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# Hemodynamic Optimization Strategies in Anesthesia Care for Liver Transplantation

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Alexander A. Vitin, Dana Tomescu and  
Leonard Azamfirei

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.68416>

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## Abstract

In this chapter, aspects of hemodynamic regulation in the end-stage liver disease (ESLD) patient, factors, contributing to the hemodynamic profile, coagulation-related problems, blood products transfusion tactics and problems, and hemodynamic optimization strategies during different stages of liver transplantation procedure—specifically what, when, and how to correct, with special attention to vasoactive agents use, will be discussed.

**Keywords:** liver transplantation, anesthesia, hemodynamic optimization, vasoactive agents, transfusion management

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## 1. Introduction

Inseparable part of liver transplantation procedure, anesthesia, and perioperative care for the liver transplant recipient has made a remarkable progress during last decades, becoming a clinical specialty with well-defined goals, requirements, and approaches. Today, with a rapid expansion of liver transplant programs worldwide and growing numbers of liver transplant procedures performed, many aspects of anesthesia care, complicated and risky in the relatively recent past, have become routine and safe. And yet some problems remain unresolved, still posing a challenge for anesthesiologist in the field. Despite incessant and plentiful research, investigating literally every imaginable aspect and angle of the anesthesia and perioperative care for liver transplant recipient, and myriad of publications coming out every year, no consensus has been reached so far as for the best choice of anesthesia induction and maintenance, intraoperative hemodynamics management, fluid and blood products transfusion, patient's monitoring, and more. One of the most important time- and effort-consuming

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aspects of anesthesia care, expanding well beyond proper intraoperative time onto the first long hours of ICU stay, is patient's hemodynamic management. Its multicomponent nature, sometimes a very short time resolution in the decision-making process, poorly predictable course of patients reactions, overall instability with rapid, oftentimes detrimental and life-threatening changes makes management of patient's hemodynamics an extremely challenging and complicating task.

## 2. Factors contributing to hemodynamic profile of the ESLD patient

Typical hemodynamic pattern of end-stage liver disease (ESLD) patients includes high cardiac output (CO)/cardiac index (CI)—hyperdynamic circulation pattern, with normal-to-low mean blood pressure, variable central venous pressure (CVP), along with general arterial and venous vasodilatation due to substantially decreased systemic vascular resistance (SVR). The hyperdynamic circulation is thought to be a compensatory change, induced by splanchnic and peripheral vasodilatation, reducing the effective blood volume. This, and also decreased perfusion pressures, leads to a diminished renal blood flow in cirrhotic patients, which in turn stimulates the renin-angiotensin-aldosterone system and antidiuretic hormone production, resulting in renal artery vasoconstriction, sodium retention, and volume expansion. Worsening liver disease results in progressive vasodilatation, making the hyperdynamic circulation and renal artery vasoconstriction more pronounced [1].

Arterial vascular tone is regulated by complex interactions of different vasoactive substances, namely catecholamines and NO complex. In ESLD patients, sensitivity of  $\beta$ -adrenoreceptors is relatively decreased, causing cardiovascular response to endogenous catecholamines substantially attenuated [2]. Plasma-free norepinephrine and epinephrine levels are significantly higher. Fraction of epinephrine, contributing to total catecholamines, increased up to 50% (normal: about 17%). Dopamine concentration is unchanged [3].

In recent years, nitric oxide (NO) has been recognized as the most important vasodilator of the splanchnic and systemic circulation. Cytokines, especially TNF- $\alpha$ , are considered to be NO inducers. Endothelial NO synthase has been found as a main source of the vascular NO overproduction in the splanchnic arterial circulation [4–6].

Augmented intrahepatic vascular resistance due to sinusoidal constriction is considered the major cause of portal hypertension. Hepatic stellate cells (HSC) provide a basis for control of sinusoidal vascular tone and an arrangement for sinusoidal constriction and hepatic blood flow (HBF) reduction. The dynamic part of hepatic resistance is caused by active contraction/relaxation of HSC. Portocaval collaterals divert up to 80% of blood flow away from liver [7].

Cardiomyopathy plays a substantial role in the hemodynamic profile and cardiovascular compensation mechanisms in a cirrhotic patient. The characteristic features of cirrhotic cardiomyopathy include an attenuated systolic or diastolic response to stress stimuli, structural and histological changes of myocardium, electrophysiological abnormalities, and increased concentrations of serum markers, suggestive of cardiac stress. The impaired cardiovascular

responsiveness in cirrhosis is likely related to a combination of factors that include among other reasons,  $\beta$ -adrenergic receptor dysfunction and reduction of  $\beta$ -adrenergic receptor density in cirrhotic patients. Recently, it has been found that, in cirrhotic patients, the control of vascular tone by  $\text{Ca}^{++}$  and  $\text{K}^{+}$  channels is altered. The calcium channel dysfunction, leading to decreased cardiomyocyte contractility, was demonstrated in an animal model study [2, 8–10].

Albeit commonly overlooked, many of these pathogenic mechanisms resulted in RV overload with gradual dilatation and impaired contractile function, leading to elevated mean pulmonary artery pressure (MPAP). Despite characteristically increased resting CO, ventricular contractile response is, actually, substantially attenuated. Cardiomyopathy may contribute to portopulmonary hypertension.

However, overt severe Congestive Heart Failure (CHF) is rare. Increased intra-abdominal pressure (ascites) contributes to both portal and PA hypertension [11].

Pulmonary vascular changes in cirrhosis are often quite substantial. They include portopulmonary hypertension (POPH) syndrome, which entails development of pulmonary hypertension in a cirrhotic patient with portal hypertension, and also hepatopulmonary syndrome, which is, essentially, increased pathological shunting and V/Q mismatch due to development of the arteriovenous malformations in the lung, resulting in hypoxemia. Portopulmonary hypertension is less prevalent than hepatopulmonary syndrome with an estimated prevalence of about 5%.

POPH is best defined as pulmonary arterial hypertension (PAH). Necessary conditions include presence of portal hypertension and absence of other secondary causes of PH, such as valvular disease, chronic thromboembolism, collagen vascular disease, or exposure to certain drugs or toxins. Current diagnostic criteria include the presence of portal hypertension (either inferred from the presence of splenomegaly, thrombocytopenia, portosystemic shunts, esophageal varices or portal vein abnormalities, or confirmed by hemodynamic measurements), but not necessarily the presence of cirrhosis; and hemodynamic parameters, specifically MPAP >25 mmHg at rest, >30 mmHg with exercise/stress, PCWP <15 mmHg, PVR >120 dynes/s/cm<sup>5</sup>, and transpulmonary gradient >10 mmHg [12–16].

A most common suggested mechanism for POPH maintains that the increased blood flow (high cardiac output) in chronic liver disease causes pulmonary vascular wall shear stress, which can trigger the dysregulation of numerous vasoactive substances. The presence of portosystemic shunts may lead to the shunting of vasoactive substances from the splanchnic to the pulmonary circulation, causing deleterious effects in the pulmonary vasculature [17, 18].

The severity of hepatopulmonary syndrome is classified according to the degree of arterial hypoxemia, specifically mild ( $\text{PaO}_2$  of 60–80 mm Hg), moderate (50–60 mm Hg), and severe (<50 mm Hg). Intrapulmonary vascular dilation leads to increased V/Q mismatching plus a degree of intrapulmonary shunting of deoxygenated, mixed venous blood. Both these mechanisms cause systemic arterial hypoxemia [19–22]. Impairment of hypoxic pulmonary vasoconstriction means that gravitational effects on pulmonary blood flow are poorly tolerated. Many authors observed at least partial resolution of the hepatopulmonary syndrome following liver transplant [23, 24].

A common complication of liver disease and portal hypertension is the accumulation of ascites, whereas the presence of significant ascites sometimes compromises respiratory function mostly by creating the restrictive pattern of lung mechanics, a more significant complication is the presence of fluid in the thorax, termed hepatic hydrothorax. Hydrothorax may exacerbate the restriction pattern even further, sometimes leading to atelectasis development, with associated V/Q mismatch and intrapulmonary shunt that adds to already pre-existing hypoxemia, and also to increase of PA pressure.

### 3. Hemodynamic changes during orthotopic liver transplant surgery

#### 3.1. Anesthesia-related factors

From the days, when the first successful liver transplantation surgery was performed to this day, anesthesiologists all over the world, despite plenty of ongoing and already published research works in the field, have not yet arrived at a consensus, let alone adopted unified guidelines or protocols of the anesthetic technique for liver transplantation surgery.

Since anesthesia-related systemic hemodynamic changes are well described elsewhere, the only aspect of these effects, specifically an impact of anesthesia factors and adjuvant drugs on hepatic blood flow (HBF) and oxygen delivery, needs to be discussed here. The degree to which the hemodynamic changes, caused by anesthetic agents, take place in patients with advanced liver disease, depends on the patient's particular hemodynamics, volume status and compensation pattern, nature of the surgical procedure, and many other factors. Patients with cirrhosis may be more sensitive to hepatic hypoperfusion, and may be more susceptible to liver injury (such as administration of a hepatotoxic drug, rapid blood loss).

It has been shown that practically all general anesthesia techniques, regardless of drug combinations, in the absence of surgical stimulation, reduce the HBF by about 30%. It appears that the systemic arterial blood pressure is a main determinant of hepatic blood as the hepatic artery exhibits almost no autoregulatory capacity [25]. Commonly used IV induction anesthetic agent, etomidate, along with maintaining well the systemic hemodynamic parameters at baseline levels, only moderately reduces the HBF in a dose-dependent manner, and causes the increase in hepatic arterial resistance (by 40%).

Propofol, however, has shown an ability to preserve baseline levels of the HBF, as long as systemic hemodynamic changes were insignificant [26].

Use of isoflurane and sevoflurane for anesthesia maintenance, albeit being associated with minimal-to-moderate global reduction of HBF, has not been found to be associated with any significant influence on arterial hepatic blood flow or oxygen transport and extraction ratio in the liver. Short-action opioids, fentanyl in particular, has shown no discernible effect on HBF [27–31].

Other potential perioperative causes of a reduction of HBF include mechanical ventilation, positive end-expiratory pressure, systemic hypotension due to hypovolemia, hemorrhage, etc., and hypoxemia. Beta ( $\beta$ )-blockers, alpha ( $\alpha$ )-agonists, H<sub>2</sub> blockers, hypocapnia, alkalosis, and hypoglycemia have been found to be associated with moderate HBF reduction.



Dopamine (3 mcg/kg/min), epinephrine (from 0.01 mcg/kg/min), hypercapnia, acidosis, and hypoxemia, however, are among the factors that actually can increase HBF [32, 33].

With a substantial variety of anesthetic techniques currently in use and with full awareness of ESLD hemodynamic profile specifics and patient-to-patient variety in that respect, it appears to be reasonable to set hemodynamic goals (i.e., hemodynamic parameters to possibly maintain) for anesthesia care for liver transplant. These should include mean arterial pressure (MAP) around 75–85 mmHg, Heart rate (HR): <100/min, Central venous pressure (CVP): <20 mmHg, Mean Pulmonary Artery Pressure (MPAP): <25 mmHg, CO/CI: >4 L/min/>2 L/min m<sup>2</sup>, Systemic Vascular Resistance (SVR): >500 dynes/s/cm<sup>-5</sup>, and mixed venous SvO<sub>2</sub>: >75%.

### 3.2. Surgery-related factors

The course of liver transplantation surgery includes four stages. During preanhepatic, or dissection phase, the diseased liver is being dissected and prepared for removal. Portal vein clamping, followed by hepatic artery and IVC clamp, heralds the start of anhepatic phase, during which part of the diseased liver is being removed from the body and being replaced by the donor's organ. Vascular anastomoses are being performed, followed by organ reperfusion phase, the shortest one with most significant hemodynamic impact. After venous blood flow restoration in the transplanted organ, postreperfusion phase include common hepatic arterial anastomosis, cholecystectomy, and bile duct reconstruction.

During preanhepatic (dissection) phase, laparotomy, often followed by ascites evacuation, causes drop of intra-abdominal pressure, with rapid splanchnic volume increase (i.e., mesenteric blood pooling) ensued. Ongoing blood loss at this stage may be very substantial, due to abundance of venous collaterals in cases with longstanding portal hypertension, and also in cases of re-do transplants, or cases with significant adhesions after previous surgeries. Decrease of venous return, ongoing blood loss, fluid shift, and developing acidosis further contribute to CO/CI and mean arterial blood pressure (MABP) decrease.

Portal cross clamp, which portends the anhepatic stage start, causes variable (20–30% of baseline) degree of venous return decrease. However, in cases of well-developed portocaval collaterals (longstanding portal hypertension), this loss of preclamp venous return may be less significant, around 15–20%, and generally well tolerated. IVC complete cross-clamp oftentimes leads to a more substantial and poorly tolerated (approximately 50%) decrease of venous return, whereas IVC partial clamp causes variable, about 25–50%, decrease of venous return [34, 35]. ESLD patients have very limited ability, if any, to compensate for the rapid decrease in venous return with systemic vasoconstriction due to inherent low SVR. Venovenous bypass (VVB) may present a possible solution to compensate for decreased venous return. Hemodynamic instability following test clamping of IVC is the most common indication for initiating VVB [36]. It has been suggested [37] that hypotension (30% decrease in MAP) or a decrease in cardiac index (50%) during a 5-min test period of hepatic vascular occlusion can be used to identify the group of patients who require VVB. Other indications of the VVB include presence of pulmonary hypertension, impaired ventricular function from previous myocardial infarction, ischemic heart disease, and cardiomyopathy [38]. In patients with pulmonary hypertension, excessive fluid loading to compensate for hemodynamic changes during anhepatic phase may result in acute right ventricular dysfunction. Patients

with cardiomyopathy have impaired left ventricular function, and consequently a limited ability to generate adequate CO in the face of the increase in SVR during the anhepatic phase. These patients, too, may benefit from ameliorative effect of the preload associated with VVB. Some centers use VVB in patients with impaired renal function (i.e., hepato-renal syndrome) in order to prevent further kidneys damage during the anhepatic phase and to reduce the need for postoperative renal support. Among the advantages of VVB, some researchers listed the ability to reduce hemodynamic instability during anhepatic phase. It is useful in patients with pulmonary hypertension and cardiomyopathy who tolerate anhepatic period poorly. VVB has been shown to maintain intraoperative renal function [39, 40]. It also helps to maintain cerebral perfusion pressure in patients with acute fulminant failure by avoiding rapid swings in blood pressure, and, at least theoretically, may reduce blood loss [41]. However, VVB is not devoid of certain disadvantages. It does not guarantee normal perfusion of abdominal organs and lower limbs, since venous return never could be maintained at prebypass levels. The pump could only provide up to 2 L/min output (most commonly, only 1.5–1.8 L/min), which is, however comparable with low-to-normal levels of CO, cannot ensure the normal or even near-normal level of preload [42]. There is neither evidence of general (patient- and organ survival) outcome improvement, nor that its use reduces or prevents the occurrence of postoperative renal failure [43]. VVB may exacerbate coagulation problems and cause excessive bleeding by inducing hemolysis, platelet depletion.

Graft reperfusion causes major hemodynamic changes along with possible substantial end-organ injury. These may include direct myocardial injury, resulting in tachy/bradyarrhythmias and cardiac arrest, profound vasoplegia, acute interstitial pulmonary oedema, leading to further RV overload/acute insufficiency, raise of pulmonary artery pressure (PAP) and CVP. Blood loss, hemodilution, hypovolemia, temperature drop, and rapidly developing lactic acidosis contribute to decreased sensitivity to catecholamines and efficiency of vasopressors. All these factors lead to rapid drop of SVR, resulting in a decrease of MABP with or without CO/CI decrease. Postreperfusion syndrome (PRS) was defined as a more than 30% decrease of MABP from that in the anhepatic stage, longer than for 1 min during the first 5 min after reperfusion of the liver graft [44–46].

In the postreperfusion period, the major factors of hemodynamic instability include ongoing blood loss, exacerbated by consumption coagulopathy in the face of very limited or almost nonexistent production of coagulation factors by the liver graft. Hypocalcemia, resulting from the effects of citrate-containing blood conservation solution, associated with transfusion of large amounts of RBC, exacerbates reduction of myocardial contractility caused by recent reperfusion. Acidemia, mostly due to lactic acidosis, substantially decreases efficacy of vaso-active agents.

## **4. Blood loss and coagulopathy management**

### **4.1. Blood loss estimation and prediction factors**

Blood loss during OLT is a well-known major factor of morbidity/mortality and overall hemodynamic instability, varying from just hundreds of ml up to dozens of liters. Predisposing

factors for major blood loss may include pre-existing + ongoing consumption and dilution coagulopathy (i.e., preoperative prothrombin time (PT), International normalized ratio (INR) and platelets numbers, factor V levels, etc.), MELD score >25, severe portal hypertension, “hostile abdomen” — postlaparotomy, re-do orthotopic liver transplant (OLT), long ischemia times, aged/marginal quality donor organ, donor-recipient organ size discrepancy, long, traumatic liver dissection, and surgeon-related factors.

Substantial number of studies reported no statistically significant correlations between blood loss and most of aforementioned parameters, particularly in respect to MELD score [47] and INR [48].

To date, blood loss and associated massive blood transfusion during OLTs remain difficult to predict [49]. Intraoperative blood salvage technique provides at least some way for blood loss estimation, with considerable approximation. Correspondent guidelines, based on calculations of hematocrit during blood loss (25–30%) and that of returned red blood cells by Cell-Saver (approximately 55–65% depending on Cell-Saver model), have been developed. Authors calculated estimated blood loss by multiplying the total volume of Cell-Saver returned RBCs by factor 3.4–4.0 [50, 51].

#### **4.2. Coagulopathy: mechanisms and assessment**

Of all the aforementioned factors, coagulopathy presents by far the most important and potentially most correctable problem, contributing to overall blood loss and, therefore, hemodynamic instability. Bleeding during OLT is multifactorial due both to surgical trauma and to coagulation defects. Coagulation defect in ESLD patients include impaired coagulation factor synthesis, dysfunction of coagulation factors, increased consumption, and fibrinolysis. Commonly, the levels of factor VII and protein C decrease first, followed by reductions in factors V, II, and X levels [52]. Platelet function is also affected by liver disease, and thrombocytopenia is common. Predisposing factors include hypersplenism secondary to portal hypertension, decreased thrombopoietin synthesis, immune complex-associated platelet clearance, and reticuloendothelial destruction [53].

During the dissection phase of the transplant, excessive bleeding is related to the technical difficulties during the liver dissection, and presence of portal hypertension, with large dilated collaterals [54].

During the anhepatic phase, coagulation factor synthesis is practically nonexistent, and ongoing factors consumption exacerbate the bleeding.

Right after graft reperfusion, profound coagulation abnormalities are very common. Factors that contribute to excessive bleeding in postreperfusion period include platelet entrapment in the sinusoids of the donor liver, a global reduction of all coagulation factors (mainly due to increased consumption, and partially due to hemodilution), and decreased level of antifibrinolytic factors [55, 56].

Method of thromboelastography (TEG) allows a rapid graphic assessment of the functional clotting status and degree of fibrinolysis. In various studies, the amount of RBCs and fresh



frozen plasma (FFP) usage has been significantly reduced when TEG monitoring that was compared to the conventional “clinician-directed” transfusion management [57, 58]. Although the usefulness of TEG in complex coagulation defects has been questioned [59], recent studies have shown, that the use of TEG can reduce the number of blood products transfused [58].

### 4.3. Hemotransfusion requirements and strategies

Blood transfusion therapy remains a critical component of anesthetic management and perioperative care in OLT. Multiple studies have shown a large variability in the use of blood products among different centers and among individual anesthesiologists within the same center [60]. The decision of when to transfuse RBCs, remains debatable. Some authors recommend keeping the hematocrit between 30 and 35%; others think it advisable and acceptable to maintain it between 26 and 28% [61, 62]. The modern trends have shown a substantial change from a transfusion of 10–20 units to 0–5.

The standard indication for fresh frozen plasma (FFP) infusion is coagulation defect treatment. FFP is expected to improve complex coagulation disorders in case of severe bleeding as it contains all coagulation factors and inhibitors. However, Freeman et al. [62] maintain that FFP administration is not essential during OLT, and that platelets and fibrinogen concentrates may be given when platelet count and fibrinogen level fall below 50,000 mm<sup>3</sup> and 1 g/L. In some centers, the trigger point is INR lower than two, which remains controversial. It has been shown that TE-guided coagulation defect management generally lowers the FFP amount. There is currently no consensus on the volume of FFP or rate of infusion required; in common practice, 10–15 mL/kg are usually administered. Because of the lack of universally accepted guidelines, the amount and timing of FFP administration during OLT are still guided by experienced clinical judgment, local practices, and coagulation tests (including TEG).

Although there is no consensus regarding the appropriate threshold value [64], platelet concentrates are frequently administered during OLT to address “oozing” on the operation field that likely could be attributed to the lack clot formation ability. Inter-center indications for platelet transfusion vary, but it seems that the current trend is to administer platelet transfusions pretty much regardless of the absolute PLT count.

It has been shown in many studies that the massive use of blood products during OLT is associated with increase in morbidity and mortality [65, 66]. It has been demonstrated that the intraoperative transfusion of red blood cells (RBCs) is associated with increase of postoperative mortality, specifically reduce survival rates at six months (63.8 vs. 83.3%) and at 5 years (34.5 vs. 49.2%), thus became a major prediction factor of mortality [59, 67, 68]. Higher intraoperative RBC transfusion requirements are associated with higher reintervention rates. Patients, who undergo reintervention, have three times higher mortality than those who do not have reinterventions [69, 70]. All blood products (RBCs, fresh frozen plasma (FFP), and platelets) have been shown to be negatively associated with graft survival at 1 and 5 years by univariate analysis [71]. Recent studies show that FFP and platelet transfusions are linked to the development of ALI/ARDS [71]. Pereboom et al. demonstrated, that platelet transfusion during OLTx is associated with increased postoperative mortality due to transfusion-related

acute lung injury (TRALI)/ARDS [63]. Intraoperative platelet transfusions have been identified as a strong independent risk factor for patient survival after OLT in addition to RBCs [72]. Studies have demonstrated that platelets are involved in the pathogenesis of reperfusion injury of the liver graft by inducing endothelial cell apoptosis. This effect is independent of ischemia-related endothelial cell injury [73].

#### 4.4. Ways of blood loss reduction

Ways of blood loss reduction include surgical techniques such as Piggy-back technique with IVC preservation—partial Inferior vena cava (IVC) clamp, and anesthesia management options, such as maintaining the low CVP, minimal hemodilution with limited crystalloids infusion, and vasoactive agents use. Discussion of surgical techniques is beyond the scope of this review; however, anesthetic management options and techniques, intended to reduce blood loss during OLT are in the focus of discussion.

##### 4.4.1. Fluid management and “low CVP” paradigm

Balanced fluid administration and maintaining relative hypovolemia have been advocated by many authors. A low CVP has been recommended to minimize blood loss during dissection stage of the liver transplantation. Massicotte et al. [74, 75] reported that maintaining a low CVP before the anhepatic phase was an efficient technique to decrease blood loss and transfusion rate. However, low CVP is associated with increased risk of complications, such as tissue hypoperfusion, development of lactic acidosis and renal failure, and also significant morbidity and mortality [76]. As it has been observed, increase in serum creatinine level, indications for dialysis, and 30-days mortality were higher in group of liver transplant patients, where CVP has been kept at low levels (around 3–5  $\text{smH}_2\text{O}$ ), in order to avoid venous congestion of the graft. However, no supportive evidence has been found for decreasing CVP and effective circulating blood volume during OLT levels, currently accepted in some centers for liver resection [77]. Due to the lack of adequately powered, randomized, prospective controlled trials further investigations are needed to determine which patients would benefit from restrictive volume management in the intraoperative period of OLT.

##### 4.4.2. Blood salvage technique during OLT

The use of intraoperative blood salvage and autologous blood transfusion has been for a long time an important method to reduce the need for allogeneic blood and the associated complications [78]. It has been demonstrated, that, for systematic use of Cell Saver salvaged blood in 75 OLT cases, retransfusion volume was enough and adequate in 65% of the cases [79].

The resultant hematocrit after Cell Saver processing ranges between 50 and 80% [80]. The safety of cell-salvaging procedure has been widely demonstrated [81]. Use of intraoperative autologous transfusion resulted in conservation of RBCs and reduction in exposure to homologous blood and blood components [82, 83]. Use of Cell Saver during OLT made it possible to recover up to 50% of blood loss [84]. Substantial reduction in FFP and a lesser reduction in platelet requirement have also been seen.

Nonetheless, blood-salvaging techniques during OLT are still being considered as controversial. Some studies have reported relatively higher blood loss, increased incidence of fibrinolysis, and cost rise [85, 86]. The increased blood loss in recipients, receiving Cell Saver blood has been attributed to the release of fibrinolytic compounds from blood cells in the collected blood and/or from the transplanted liver [87]. These findings, however, have not dissuaded the anesthesiologists from using Cell Saver during OLTs; in fact, this method is gaining wider popularity, and becoming almost a standard of care in many centers around the world.

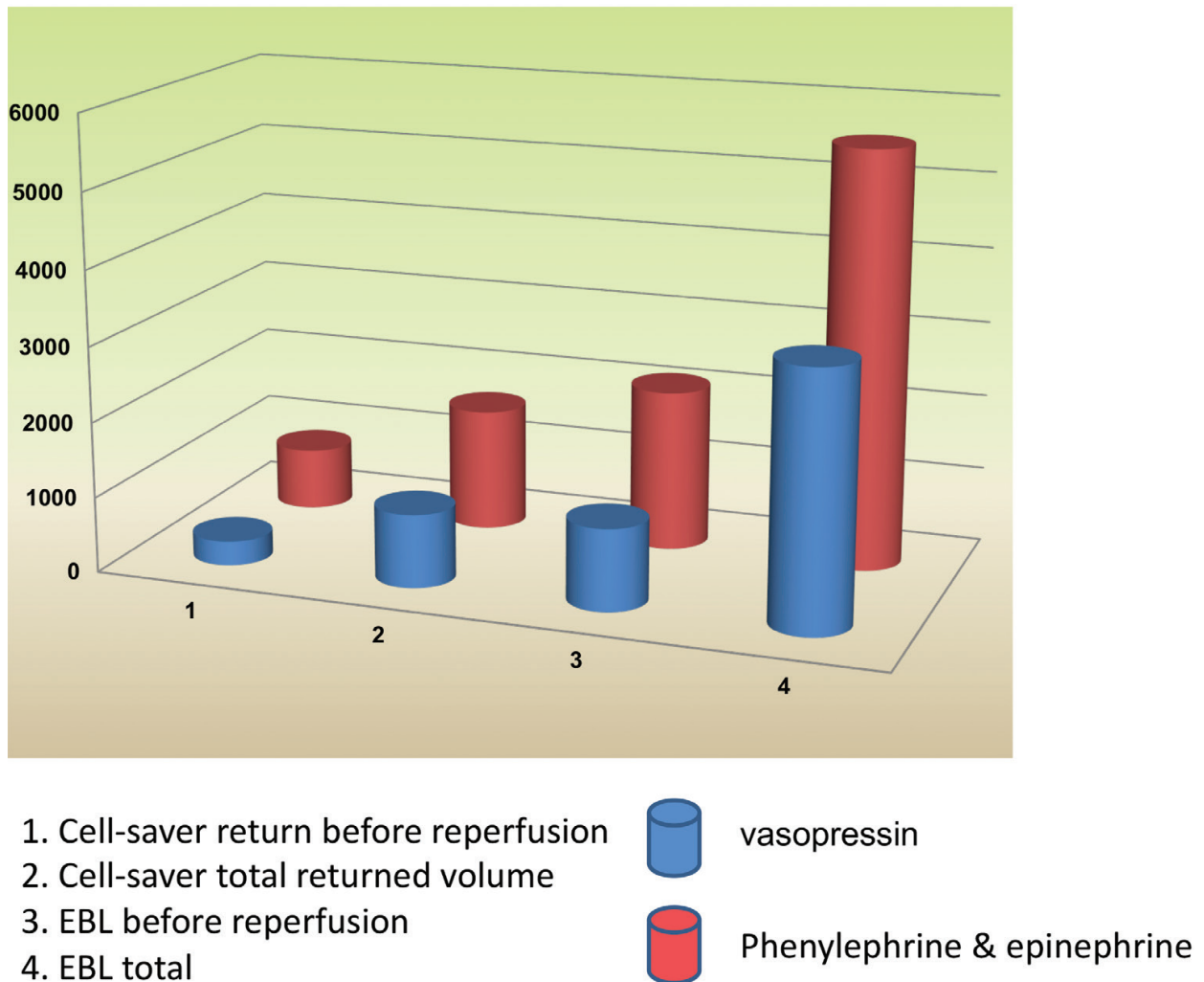
## 5. Vasoactive agents applied pharmacology and use in hemodynamic management during OLT

Hemodynamic instability during OLT due to blood loss, graft reperfusion, and postreperfusion vascular tone adjustment, substantial fluid shift oftentimes necessitates the use of vasoactive agents. Different vasopressors, such as dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, vasopressin, and, more recently, terlipressin and octreotide have been used for hemodynamic optimization and end-organ perfusion improvement during OLTs for decades [88, 89].

Norepinephrine and phenylephrine have a universal vasoconstrictor effect due to  $\alpha$ -receptor stimulation, thus effectively increasing systemic vascular resistance, while decreasing cardiac index, peripheral and portal blood flow [90–93]. However, norepinephrine in higher doses causes severe peripheral vasospasm and promotes metabolic (lactic) acidosis [88]. Phenylephrine increases SVR and MPAP, while it decreases CO/CI, peripheral, and portal BF [93], and does not affect portal VP during the dissection phase. CVP is often increased and does not seem to reflect cardiac filling [94].

Epinephrine and norepinephrine decrease liver and kidney tissue perfusion, thereby reducing lactate clearance, promote lactic acidosis, cause temporary alterations of hepatic macro- and microcirculation (return to baseline 2 h after onset of infusion). Dose-dependent progressive decline of hepatic macro- (33–75% reduction) and microcirculation (39–58% reduction) was found in transplanted livers. Norepinephrine has a direct constrictor effect on liver sinusoids, thereby reducing hepatic blood volume/flow and aggravating portal hypertension, and demonstrates effects similar to those of vasopressin effects on CO/CI and SVR [95], does not increase HBF, hepatic DO<sub>2</sub> or VO<sub>2</sub>, and does not improve the hepatic lactate extraction ratio [96]. Vasopressin increases SVR, decreases MPAP; normalizes CO/CI, and potentially, CVP; maintains mean BP; decreases portal pressure, HBF, and systemic blood flow (SBF); improves impaired renal function; enhances diuresis, and thus improves Na balance and lactate elimination; enhances platelet aggregation; and increases levels of Profactor VIII and von Willebrand factor, and does not promote lactic acidosis. Its use after reperfusion, albeit having been shown beneficial by many authors, remains controversial, mainly due to splanchnic flow restriction effect with potential impairment of portal flow to the graft. Vasopressin has been demonstrated to have a dose-dependent vasoconstrictor effect on the peripheral vasculature with substantial SVR increases, while having little effect on heart rate, systemic arterial blood pressure, and CI in normotensive patients [97]. The ability of vasopressin to selectively

constrict splanchnic vasculature, and thus decrease portal blood flow, is thought to constitute a physiological basis for variceal bleeding control by a higher vasopressin (0.4 U/min) dose [98, 99]. Vasopressin decreases portal vein pressure and flow in the native liver during liver transplantation [100]. Authors' own study has shown that use of low-dose vasopressin (0.04 U/min) infusion in an attempt to reduce blood loss seems to be a promising and a feasible technique. Vasopressin decreases portal vein pressure and blood flow in the native liver, as do terlipressin and octreotide [101]. A low-dose vasopressin (0.04 U/min) infusion apparently exerts only a minimal effect on the general hemodynamics. Low-dose vasopressin infusion is proved to be safe: to date, no cases of liver graft damage have been documented. To the contrary, cases where a high-dose of vasopressin (0.8 U) bolus, followed by a vasopressin infusion (4U/h) to attenuate refractory hypotension secondary to graft reperfusion, was used without causing any identifiable liver graft damage, have been reported [102]. Vasopressin has been shown to have a stimulation effect on lactate production by liver cells and adipose tissue in the septic model [103], and to be able to decrease blood loss during pre- and anhepatic phases of OLT (namely, EBL before graft reperfusion has been decreased by 50.2% [104] **Figure 1**)



**Figure 1.** Blood loss decrease in pre-reperfusion stages of OLT: comparison of low-dose vasopressin and phenylephrine infusions.



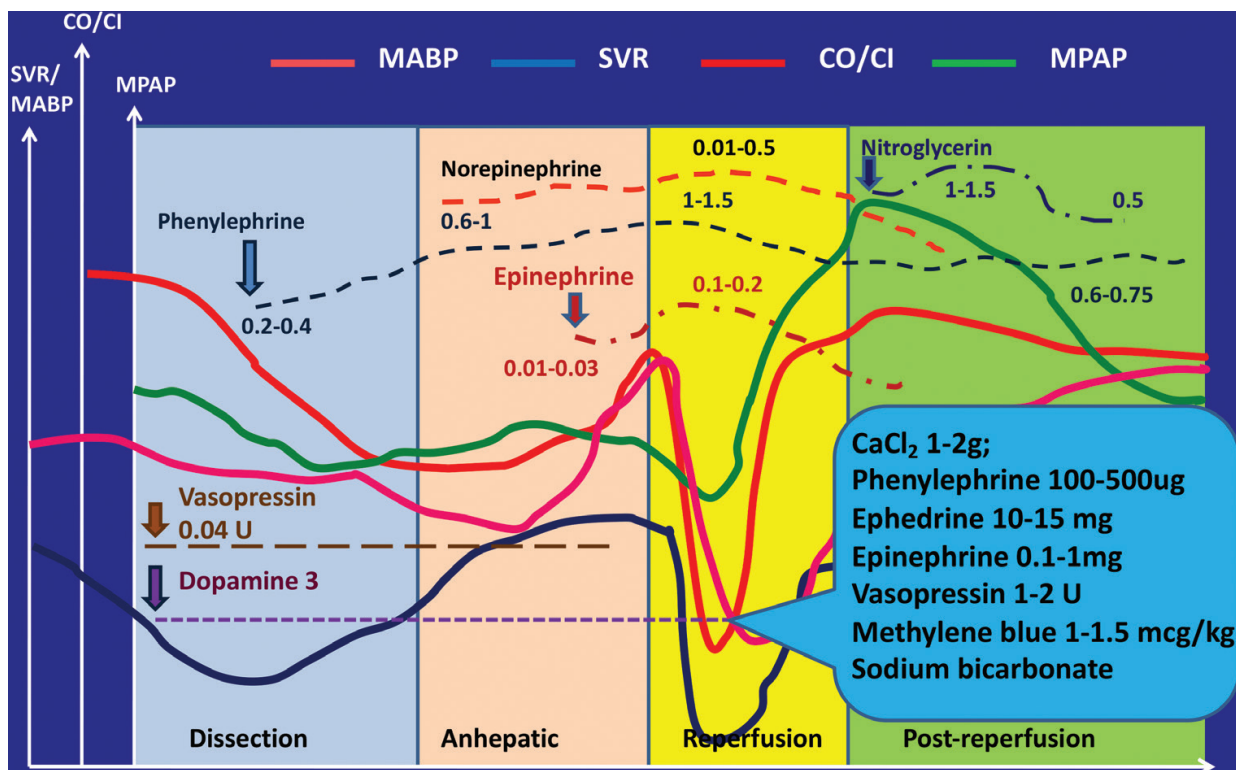
### 5.1. Suggested algorithm of vasoactive agents used during anesthesia for OLT

Phenylephrine, epinephrine, norepinephrine, dopamine, and vasopressin are commonly used during different stages of OLT. The task of attaining hemodynamic stability sometimes dictates concomitant use of two or more vasoactive agents (**Figure 2**).

Intraoperative use of dopamine, 3 mcg/kg/min in OLT is intended to preserve and protect the adequate renal function, especially in cases of hepatorenal syndrome [105]. Higher rates of dopamine infusion, 5–10 to 20 mcg/kg/min, increase cardiac output and SVR. However, gaining CO/CI increase at the expense of tachycardia and, potentially, some rhythm disturbances makes dopamine a less desirable agent.

Early in the perunhepatic (dissection) stage of the surgery, phenylephrine infusion may be started, along with already running dopamine and low-dose vasopressin. Due to phenylephrine's almost purely  $\alpha$ -mimetic activity, its use actually addresses the low SVR problem, a main culprit for low MABP in majority of cases, provided that volume status correction and maintenance is being performed properly. In the majority of cases, phenylephrine infusion continues throughout the case. Providers in the other centers prefer and advocate early norepinephrine-only infusion be started, while others combine these agents [106].

Anhepatic stage often presents a challenge in terms of maintaining of hemodynamic stability. Rapid decrease in venous return; therefore, potential drop of CO, exacerbated by significant blood loss, usually necessitates more aggressive approach. Along with increase of norepinephrine (and phenylephrine, if its infusion is running along with the former), epinephrine may be added, with the purpose of using its  $\beta$ -stimulation activity. In preparation graft reperfusion,



**Figure 2.** Use of different vasoactive agents throughout the whole of the OLT procedure.



some authors actually recommend “pretreatment” [107] with epinephrine and phenylephrine combination for postreperfusion syndrome prevention.

Graft reperfusion and postreperfusion syndrome presents a most significant challenge for hemodynamic management. Many different techniques and drug combinations has been tested and recommended for rapid hemodynamic recovery after liver graft reperfusion. Along with vasoactive agents and their combinations that are already in use by the time of a graft reperfusion, other agents has been successfully used (Figure 1). Vasopressin in small boluses, 1–2 U, may be highly efficient in opposing the significant and rapid decrease of SVR, and calcium chloride, up to 100 mg, may enhance inotropic effects of epinephrine [108]. Another agent, namely Methylene Blue, 2 mg/kg, has been reported as very efficient and “last resort” drug for prolonged and profound hypotension, refractory to treatment with other vasoactive drugs [109].

The presence of significant metabolic, mainly lactic, acidosis is a well-known cause of decreased vasoactive agent’s efficiency [110]. To overcome hyporesponsiveness to vasopressors, sodium bicarbonate infusion may be necessary. THAM infusion provides a fast and efficient way of acidosis reversal and returning pH closer to the physiological range [111].

In certain cases, shortly after even seemingly uneventful graft reperfusion, PAP and CVP start to rise and graft congestion ensues. Reasons for this pulmonary pressure surge include postreperfusion left ventricle diastolic dysfunction as a result of direct myocardial injury, caused by free oxygen radicals containing metabolic substances, relative overload due to rapid transfusion of substantial amounts of blood products, interstitial pulmonary edema with PVR increase, and more. Graft congestion causes substantial perfusion and oxygen delivery impairment in the newly transplanted liver, that delays normal function restoration, specifically restart of coagulation components synthesis, which, in turn, exacerbates and prolongs the coagulation deficit. To address this problem, infusion rates of vasoactive drugs should be adjusted to the best possible balance of MAP and PAP, blood products transfusion rate (but not necessarily volume) should be decreased, diuretics (Furosemide) may be administered, and infusion of nitroglycerin, starting at 1 mcg/kg/min, may be commenced, as blood pressure tolerates. Nitroglycerin has proved to be an effective agent for treatment of pulmonary hypertension. It has been shown that nitroglycerin infusion resulted in pulmonary vascular resistance decrease by 43%, and mean pulmonary artery pressure decrease by 19% [112].

Hemodynamic management of postreperfusion stage of liver transplantation procedure consists of continuation of vasoactive agents infusion and usually involves a gradual decrease of infusion rates and also weaning from most aggressive vasopressors, like epinephrine. In substantial percentage of the cases, despite the adequate volume status restoration and coagulation defect complete reversal, the necessity for vasoactive drugs persists. Hemodynamic optimization continues well beyond the actual end of the surgery, oftentimes for a few days in critical care units.

Choice and dosage of vasoactive agents at every stage of OLT depend and should be guided by hemodynamic parameters. We suggest the allocation to all the patient population undergoing liver transplantation surgery, in three groups, according to hemodynamic parameters: compensated (MAP 80–100 mmHg, SVR > 600 dynes/s/cm<sup>5</sup>), subcompensated (MAP 60–70 mmHg, SVR 300–600 dynes/s/cm<sup>5</sup>), and decompensated (MAP <50 mmHg, SVR <200–250 dynes/s/cm<sup>5</sup>)

Suggested algorithm of vasoactive agents use and dosage is summarized in **Table 1**.

OLT stage	Hemodynamics					
	MAP 80–100, SVR>600		MAP 60–70, SVR 300–600		MAP<50, SVR <200–250	
	Agent	Dose	Agent	Dose	Agent	Dose
Dissection	Dop	3	Dop	3	Dop	5–10
	Phen	0.2–0.4	Phen	0.4–0.6	Phen	0.6–1.0
	Vas	0.04	Vas	0.04	Vas	0.04–0.08
				NE	0.01–0.03	
An-hepatic	Dop	3	Dop	3	Dop	5–10
	Phen	0.2–0.4	Phen	0.4–0.8	Phen	0.8–1.2
	Vas	0.04	NE	0.01–0.03	NE	0.04–0.08
		Vas	0.04	Epi	0.01–0.03	
				Vas	0.04–0.08	
Reperfusion	Dop	3–5	Dop	3–5	Dop	3–5
	Phen	0.2–0.6	Phen	0.6–0.8	Phen	0.8–1.2
	Ca	500	NE	0.04–0.08	NE	0.06–0.1
		Epi	0.02–0.04	Epi	0.04–0.08	
		Ca	1000	Vas	3–5	
		Vas	1–2	Ca	1000–2000	
				MB	1–1.5	
				Bic	50–100	
Post-reperfusion	Dop	3	Dop	3	Dop	3–5
	Phen	0.02–0.06	Phen	0.4–0.8	Phen	6–1.0
			NE	0.02–0.04	NE	0.08–0.1
				Epi	0.02–0.04	

Dop—dopamine; Phen—phenylephrine; NE—norepinephrine; Epi—epinephrine, all dosage in mcg/kg/min; Vas—vasopressin, units/min; Ca—calcium chloride, mg; MB—Methylene Blue, mg/kg; Bic—sodium bicarbonate, mEq.

**Table 1.** Algorithm of vasoactive agents use and dosage during OLT.

## 6. Conclusion

Hemodynamic optimization during liver transplant surgery presents very complex, challenging, sometimes formidable task, many aspects of which remain unclear, thus warrant further research. A wide variety of anesthetic techniques and standards, institutional policies,

hemodynamic triggers for vasoactive agents use and transfusion thresholds, arriving at the even nation-wide consensus, let alone worldwide, remain extremely difficult, if not mere a unrealistic task. Nonetheless, introduction of comprehensive guidelines, based on most common clinical practices and realities of perioperative hemodynamic management appears to be not only conceivable but rather timely and a necessary enterprise. Once introduced, such guidelines may lay the ground for successful and safe intra and perioperative practices and also provide support for much-needed research efforts in this complicated area of transplant anesthesia practice.

## Author details

Alexander A. Vitin<sup>1\*</sup>, Dana Tomescu<sup>2</sup> and Leonard Azamfirei<sup>3</sup>

\*Address all correspondence to: [vitin@uw.edu](mailto:vitin@uw.edu)

1 Department of Anesthesiology, University of Washington, Seattle, WA, USA

2 Department of Anesthesia and Intensive Care “Carol Davila”, University of Medicine and Pharmacy, Fundeni Clinical Institute, Bucharest, Romania

3 University of Medicine and Pharmacy Tîrgu Mureş, Tîrgu Mureş, Romania

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