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Importance of Hepatic Flows in Liver Transplantation

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Abstract

Establishing appropriate dual blood supply in liver transplant is important to ensure optimal graft survival and post-operative outcomes. The hemodynamic changes in cirrhotic patients render the patients with hyperdynamic circulation and this environment raises the portal venous flow through the graft immediately after transplant. In deceased donor liver transplantation, lower hepatic flows are associated with detrimental outcomes. Lower measured hepatic artery flow has been associated with lower graft survival and higher rate of arterial complications. Lower portal venous flow of less than 1-1.3 L/min has been associated with lower graft survival. Lower hepatic artery flow is associated with increased rate of biliary complications after deceased donor transplantation. In live donor liver transplantation, portal hyperperfusion is implicated in small for size syndrome. Maneuvers to decrease portal venous flow such as splenic artery ligation, splenectomy or portacaval shunt have been associated with improved outcomes after live donor liver transplantation. It appears that relationship between higher portal flows and poor outcomes is not yet firmly established in that the live donor liver graft may tolerate higher PV flows when the outflow of the graft is well established and if the higher PV flow is not accompanied by portal hypertension. The importance of blood flow in liver transplantation is undeniable. Further studies are required to establish the relationship between the portal and hepatic arterial flows to biliary and arterial complications after liver transplantation.

Keywords: Liver transplant; Hepatic flows

Introduction

Although the liver is only 2.5% of body weight, it receives 25% of the cardiac output [1]. Of the total hepatic flow of 100-130 ml/min per 100g of liver tissue, 25% of it is supplied by the hepatic artery (HA) and 75%, by the portal vein (PV) [2]. The PV system is a valveless, low pressure, low resistance system. PV flow is affected by the venous drainage from the visceral organs (e.g. intestines, spleen, pancreas, stomach and omentum), mesenteric arterial inflow and the intrahepatic vascular resistance. The average portal flow in healthy subjects appears to be around 700 - 850 mL/min [3,4] and the portal pressure ranges from 5-10 mmHg [5-7]. The liver is not capable of directly controlling the PV flow but there are indirect mechanisms of maintaining total hepatic flow in cases where the PV is decreased. A reduced PV flow allows accumulation of adenosine in the space of Mall that surrounds the terminal branches of the hepatic artery and the portal vein. Adenosine, a potent vasodilator, is secreted at a constant rate and is washed away by PV flow. A reduced PV flow leads to accumulation of adenosine and subsequent HA vasodilation. This phenomenon is called the hepatic artery buffer response (HABR) [2].

In contrast to the PV system, HA system is a high pressure, high resistance system with an average flow of 400 mL/min [8,9]. Its flow is affected by the HABR, but also other stimuli can affect its flow. Norepinephrine, and angiotensin cause HA vasoconstriction. This lowers HA flow without affecting PV flow [10]. The vasoconstricting effects of these agents can be reversed by high doses of intra-arterial adenosine [10]. In addition to the external agents, sympathetic nerve activation also results in HA vasoconstriction [10].

Hepatic Hemodynamic Changes in Cirrhosis

With cirrhosis, intrahepatic endothelial cells produce less nitric oxide (NO), resulting in portal hypertension. In the extra hepatic, mesenteric vascular beds, portal hypertension causes progressive vasodilation's of splanchnic vasculature from the release of vasodilators such as NO [11]. This results in an increased portal flow which can contribute to worsening of portal hypertension. Formation of portosystemic collaterals is likely an attempt to compensate for portal hypertension and is a result of dilation of preexisting vascular connections and vascular remodeling [11,12]. The important mediators appear to be endothelial nitric oxide synthase and vascular endothelial growth factor (VEGF) [13].

In addition to the increase in portal flow, there is sodium and fluid retention through the activation of hepatorenal reflex [14]. Cirrhosis increases the renal sympathetic nerve activity, thereby promoting sodium and water retention [1]. Overall fluid retention and pooling of blood volume in the splanchnic vasculature contribute to the hyperdynamic hemodynamic state of cirrhotic patients that mirrors the picture of a patient in septic shock. In a cirrhotic patient, the total blood flow stays around 25% of the cardiac output but usually has a disproportionately high portal component (85%) [15].

Hemodynamic Changes after Liver Transplantation

Prior to transplantation, due to the increased resistance in the cirrhotic liver, the portal flow remains around 1 L/min [3,4,16]. This value is not much higher than the non-cirrhotic counter parts. Once the cirrhotic liver is replaced by a liver allograft, lower resistance in the graft allows better portal flow. The portal flow increases to 1.8-2.8 L/min after implantation of the liver allograft [3,15-17]. The mean hepatic artery flow appears to have a range from 268 to 584 ml/min

[15,16] (Table 1). Due to the patient's hyperdynamic circulation, the cardiac output (10 L/min) remains high in the immediate post-operative period. This reflects the hyperdynamic circulation that is higher than what is observed in non-cirrhotic patients [17,18]. The elevated PV flow appears to persist but eventually returns to the pre transplant values at 1-2 years. The reason for this length of time is mainly due to persistently high splenic flow in the post-transplant period [3,4,19].

Author	N	Cardiac output (L/min)	PV flows before implantation (ml/min)	PV flows after implantation (ml/min)	HA flows (ml/min)
Bolognesi, 2002 [3]	41	10.1 + 3.2	808 + 479	2817 + 1153	NA
Henderson, 1992 [15]	34	9.5 + 2.8	NA	1808 + 929	268 + 157
Paulsen, 1992 [16]	282	8.9 – 10.1	1241 + 65	1977 - 2348	571 - 584

Table 1: Measured hemodynamic parameters in deceased donor transplantation.

In patients who undergo liver transplantation for acute fulminant failure, because they do not have underlying cirrhosis, the hemodynamic parameters resemble what is observed in healthy patients with lower PV flows when compared to the patients with cirrhosis (1.15 vs. 1.96 L/min) [19].

Relevance of Flows in Liver Transplantation

A successful liver transplant is dependent on good blood supply to the transplanted liver. Establishing optimal dual blood supply (HA and PV) is essential for immediate graft function and long-term survival. What the optimal flow values for the respective vessels are still to be determined. Limited literature sheds some light on what these values may be. In general, in deceased donor whole liver transplantation, lower blood flows appear to be detrimental. Lower HA and PV flows appear to be associated with lower graft survival after liver transplantation. Pratschke et al. documented that HA flows <100 mL/min or 100-240 mL/min were associated with worse graft survival than HA flows >240 mL/min [20]. Portal vein flows of <1300 mL/min was found to be a significant factor in univariate but not in multivariate analysis [20]. Other reports have suggested that at least 1000 mL/min of PV flow is required for better survival. Spitzer et al., found that >1000 mL/min of PV flow was associated with better patient survival at 30, 60 and 365 days post-transplant in the deceased donor transplantation [21]. In the same study, HA flow of >400 mL/min was predictive of better survival [21].

It is difficult to glean from these two studies what contributed to lower PV flow. Some of the possibilities are (1) unrecognized portal, mesenteric and/or splenic vein thrombosis that can eliminate the tributaries to the portal flow; (2) inadequate portal vein thrombendvenectomy; (3) unaddressed large Porto-systemic collaterals. Decreased HA flow found intraoperatively may be due to a number of reasons: (1) a technical problem with the arterial anastomosis; (2) a manifestation of the arterial steal syndrome (gastroduodenal artery or splenic artery) [22]; (3) manifestation of the celiac artery stenosis; (4) general hypoperfusion from under resuscitation.

Portal Vein Flow

In cirrhotic patients, establishing portal flow is important for two reasons: (1) decompression of the portal system to relieve portal hypertension and (2) provide the liver with perfusion from the mesenteric venous system. As mentioned above, optimal PV flow appears to be greater than 1000 ml/min [20,21]. If the PV flow is felt to be inadequate, the assumption is that the portal vein flow is being shunted to the systemic circulation via the collaterals. To increase the PV flow, these collateral veins would need to be ligated. Common veins to ligate include coronary vein, inferior mesenteric vein, gastroepiploic veins, splenorenal shunt or retroperitoneal varices. In cases where there are large coronary vein varices are present (>1 cm in diameter), ligating these may increase the PV flow by 55-140% depending on the relative size of the varix. This prevents the "steal" by the coronary vein, and diverts the flow to the main PV [23]. Large splenorenal shunt can be addressed by percutaneous embolization or ligation of the left renal vein [24,25].

Hepatic Artery Flow and Arterial Complications

Hepatic artery flow has been studied to correlate measured flow with hepatic artery complications and graft survival (Table 2). Abbasoglu et al. first documented that in patients with HA flow <400 mL/min were five times more likely to develop HA complications [26]. In patients with HA flow of <400 mL/min had 11% early HA complications (first 100 days) whereas patients with HA flow >400 mL/min had 5% early HA complications [26]. The update of the study documented that HA stenosis was associated with lower HA flows (452 mL/min vs. 512 mL/min, P=0.025) [27]. Early hepatic artery thrombosis (HAT) after deceased donor liver transplantation was associated with lower HA flow (93.3 mL/min vs. 187.7 mL/min, P<0.0001) [28].

Author	N	Hepatic artery complications
Abbasoglu, 1998 [26]	411	HA flow >400 ml (5%) vs. HA flow <400 ml/min (11%), early (100 days)
Molmenti, 2002 [27]	1038	HA stenosis associated with lower HA flows (452 vs. 512 ml/min, P=0.025)
Marin-Gomez, 2012 [28]	110	Early HAT (1 month) associated with lower HA flow (93.3 vs. 187.7 ml/min), P <0.0001).

Table 2: Impact of hepatic artery flows on hepatic artery complications in deceased donor liver transplantation.

One of the well-described strategies to improve HA flow is splenic artery occlusion. Troisi et al. described the increase in HA flow (from 87 + 39 to 152 + 64 mL/min, P=0.0035) in adult right lobe live donor liver transplant (LDLT) when splenic artery was ligated at its origin from the celiac artery [29]. This increase in the HA flow was a result of a 33% decrease in PV flow by HABR. Other groups have documented this phenomenon in deceased donor liver transplantation where portal

hyperperfusion induced hepatic artery constriction was treated by splenic artery embolization thereby increasing the HA flow [30]. Splenic artery ligation or embolization may increase the HA flow but the mechanism may be from decrease in PV flow not by diversion of splenic arterial flow to the HA [31].

Splenic artery steal is a real phenomenon where hepatic hypoperfusion occurs in the setting of preferential arterial flow to the splenic artery, thereby "stealing" the blood from the hepatic artery even in the setting of a patent hepatic artery. The diagnosis is suspected when there is graft dysfunction with a patent hepatic arterial anastomosis. The angiographic diagnosis is made when the splenic artery fills first with contrast and the hepatic artery is visualized during the portal venous phase of the angiogram [32]. Gastroduodenal artery (GDA) also may "steal" the blood from the hepatic artery [33]. There has been a suggestion that splenic artery steal occurs as a consequence of portal hyperperfusion rather than diversion of arterial flow [30]. The arguments against this explanation for the splenic artery steal are twofold. The GDA steal can occur even though GDA does not contribute significantly to the portal flow. Splenic steal does not appear to occur in patents with aortohepatic conduit even though they may have portal hyperperfusion [31].

Based on the available data, it is difficult to know whether there is truly a cause and effect relationship between the HA flow and the outcomes. It may be that the HA flow is a reflection of the overall donor quality.

Impact of Flows in Biliary Complications

Historically, the hepatic artery was thought to be the sole blood supply to the bile duct [34-36]. Consequently, hepatic arterial problems such as hepatic artery thrombosis or hepatic artery stenosis have been associated with biliary complications after liver transplantation. Lower measured hepatic artery flows have been associated with higher rate of biliary complications after liver transplantation (Table 3). Our group had documented that HA flow per recipient body weight ratio of <5 mL/min/kg was associated with a significantly higher rate of biliary complication rates after liver transplantation [37]. O'Loughlin et al. observed that the pediatric patients with biliary strictures after spilt liver transplants had lower HA flows than the patients without biliary strictures (88 mL/min vs. 126 mL/min, P<0.02). In addition to the actual flows, the HABR has also identified as a potential factor in flow related biliary complications. Hashimoto et al., reported that lower HABR was associated with a higher rate of early (<60 days) biliary anastomotic structures (15% vs. 5.1%, P=0.0168) [38]. The authors used buffer capacity (BC) defined as (augmented HA flow – basal HA flow)/PV flow as a surrogate marker of HABR [39,40]. Augmented HA flow was achieved by temporarily clamping the PV.

Author	N	Effect
Hashimoto, 2010 [38]	234	Lower HABR associated with higher early biliary strictures (15% vs. 5.1%, P=0.0168)
Kim, 2014 [37]	268 4	HA flow per weight <5 ml/min/kg associated with higher rate of biliary complications.
O'Loughlin, 2010 [59]	46	Patients with split grafts with biliary strictures had lower HA flow 88 vs. 126 ml/min, P<0.02)

Table 3: Impact of hepatic artery flows on biliary complications in deceased donor liver transplantation.

Contrary to the dogma in transplantation, the hepatic artery may not be the sole bloody supply to the bile duct. In a recent study in an adult pancreaticoduodenectomy model, PV flow was found to be 40% of the total blood flow to the common bile duct measured by a combination of laser Doppler flowmetry and reflectance spectrophotometry [40,41]. Lack of portal flow appears to be a significant factor in biliary complications even when the arterial blood supply is intact [42].

Although aforementioned studies have demonstrated a relationship between decreased HA flow and increased biliary complications after liver transplantation, it is difficult to establish a clear cause and effect relationship between the measured intraoperative HA and biliary complications after liver transplantation. More studies are required to further clarify this relationship.

Importance of Hepatic Flows in Live Donor Liver Transplantation

The importance of optimal flows in live donor liver transplantation is underscored by small for size syndrome (SFSS). Small for size syndrome is defined by dysfunction of a "small" partial liver graft (graft to recipient weight ratio; GRWR <0.8%) during the first post-operative week after exclusion of other causes such as technical, immunological and infectious [43]. Pathogenesis is multifactorial. In addition to the overall quality of the graft, graft volume is an important factor. Hepatic flow, in particular, portal hyperperfusion has been implicated as an important factor in development of SFSS [29,44]. Live donor grafts are smaller than the deceased donor whole grafts and are subject to the portal flow destined for the whole liver. In combination with a hyperdynamic portal circulation, this results in a relatively high portal flow. In addition, smaller grafts may have a higher resistance compounding the problem of portal hyperperfusion. Portal hyperperfusion is thought to cause shear stress to the hepatocytes; a hypothesis which is supported by the presence of sinusoidal congestion and hemorrhage within few minutes of reperfusion [45,46]. In addition, portal hyperperfusion results in the decreased hepatic artery flow by HABR [47,48] which may further contribute to the graft injury.

Various maneuvers have been described to modulate portal vein flow such as splenic artery ligation [49], splenectomy and portacaval shunts to prevent SFSS from occurring. The challenge is to establish the criteria by which a LDLT team can modulate the portal flow. Absolute portal pressure of 15 mm Hg has been described to be a potential target to improve survival after LDLT [50]. Intentional portal pressure control was performed by splenectomy and at times portacaval shunt to decrease the final portal pressure to <15 mmHg to improve survival in LDLT [50].

Earlier studies have suggested that lower PV flow 190 mL/min/100g graft tissue with portacaval shunt is beneficial to the patient compared to higher flows of 401 mL/min/100g [51] (Table 4). Authors of other studies have recommended modulation of portal flow if the flow is greater than 250 mL/min/100g [29]. However, other studies have found portal flow of 318 mL/min/100 g of graft liver in right lobe LDLT with middle hepatic vein was found to be safe as long it was not associated with portal hypertension [52]. They found that performing portal flow modulation for persistent portal hypertension resulted in favorable results. Portal flow after implantation was associated with portal pressure prior to recipient hepatectomy. The seemingly high portal flow in this study may not have had deleterious effects on the allograft due to good outflow provided by the middle hepatic vein and

the lack of persistent portal hypertension. Another study reported that mean PV flows of 301 mL/min/100g of liver in patients with left lobe live donor liver transplantation was safe and were not associated with SFSS [53].

Author	N	Donor (right portal vein flow)	Recipient (post implantation)PV flow	Results
Troisi [51]	13	112-117ml/min/100g	401 to 190 ml/min/100g with hemiportacaval shunt	Better results with reduction of PV flow.
Ishizaki [53]	54	NA	301 ml/min/100g	Portal hyperperfusion not deleterious.
Troisi [29]	17	91 ml/min/100g	360 to 241 ml/min/100g with splenic artery ligation	PV flow modulation resulted in better outcomes
Botha [57]	16		1018 ml/min	Good outcomes with hemi-portacaval shunts in left lobe LDLT
Chan [52]	46	81 ml/min/100g	318 ml/min/100g	High portal flow without portal hypertension can have good outcomes

Table 4: Impact of portal vein flow modulation in live donor liver transplantation (LDLT).

Splenic artery modulation is usually the first step in portal flow modulation. Initial studies have suggested that splenic artery was found to reduce portal flow by 52% [54]; however, more recent studies in LDLT suggested that splenic artery ligation results in reduction of 30% flow [29]. A less invasive procedure is splenic artery embolization (SAE). Gruttadauria et al. reported 6 patients with suspected SFSS in LDLT who were treated with SAE [55]. Prophylactic splenic artery modulation (preoperative embolization and intraoperative ligation) appeared to help reduce the incidence of SFSS in adult LDLT recipients with graft recipient weight ratio (GRWR) of less than 0.8 (28% vs. 5%, P=0.038) [56].

The alternative to splenic artery modulation is hemi-portacaval shunts to divert portal flow from the graft and to further relieve portal hypertension. A significantly better survival was observed in patients with LDLT with GRWR of equal to or less than 0.8 when hemi-portacaval shunts were performed [51]. Botha et al. described a series of 16 patients with left lobe LDLT with hemi-portacaval shunts with good outcomes and a low (one patient, 6.3%) rate of SFSS [57].

The truth may be that the combination of high portal pressure and high portal flow is responsible for shear stress on the hepatocytes whereas high portal flow with low portal pressure is not as deleterious as once thought.

The role of arterial hypoperfusion from portal hyperperfusion in the development of SFSS is still to be further defined. In a porcine model, adenosine was able to inhibit the HABR and reduce further graft injury [58,59]. Although this is an interesting finding, adenosine is not routinely used in clinical practice.

Conclusions

The complex hemodynamic changes that occur after liver transplantation in a cirrhotic patient are challenging to deal with. In most cases, no flow modulation is required and the outcome of the patient is determined by recipient and donor selection. However, there are clinical syndromes where too much or too little portal flow can be detrimental to the graft. In general, low hepatic artery flow appears to be detrimental to arterial, biliary complications and survival after liver transplantation. It is difficult to make decisions for corrective action without having the flow data. Therefore, we advocate for routine measurement of PV and HA flow during liver transplantation.

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