12 Liver Transplantation: Hemodynamic Changes, Cardiac Output Monitoring and Inotropic Support

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Introduction

Liver transplantation (LT) poses distinct challenges to the anesthesiologist. Patients presenting for LT constitute a high-risk surgical group with unique problems and require meticulous attention to their perioperative management.

End-stage liver disease (ESLD) is the most common indication for LT and presents complex pathophysiological changes involving various organ systems. The severity of such changes varies enormously between cases. A further level of complexity is seen in patients presenting with decompensated ESLD and in those presenting with acute hepatocellular failure. Cardiovascular, respiratory, renal, neurological, gastrointestinal and inflammatory changes all interact to produce a complex picture. Portopulmonary hypertension, ascites, varices and dyselectrolytemia are some of the myriad problems associated with liver disease that require special consideration before anesthetising patients for LT.

In this chapter, we discuss cardiovascular changes occurring at various stages of LT, modes of hemodynamic monitoring and use of inotropes and vasopressors.

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Cardiovascular Changes During LT

Physiological Considerations

To understand fully the hemodynamic changes during LT, it is worth considering the physiological principles of liver blood flow. In health, autoregulation smoothes out potentially major changes in hepatic blood flow (HBF) and protects normal hepatic physiology and function. The precise mechanisms that regulate HBF are poorly understood. However, there are several hypotheses to explaining *intrinsic* and *extrinsic* factors affecting hepatic flow [1]. The liver has limited inherent ability to control portal venous blood flow (PBF); however, multiple integrated processes determine PBF, including anatomical and pathological changes altering portal vascular resistance.

Intrinsic Factors—PBF acts as a main intrinsic factor regulating HBF. The hepatic arterial blood flow buffers any changes in PBF through the "hepatic artery buffer response" to maintain a constant total HBF. This buffer response seems to be independent of the metabolic demands of the liver [2]. Myogenic and chemical mechanisms have been postulated to explain this mechanism. As in most other organs, the vascular resistance of the hepatic artery (HA) is inversely proportional to blood flow, and a*denosine* plays a key role in the chemical autoregulation of HBF. Sinusoidal adenosine concentrations, determined largely by portal venous washout, are inversely proportional to HA tone. Thus a reduc-

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tion in PBF causes accumulation of adenosine and ensuing local vasodilation of the HA [3]. The liver also has a unique property of matching its mass to the blood supply it receives by either *proliferation* or *apoptosis* of hepatic cells possibly mediated via portal flow-dependent growth factors. Adenosine furthermore activates the *hepatorenal reflex* causing fluid retention [4].

Extrinsic Factors—Animal experiments have revealed multiple extrinsic factors regulating HBF including:

- Sympathetic nervous system
- Catecholamines
- Gastrointestinal hormones (secretin, glucagon, cholecystokinin, etc.)
- Autacoids (histamine, serotonin, bradykinin, prostaglandins, etc.)
- Vasoconstrictor peptides (angiotensin-2 and vasopressin) [1]

Hemodynamic Changes

Patients with ESLD demonstrate characteristic cardiovascular system (CVS) changes such as a hyperdynamic or hyperkinetic state secondary to a reduction in systemic vascular resistance (SVR) and a compensatory increase in cardiac output (CO) [5]. There may be a coexisting cirrhotic cardiomyopathy particularly in alcoholic liver disease, chronic portal and/or pulmonary hypertension, ascites, hypoproteinemia and dyselectrolytemia. These CVS changes worsen as disease progresses [6], and conditions inducing a neurohumoral stress response, such as trauma, surgery and sepsis, may induce or aggravate such complications as hepatorenal syndrome, variceal bleeding and circulatory failure [7].

Pathogenic Mechanisms

Liu et al. have reviewed the pathophysiological processes contributing to the CVS changes in liver disease [7]. The salient features are summarised in Table 12.1.

The exact pathogenic mechanisms causing significant hemodynamic changes in the perioperative period of LT, however, remain unclear.

Measurement of Cardiac Output

Although a full discussion of CO monitoring techniques is discussed elsewhere (Chapter 9) in this book, it is important to understand their importance and limitations. Estimation of CO is important as it helps guide fluid and inotrope management. Hypotension may result from low SVR, poor cardiac contractility, reduced stroke volume or a combination of these factors; (relative) bradycardia may also contribute to low CO, and hence hypotension even in the presence of adequate filling. This is particularly important in LT as bradycardic hypotension is frequently associated with high central venous pressure, which may compromise the pressure gradient between the portal and central venous systems, compromise graft blood flow in the immediate post-reperfusion phase and result in primary nonfunction.

Cardiac function may be further compromised by pleural or pericardial effusions or pre-existing pulmonary hypertension with right ventricular dysfunction. Furthermore, cardiac filling may be impaired by diastolic dysfunction, either *irreversible* (e.g. as a result of an established infarct with a fibrotic area), *mechanically reversible* (e.g. due to pericardial effusions) or *physiologically reversible* (e.g. lusitropic and pseudo-lusitropic effects secondary to the effects of transfusion on anemia-induced myocardial ischemia or due to ventricular septal shifts following "venodilatation").

The method for CO monitoring selected should take account of the patient's needs and the expected severity and nature of cardiovascular derangement. For example, the patients at risk of micro-embolic phenomena at reperfusion, or patients thought to have an inducible regional wall motion abnormality, or pericardial effusion, may be best monitored using trans-esophageal echocardiography (TEE) [8], but the patient with pulmonary hypertension, however, may benefit from the use of a pulmonary artery catheter (PAC). For routine use in patients with previously good cardiac function and no structural abnormality, pulse pressure or pulse power analysis

Table 12.1 Proposed pathogenic mechanisms that contribute to hemodynamic changes in liver disease. cGMP—3′, 5′ cyclic guanosine monophosphate, CVS – cardiovascular system

Central neural activation	Plays a vital role in development of CVS changes in portal hypertension. Exact route of signaling from periphery to central nervous system remains unclear.
Endogenous cannabinoids (CB)	Lipid-like substances, acting on G protein-coupled receptors CB1 & CB2, show negative inotropic effect (for example, Anandamide levels increased in cirrhosis) and induce apoptosis in hepatocytes. This could alter microcirculation and lead to portal hypertension and hyperdynamic state.
Nitric oxide (NO)	Changes in NO activity affect CVS in different ways. Increased systemic NO production causes peripheral arterial vasodilation and negative inotropic effect. Cirrhotic rat models show reduced local expression of liver NO synthase and a corresponding drop in portal venous pressure
Carbon monoxide	Mainly produced by the action of heme oxygenase (HO), and activates soluble guanylate cyclase resulting in increased levels of cGMP. There is association between raised cGMP and heart failure in animal models of cirrhotic cardiomyopathy
Beta-adrenergic signaling	Expression and responsiveness of beta-adrenergic receptors and post-receptor signaling pathways are impaired at various levels in cirrhotic cardiomyopathy
Autacoids	Various potent autacoids (bradykinin, serotonin, histamine and prostaglandins) are less likely to play a significant role in systemic CVS changes due to their short half-life

may be sufficient, for example, using pulse contour cardiac output (PiCCO™) or lithium dilution cardiac output (LiDCO™) systems [9] In the authors' institution, use of LiDCO™ is standard, with PAC and TEE when indicated.

Classification of Inotropes and Vasopressors

An understanding of the specific pharmacology of inotropes and vasopressors and the (sometimes subtle) differences between them increases their utility during LT in situations of varying physiological patterns and derangements at various stages of the transplant procedure. The key attributes of commonly used agents are summarised in Fig. 12.1.

Other agents with hemodynamic effect include vasopressin analogues such as terlipressin and octreotide. Both agents have important effects on reducing portal pressure and potentially limiting portal venous bleeding [10, 11] which can be of great value during the dissection phase of surgery. In addition, terlipressin has a direct vasopressor effect through its action on vasopressin receptors [12], enhancing the effects of alpha-adrenergic agents. This may be particularly valuable in patients with low SVR, who may have exhausted pituitary stores of vasopressin and consequently show a reduced responsiveness to alpha-adrenergic stimulation. This effect has been observed in prolonged septic shock [13] and is also hypothesised as one cause of the vasodilatory state in liver failure [14]. Vasopressin or its analogues can be useful during liver transplantation to maintain SVR and is commonly used in the perioperative management of patients with hepatorenal syndrome.

Calcium supplementation is also frequently required during LT because the concentration of ionised calcium in the circulation falls rapidly, particularly during the anhepatic phase. This is due to chelation by citrate added to blood products at a time when there is no metabolic route for citrate [15]. Administration of calcium at this time, to maintain an ionised calcium value above 0.9 mmol per litre, has both a dramatic positive inotropic effect and a vasopressor effect and is of value in maintaining normal perfusion pressure [16].

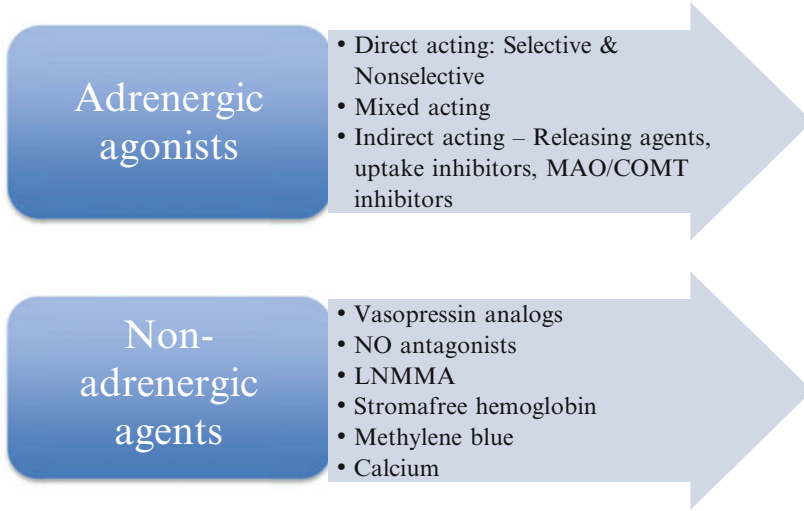

Fig. 12.1 Classification of vasopressors and inotropes. MAO – monoamine oxidase, COMT – catechol-o-methyl transferase, NO – nitric oxide, LNMMA – L-NG-monomethyl arginine citrate

Free radical scavengers such as mannitol and N-acetylcysteine have also been described as helping improve hemodynamic stability during LT, particularly in the period following graft reperfusion. Similar claims have been made for aprotinin, a broad-spectrum serine protease inhibitor, generally used for prevention of fibrinolysis and maintenance of clotting [17].

Methylene blue has been used as an inhibitor of the NO pathway and acts by inhibition of guanylate cyclase. Used as a bolus at the time of reperfusion, this may increase the blood pressure, but its overall effect on outcome is unclear [18]. The biological role of NO inhibition in sepsis is controversial as NO also appears to exert a protective effect.

Clinical Features of Hemodynamic Disturbance and Their Management

Pre-existing cardiovascular changes in liver disease are further affected during induction and maintenance of anesthesia as intravenous and volatile agents frequently reduce CO and SVR. ESLD is associated with low SVR which may decrease even further with induction of anesthesia typically reaching a value around 250 dyn s cm^{-5}. This is in part offset by an increase of CO which contributes to a "hyperdynamic state." Nevertheless, the CO achieved is a reflection of the low SVR, a consequence of left shifting of pressure–volume loops and may coexist with reduced cardiac contractility. The extent to which the CO can compensate for a low SVR is further dependent on adequate ventricular filling, a function of venous return (dependent in part on vascular tone in capacitance vessels) and ventricular diastolic function. In ESLD, diastolic function may be abnormal due to cirrhotic cardiomyopathy [19], the presence of pleural or pericardial effusions, or myocardial ischemia. Consequently, close physiological monitoring and an intelligent approach to multimodal cardiovascular manipulation are required. The nature and magnitude of these CVS changes may necessitate intervention with fluids, inotropes or vasopressor agents. The hemodynamic changes during the various phases of LT and their causes are summarised in Table 12.2.

Intraoperative Changes

Hemodynamic changes will be discussed in type and a suggested therapeutic/inotrope strategy in smaller font.

Table 12.2 Cardiovascular changes during various phases of liver transplantation (LT). CO—cardiac output, PV – portal vein, IVC – inferior vena cava.

Phase of LT	CO	Causes for change in CO
Dissection/pre-anhepatic	↓	Hypovolemia, transient IVC compression, fluid shift with ascitic decompression
Anhepatic	↓	Reduced venous return due to clamping of PV and IVC, acidosis
Reperfusion/neohepatic	↑	Hyperkalemia, release of vasoactive substances, diuresis

During the course of the surgical dissection phase (pre-anhepatic phase), there may be further hemodynamic compromise due to decompression of ascites, hemorrhage and gut translocation. These issues are further exacerbated by lifting and rotation of the liver causing transient caval compromise. This may include introduction of portal bypass as part of the veno–venous bypass technique; complete cross-clamping of portal vein in techniques not using bypass, with consequent loss of venous return; or the creation of a portocaval shunt. The specific technique used, and therefore its hemodynamic consequences, will vary according to patient anatomy, surgeon preference and local protocol as discussed elsewhere (Chapter 11) in this book. Drainage of potentially massive ascites at the beginning of surgery is frequently accompanied by a reduction in aortocaval compromise and hence an improvement in overall systemic hemodynamics. This may further be enhanced by a reduction in pulmonary artery pressure (PAP); however, it is not uncommon to observe substantial hypovolemia at this time as well.

Prior to the anhepatic phase of the procedure, fluid and inotrope requirements vary considerably between patients. The principles of management are maintenance of an adequate perfusion pressure and hemodynamic optimisation. Significant volume loading may be necessary to achieve an optimal stroke volume. However, it is important also to pay attention to filling pressures and electrolyte changes; excessive elevation of filling pressure or PAP may both lead to reduced right ventricular performance and increased bleeding. For this reason, cardiovascular monitoring is important at this stage, and the use of inotropes or vasopressors may help mitigate excessive fluid administration. Agents commonly employed at this stage, both to help optimise stroke volume and to fine-tune fluid administration, include norepinephrine, phenylephrine or dopamine.

The problems of the dissection phase may be further exacerbated by portal hypertension and variceal bleeding. A logical combined approach to the hyperdynamic state similar to sepsis and bleeding secondary to portal hypertension is the use of vasopressin or a suitable analogue. Vasopressin by infusion, terlipressin and octreotide have all been used in these situations, and they have the advantage of enhancing catecholamine sensitivity while at the same time promoting splanchnic vasoconstriction and reducing portal hypertension. There may be an additional theoretical advantage in the reduction in portal flow around the time of graft reperfusion that may help minimise the potential for the "small for size" syndrome [20].

During the anhepatic phase, there is a progressive reduction in body temperature and worsening of coagulopathy and fibrinolysis. These effects interact with the hemodynamic situation. In those techniques involving partial caval clamping, either side clamping or cross-clamping in the absence of veno–venous bypass, there is additionally the effect of reduced venous return. While this can, to some extent, be offset by fluid administration, any improvement seen is generally transient and may overall contribute to a worsening of the clinical situation because gut edema and fluid overload may ensue which becomes manifest after clamp removal and graft reperfusion.

The extra fluid volume required to maintain hemodynamic stability has been estimated at around 4 L or more [21]. Vasopressors can be used to reduce fluid requirement to maintain hemodynamic stability during the anhepatic phase, especially in the presence of caval occlusion. Norepinephrine and phenylephrine by infusion are generally the drugs of choice; they help maintain blood pressure both by raising SVR and, importantly, through action on venous capacitance vessels resulting in modestly improved venous return and cardiac filling. This is particularly important in the presence of partial caval clamping. Hemodynamic consequences of IVC

occlusion, and therefore the effectiveness of alpha-agonists, are dependent on the extent to which the variceal circulation has resulted in collateralisation, facilitating venous return in the absence of vena cava flow.

At the time of graft reperfusion, caval blood flow is restored, resulting in an improvement in hemodynamics, but immediately thereafter is a return of blood flow from the graft. The initial stages are affected by the washout of cold fluid from the graft, potentially containing high concentrations of potassium and traces of preservation fluids which include adenosine in the case of University of Wisconsin solution. Therefore, the immediate effect is due to acute myocardial cooling and exposure to potassium and adenosine, possibly resulting in transient bradycardia, dysrhythmias and myocardial depression. As liver cell membranes become more functional, there is rapid sequestration of potassium into intracellular locations. Cardiac output rises, but the effects of complement activation and release of inflammatory mediators, together with generation of oxygen-derived free radicals, result in the "post-reperfusion syndrome" [22, 23]. This is characterised by hypotension and low SVR occurring five minutes or more after reperfusion and lasting at least 1 h [24].

A number of strategies may be employed to offset dramatic hemodynamic changes that can be seen at the time of graft reperfusion. The younger patient who is otherwise cardiovascularly fit or patients who do not have significant metabolic derangement and those where the graft ischemic time is particularly short may display only minimal and transient hemodynamic changes and require no specific inotrope or vasopressor at this time. However, such patients represent a minority in routine clinical practice.

In general, management of the immediate reperfusion phase consists of both pre-emptive and reactive elements. The pre-emptive element includes administration of a bolus of calcium, either as calcium chloride or gluconate, immediately prior to graft reperfusion. This has combined effects on protecting the myocardium against a potassium surge, while at the same time replenishing or restoring deficient calcium ion concentration to a physiological level. Hypocalcemia during the late anhepatic phase is common, as a consequence of citrate accumulation, and this may be clinically significant [19]. A bolus of 10 mmol of ionised calcium at this stage is highly effective. In some cases, a bolus of sodium bicarbonate may also be of value to control peri-reperfusion hyperkalemia and helps maintain pH above 7.2. This is important to maintain vasopressor receptor responsiveness. Appropriately judging the use of these agents mandates blood gas analysis immediately prior to graft reperfusion.

The reactive components of management of the reperfusion process depend on the extent to which hypotension occurs. Small, incremental boluses of epinephrine may be required. Depending on the specific clinical situation, fluids may also be needed, for example, where the patient is relatively hypovolemic or if there is unexpected bleeding at reperfusion.

Cases who have been managed without veno–venous bypass may have received significant fluid loading during the anhepatic phase, depending on the degree of vena caval occlusion and whether or not a temporary porto-systemic shunt has been created. As a result, there may be an increased venous return as the vena caval clamps are removed; such patients may show elevated right heart pressures in the seconds and minutes following liver reperfusion and therefore, fluid administration is inappropriate in this group. Epinephrine is generally a more suitable choice of agent rather than phenylephrine in this situation. Constriction of venous capacitance vessels can further contribute to fluid overload. Occasionally, it is necessary to combine epinephrine with a nitrate to achieve simultaneous improvement in cardiac function and venous offloading. This, however, is a strategy which requires considerable experience and very close monitoring. Injudicious use of nitrates at this stage can result in catastrophic hypotension.
Other agents that have been used experimentally to offset the hypotension and graft reperfusion include methylene blue, though there is very limited evidence to support the use of this agent and therefore, its use cannot be advocated in routine clinical practice.

Following reperfusion, reduction in SVR results in an elevation in CO. This, in turn, is accompanied by (and is related to) progressive elevation of PAP. This is probably a feature of a fixed or moderately elevated pulmonary vascular resistance in the presence of a rising CO [25]. An increase in left ventricular stroke volume is also frequently seen at this stage. Patients with pre-existing pulmonary hypertension or right ventricular dysfunction are at particular risk of

decompensation secondary to elevation of PAP with a subsequent shift of the right ventricular pressure flow-volume loop to the right. In these situations there is a substantial risk of right heart failure resulting in very high venous pressures and graft failure as a result of the loss of a pressure gradient between the portal and central circulations. Graft blood flow is further compromised by the potential low CO state and hypotension that can result from inadequate left ventricular filling secondary to right heart failure.

Standard management of persistent hypotension following liver graft reperfusion is the use of an alpha-agonist, commonly norepinephrine by infusion. Epinephrine may be a suitable alternative where a reduced or inappropriately low CO is also a feature. Patients who exhibit right heart failure at this time may benefit from administration of epinephrine and a nitrate. There may also, in such situations, be a role for dobutamines for inotropic support, but because of the vasodilatory properties of dobutamine, caution should be exercised. Dobutamine is unpredictable in this situation, as it is a racemic mixture, whose isomers exhibit a differential alpha-agonist effect.

An important and often overlooked contribution to maintain hemodynamic stability during vasodilating states and major hemorrhage is plasma viscosity (a function of hematocrit) among other factors. Although conventional teaching has been that a lower hematocrit is associated with reduced plasma viscosity and hence less tissue perfusion, current evidence questions this. At low plasma viscosity, reduced vascular sheer results in altered signalling, probably via a NO pathway among others, which can in turn result in vasoconstriction and reduced tissue perfusion [26]. Maintaining an adequate hematocrit is also beneficial in preserving diastolic function and hence helping to avoid the catastrophic rise in right heart pressure, which could compromise hepatic perfusion at a stage when the liver is entirely dependent on portal venous flow.

Classically, diuresis is described during the neohepatic phase; however, this depends on the quality of the liver graft function, adequate perfusion pressure and the absence of preoperative renal impairment. Additionally, perioperative factors such as massive hemorrhage during the dissection phase may compromise renal function and limit the potential for a diuresis. To some extent, decisions on volume replacement and potassium supplementation depend on observation of an adequate urine output and decreasing serum potassium at this stage of the procedure. Clearly, the inotrope and vasopressor requirements at the time of graft reperfusion differ from those required for support in the ensuing time period.

Cardiovascular changes persist well into the postoperative period. SVR remains low for up to 24 h after surgery, but they will gradually normalise over the next 24–48 h. The normalisation of SVR seems to be independent of the reduction in CO, which also self-corrects over a slightly greater time course. It is therefore not entirely clear whether the reduction in CO is compensatory or a consequence of separate neurohumoral regulation [27]. In patients with increased postoperative PAP and wedge pressure, these usually remain high for at least 4 days after surgery. Therefore, there is frequently an ongoing requirement for vasopressor support, although these can usually be decreased in the hours following surgery. Spontaneous improvement in mean arterial pressure and organ perfusion is associated with significant diuresis during the process of weaning from artificial ventilation. In most units, this is feasible within few hours after surgery. In units with fast track protocols, ventilation and extubation at the end of surgery are feasible when intraoperative fluid requirements and the absence of pulmonary fluid overload are taken into account [28]. Therefore, judicious use of inotropes and vasopressors at this stage of the procedure directly influences the need for postoperative ventilation and the time course of critical care unit discharge.

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