Section A-Research paper

Brief Overview About Different Methods of Fluid Management During Hepatectomy

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Abstract

Background: Fluid therapy is a cornerstone in the perioperative care of patients undergoing hepatectomy with a major controversy regarding which, when and how much fluid should be given peri-operatively. Fluid management strategies have undergone several shifts over the past 50 years. The choice of fluid became the subject of intense debate and continued until today, using colloid versus crystalloid and applying fluid restriction strategy or less restrictive strategy. Recently, there is interest in the concept of achieving a supernormal oxygen delivery and avoiding anesthesia-related harm after surgery such as prescribing individualized goal-directed fluid therapy (GDFT).

Keywords: Fluid management, Hepatectomy

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- **Physiology of body fluids:**

A) Compartment, fluid distribution and permeability:

Accurate replacement of fluid deficits requires an understanding of the distribution volume of body fluids. For a person weighing 70 kg, total body water (TBW) is about 42 L (60% of weight in kg). Two-thirds of the TBW (28 L) is intracellular water. The remaining third (14 liters) in the extracellular compartment is divided into the intravascular (5L: one third) and extravascular (9L: two-thirds) compartments. Blood is composed of around 60% plasma and 40% red, white blood cells and platelets. The cell wall separates the intracellular compartment from the extracellular compartment [2].

Endothelial glycocalyx layer (EGL) play an important role in microvascular permeability. It is an approximately 2-µm-thick, membrane-bound, sponge like mesh consisting of glycoproteins and proteoglycans. The EGL covers the entire vascular lumen, occupying 700–1,000 ml of the intravascular space. The soluble components of the plasma (mainly albumin) are embedded within the EGL meshwork. The combination of the meshwork and the trapped albumin opposes trans-capillary filtration and has a regulatory role in leukocyte and platelet adhesion on the endothelial surface [3].

Water moves freely through cell and vessel walls and is distributed throughout all these compartments. EGL is freely permeable to small ions such as Na and CL and excludes molecules larger than 70 kilo Dalton (kDa) such as albumin and the semisynthetic colloid. However, plasma proteins may leak into the interstitium through a relatively small number of large pores that are responsible for increased trans-capillary flow occurred in the early stage of inflammation. The trans-capillary escape rate of albumin to the tissues is an index of vascular permeability and is normally 5% of the plasma albumin per hour. This rate can increase in various pathophysiological states such as ischemia-reperfusion injury, trauma, major abdominal surgery and

rapid infusion of fluids allowing protein-rich plasma to move across the vascular wall, leading to development of interstitial edema, hypovolemia and organ dysfunction [3].

B) Fluid distribution kinetics during surgery:

The interstitium is filled with a fine gel fiber matrix "proteoglycan filament", which have low compliance due to the viscoelastic properties of the fibers in the meshwork. These filaments may prevent fluid from flowing easily through the gel, resulting in slow fluid distribution over 30 minutes. The slow distribution of crystalloids is beneficial as they considered a good plasma volume expander with an efficiency of 50%–75% as long as infusion is continued. However, during surgery, the matrix loses much of its elastic quality, causing the distributed fluid to remain in the interstitial tissue for a prolonged period leading to significant interstitial edema [4].

Initially, the infused crystalloids are distributed in the intravascular space. When capillary pressure is higher than normal, the crystalloids increases fluid movement across capillary wall (JV) more than does the same volume of colloids. In contrast, when capillary pressure is low, such as during acute hypotension after induction of anesthesia and during hypovolemia, JV declines to close to zero. Therefore, distribution of the infused fluid to the interstitial space is stopped, with fluid efficiency reaching 100% [4].

Elimination of infused fluid under anesthesia is approximately 10%–20% of that in a conscious state. Surgery and stress significantly alter the fluid balance, leading to fluid retention through modulation of adrenergic activity and levels of renin, antidiuretic hormone and aldosterone. Isoflurane lowers renal clearance for crystalloids by 50%. The half-life ($T_{1/2}$) of crystalloids is as much as 10 times longer during surgery under general anesthesia leading to augmented plasma volume expansion with a risk of peripheral fluid accumulation [4].

- **Choice of fluids:**

The composition of administered fluids will dictate their distribution. Pure water expands all body fluid compartments and therefore provides minimal expansion of the intravascular volume. Isotonic solution of sodium chloride expands the extracellular compartment only and increases intravascular volume by about one-fifth of the volume infused. Colloid solutions containing large molecules are maintained within the circulation and provide greater intravascular volume expansion per unit infused [2].

A) Crystalloids:

Crystalloids are categorized into unbalanced (normal saline) and balanced (e.g., Ringer's lactate, Ringer's acetate, and Plasma-Lyte) solutions. Normal saline contains a chloride concentration 50% higher than that of plasma and a strong ion difference of zero (unbalanced). Rapid administration of large amounts of saline produces hyperchloremic metabolic acidosis and undesirably affects renal function "reduced glomerular filtration rate and renal blood flow" especially in the major abdominal surgery. Saline is reserved for special indications, such as hyponatremia "hypochloremic metabolic alkalosis" associated with vomiting. Saline may also be used for irrigation and as a vehicle for IV administration of drugs [5].

Balanced solutions are crystalloids that contain electrolyte compositions closer to that of extra-cellular fluid. The solutions are the cornerstone of fluid administration in perioperative settings and should be used when saline is not indicated. Ringer's lactate substitutes a portion of chloride content with L-lactate buffer, providing a more physiologic chloride concentration. However, Ringer's lactate is slightly hypotonic relative to the plasma therefore, increase intracranial pressure and worsen cerebral edema in patients with brain injury. During liver resection, ringer's lactate may not be a choice in patients with liver hypo-perfusion or insufficiency since lactate metabolism entirely depends on preserved liver function. To overcome this problem, usage of ringer's acetate is ideal as the L-lactate is replaced with acetate, which is rapidly oxidized by the liver, muscle and heart to produce bicarbonate. To date, evidence of acetate toxicity after volume resuscitation has not been reported [5].

B) Colloids:

Colloids are crystalloid electrolyte solutions with macromolecules such as albumin and synthetic colloids (e.g., HES, gelatin, and dextran). However, the relatively higher cost and occasional complications may limit their use. Colloids are should be considered when crystalloid replacement exceeds 3–4 L prior to transfusion in patients

dalton (kDa) and molar substitution ratio of 0.38– 0.45 [7].

- **Optimal amount of fluid:**

Both hypovolemia and hypervolemia have a negative impact on patient outcomes. Hypovolemia decreases circulating blood volume and oxygen delivery to organs and peripheral tissues, causing organ dysfunction, whereas fluid overload causes tissue edema with increased risk of postoperative pulmonary complications, wound infections, and organ dysfunction [5].

Patients undergoing major abdominal surgery have often been administered a large volume of crystalloids during and after surgery due to preoperative fasting and third-space loss. Surgical patients are fasted for too long from midnight before the surgery. Current guidelines recommend oral intake of clear fluids or carbohydrate drinks up to 2 hours prior to surgery, reducing the need for supplemental fluid. Perioperative fluid loss consisting of diuresis, insensible perspiration, evaporation from the wound, and accumulation in the traumatized tissue. In addition, general anesthesia inhibits the autonomic control of the cardiovascular system, possibly inducing a type of distributive shock. Therefore, the current recommendation is to administer 3–5 ml/kg/h of crystalloids during surgery. A volume kinetic simulation of crystalloid infusion in this range shows a plasma volume expansion of 50–170 ml at 3 hours after surgery [5].

The rates of distribution and elimination of infused fluid are significantly delayed under general anesthesia enhancing fluid efficiency. This concept may shift the current fluid strategy toward more restrictive fluid amounts. The restrictive strategy aiming for "zero-balance" based on replacement of measured intraoperative blood and fluid loss only to reduce postoperative complications such as interstitial edema in patients undergoing abdominal surgeries. However, many studies compared the restrictive versus liberal fluid therapy in major abdominal surgery resulting a high incidence of postoperative oliguria and acute kidney injury (AKI) in restrictive groups despite similar survival rates between groups. These results are in conflict with a recent trend toward a more restrictive fluid approach during major surgery, indicating that aiming for "zero fluid balance" is too restrictive, and liberal approach may be needed. Goal-directed fluid therapy is a method of optimizing fluid and hemodynamic status for at-risk patients, using monitors to predict which patients will show hemodynamic improvement after fluid administration "fluid responsiveness". Recently, this fluid therapy is based on objective feedback regarding patient fluid responsiveness was shown to improve patient's clinical outcomes [8].

- **Role of lactate in fluid management of hepatectomy:**

Peri-operative increase of lactate concentration especially after hepatectomy is associated with higher morbidity and mortality rates. Hyperlactaemia means a level of lactate between 2 to 5 mmol/L and severe hyperlactaemia indicates lactate level more than 5 mmol/L. Patients with high serum lactate usually had longer surgery and ischemia duration, larger blood losses and higher requirements of fluids and blood transfusions. During surgery, hemoglobin concentration and oxygen delivery (DO2) decreased more significantly in those patients that is a landmark of tissue hypo-perfusion [9].

The liver has the greatest ability to metabolize lactate, while the kidneys, skeletal muscle, and heart contribute to lactate clearance. Different mechanisms may affect lactate metabolism in liver resection. Restrictive fluid therapy techniques such as (low CVP) that is used to minimize blood loss promotes local and systemic hypo-perfusion that lead to hyper-lactaemia. Hypoperfusion may be induced by administration of diuretics and vasodilators, epidural anesthesia, volatile anesthetics especially with a diseased liver. Intermittent clamping of the hepatic pedicle during parenchymal resection induces ischemia and ischemia-reperfusion of hepatic cells and decreasing the liver ability to metabolize blood lactate leading to hyper-lactaemia. In addition, the liver manipulation itself results in a significant cytokine release, finally leading to an increased lactate production [9].

- **Monitoring Fluid volume status:**

Estimation of hemodynamic responses is classified into static and dynamic measures. Static measures including (central venous pressure, pulmonary artery occlusion pressure, global end-diastolic volume and inferior vena cava diameter) and they poorly predict fluid responsiveness. Instead, dynamic measures in which changes cardiac output are observed in response to changes in cardiac preload by changes during the respiratory cycle such as; pulse pressure variation (PPV), systolic pressure variation (SPV) and stroke volume

variation (SVV). Changes in cardiac preload may be evoked by certain maneuvers such as; passive leg raise to 30°, end-expiratory occlusion test for 15 seconds and small fluid bolus of 3 ml/kg, which are currently, favored by anesthesiologists [10].

A) Static measures:

1) Blood pressure and heart rate:

The clinical diagnosis of hypovolemia is still often based on reflect hemodynamic stability despite of the limitations in assessing changes in heart rate and blood pressure during blood loss. A healthy patient may lose up to 25% of blood volume before occurrence of hypotension and tachycardia. Volume expansion-induced changes in arterial pressure-derived parameters are indecisive for the detection of an increase in cardiac output and do not predict the development of complications. Therefore, it should not be used for evaluation of fluid responsiveness in patients undergoing high-risk surgery such as liver resection [11].

2) Urine output (UOP):

Urine output should be maintained above a certain level to prevent acute kidney injury (AKI); therefore, low urine output should be treated with crystalloid boluses. Oliguria is defined as UOP < 0.5 ml/kg/h and it is extremely common in perioperative period due to a neuro-hormonal response to surgical stress. In addition, permissive oliguria during low CVP (LCVP)-assisted hepatectomy is associated with a transient biochemical alteration in estimated glomerular filtration rate without clinically relevant renal dysfunction. Therefore, it is an unreliable marker of volume status [12].

3) central venous pressure (CVP):

Although central venous pressure (CVP) is used to guide fluid therapy in hospitalized patients, there is little evidence that supports the use of CVP as a guidance for perioperative fluid therapy. CVP and pulmonary capillary wedge pressure estimate volume status of the right and left ventricles. Dramatic changes in systemic hemodynamics may not be associated with any significant changes in CVP. The venous system contains approximately 70% of the total blood volume and is 30 times more compliant than arterial system; therefore, changes in blood volume within the veins are associated with small changes in venous pressure. If fluid resuscitation is guided by CVP, it is likely that patients will have volume overload and pulmonary edema [7].

B) Dynamic measures: (Goal-directed therapy)

Early goal-directed therapy (GDT) is a term that has been used to describe oxygen targeted GDT which used the pulmonary artery catheter (PAC) to augment oxygen delivery (DO2) to supra-normal levels in high-risk surgical patients. Many studies showed that targeting DO2 values above (600 ml/min/m^2) before the stress of surgery could decrease morbidity and mortality in high-risk surgical patients. Recently, modern GDT with fluid alone targets to maximize stroke volume (SV) and cardiac output (CO) using a minimally invasive CO monitor. Major surgery like liver resection exposes patients to periods of cardiovascular insufficiency due to anesthesia-induced loss of vasomotor tone, blood loss and mechanical obstruction to blood flow. This leads to decrease in cardiac output, stroke volume, global oxygen delivery (DO2) and then end-organ dysfunction may occur. In addition, trials for aggressive resuscitation and vasoactive drug therapies needed to achieve targeted levels of DO2 associated with risks on patient's outcome [7].

Perioperative goal-directed fluid therapy (PGDT) is a clinician-guided protocol that uses measurements of advanced hemodynamic parameters during surgery to guide fluid management. The accurate assessment of hemodynamic parameters [stroke volume (SV), stroke volume variation (SVV) and cardiac output (CO)] allows for individualized volume management and decreases variability among clinicians because fluids are given only when there is demonstrable fluid responsiveness. PGDT is based on the physiological principles of the frank-starling curve (Figure 1) that describing the relationship between stroke volume as one of two determents of cardiac output and preload. Therefore, the only reason to give a patient a fluid challenge is to increase the stroke volume [13].

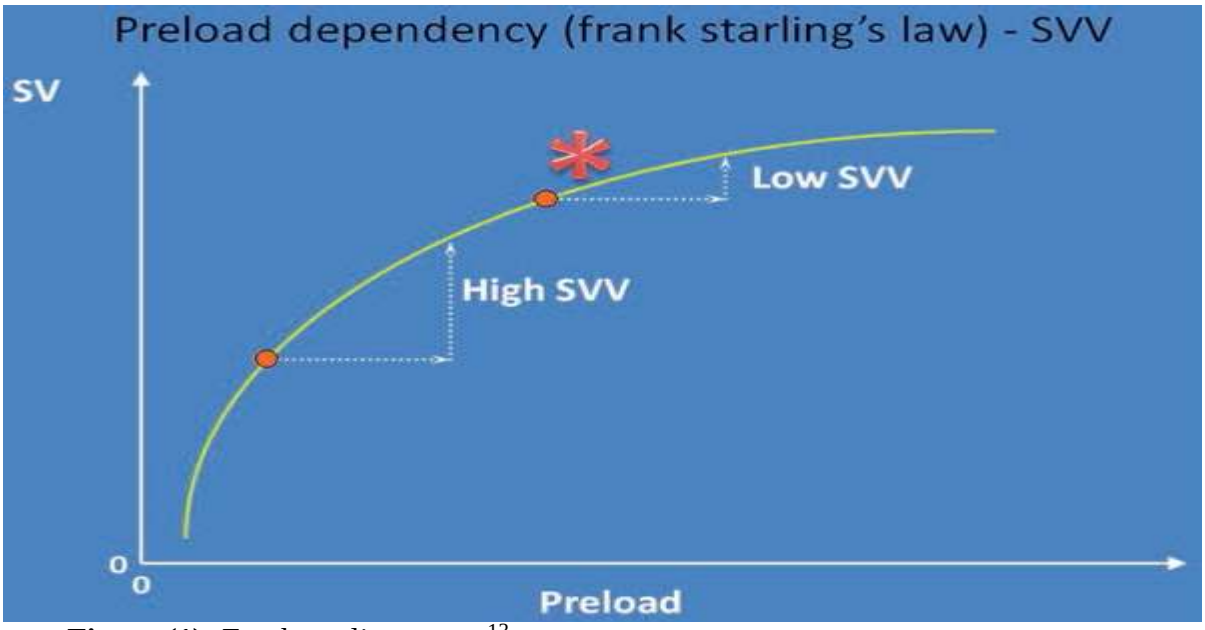

Figure (1): Frank starling curve [13].

This curve assumes that when the patient is on the ascending portion of curve and so, has "recruitable" cardiac output. Once the left ventricle is functioning near the plateau on the frank-starling curve, fluid loading has little effect on cardiac output and only leads to more tissue edema. Therefore, giving fluid until the patient has reached the plateau of the frank-starling curve may be the way of preventing both hypovolemia and fluid overload. Patients who respond to a fluid challenge with an increase in SV of more than 10% are considered fluid responsive and need more fluid. However, patients who respond to a fluid challenge with a change in SV < 10 % are considered replete and fluid administration should stop. Positive pressure ventilation induces cyclic changes in intra-thoracic pressures that transiently affect venous return, resulting in cyclic changes in stroke volume [13].

The degree of respiratory variations in systolic pressure, pulse pressure and stroke volume reflects volume (preload) responsiveness. Therefore, these dynamic predictors called systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV). High respiratory variations reflect that the heart is working on the steep part of the curve (preload dependence), But low respiratory variations means the heart is working on the plateau of the relationship (preload independence). These dynamic flow-related parameters are more accurate in assessment of fluid responsiveness than static parameters. Preload dependence optimization (SVV or PPV minimization) dictates the fluid boluses aiming at keeping the value below a threshold number. There is a wide range of perioperative protocols available according to patient's health, type of surgery and the type of hemodynamic monitoring (Figure 2) [14].

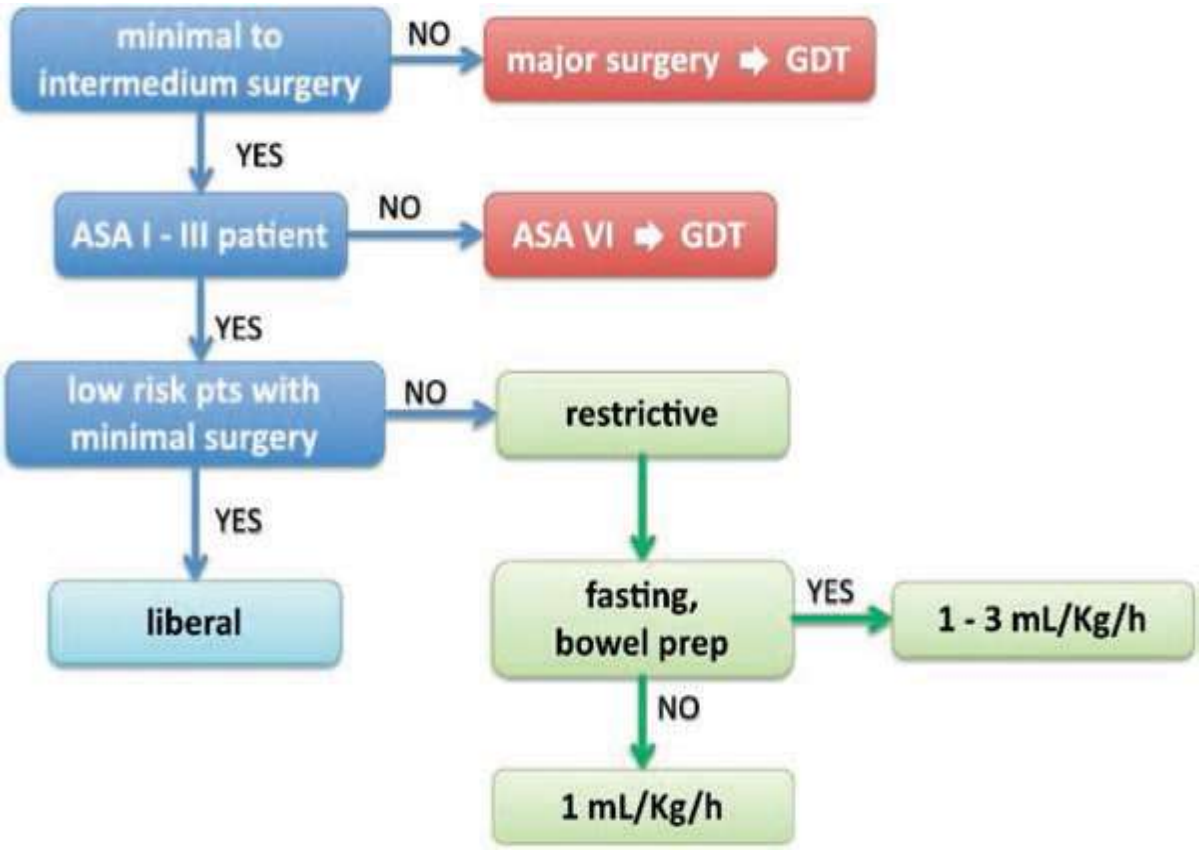

Figure (2): Pre-operative protocol for fluid therapy (Fluid flow chart) [14].

- **Stroke volume variation (SVV):**

Stroke volume variation (SVV) is one of the dynamic parameters of hemodynamic monitoring used to access the volume status and fluid responsiveness in mechanically ventilated patients. Now, SVV accepted as a simple and sensitive indicator for evaluating fluid responsiveness and the preload status in various clinical settings [15].

Many studies discussed SVV as an independent hemodynamic predictor of intraoperative blood loss and a valuable functional preload index during hepatectomy. The results demonstrated that CVP values significantly correlated to SVV value, so implying that SVV can used as an alternative to CVP monitoring. In addition, when IVC with or without the portal triad was clamped during hepatic resection, the SVV was significantly higher in patients with lower blood loss than in those with higher blood loss. Therefore, SVV may be used as a guide for fluid management in order to reduce blood loss during liver resection [16].

SVV reflects the variation of stroke volume (SV) in 30 second and was considered a reliable parameter during surgeries with closed chest. It represents the effect of respiratory movement on venous return. During inspiration of positive pressure ventilation, the increase of intrapulmonary pressure significantly decreases the negative intra-pleural pressure, thereby decreasing venous return and CO. During expiration, the opposite changes occur. When the body has insufficient circulating blood volume, the variation of SV fluctuates obviously with the switching between inspiratory and expiration. Thus, the fluid responsiveness can be predicted according to SVV, to judge the condition of blood volume. SVV is the ratio of the difference between the maximum and the minimum of the SV and the mean of the SV during 30 second as follows:
$SVV = (SV_{max} - SV_{min})/SV_{mean}$ [17].

- **Conclusion: important points in fluid management of hepatectomy:**

Maintaining effective intravascular volume to ensure tissue perfusion and cellular oxygenation is the physiological goal independent of the type of surgery. This consideration also applies to major liver surgery (resection, transplantation), with particular emphasis on liver perfusion and oxygenation. Fluid therapy has to be balanced between underuse leading to hypovolemia and inappropriate tissue perfusion and, administration of excessive fluids with subsequent risks of pulmonary and peripheral edema and hepatic

congestion. For a few years, fixed regimens of fluid infusion (measured in milliliters per kilogram per hour) that can be liberal or restrictive were used but a growing body of evidence suggests now that intraoperative hemodynamic goal-directed therapy to increase blood flow may best to reduce postoperative morbidity and mortality in the higher-risk groups of patients. Fluid therapy should therefore be individualized by using specific goals of care (such as stroke volume or cardiac output optimization) to allow early correction of fluid deficits and avoid excessive administration by fluid titration [18].

The use of low CVP as an index of preload has been popular in hepatic surgery. Although CVP may indirectly reflect volume status, it is not a reliable predictor of the response to fluid loading and associated with many limitations in hepatic surgery. Because CVP is thought to reflect hepatic sinusoid pressure, lowering CVP during liver resection can reduce hepatic parenchymal congestion and subsequent blood loss by helping to control hepatic venous hemorrhage [18].

High CVP values (>10 mmHg) may cause uncontrollable retrograde bleeding occurring during clamping of the portal triad, but whether CVP can be recommended as a monitor or endpoint to guide the hemodynamic management of patients undergoing major hepatic surgery (liver resection or transplantation) remains a matter of debate. Continuous monitoring of CVP has been justified for a long time in liver surgery because of several studies suggested that maintaining a CVP below 5 mmHg was associated with improved outcome and a decreased transfusion requirements during liver resection or transplantation. Noteworthy, most of the studies that support a low CVP strategy have some major methodological flaws, as they were either retrospective or prospective nonrandomized cohorts with a low number of patients or underpowered randomized controlled trials. Surgical situations can affect CVP measurement reliability: wrong placement of the pressure transducer, liver manipulation, occasional clamping of inferior vena cave, hepatic veins or even portal vein by the surgeon, changes in pericardial, intra-thoracic (in particular positive and expiratory pressure, PEEP) and intra-abdominal pressure and frequent patient position changes. Measured CVP may therefore not always reflect hepatic vein or transection zone pressures. Moreover, a meta-analysis including all randomized clinical trials comparing various cardiopulmonary interventions aimed at decreasing blood loss and transfusion requirements in patients undergoing liver resection and showed no significant beneficial impact of the "low CVP" strategy on transfusion, surgical complications or mortality. Thus, the benefit of "low CVP" technique seems only controversial while its morbidity remains poorly evaluated. Potential fatal consequences of the low CVP technique during hepatectomy include air embolism and unnecessary hypo-perfusion [18].

Briefly, reducing CVP can only be obtained by rendering the patient hypovolemic, by hemorrhage, partial clamping of the inferior vena cava, elective addition of diuretics or vasodilators, intraoperative epidural analgesia or increasing depth of anesthesia. This is feasible in minor or intermediate liver resection or in young healthy patient but not in older patients with severe comorbidities undergoing major liver resection. Some studies employed strategies to reduce CVP included the use of diuretics and even severe hypovolemia requiring high-dose vasopressors to maintain blood pressure. This strategy increases the risk of postoperative renal failure and is not recommended for routine use. In general, minimizing fluid administration until the resection is completed (regardless of the CVP) is likely useful to decrease bleeding and improve visualization of the surgical field. This is usually well tolerated as long as the patient is relatively healthy and fluid deficits are corrected after resection and hemostasis are completed [18].

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