Dextrans

Dextrans are glucose polymers of different size, mainly used in USA, which can lead a 100–150% volume increase of the IVS. Only a small fraction transiently passes into ISS (Agrò 2013; Agrò et al. 2018a, b). Their main clinical use is the maintenance of hemodynamic stability in different types of shock, improving both tissue perfusion and microcirculation. However, they can have different side effects. In fact, they have the greatest risk of anaphylactoid reaction compared to other colloids, can cause renal failure especially in elderly and dehydrated patients or with pre-existing renal dysfunction. Finally, dextrans may cause bleeding disorders, as they can alter platelet function, reduce factor VIII and increase fibrinolysis (Feldschuh and Enson 1977; Haeberle et al. 2006; Feldschuh and Katz 2007).

Gelatins

Gelatins are polydispersed peptides derived from bovine collages (6 L), available in most European and Asian countries. Gelatins' MW is about 30–35,000 and they are based on unbalanced, hypotonic solutions (Agrò 2013; Agrò et al. 2018a, b).

Particularly, there are three types of gelatins currently available:

- Cross-linked or oxypolygelatins, generally containing Na+ 145, K+ 5.1, Ca++ 6.25 and Cl– 145 mmol/L
- Succinylated or modified fluid gelatins, containing Na+ 154, K+ 0.4, Ca++ 0.4 and Cl– 120 mmol/L
- Urea cross-linked gelatins

Gelatins have a shorter duration effect than any other colloid, with a similar IVS volume- expanding power between them and a half-life of about 2.5 h (12). Therefore, they are associated with a lower risk of kidney injury compared to starch solution and there are no dose limitations, in contrast to other colloids. On the other hand, potential adverse effects are:

– Anaphylactic reaction
– Hemodynamic impairment, particularly after massive paracentesis in ascitic patients, due to increased plasma aldosterone and renin activity
– Coagulation disorders, which however do not have great clinical significance (Kato et al. 2001; Haeberle et al. 2006; Levi and Jonge 2007; Ertmer et al. 2009; Mitra and Khandelwal 2009; Hartog et al. 2011).

Hydroxyethyl Starches (HES)

HES are modified natural polysaccharides derived from maize or potatoes amylopectin, with hydroxyethyl groups at the C2, C3 and C6 carbon position of anhydroglucose residues instead of hydroxyl groups, which confers resistance to degradation by plasma amylases and greater solubility.

HES are described by a series of numeric parameters that reflect their pharmacokinetics (Barron et al. 2004; Agrò 2013; Perel et al. 2013; Agrò et al. 2018a, b)

– The first number represents the solution concentration that influence the volume expansion power (3, 6, 10%). HES at 6% concentration is iso-oncotic and have a 100% volume-expanding power; HES at 10% concentration are hyper-oncotic and have a volume- expanding power > 100%
– The second one relates to the mean MW (lower MW: 70 kDa, medium MW: 130–270 kDa, high MW: >450 kDa). MW determines the duration of volume-expansion, as lower MW is associated with faster elimination
– The third number is the molar substitution rate (MRS): low MRS is 0.4–0.5; high MRS is 0.62–0.7. MRS is the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units. It is inversely proportional to the rate

of degradation, while it is directly proportional to the duration of the volume effect and to the incidence of adverse effects

– The fourth is the C2/C6 ratio: it represents the quotient of the total number of hydroxyethyl groups on carbon atom 2 and the total number of hydroxyethyl groups on C6. The higher the ratio, the more groups will be present in C2 and the greater will be the resistance to plasma amylase and, therefore, the volume effect

HES solutions have a high hemodilution power, which leads to a reduction in vascular resistance and an increase in venous return. For this reason they have been widely used in hypovolemic patients, even in critically conditions, thanks to the low rate of infection related to HES administration.

Furthermore, HES administration is potentially associated with risks and side effects. HES can cause a reduction in von Willebrand factor, fibrinogen levels and thrombin generation with a severe increase in the bleeding risk. Another side effects of HES is impaired platelet function. However, there is a wide debate about the clinical impact on coagulation with the use of HES with a medium MW and a low MRS (Agrò 2013; Agrò et al. 2018a, b).

In cardiac and orthopedic surgery patients new-generations HES increase von Willebrand factor levels, resulting in a reduction of bleeding risk and transfusion need. Similar results were reported for minor elective surgery. Administration of HES increases the risk of kidney failure, especially in patient treated with high MW and high MRS HES and in elderly patient with previous renal dysfunction or other comorbidities. Kidney damage appears to be related to tubular obstruction caused by hyper-oncotic urine. Adequate hydration with crystalloids could prevent this damage. However, recent literature suggests that the latest generation of HES is the best colloid solution in kidney protection from oncotic damage, although the influence of HES on kidney function remains controversial. A decreased incidence of anaphylaxis with HES is found compared to other colloids. Prolonged administration of large amount of HES may cause itching. Itching is due to storage of the material in small peripheral nerves and appears weeks or even months after HES administration. Finally, since HES are similar to glycogen, they have potential to interfere with blood glucose levels (Kozek-Langenecker et al. 2008; Liu et al. 2009; Lindroos et al. 2010; Agrò 2013; Agrò et al. 2018a, b).

Goal-Directed Fluid Therapy

The administration of fluids to obtain better oxygenation and tissue perfusion is an elaborated strategy called Goal-Directed Therapy (GTD). GTD allow doctors to dose fluids and various drugs (e.g. inotropic, vasoactive, etc.) and administer them at the right time, only to those patients who need them, thanks to hemodynamic monitoring. GDT permits a personalized fluid therapy, based on the need of every single patient. Fluid responders will generally demonstrate an increase in their SV by >10–15% after a fluid challenge; the definition of fluid challenge typically refers

to a fluid volume administered over a short period of time (example a bolus of 500 mL or more in 10 min or less). It is important to understand that being a fluid responder is not equal to being hypovolemic (Miller et al. 2015; Yamada et al. 2018; Kendrick et al. 2019).

Physiology

The principle behind GDT is to optimize peripheral oxygen delivery without fluid overload. Oxygenation and tissue perfusion are both vitals for elective surgery and critical ill patients. DO2 (oxygen delivery) must be assured in adequate quantity every minute by respiratory and cardiovascular system (Miller et al. 2015; Kendrick et al. 2019).

$$\mathrm{DO2}\left(\mathrm{mL/min}\right)=\mathrm{CO}\left(\text{Cardiac Output}\right)\times\mathrm{CaO2}\left(\text{arterial oxygen content}\right)$$

$$\mathrm{DO2}=900-1000\,\mathrm{mL/min}\,\text{or}\,500-600\,\mathrm{mL/min/m^2}\,\text{under physiologically conditions.}$$

CO and CaO2 are determined by various factors; CO depends on heart rate (HR) and stroke volume (SV), CaO2 depends on the amount of Hb in g/dL, the number of mL of oxygen carried by every g of Hb (1.34), the O2 saturation of arterial blood and the O2 partial pressure of arterial blood. Considering all these factors, the previous equation can be rewritten as follow:

$$\mathrm{DO2}\left(\mathrm{mL/min}\right)=\left(\mathrm{HR}\times\mathrm{SV}\right)\times\left[\left(1.34\times\mathrm{Hb}\times\mathrm{SaO2}\right)+\left(0.003\times\mathrm{paO2}\right)\right]$$

where 0.003 is the solubility coefficient of O2 in blood.

SV can be modified using vasoactive, inotropic drugs or fluid administration; Hb by blood transfusion; SaO2 and paO2 by mechanical ventilation.

VO2 is the oxygen consumed by tissue per minute (mL/min). VO2 is usually increased during stressful situation, like surgery and critical conditions.

$$\mathrm{VO2}\left(\mathrm{mL/min}\right)=\mathrm{CO}\times\left(\mathrm{CaO2}-\mathrm{CvO2}\right)$$

where CvO2 is venous O2 content. It can be rewritten as follow:

$$\mathrm{VO2}\left(\mathrm{mL/min}\right)=\left(\mathrm{FC}\times\mathrm{SV}\right)\times\begin{bmatrix}\left(1.34\times\mathrm{Hb}\times\mathrm{SaO2}\right)+\left(0.003\times\mathrm{paO2}\right)\\-\left(1.34\times\mathrm{Hb}\times\mathrm{SvO2}\right)+\left(0.003\times\mathrm{pvO2}\right)\end{bmatrix}$$

where SvO2 is the O2 saturation of venous blood; PvO2 is the partial O2 pressure of venous blood. Normally, VO2 is around 200–300 mL/min; it could increase

for 4–6 times under stress conditions. The fraction of DO2 released to the peripheral tissues per minute is called O2 extraction. It can be expressed as follow:

$$O2ER = VO2 / DO2.$$

Normally, O2ER is 0.25, but it could increase. Below a critical value of DO2, O2ER can not increase anymore, and the flow become a VO2 determiner; tissue hypoxia could appear and anaerobic metabolism starts. This process can cause a discrepancy between ATP request and production. cAMP and cGMP decrease cause an activation of the endothelium and the release of pro-inflammatory cytokines that lead to capillary leak syndrome; the endothelial barrier falls, exposing the blood to leukocyte adhesion molecules and pro-coagulant factors. The leukocytes activation lead to a systemic inflammation, organ hypoperfusion and failure. It is clear that Hypoxia must be early detected and prevented when possible; this can be done with a correct approach to fluid therapy (GDT). A lack in the compensatory system of VO2 increasing due to vascular comorbidities, can lead in some patients to a higher probability of a fall of DO2 during stress conditions; a GTD approach can be crucial in these patients (Lees et al. 2009; Kendrick et al. 2019).

Hemodynamic Variables

In the GDT approach, it is crucial to predict the fluid responsiveness. The target is to identify the responders, patients who would benefit from high fluid administration in terms of DO2 and hemodynamic parameters, giving fluid boluses only to the ones who need them. To identify the responders, it is important to define hemodynamic variables that can be split into static and dynamic. A static variable for example can be the cardiac index obtained during a single thermodilution, thanks to the Swan-Ganz catheter. It indicates a hemodynamic status at a specific time. On the other hand, dynamic variables are hemodynamic changes due to a periodic pre-load variation; they are the best way to understand if a patient is a responder or not (Lees et al. 2009; Miller et al. 2015; Kendrick et al. 2019).

The CVP measurement is still widely used to guide intravascular volume therapy. Some recent studies, however, have shown that CVP is not a good pre-load indicator and is not effective in predict fluid responsiveness. PPV (pulse pressure variation) has also been recently considered; it defines the difference between diastolic and systolic pressure at different heart beats. It is defined by variation of intrathoracic pressure due to mechanical ventilation. This variation cause a change in pre-load volume; it has been demonstrated that PPV can be used to guide volume therapy (Drage and Boyd 2007; Lopes et al. 2007; Abbas and Hill 2008; Cavallaro et al. 2008; Malbouisson et al. 2017).

Other useful parameters are SVV (stroke volume variation) and CI; they can be obtained by the analysis of the pulse wave. To calibrate the pulse wave analysis, intermittent transpulmonary thermodilution can be used, enhancing the trustworthiness of CI measurements. It can also be used to measure ELVW (extravascular lung water), SVV (stroke volume variation), GEDV (global end diastolic volume); these three are called "the golden triangle", and can be used together for GDT assessment.

$$\mathrm{SSV} = \left(\mathrm{SV\,max} - \mathrm{SV\,min}\right) / \mathrm{SV\,mean}$$

SVV is simile to PPV but more precise; it is based on cyclic changes in SV caused by intrathoracic pressure oscillation during mechanical ventilation. With other variables, it can indicate the real-moment position on the Frank-Starling curve. The intrathoracic pressure variation cases changes in pre-load and SVV (SVV > 13%) when the heart operate on the ascending tract on the Frank-Starling curve; this indicates a good pre-load reserve and CI improvement after the administration of fluid, identifying the fluid responders. Very little variation of CI after fluid loading is noticed at the Frank-Starling curve plateau, with small SVV change (SVV < 13%) after intrathoracic pressure change, suggesting a small pre-load reserve; inotropes may be useful in these patients (Lees et al. 2009; Reuter et al. 2010; Agrò 2013; Agrò et al. 2018b).

SSV has some limitations that may exclude his use:

- Arrhythmias
- Right ventricular failure
- Spontaneous breathing
- Ratio heart rate/respiratory rate < 3.6
- Low tidal volume (<8 mL/kg)

GEDV is a good indicator of pre-load; it is a static variable that is unable to determinate the patient fluid responsiveness. EVLW can be used in case of acute lung injury or left ventricular failure. It is a predictor of patient's survival. Its use in GDT speeds up the treatment of lung edema, caused by increased vascular permeability or hydrostatic pressure (Drage and Boyd 2007; Goepfert et al. 2007; Lopes et al. 2007; Mutoh et al. 2007; Kapoor et al. 2008; Lees et al. 2009; Malbouisson et al. 2017; Kendrick et al. 2019).

A positive post-operative outcome could be seen if a GDT approach (GEDV > 800 mL/m^2; EVLW = 10–12 mL/kg) is used in cardiac surgery patients. In order to prevent secondary brain injury, CI was maximized using GEDV and EVLW, in patients with subarachnoid hemorrhage; during GDT protocol no congestive heart failure was observed (Chytra et al. 2007; Drage and Boyd 2007; Goepfert et al. 2007; Abbas and Hill 2008).

Monitoring System

Due to the risk associated with excessive fluid administration, it is important to predict whether a patient is a fluid responder without actually giving fluid. Checking the response to a 30° Trendelenburg position is an option to do that (Miller et al. 2015; Kendrick et al. 2019).

The hemodynamic monitoring is fundamental in GDT; obviously, the perfect system of monitoring should be non-invasive, simple, safe for the patient, precise and immediate, but unfortunately an ideal system has not been found yet. Recently, anyway, a lot of systems have been proposed; all of them have to be compared with the gold standard, the Pulmonary Artery Catheter (PAC) or Swan Ganz, which is not recommended in the routine operative settings, even if GDT is used. It is invasive, it exposes the patient to a not justified risk and requires high skills and experience for its placement; its fame in clinics practice has fallen, especially in the last years, thanks to the advent of less invasive techniques (Lees et al. 2009; Agrò 2013; Agrò et al. 2018b).

The new technologies permit the measurement of more precise filling volume values related to pre-load and fluid responsiveness; for example, arterial pressure wave form analysis and Doppler technologies are less invasive and permit an accurate measurement of cardiac output or SV.

ED (Esophageal Doppler) can be used for the measurement of blood flow time (FTc) in the descending aorta, which corresponds to the SV. FTc is normally 330–360 ms. If FTc is lower, hypovolemia should be suspected. This technique requires less training and does not require calibration; on the other hand, like any ecographic technique, it is operator-dependent and is difficult to use on an awake and not compliant patient. The use of ED has shown to improve patients outcomes during GDT, reducing blood lactate levels, infections, duration of the ICU and hospital stay in trauma patients and reducing complications, requirement of inotropes, ICU admissions and hospital stay in patients undergoing major abdominal surgery (Chytra et al. 2007; Drage and Boyd 2007; Mutoh et al. 2007).

PiCCO (Pulsion Medical System) and EV1000 System: they provide parameters that improve GDT, combining pulse wave analysis and trans-pulmonary thermodilution. They require invasive arterial cannulation and CVC, but they still are less invasive than PAC.

PiCCO analyzes thermodilution curves to find GEDV and EVLW, while EV1000 calculate GEDV thanks to the maximum gradient of the thermodilution curve ascent and descent. The recent findings demonstrate that the two devices are comparable. PiCCO PLUS (an evolution of PiCCO) evaluation of SVV can precisely indicate fluid responders among patients (Drage and Boyd 2007; Goepfert et al. 2007; Lopes et al. 2007; Mutoh et al. 2007; Cavallaro et al. 2008; Lees et al. 2009; Reuter et al. 2010).

FloTrac/Vigileo system: it performs the wave analysis with Langewouters' algorithm and does not required thermodilution, so it can be used with a normal arterial line and nothing else, connected to the FloTrac sensor. GDT protocol through

FloTrac/Vigileo has demonstrated hospital stay and incidence of complications reduction in high risk patients undergoing major abdominal surgery. The Vigileo limits involve the fact that the analysis of the wave pressure and SSV values are valid only in patients who are mechanically ventilated (Benes et al. 2010; Reuter et al. 2010).

Nefxin HD monitor: is a new non-invasive monitor that measure continuous CO by an inflatable finger cuff. It continuously measures finger blood pressure and converts it into the blood pressure wave of the brachial artery. It can be used in awake and not mechanically ventilated patients.

Conclusion

Decision regarding fluid therapy are among the most challenging and important tasks that a clinician face every day. Maintenance of intravascular euvolemia throughout the perioperative period is ideal. The main hemodynamic goal in critically ill patients is an optimization of administration of fluids by assessing fluid responsiveness. Load intravenous fluid is required in patients with reduced circulating volume and fluid responders. It seems more rational to give fluid when hypovolemia occurs, and not before it, because the volume effects is more sensitive. It has been demonstrated that GDT is an effective strategy for fluid administration, based on hemodynamic evaluation of the patient.

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