HPB, 2008; 10: 196–203

informa
healthcare

REVIEW REVIEW

The need for venovenous bypass in liver transplantation

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Abstract
Since introduction of the conventional liver transplantation (CLTx) by Starzl, which was based on the resection of recipient inferior vena cava (IVC) along the liver, the procedure has undergone several refinements. Successful use of venovenous bypass (VVB) was first introduced by Shaw et al., although in recent decades there has been controversy regarding the routine use of VVB during CLTx. With development of piggyback liver transplantation (PLTx), the use of caval clamping and VVB is avoided, leading to fewer complications related to VVB. However, some authors still advocate VVB in PLTx. The great diversity among centers in their use of VVB during CLTx, or even along the PLTx technique, has led to confusion regarding the indication setting for VVB. For this reason, we present an overview of the use of VVB in CLTx, the target of patients for whom VVB could be beneficial, and the needs assessment of VVB for patients undergoing PLTx. Recent studies have shown that with the advancement of surgical skills, refinement of surgical techniques, and improvements in anesthesiology, there are only limited indications for doing CLTx with VVB routinely. PLTx with preservation of IVC can be performed in almost all primary transplants and in the majority of re-transplantations without the need for VVB. Nevertheless, in a few selective cases with severe intra-operative hemodynamic instability, or with a failed test of transient IVC occlusion, the application of VVB is still justifiable. These indications should be judged intra-operatively and the decision is based on each center's preference.

Key Words: *Conventional liver transplantation, piggyback liver transplantation, venovenous bypass*

Introduction

Conventional liver transplantation (CLTx) has undergone continual improvement since it was first performed by Starzl in 1963 [1]. The technique includes resection of the recipient's inferior vena cava (IVC) along the liver, clamping of the portal vein, and end-to-end cavo-caval anastomosis. This technique yields severe hemodynamic instability because of complete cross-clamping of the IVC and a huge reduction of cardiac preload, as well as congestion of the gut due to portal clamping. Therefore, a need was felt for a system that would maintain venous return to the heart and decompress intestinal venous stasis. In this regard, the necessity of using a bypass circuit was first described by Moore in 1960 [2], and thereafter an experimental temporary portocaval shunt combined with a passive femoral-jugular venous bypass system was developed [3–5]. Ever since that time, different bypass systems have been applied, including passive venous shunts [6] and the partial cardiopulmonary bypass introduced by Calne et al. in 1979 to keep the hemodynamic status stable [7]. In 1983, Griffith et al. [8] introduced the first VVB system with centrifugal force pump and heparin-bonded tubing. The clinical efficacy of this technique was confirmed one year later by Shaw et al., who showed an improved hemodynamic stability, better perfusion of vital organs such as kidney and intestine, decreased need of blood transfusion, a longer anhepatic phase allowing the surgical team more time for CLTx, and improved short-term patient survival (91% vs. 73% in non-bypass group) [9–12]. With this technique, the blood flow was withdrawn from portal and femoral veins and returned to the central circulation via axillary or subclavian veins. In the course of time, the technique has undergone some improvements, including the use of single-limb bypass (caval) instead of double-limb (portal and femoral), use of the

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(Received 28 January 2008; accepted 29 January 2008)

ISSN 1365-182X print/ISSN 1477-2574 online
DOI: 10.1080/13651820801953031

Seldinger percutaneous technique under ultrasonographic guidance [13] and the technique introduced by Oken et al. in 1994 to access the inflow vein through internal jugular or subclavian veins [14] without performing surgical cut-downs. This technique reduced the incidence of complications associated with open dissection of the axilla, including seroma and lymphocele formation, wound infection, thrombosis and nerve injury [15].

With the introduction of the piggyback technique of liver transplantation (PLTx) by Calne et al. in 1968 [16] and routine clinical use by Tzakis 20 years later [17], as well as modification of the technique by Belghiti et al. in 1992 [18], partial IVC clamping with preservation of venous return provided the possibility of a very selective use or avoidance of VVB [19–21]. During LTx, the portal vein of the recipient has to be clamped, which can lead to severe intestinal congestion resulting in disruption of the intestinal mucosal barrier, bacterial translocation, bacteremia, septic complications and multiorgan failure. A temporary portosystemic shunt was therefore needed [22]. For this reason, Belghiti et al. modified their technique with the use of a temporary porto-caval shunt to preserve portal flow and to maintain splanchnic venous drainage [12,23]. During recent decades, a great diversity among centers in using VVB during CLTx, or even applying it along with the PLTx technique, has led to confusion regarding the indication settings for use of VVB during LTx. We therefore present an overview of the use of VVB in patients undergoing CLTx or PLTx.

Impact of VVB on liver transplantation

In early experiences of CLTx without VVB, mortality and morbidity were high due to hemodynamic instability resulting from complete cross-clamping of IVC and the portal vein. The rationale for using VVB during CLTx was to maintain hemodynamic stability, to preserve cardiac, pulmonary, cerebral, renal and intestinal flow and function, to reduce the need for blood transfusion, to provide a longer anhepatic phase for better surgical performance, and to improve patient survival. The only contraindication for using VVB was reported to be Budd-Chiari syndrome [9]. Studies on the effectiveness of VVB in LTx have shown that the routine use of VVB varies widely across institutions [24], categorizing them into three groups. Some centers never use VVB, claiming that performing the PLTx technique obviates the need for VVB in all circumstances. Some use VVB only in selected patients based on their surgical conditions, preferably in the event of fulminant hepatic failure (FHF), severe portal hypertension, volume overload, or in patients who cannot tolerate the test cross-clamp of the IVC intra-operatively [25]. The third group comprises centers that perform CLTx routinely and advocate the application of VVB [26]. The LTx technique varies among transplant centers between routine and selective use of IVC preservation [27], between temporary portocaval shunt and VVB use and non-use [20,28], and between different types of anastomosis [29,30]. This has led to a variable application setting among centers, including avoidance and using VVB routinely or selectively.

During recent years, some few data have been presented in support of any substantial improvements in the above-mentioned factors following the use of VVB in CLTx. However, advancements in transplant anesthesiology, technical refinements of the LTx procedure, and improvements in surgical skills have led to CLTx being performed without VVB, and with an acceptable long-term outcome. Additionally, serious side effects due to the use of VVB (reaching 10–30%) have limited its use at many transplant centers [27]. Nevertheless, even with the introduction of PLTx leading to avoidance of VVB at many transplant centers, there are still transplant surgeons who perform CLTx with the use of VVB routinely or selectively.

Venovenous bypass in CLTx

Different studies in CLTx have shown that the main proposed indications for using VVB are hemodynamic instability following test clamping of the IVC, impaired cardiac and renal function, fulminant hepatic failure (FHF), severe portal, massive bleeding during hepatectomy due to severe portal hypertension, and in cases with familial amyloidotic polyneuropathy during hepatectomy [15,27,31–37]. Proposed indications and their presumed pros and cons for the use of VVB are summarized in Table I, and claimed advantages and disadvantages of its use by different authors in Table II.

Regarding hemodynamic instability following IVC test clamping, Veroli et al. advocated the use of VVB in patients with $>30\%$ drop in mean arterial pressure and $>50\%$ decrease in cardiac index during a 5 min test-clamping period [34]. However, several studies have failed to show any increased rate of morbidity or mortality in these patients with or without the use of VVB [38,39]. Although cross-clamping of both portal and IVC veins reduces the venous return and cardiac output to 50%, the severity of hemodynamic instability depends on the preload status before cross-clamping, the presence of underlying cardiovascular disease, and the extent of collateral veins [12]. In patients with normal cardiac status, the compensatory mechanisms, such as increase in heart rate and vascular resistance, may partially overcome this problem [38]. Furthermore, administration of vasopressors and strict volume adjustment can help to maintain preload and hemodynamic stability without an increased risk of volume overload and pulmonary edema following reperfusion of the liver [15,40,41]. Meanwhile, the majority of patients undergoing LTx have liver

Table I. Overview of proposed indications for the use of VVB during LTx.

Proposed indications for the use of VVB	Pros for using VVB	Cons for using VVB
Hemodynamic instability during test cross-clamping of the vena cava inferior	Chari et al. [27] Veroli et al. [34]	Schwarz et al. [38] Wall et al. [33]
Impaired cardiac function such as		
pulmonary hypertension	Chari et al. [27]	
impaired ventricular function	Gifford et al. [46]	Hilmi et al. [12]
myocordial infarction	Beltran et al. [47]	
ischemic heart diseasecardiomyopathy	Stock et al. [48]	
Renal dysfunction	Shaw et al. [9] Grande [49] Estrin et al. [51]	Wall et al. [52] Johnson et al. [53] Corti et al. [54] Cabezuelo et al. [55]
Fulminant hepatic failure (FHF)	Shaw et al. [11] Belghiti et al. [80]	Pere et al. [56] Prager et al. [57] Wojcicki et al. [81] Steib et al. [82]
Severe portal hypertension	Reddy et al. [15]	Belghiti et al. [80]
Severe bleeding during hepatectomy	Shaw et al. [9] Chari et al. [27] Wall et al. [33]	Fan et al. [42] Johnson et al. [53] Stegall et al. [83]

cirrhosis with well-developed portal venous collaterals; the effect of portal clamping on hemodynamic status is therefore marginal [12]. However, Shaw et al. stated that the presence of portal hypertension does not necessarily protect patients from hemodynamic instability [10] and some authors have advocated the use of VVB in the event of severe portal hypertension [15]. The rationale has been that large varices, especially in the retrohepatic area, can cause severe bleeding during hepatectomy.

Table II. Claimed advantages and disadvantages of using VVB during LTx.

Claimed advantages of using VVB	References
- Maintaining the cerebral flow, especially in FHF cases	9
- Preserving the cardiac and pulmonary flow	9
- Maintaining the renal flow and kidney function	49
- Maintaining hemodynamic stability during the anhepatic phase	9, 27, 34, 84
- Providing longer anhepatic phase for better surgical performance	9
- Reduction of intraoperative blood loss	9, 34
- Improving the clinical outcome	9, 34
Claimed disadvantages of using VVB	
- Pulmonary or air emboli, thrombosis	9, 15, 27
- No evidence of maintaining normal perfusion of abdominal organs	27
- No evidence on preserving renal function	38, 39, 49, 55, 83
- Longer operative and warm ischemia time	42, 83
- Higher rate of post-reperfusion syndrome	37, 51, 58
- Hypothermia	15, 85
- Risk of bleeding due to the hemolysis and fibrinolysis in bypass tubes	35
- Nerve injury, lymphocele, hematoma, wound infection	9, 15, 27
- No evidence for improving the clinical outcome	38, 39, 49, 56, 74, 76, 83
- Higher transplant cost	12, 35

Cardiopulmonary disorders, including pulmonary hypertension, ventricular dysfunction, myocardial infarction, ischemic heart disease and cardiomyopathy, have been proposed as indications for VVB [41,46–48]. However, several studies have shown that application of VVB still decreases cardiac output and increases systemic vascular resistance with little or no change in cardiac filling pressure [49,50]. Furthermore, one study reported that with intravascular volume expansion using a rapid-infusion device the VVB could be avoided [48]. Therefore, the role of VVB for cardiac protection remains controversial.

One of the most challenging parts of VVB is preservation of renal function during the CLTx. In a retrospective study by Shaw et al., the VVB led to lower creatinine levels 3 days after LTx and a decreased rate of post-LTx hemodialysis compared with patients in whom VVB was not used [11]. In contrast, later studies showed that in patients with pretransplantation normal renal function, cross-clamping of the IVC without the use of VVB did not lead to renal dysfunction [34,49]. However, in patients with prior impaired kidney function, there is a diversity among authors, some advocating the use of VVB [49,51,52], others not showing any significant difference in terms of renal function [53,54]. Johnson et al. found no substantial changes in peri- and postoperative renal function and in short-term survival when VVB was not used [53]. Another study has shown that the use of VVB, the presence of post-reperfusion syndrome (PRS), and transfusion of fresh frozen plasma were the risk factors for renal failure in CLTx [55].

To maintain cerebral perfusion, several authors argue for the use of VVB, especially in the event of FHF. These reports indicate that 75% of patients with FHF develop cerebral edema during CLTx. The postulated causative factor reported was the lack of an adequate collateral venous system leading to severe hemodynamic instability. Consequently, owing to cerebral blood flow impairment volume substitution is needed to compensate for the hemodynamic instability, which can result in fluid overload and cerebral edema. Moreover, release of carbon dioxide during reperfusion of the liver may lead to cerebral vasodilatation and increasing intracranial pressure [15]. Therefore, some surgeons have suggested the routine use of VVB in patients with FHF. Nevertheless, there are authors who have shown that cerebral perfusion can be preserved by careful and adequate anesthesiological management without the use of VVB in such patients [56,57].

PRS, first described by Aggarwal et al. in 1987 [58], is a syndrome of cardiovascular collapse related to systemic vasodilatation due to the release of vasoactive substances from the reperfused liver, acidosis, hyperkalemia, hypercarbia and hypothemia [37,58,59]. The definition was then refined by Estrin et al. as bradycardia, ventricular dysfunction, and mean arterial pressure below 60 mm Hg in adults, and below 50 mm Hg in children after liver reperfusion [51]. It has been shown that the use of VVB is associated with an increased rate of PRS to 30% and the rate of PRS in patients without VVB was 3.7–3.8% [37,51,58]. In a study by Zaballos et al., avoidance of VVB was associated with a decreased incidence of PRS [37]. They speculated that lower serum kalium value in patients without VVB might have contributed to lower rate of PRS in these patients.

Morbidity of the VVB technique

Overall incidence of complications due to the use of VVB is reported to be between 10% and 30% [27]. VVB can lead to fatal complications, such as decannulation of the bypass circuit and air or thrombotic pulmonary emboli. Other side effects include hypothermia, blood clotting in the bypass system and vessel thrombosis, lymphocele formation, hematoma, vascular and nerve injury as a complication of catheter placement, wound infection or dehiscence, infected vascular suture lines, hemothorax after insertion of a large bore cannula percutaneously, and prolonged operative and warm ischemia time [15]. It has been shown that hypothermia has deleterious effects on myocardial functioning and hemodynamic status. Some authors suggest that the use of a heat exchanger is a good option, but that this can increase the incidence of pulmonary embolism [12]. There are a few reports indicating that VVB is associated with an increased rate of red blood cells transfusion (15 vs. 8 units without VVB) due, presumably, to fibrinolysis, hemolysis and bypass-mediating platelet adhesion [42–45]. In contrast, Kuo et al. have pointed out that the absolute amount of administered blood products was no different between the groups using or avoiding the VVB [35]. In published studies, the morbidity of VVB was similar in the two groups with routine or selective use of VVB, i.e. 13.4% and 18.8%, respectively [27].

Regarding outcome following the use of VVB, although Shaw et al. showed an improved 30-day survival in patients who underwent CLTx with VVB, some authors have not been able to demonstrate better short-term or long-term outcome when this technique was not used routinely [53]. In contrast, selective use of VVB has shown significantly better 1-year patient survival than is the case in patients in whom the VVB is used routinely. Chari et al. reported that the outcome of CLTx was not influenced by the policy of routine or selective use of VVB [27]. Table III gives an overview of the controversies regarding the claimed advantages of using the VVB during LTx as reported by different transplant centers.

Venovenous bypass in PLTx

Introduction of the PLTx technique as an IVC preserving procedure led to a limited need for VVB in the majority of transplant cases [60]. Nonetheless, some centers still use VVB in such patients because of partial venous obstruction resulting from side-clamping of the IVC leading to intestinal congestion and increased risk of instability after declamping as well as bacterial translocation [15]. In fact, the unwillingness to use PLTx without VVB or temporary passive shunt at some small transplant centers is mainly due to their fear of venous complications without the use of VVB [61,62]. Moreover, they believe that with the use of meticulous approaches, e.g. precise management of volume and electrolyte substitution in recipients, having the opportunity to put the venous dialysis system on the circuit, using the Seldinger technique for percutaneous cannulation of inflow veins, and active warming during the extra-corporeal circulation, this procedure can be a safe option for preventing renal dysfunction and for maintaining normothermia as well as a normal blood and electrolyte balance in transplanting patients [26]. Nevertheless multicenter studies show that PLTx can be performed with a low incidence of hepatic venous complications [63]. Problems of anastomotic stenoses or thromboses using the hepatic venous cuff can be overcome by making a large latero-lateral anastomosis, the so-called modified PLTx technique of Belghiti [18]. Moreover, outflow complications can be managed with surgical [64] or interventional radiological procedures [65]. The IVC-preserving technique without VVB can also be performed in the vast majority of re-transplantations [66], because the plane between the previous donor's IVC and allograft may be more

Table III. Controversies regarding the claimed advantages of using VVB during LTx.

	Controversies regarding the claimed advantages for using VVB							
Authors	Hemodynamic stability	Cardiac function	Renal function	Cerebral blood flow	Pulmonary function	Transfusion	Surgical exposure	Outcome
Shaw et al. [9,11]	↑	↑	↑	↑	↑	↓	↑	↑
Veroli et al. [34]	↑	↑	↑ in preoperative normal function ↔ in preoperative renal dysfunction	n/a	n/a	↓	n/a	↑
Schwarz et al. [38]	↔	↑	↔	n/a	n/a	n/a	n/a	↔
Wall et al. [39]	↑	↑	↔	n/a	n/a	↓	n/a	↔
Cheema et al. [41]	↔	↔	n/a	n/a	n/a	n/a	n/a	n/a
Fan et al. [42]	↓	n/a	↓	n/a	↓	↑	↑ operative time	↓
Grande et al. [49]	↑	↑	↔	n/a	↑	↔	n/a	↔
Cabezuelo et al. [55]	n/a	n/a	↓ versus PLTx	n/a	n/a	n/a	n/a	n/a
Pere et al. [56]	↔	↑	n/a	↔	n/a	n/a	n/a	↔
Prager et al. [57]	n/a	n/a	n/a	↔	n/a	n/a	n/a	n/a
Jovine et al. [69]	↔	n/a	↓ versus PLTx	n/a	n/a	↔ versus PLTx	↔ operative time	↔ versus PLTx
Isern et al. [74]	n/a	n/a	n/a	n/a	↔ ↓ infiltrates vs. PLTx	↔ versus PLTx	n/a	↔ versus PLTx
Golfieri et al. [75]	n/a	n/a	n/a	n/a	↓ noninfection complications vs. PLTx	n/a	n/a	n/a
Carvalho et al. [76]	n/a	n/a	n/a	n/a	↔ ↓ infiltrates vs. PLTx	n/a	n/a	↔ versus PLTx
Stegall et al. [83]	↑	↑	↔	↑ intracranial pressure	↓	↔	↑ operative time	↔
Shokouh-Amiri et al. [86]	↔	n/a	↔ versus PLTx	n/a	n/a	↑ versus PLTx	↑ operative time	↓ versus PLTx
Khan et al. [87]	↔	n/a	↔ versus PLTx	n/a	↑ ventilatory support vs. PLTx	↑ versus PLTx	↔ operative time	↔ versus PLTx

Table IV. The advantages of using the PLTx technique without VVB as published by different authors [69–72, 86–88].

- obviating the need for VVB
- more hemodynamic stability without a large-volume fluid infusion
- less impact on renal function
- shorter anhepatic phase, warm ischemia time, and operation time
- lower blood product use
- less postoperative ventilation requirement
- shorter length of intensive care unit and hospital stay
- lower operation and hospital charges

accessible [67,68]. The advantages of the PLTx technique without VVB are summarized in Table IV [69–72].

It has been shown that the cardiac function can be preserved during PLTx even without the use of temporary portosystemic shunt. Moreover, there is less renal flow disturbance due to partial preservation of IVC flow. PLTx has also been shown to decrease the warm ischemia time [70], anhepatic phase, operating time [61], and hospital stay [73]. Furthermore, the PLTx technique has been attributed with better tissue perfusion attenuating the risk of cerebral perfusion problems. Regarding the rate of pulmonary complications, a study by Isern et al. showed no significant differences between CLTx with VVB and PLTx without VVB, but other studies noted that extensive fluid administration in PLTx with the absence of VVB on one side and bacterial translocation because of portal clamping on the other led to a higher trend of complications, including pneumonia, pulmonary edema and infiltrates, atelectasis, and pleural effusion, which could subside by precise volume optimization as well as performing temporary porto-systemic shunts [74–77]. Nevertheless, there were no significant differences regarding pulmonary gas exchange, pulmonary compliance, duration of mechanical ventilation, length of hospital stay, or patient mortality [74].

It can be speculated that CLTx without VVB has a similar hemodynamic condition compared to CLTx with use of VVB [32,66,78]. Additionally, there are no significant differences in perioperative parameters, postoperative renal function, or short-term survival when surgeons do not use VVB [53]. Avoiding VVB also decreases the need for excessive fluid administration and prolonged ventilatory assistance in the majority of cases [79]. Furthermore, the extra cost of VVB and the presence of more effective and cost-benefit procedures such as PLTx have limited application of the VVB to only highly selective cases in which using VVB provides better surgical exposure or in cases in which its avoidance may be life-threatening [12] such as in cases of FHF or severe portal hypertension.

Conclusions

In summary, there are some proposed theoretical benefits of using VVB that could not be constantly demonstrated in different studies. Although the use of VVB is still under debate among transplant centers, many centers have realized that due to the higher rate of complications with VVB and continuous advancements in surgical techniques as well as anesthesia, its routine use is no longer necessary. At present, only a few transplant centers still use VVB as a standard approach. With popularization of the PLTx technique, VVB has been abolished or limited to selected cases. The PLTx procedure can be performed in nearly all primary recipients and in the majority of retransplantations. Finally, avoiding VVB or using it as a routine or selective approach is based on the surgical experience of the transplant team and each centre's preferences.

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