Review

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Mechanisms and management of graft inflow and outflow in liver transplantation

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Summary

Effective management of the liver graft's dual vascular supply is increasingly recognised as critical to optimising graft function in liver transplantation (LT). In this narrative review, we explore the relationship between graft inflow and outflow within the context of hepatic haemodynamic autoregulation, highlighting key mechanisms such as the hepatic artery buffer response (HABR) and the influence of portosystemic circulatory changes on graft perfusion. This review synthesises current literature and incorporates the authors' clinical experience to provide guidance on the surgical management of both common and complex vascular conditions post-transplantation. Portal hyperperfusion – often due to reduced intrahepatic adenosine and HABR-mediated arterial vasoconstriction – is the most frequent issue and a primary cause of small-for-size syndrome. Portal inflow modulation strategies such as splanchnic vasodilators, splenic embolisation, or splenectomy are recognised treatments for portal hyperperfusion. In contrast, management of portal hypoperfusion remains poorly defined, with only isolated reports of portal inflow augmentation. Graft outflow is also examined, particularly its role in enhancing graft function in living donor LT. Overall, a deep understanding of hepatic vascular regulation is essential for improving graft outcomes and expanding access to LT globally.

Introduction

Liver transplantation (LT) is the only curative-intent therapy for cirrhosis and/or end-stage liver disease.[1] Liver grafts have dual vascular inflow from the portal venous and hepatic arterial systems. The portal vein (PV) drains the visceral organs including the bowel, pancreas, peritoneum, and spleen, supplying 75% of the blood to the liver, though this is mostly deoxygenated blood.[2,3] The hepatic artery (HA) arises from the celiac artery and carries approximately 25% of hepato-petal blood flow and is the primary source of oxygenated blood to the liver.[2,3] There is notable variation in HA anatomy, which is itself a significant contributor to vascular complications.[4] Finally, the hepatic veins (HV) drain the liver to the inferior vena cava (IVC), which then returns blood to the right side of the heart.

The relative blood supply to the liver under normal and peri-transplant conditions is mediated by the HA buffer response (HABR).[5–10] The combination of the HABR and the liver's venous outflow have clinically relevant impacts for patients receiving a liver transplant, and thus a detailed understanding of these phenomena is critical for both transplant surgeons and hepatologists. Escalating series of interventions for these concerns have been described throughout the years, yet there has never been a comprehensive review of the mechanisms and interventions available for the management of peri-transplant hepato-petal haemodynamics.

The 2023 International Liver Transplant Society-International Living Donor Liver Transplant (LDLT) Society-Liver Transplant Society of India (ILTS-iLDLT-LTSI) consensus guidelines established effective guidance for the prevention of small-for-size syndrome (SFSS) in LDLT recipients.[11] However, to our knowledge, no comprehensive review has yet addressed hepatic vascular autoregulation and its management in both living and deceased donor liver transplantation. We review a range of conditions, including portal and arterial hyperperfusion and hypoperfusion, as well as outflow obstruction and augmentation. While these topics relate to SFSS, this review expands well beyond this single topic, focusing on the mechanisms by which liver grafts autoregulate haemodynamics in the peri-transplant period, and providing summary protocols for clinical intervention that can guide surgeons in both partial liver and whole liver transplantation.

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Keypoints

- The hepatic artery buffer response (HABR) mediates relative portal and hepatic arterial flow via adenosine washout and cAMP-mediated vasoconstriction.
- Portal hyperperfusion leads to arterial vasoconstriction, endothelial damage, and small-for-size syndrome.
- Portal hypoperfusion is also highly dangerous. Portal flows should be measured routinely in all cases.
- Functional graft size (FGS) can guide the requirements in living donor transplant, by accounting for actual graft size, recipient disease, donor graft quality, technical graft inflow and graft outflow.
- Portal inflow modulation regulates arterial and venous inflow; options include medications, splenic embolisation/ligation, porto-caval shunt, or splenectomy.
- Even a small degree of liver outflow obstruction causes impaired inflow and graft congestion; outflow should be maximised in all cases.

Methodology

This narrative review of the literature, combined with the editorial input/practices of the authors, aims to guide surgeons and hepatologists alike. Although not a systematic review, a standardised strategy was applied. Generally, PubMed, Scopus, and Web of Science were reviewed using search terms such as “Liver Transplantation” AND “Graft In-flow”, “Graft Out-flow”, “Functional Graft Size”, “Portal vein”, “Hepatic Artery”, “Graft Perfusion”, “Portal Hyper-perfusion”, and “Portal Hypo-perfusion”. Articles reporting clinical outcomes were prioritised although animal studies were included if they supported mechanistic understanding. Review articles were also included as were clinical practice guidelines. Articles on LDLT and deceased donor LT (DDLT) were included. References from identified articles were reviewed to supplement the search strategy and maximise review of the literature.

Mechanisms and clinical impacts of hepatic haemodynamics

Inflow regulation

The baseline hepatic requirements for blood flow are relatively well described. PV pressure (PVP) refers to the intravascular pressure in the PV and PV flow (PVF) refers to the volume of blood flowing through the PV per unit time. The PV typically carries about 75% of hepato-petal blood flow, and livers generally require 90-130 ml/min/100 g of liver weight.[12–14] The HA flow is expected to be 25-30% of the PVF, or 20-35 ml/min/100 g of liver.[15] The PV is a low-pressure and valveless system and, critically, there is no ability to autoregulate flow in the PV as veins lack a muscular layer. However, we must also consider resistance in the HA, which is mediated through myotonic contraction. The resistance of the HA is usually reported as the resistive index (RI), defined as: (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Normal ranges for HA-RI in non-transplant patients are 0.6-0.8.[16]

HABR is a critical concept in both interpreting RIs and managing peri-transplant vascular flow. The HABR was described in 1985 by Lautt *et al.*, who identified an inverse relationship between HA and PV flow; this is mediated at high PVF by adenosine washout and norepinephrine-related vasoconstriction, and at low PVF by a high degree of adenosine leading to HA vasodilation.[17,18] More specifically, PV and HA flow mix in the Space of Disse within the hepatic sinusoids. At increased PVF, adenosine experiences more rapid washout. Adenosine is a very potent cAMP-mediated vasodilatory agent; thus, at high PVF, there is a compensatory vasoconstriction in the HA (Fig. 1).[10,17,19] This was demonstrated to be somewhat dys-regulated in patients with cirrhosis because of portal hypertension.[15]

Portal hyperperfusion

While arterial hypoperfusion has long been known to cause graft failure, as late as the early 2000s this was thought to result from “arterial steal syndromes”, where blood was being “stolen” by the spleen, gastroduodenal artery or other visceral arteries leaving inadequate supply to the HA.[20,21] Interestingly, the management for this was coil embolisation of the suspected culprit artery, which was indeed effective, despite targeting the incorrect mechanism.[21] Elucidation of the role of the HABR in 2008[10] allowed for the use of somatostatin or octreotide to reduce portal venous circulation, which in turn enabled HA vasodilation by reducing adenosine washout. The reduction of PVF by either medical or surgical approaches is collectively referred to as portal inflow modulation (PIM), which will be reviewed in detail in the management section. In liver transplant cases where graft arterial inflow is established via an aortic jump graft, there is no direct anatomical connection between the splenic artery and jump graft, but liver graft arterial flow improves after proximal splenic artery embolisation. This phenomenon demonstrates that the mechanism underlying graft arterial insufficiency is portal hyperperfusion not splenic artery steal.

SFSS has been the most critical historical limitation of LDLT, resulting from a relatively insufficient liver volume to sustain life.[22] The first step in avoiding SFSS was understanding that the relative liver volume requirement stemmed from both the graft volume and size of the recipient, leading to calculation of the graft-to-recipient weight ratio (GRWR).[23] A GRWR <0.8 is generally regarded as a small liver graft at increased risk of SFSS, and this cut-off was included in the original definition of SFSS by Dahm *et al.*, which was appreciated first in the early 2000s.[23,24] Cases of SFSS frequently present with clear intrahepatic ischaemia, severe cholestasis, and cellular ballooning on histopathology, demonstrating vascular and biliary manifestations of SFSS.[24] The need to

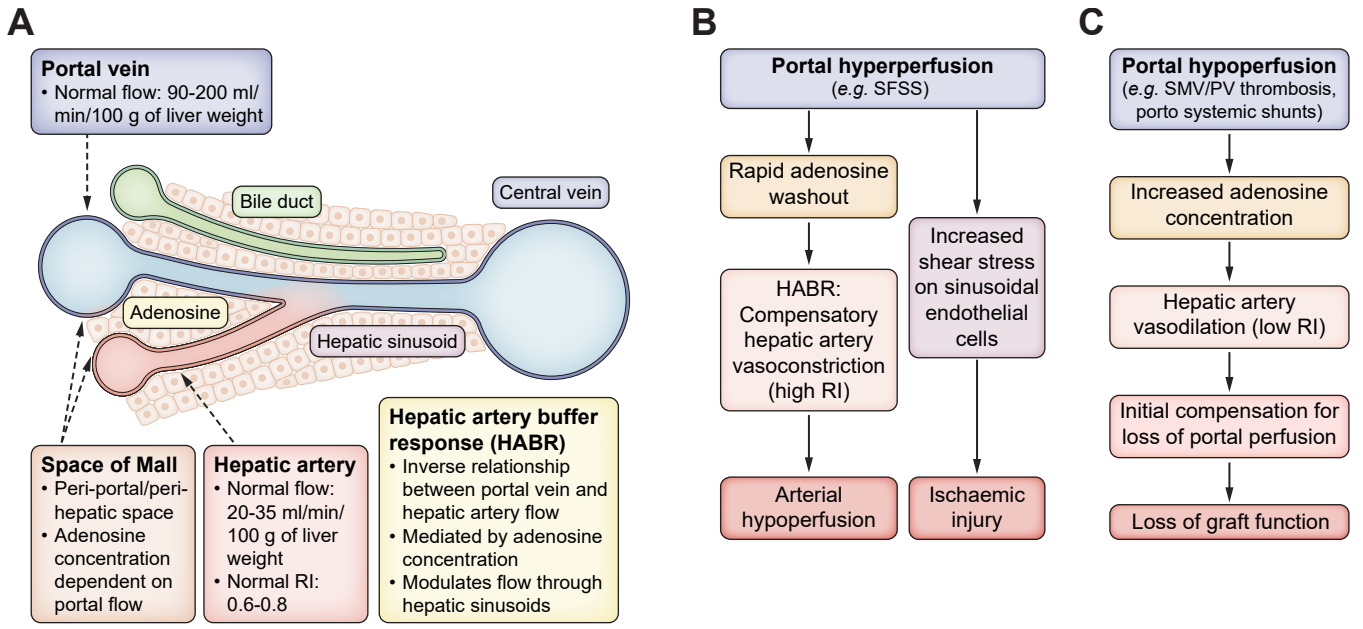

Fig. 1. Mechanisms of the HABR and inter-relationship between portal venous and hepatic artery flow. HABR refers to the competitive flow between the portal vein and hepatic artery. Increased PV flow leads to increased adenosine washout from the Space of Disse, which in turn causes cAMP and nitric oxide-mediated vasoconstriction of the hepatic artery. HABR, hepatic artery buffer response; PV, portal vein; RI, resistive index; SFSS, small-for-size syndrome; SMV, superior mesenteric vein.

sustain life in the donor limits the degree to which this parameter can be controlled.[25] This phenomenon is exacerbated by the hyperdynamic circulation associated with cirrhosis, which increases splanchnic and portal flow – particularly in the immediate post-transplant period, when a small liver graft is most vulnerable.[26] Indeed, SFSS has even been referred to as "small for flow" syndrome, wherein hyperperfusion leads to sinusoidal endothelial damage and simultaneous HA-insufficiency.[27,28] In LDLT, elevated PVP and PVF, both intra- and post-operatively, have been directly linked to additional morbidity, including bacteraemia, cholestasis and ascites.[28]

Portal hyperperfusion leads to HA vasoconstriction and to direct hepatic graft injury in multiple critical ways, including endothelial over-activation, sinusoidal and endothelial cell shear stress, and unbalanced nutrient levels (Fig. 2). Shear stress secondary to hyperperfusion is associated with microscopic changes consistent with increased gaps in the sinusoidal endothelial lining, mitochondrial swelling, vacuolar hepatocyte changes, and massive microvesicular degeneration contributing to SFSS.[29,30] Hepatocyte regeneration is required for low GRWR grafts to sustain life, and the largest changes in hepatic volumes have been shown to occur in the first week after transplant.[22,31] Regeneration has been shown

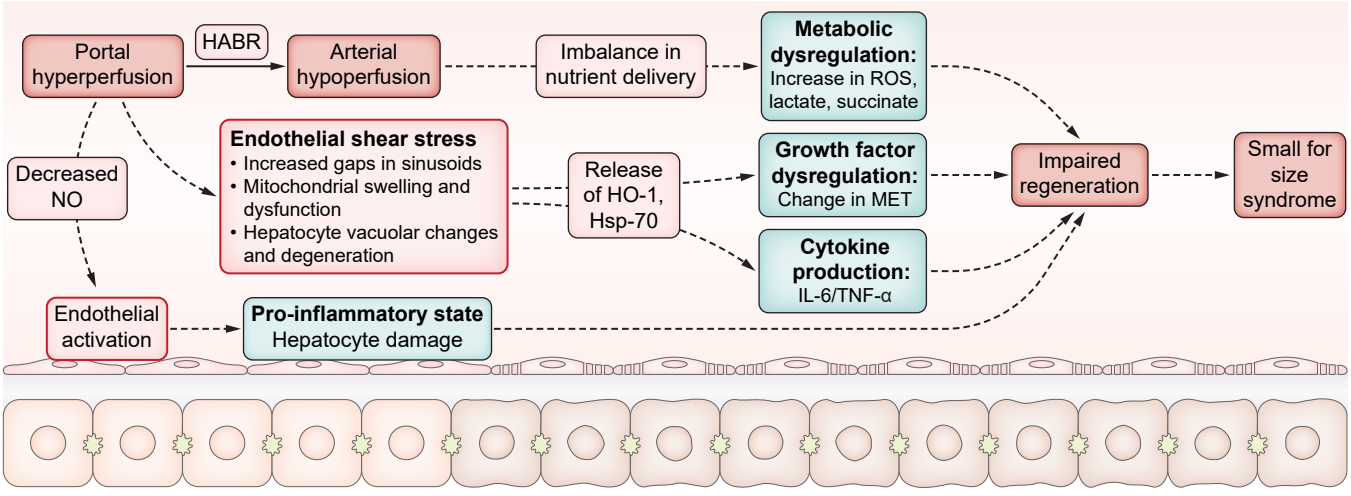

Fig. 2. Mechanisms underlying portal hyperperfusion-mediated hepatic graft injury. Direct sinusoidal and endothelial sheer stress and endothelial activation lead to HSP-70 and HO-1 release and growth factor dysregulation, which in turn impairs hepatic regeneration. This combined with HABR-mediated arterial vasoconstriction is the aetiology for portal hyperperfusion-induced small-for-size syndrome. HABR, hepatic artery buffer response; ROS, reactive oxygen species.

to relate directly to three cascades: cytokine, growth factor, and metabolic.[32,33] Hyperperfusion-associated reduction in nitric oxide leads to direct endothelial cell activation, triggering a local intravascular inflammatory response that damages the liver. Animal models described by Cantre *et al.* demonstrated that this effect could be reversed with nitric oxide substitution, which in turn led to increased hepatocellular proliferation and reduced aminotransferase release.[34] Growth factor dysregulation leads to a change in the mesenchymal-epithelial transition factor pathway, which could even be augmented with a hepatocyte growth factor-mimetic antibody.[33] Further, warm and cold ischaemia both impair regeneration, and indeed interact with the sheer stress associated with portal hyperperfusion to interfere with production of IL-6 and TNFa, which in turn prevents cellular proliferation.[35–37]

The described microscopic changes (endothelial gaps, vacuolar changes, mitochondrial swelling) also induce a stress response via HO-1 and heat-shock protein 70, which further dysregulate the cytokine and growth factor response.[38] Metabolic dysregulation results from the relative imbalance of nutrient delivery, specifically the increased delivery of deoxygenated blood, lactate, succinate and reactive oxygen species via the portal system *vs*. what would be present with greater arterial delivery (Fig. 2).[22] Collectively, these factors contribute to both direct and indirect disruption of hepatic regeneration, leading to SFSS, a process closely linked to mitochondrial (dys)regulation. While studies have identified certain molecular targets for intervention, clinically speaking the most significant advances have involved modifying hepatic perfusion to mitigate such damage ideally before, or worst case soon after, it presents.

Significant work has linked these *in situ* observations to *ex situ* machine perfusion. Li *et al.* reported *ex situ* perfusion as inducing hepatocyte proliferation via a β1 integrin-YAP mechanotransduction mechanism. Furthermore, both Lau and Eshmuminov *et al.* have reported on the proliferative and regenerative benefits of long-term *ex situ* perfusions, both mediated by restoration of cellular energy and endothelial regeneration.[39–41] Hypothermic oxygenated perfusion (HOPE) has been proposed to mitigate the perfusion-induced endothelial stress associated with normothermic perfusion via its protective effects on mitochondrial function and ischaemia-reperfusion injury.[42] However, interestingly, excessive perfusion pressures during HOPE have been shown to negatively affect sinusoidal endothelial cells, emphasising the importance of haemodynamic regulation.[43] The viscosity of perfusion solutions is also a potentially critical factor, with blood-based solutions exhibiting higher viscosity than non-cell-based alternatives. The impact of single-*vs*. dual-vessel perfusion has not been robustly demonstrated, though some propose that dual-vessel perfusion offers benefits due to competitive haemodynamic regulation, even under *ex situ* conditions.[44]

Interestingly, the described mechanisms have also been reapplied to establish the RAPID procedure, consisting of simultaneous liver resection and partial liver (segment 2-3) transplantation, followed by delayed total hepatectomy.[45,46] This is mechanistically interesting in this context, because the transplanted graft must regenerate efficiently to eventually sustain life independently. Portal flow diversion to the auxiliary graft and right portal vein ligation in the RAPID procedure acts as a stimulus for regeneration. However, hyperperfusion is quite likely in this very small auxiliary graft, and thus Line *et al.*, who first described the procedure, advocate close monitoring of the arterial flows to prevent relative arterial ischaemia.[46] This balance is particularly delicate for very small grafts involving two segments (II and III) or three segments (II, III, and IV A/B), illustrating the need for careful monitoring of haemodynamic interplay, especially in the setting of partial liver transplantation. However, to date, the concept of venous outflow augmentation has not been applied to the RAPID procedure because the right HV of the recipient cannot be included as the initial liver remains *in situ*, which is a factor that potentially limits the application of functional graft size (FGS) in this setting.

In addition to the PVF, studies have also identified older donor age and extended preservation time as factors associated with increased post-LT RIs.[16] Although this was originally stated to lack clinical significance, these two factors have since been shown to relate to functional graft volume, which is an advancement of the well-described consequences of SFSS. The utility and clinical implications of functional graft volume are described later.

Portal hypoperfusion

Conversely, portal hypoperfusion may also occur in patients with cirrhosis. Such a conundrum is not uncommon and is often unrecognised by clinicians, but it can be more dangerous than hyperperfusion not only in partial liver transplantation, but also when a whole liver graft is used. Hypoperfusion is commonly secondary to unidentified portosystemic shunts, which divert blood into venous pathways that bypass the liver graft.[47,48] This can also result from PV or mesenteric venous thrombosis, which further reduces PVF.[49–51] In these cases, the HABR leads to HA dilatation and very low RIs in an attempt to increase hepatic blood flow, and it is notable that in many cases an increased HA flow can compensate for relatively poor PV flow.[52] However, the HA is typically unable to sustain the volume of flow required for hepatic graft viability, thus making portal hypoperfusion a critical issue. One study by Matsushima *et al.* highlighted an increased rate of graft loss when PV flow was either <65 ml/min/100 g or ≥155 ml/min/100 g, which can guide assessment of both hypo- and hyperperfusion.[53] This complication may be recognised and mitigated intraoperatively by routine measurement of PV and HA flows.

Venous outflow

The liver graft outflow is also a critical issue to consider. Continuous delivery of oxygenated blood from either inflow source depends on adequate outflow. This relationship has been recognised since at least 1939 in the context of cardiac congestive hepatopathy or cardiac cirrhosis.[54] Similar concepts have also been described in LDLT and DDLT since 2000, though this is most relevant in LDLT, where venous outflow obstruction is a well-described cause of graft loss.[55,56] While outflow obstruction has a clear and direct relationship to graft loss, the functional size of a liver graft is dependent not just on the binary presence of “obstruction”, but also on the degree of outflow patency needed to maximise venous drainage. The latter has since been described, along with four other factors, as part of the pentagon which collectively contribute to the true functional size of a liver.

Functional graft size

Finally, we introduce the concept of FGS in partial liver transplantation (Fig. 3). FGS refers to a more comprehensive consideration of the size of a liver graft, taking into account both its actual size and its relative ability to sustain life, factoring in functional and technical considerations.[57] The so-called pentagon of FGS was first defined by the actual size of the graft, as this is a relatively immutable factor. This must be placed in the context of the recipient hepatic demand using the GRWR. However, recipients are not equal, and thus recipient sickness (model for end-stage liver disease [MELD] score, intensive care unit status, sarcopenia, *etc.*) must also be considered as a point of the pentagon.[11] MELD is a non-modifiable representation of recipient disease severity, with patients who have higher MELD scores generally requiring greater FGS. As a known mechanism underlying SFSS, hyperperfusion is perhaps the most critical component of recipient disease to consider when evaluating

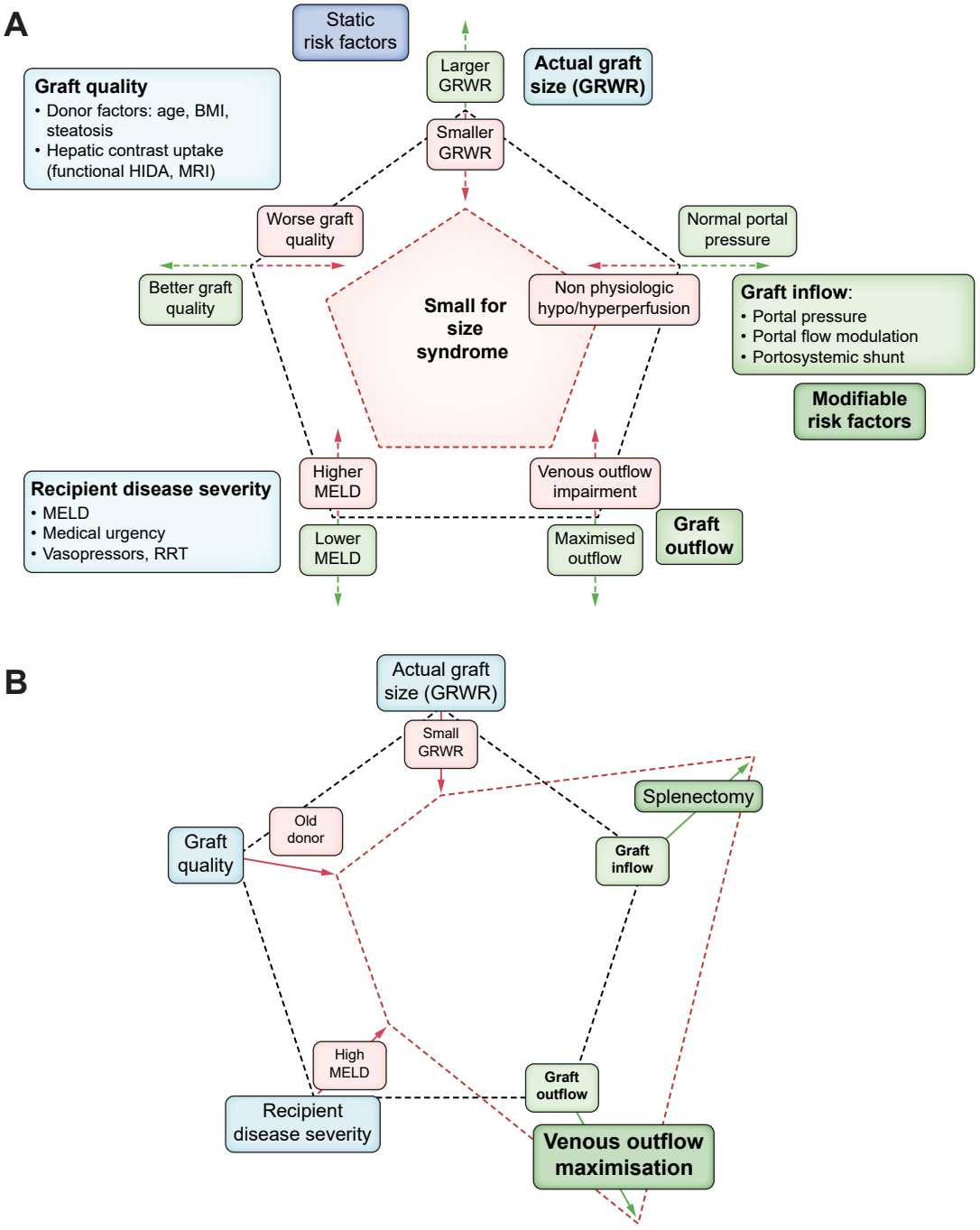

Fig. 3. The concept of functional graft size. (A) Factors associated with risk of small-for-size syndrome in all cases. Dotted red line = technical modifiable factors. (B) Conceptual approach to mitigation of small-for-size syndrome in small grafts using technical modifications of portal inflow modulation and outflow augmentation. GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; RRT, renal replacement therapy.

a donor-recipient-graft combination in LDLT. Furthermore, portal hypertension should also be considered as related to graft inflow and thus should be a key consideration when evaluating modulation techniques.

In addition to their direct impact on FGS, donor/graft factors (*e.g*. steatosis, donor age, ischaemic time) influence graft compliance, which in turn modifies haemodynamics. Therefore, these factors must be considered both in terms of their impact on the required FGS and their contribution to increased resistance to flow, which itself is a risk factor for haemodynamic compromise. Similarly, post-transplant complications (*e.g*. rejection, cholangiopathy, re-fibrosis) can also increase graft resistance to flow and thereby lead to a re-occurrence of intrahepatic portal hypertension. Treatment of the primary underlying condition is most critical, though flow modulation might also be necessary if the complications are severe enough. Unfortunately, the impact of either of these donor factors or post-LT complications has not yet been quantified.

An international study of ultralow GRWR (≤0.6%) did not highlight portal hypertension as a negative risk factor, but did identify renal dysfunction as an important predictor of survival; this too should be considered in recipient evaluation.[58] Nearly 50% of patients in this study received PIM, and portal flow measurements were used intraoperatively in included cases, possibly explaining why PIM was not predictive as it was guided by proper intraoperative analysis. Recipient weight and ascites remain additional relevant factors. Weight should be considered not just for the calculation of GRWR, but also in terms of its distribution, as patients with external adiposity may have artificially elevated weight. The Riyadh group, for example, uses ideal body weight rather than total body weight for this reason, although large investigations have not been published. Finally, ascites represents a clear manifestation of portal hypertension and must be considered.

Additionally, liver function in the donor must be considered, which may be measured with variables such as donor age, graft steatosis and ischaemic time, with older age donors and increased graft risk reducing the functional size of the graft. Two technical factors related to vascular flow comprise the final two points: graft inflow and outflow (Fig. 3). For a given donor-recipient combination, the former three points (graft size, graft quality, and recipient disease) are relatively unchangeable. However, the latter two (graft inflow and outflow) are technically modifiable, as we will discuss in the coming sections.

Approaches to management

How to assess the vasculature

Within our multicentre transplant enterprise, we view the routine numeric assessment of graft inflow and outflow as mandatory in all cases. Intraoperative PV and HA flows are measured using a MediStim (MediStim, Oslo, Norway) vascular flow device with sterile operative probes. The presence of portosystemic collaterals is assessed pre-operatively with contrast-enhanced imaging and intraoperatively by a test-clamp of the infrahepatic IVC, which will result in increased PVF only if such shunts drain into the infrahepatic IVC. There is no established cut-off for when shunt ligation should be performed or consensus on which technique to use. Despite the lack of data, one might consider techniques to assess the presence of low PVF (<1 L/min and/or 25-50 ml/100 g/min). On clamping, we assess for an increase in PVF, with an increase of >20% being considered significant and prompting further exploration for unidentified shunts. Shunt ligation may also be considered when the PV waveform on the flowmeter machine becomes less phasic after temporary caval clamping. Such a change happens when there is a haemodynamically significant shunt(s). In contrast, coronary shunts (*e.g.* left gastric vein), which drain into the superior vena cava via the azygous system would not appear with this approach, highlighting the importance of careful pre-operative image evaluation. HA augmentation can also be measured if there is concern regarding hyperperfusion. This refers to a PV test-clamp to assess for increased HA flow regulated by the HABR.

Intraoperative PVP measurement was introduced as an assessment tool in 2003 by Ito *et al.*, who demonstrated that elevated PVP intraoperatively and during the first post-operative week led to worse outcomes in small grafts.[59] The Kyoto group developed their approach to PIM based on PVP assessment.[60] PVP measurements have also been externally validated in multiple centres, and shown to directly predict SFSS, morbidity, and even graft regeneration.[61,62]

Furthermore, daily liver vascular ultrasounds (LVUS) are obtained post-transplant for at least 7 days in partial liver recipients, and routinely though not always for a complete 7 days in whole liver recipients. Portal hyperperfusion frequently presents as arterial vasoconstriction evidenced by increased RI. These ultrasounds also assess waveforms, peak velocities and cumulative flow volumes of the HA, PV and HV, which can help gauge and thus correct issues with inflow or outflow.

Approaches to portal inflow modulation

For both LDLT and DDLT, there are generally three categories of interventions for PIM: pharmacologic, procedural, and surgical. Pharmacologic interventions are generally focused on somatostatin or its analogues (*e.g.* octreotide). Such medications decrease splanchnic blood flow, reducing PVP and PVF.[63,64] Indeed, Hessheimer *et al.* reported a porcine 20% LDLT model in which PVF increased fourfold after graft reperfusion, but this rise was reduced to a 2.7- to 3-fold increase with the addition of somatostatin.[64] This, in turn, led to a demonstrable reduction in aminotransferase levels, SFSS, and even histopathologic sinusoidal damage. Such findings have been extended to non-transplant models, where somatostatin has been proposed as a prophylactic treatment in major liver resections, especially in patients with cirrhosis.[63,64]

Approaches to PIM are described in Table 1 and Fig. 4 with reference to major relevant literature, timing of interventions, and the pros and cons of each approach. Each approach has utility in various settings and must be carefully considered in the context of the timing of the intervention and the relative morbidity *vs.* potential efficacy of each approach.

Procedural interventions may be performed in the post-operative period in pursuit of PIM. This is primarily performed by interventional radiology (IR) using IR-guided splenic artery embolisation (SAE), which has been described since the mid-2000s as a treatment for SFSS.[65–67] Several important technical considerations exist for SAE in the early postoperative period. First, SAE should be performed by experienced IR physicians, as inadvertent damage to the HA anastomosis through the celiac

Table 1. Timing, pros and cons of portal inflow modulation techniques.

Technique [Citations]	Timing	Pros	Cons
Medical			
Octreotide analogues[10,27,64,147]	Generally post-op; can be started during surgery	Does not require procedure, lowest complication rate	Effects limited to duration of medication infusion Lowest impact on portal flow
Procedural			
Splenic artery embolisation (SAE)[8,9,67,68,101]	Postoperative	Percutaneous; non-operative intervention Incomplete splenic devascularisation (avoids thrombotic/infectious complications)	Less significant reduction in inflow *vs.* splenectomy or devascularisation
Surgical			
Splenic artery ligation (SAL).[71,72,74,78,79,148]	Intraoperative*	Immediate reduction in PVF up to 70% (avoids portal hyperperfusion immediately during operation) Incomplete splenic devascularisation (avoids thrombotic/infectious complications) Avoids potentially bloody splenic dissection	Less significant reduction in inflow *vs.* splenectomy or devascularisation, though some studies report similar reduction to splenectomy
Devascularisation[70]	Intraoperative*	Three-fold reduction in PVF Larger impact on PVF *vs.* SAE/SAL	More aggressive/morbid surgical procedure *vs.* SAL Potential immunologic, infectious or thrombotic complications
Hemi-portocaval shunt (HPCS)[69,75,80,149,150]	Intraoperative*	Three-fold reduction in portocaval gradient Avoids complications of splenectomy/splenic occlusion	Challenging to control the degree of portal venous diversion Possible need for re-operation for shunt ligation
Splenectomy.[71,72,76,78,79,151,152]	Intraoperative*	Most significant and sustained reduction in PVF, although some studies report equivalence to SAL	Most aggressive/morbid surgical procedure Potential immunologic, infectious or thrombotic complications

*Can be performed intraoperatively before or after reperfusion, or as a subsequent operation if required.

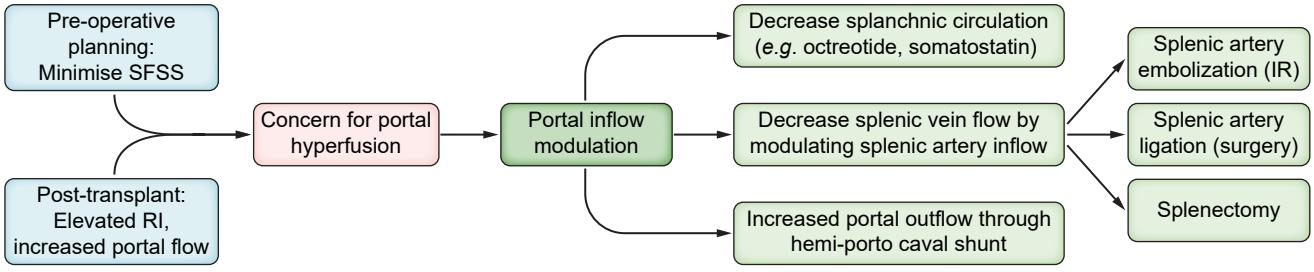

Fig. 4. Considerations and options for portal inflow modulation. Pre-operative planning along with intra- or post-transplant vascular assessment can guide the use of pharmacologic, procedural, or surgical portal inflow modulation. RI, resistive index; SFSS, small-for-size syndrome.

axis can occur. Second, a proximal SAE is usually optimal, as this approach reduces splenic blood supply, but does not lead to complete splenic devascularisation, which can lead to necrosis and infection in an immunosuppressed patient.

SAE is one type of delayed splenic artery occlusion, with the other type being splenic artery ligation (SAL), which is associated with similar outcomes.[68] The use of SAL has been widely reported in the US as a mechanism to increase the use of left lobe liver grafts (LLGs) and can result in significant PV flow reductions in up to 70% of cases, which in turn reduces early graft dysfunction. Another surgical option is the hemi-portocaval shunt (HPCS), which can result in 3-fold reductions in portocaval gradient.[69] The Asan group has described the utility of splenic devascularisation, rather than splenectomy, which functions via similar mechanisms as SAE and/or SAL, though it is proposed to have a larger effect on inflow modulation by inducing a greater reduction in splenic flow.[70]

Partial liver transplantation

We elected to begin with LDLT as this cohort offers many additional challenges due to the smaller nature of the liver graft. Within the concept of FGS, the graft inflow and outflow can be modified to optimise the haemodynamic and functional status of a certain graft (Figs 3 and 4). This is done through an escalating and thoughtful approach to PIM based on the specific donor, recipient and graft selected.

Splenectomy is utilised more liberally in Eastern centres, such as Kyushu and Kyoto, where it is used in as many as 60-80% of LDLT cases.[71,72] It is noteworthy that recent

benchmarking studies by Li *et al.* demonstrated improved outcomes in Eastern populations, including greater degrees of PIM, reduced SFSS, and reduced overall morbidity.[73] The A2ALL study by Emond *et al.* highlighted that splenectomy is relatively rare in other US practices,[74] though some US centres advocate the use of planned SAL and splenectomy as critical in cases of small grafts and/or even larger grafts with potentially less favourable transplant factors. Our group proposed an algorithm for avoiding SFSS even with very small (GRWR ≤0.7%) liver grafts using splenectomy for PIM plus, critically, outflow augmentation in all cases (Fig. 5). This work represents an advancement not just in advocating for outflow augmentation, but also in helping define the optimal timing of splenectomy based on stimulated graft size, graft quality, and

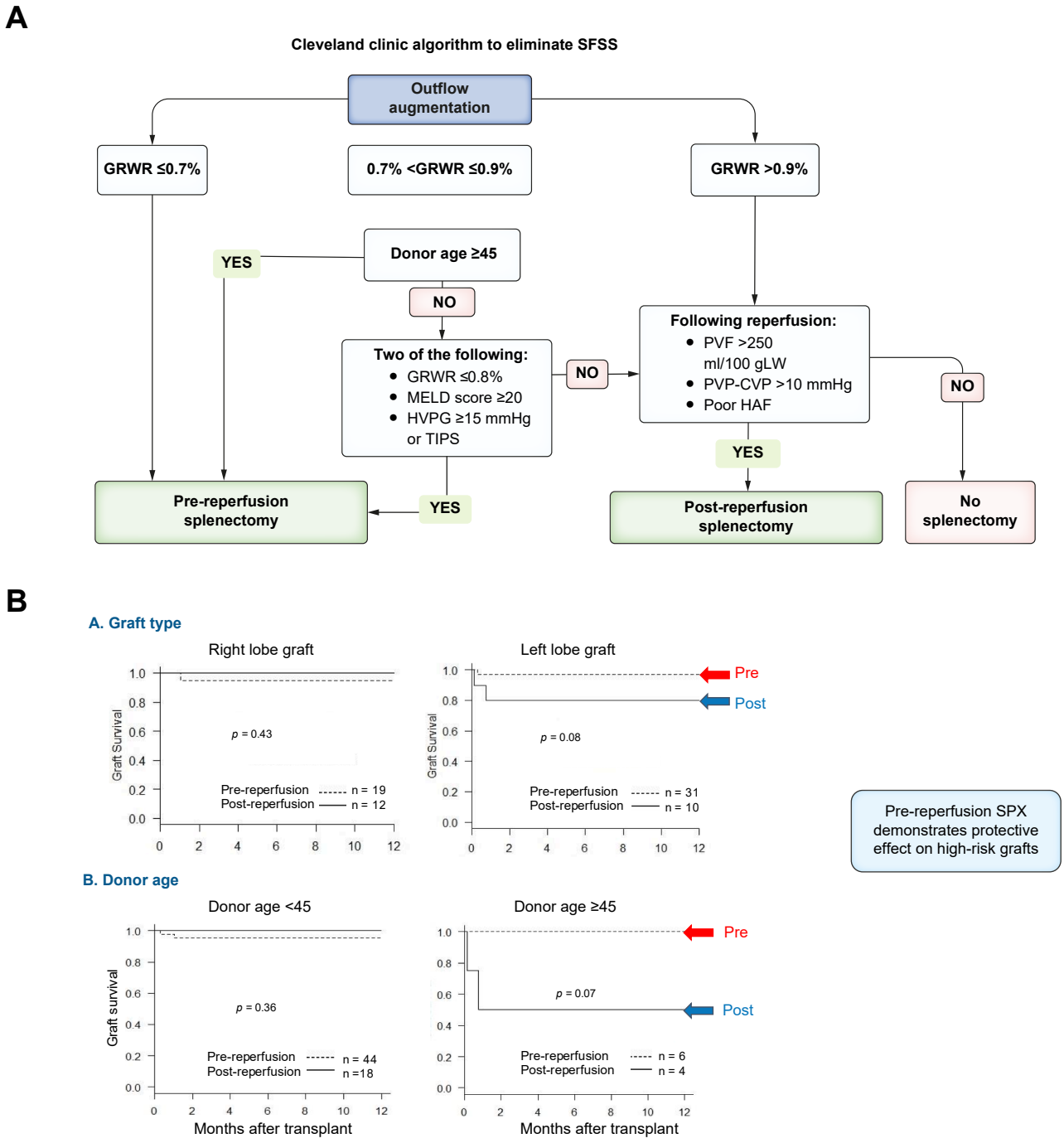

Fig. 5. Algorithm for portal inflow modulation based on donor and recipient factors in LDLT and impact of timing of splenectomy based on donor age and graft selection. Collective assessment of the graft size/GRWR, the donor factors (age, steatosis, ischaemia time), and recipient disease (MELD, portal hypertension) can guide the need for and timing of inflow modulation. Adapted from Fujiki *et al.* 2022 with permission.[76] CVP, central venous pressure; GRWR, graft-to-recipient weight ratio; HAF, hepatic arterial flow; HVPG, hepatic venous pressure gradient; LDLT, living donor liver transplant; MELD, model for end-stage liver disease; PVF, portal venous flow; PVP, portal venous pressure; SPX, splenectomy; TIPS, transjugular intrahepatic portosystemic shunt.

recipient disease, which had not previously been linked to the need for and timing of PIM. At present, there is no clear consensus on a single guiding measurement for PIM. There is clear evidence supporting both PVF and PVP measurements, with PVF >250 ml/100 g and PVP >15 mmHg being described as critical values.[60,75] In our experience, PVP is frequently quite low and may be relatively less reliable.[76,77] We therefore use PVF and PV pressure gradient (PVP-central venous pressure) since PVP may frequently be below the described 15 mmHg cut-off. However, there is no definitive guidance at present, and perhaps both approaches should be considered simultaneously in each case.

Some studies report no clear difference between surgical techniques (SAL *vs*. splenectomy) for PIM in LDLT, with recent studies demonstrating a similar reduction in portal pressure (~25%) with each technique.[78] However, early and more recent Eastern experiences suggest greater PIM with splenectomy *vs*. SAL.[71,72,79]

HPCS was first described for LDLT nearly two decades ago. Troisi *et al.* described the initial approach in 2005, and demonstrated significant reductions of 75% in PV flow with HPCS.[75] In a US study by Botha *et al.*, HPCS was associated with a very low (<5%) rate of SFSS despite a median GRWR of 0.67 [69]. Unfortunately, the extreme nature of HPCS makes it both successful and dangerous, as a 75% reduction in portal flow can lead to issues with portal hypoperfusion, which is also a feared situation. To this effect, the Delhi group described an approach to minimise the need for HPCS unless necessary by pursuing HPCS only if GRWR is <0.8% and portal pressure is >16 mmHg during the hepatic dissection phase. The group achieved a very low (2.8%) rate of SFSS and spared the need for HPCS with this approach.[80]

While LDLT is the most common reason for partial liver transplant, deceased donor split-liver transplant (DD-SLT) is also of relevance. Similar considerations apply in split liver transplantation; however, the FGS pentagon must be adjusted to account for a greater degree of ischaemic graft damage incurred during the transplant process. This is supported by overall better outcomes in LDLT *vs*. DD-SLT, and by mechanistic studies by Selzner *et al.*, which showed that ischaemic times (warm and cold) lead to an increased risk of SFSS in DD-SLT livers.[35,36,81,82] Similar vascular considerations should be considered, but with an increased tendency to pursue techniques to improve FGS. However, of relevance is the potential to improve graft quality using HOPE. More specifically, liver splitting using HOPE has been described by both Rossingnol *et al.* and Thorne *et al.* as a potential strategy to improve graft quality, with already demonstrated reductions in ischaemic time with this approach.[83–86] The HOPE-Split trial is ongoing in this context.[85,86]

Whole liver transplantation

Portal hyperperfusion is admittedly a less common concern in DDLT, but studies have shown that up to 8% of DDLT recipients require intervention. SAE is reported to lead to a 67% reduction in PV peak velocity, 18-20% reduction in HA RIs and 50-80% increase in HA flow in DDLT.[8,9] Indications may be either refractory ascites or inappropriately elevated RIs. The HA waveform should also be considered, as reversal of diastolic flow is frequently a sign of impending arterial hypoperfusion, and this may prompt intervention, first pharmacologically and then procedurally with SAE. It is very rare to require intraoperative SAL or splenectomy in DDLT, as the increased graft weight allows for a much higher portal flow at the time of transplantation.

However, the need to address portal hypoperfusion might be more common in this population. The first and most common issue arises from portosystemic collaterals, very commonly secondary to extensive portal venous thrombosis. Unlike the arterial system, which is regulated by vasoconstriction, venous drainage is pressure-regulated, and thus shunts can lead to a true vascular siphon, where blood bypasses the portal drainage to return directly to the systemic circulation. Furthermore, these shunts may be hard to access after transplantation, and they could even enlarge if liver graft compliance decreases. Thus, the standard approach to ensure adequate portal inflow is the routine ligation of portosystemic shunts and, if necessary, the use of alternative portal inflow.[47,87–89] Our group frequently pursues routine ligation of visible portosystemic shunts regardless of their measured flow. High-quality data on the need to routinely ligate all shunts is lacking, although a systematic review by Nacif *et al.* highlighted improved outcomes with routine shunt ligation.[90] Small retrospective studies have demonstrated no benefit to routine compulsory shunt ligation in LDLT.[91,92] In the absence of robust data, it is our practice to ligate reasonably accessible shunts. This can be guided by intraoperative flow measurements with shunt ligation pursued aggressively in the presence of phasic PVF changes as described.

Alternative portal inflow can be achieved with a jump graft from the superior mesenteric vein, a reno-portal bypass, coronary shunt, or rarely with cavoportal hemitransposition. Fundora *et al.* recently described a variety of complex extra-anatomical approaches to venous inflow in cases of portal vein thrombosis, demonstrating that alternative PV anastomoses can achieve favourable outcomes in otherwise technically challenging cases, including delivery of at least some splanchnic flow to the liver graft.[93] A similar French experience by Bhangui *et al.* demonstrated similar results, suggesting that hypoperfusion can be avoided through extra-anatomic vascular inflow.[94] The French experience also demonstrated how non-physiological inflow modifications in the setting of non-tumoral portal vein thrombosis can lead to proper control of prehepatic portal hypertension and modulate proper haemodynamics.[95]

Hepatic arterial flow can frequently compensate for relative portal hypoperfusion in DDLT, which can pre-empt the need for intervention in many cases of portal vein thrombosis.[52] However, sometimes portal augmentation is necessary in DDLT. When alternative inflows are unavailable, for example in cases of acute liver failure with relatively little portal hypertension, PV arterialisation is one uncommonly described but important salvage technique to ensure adequate graft flow.[50,96–98]

Intractable post-transplant ascites is a rare complication that is challenging to manage when present. This complication can generally result from intrahepatic, vascular, or extrahepatic causes. Intrahepatic causes include intrinsic dysfunction from recurrent cirrhosis, rejection or other direct liver insults. Extrahepatic causes may relatively commonly include renal dysfunction or cardiac dysfunction. Both intrahepatic and extrahepatic causes should be reviewed, including assessment of cardiac and kidney function, as many may be amenable to

intervention. Vascular causes of post-LT ascites include outflow obstruction or relative portal hypertension. LVUS and hepatic venous pressure gradient should guide vascular assessment. In the absence of outflow obstruction, vascular aetiologies of post-LT ascites may be effectively treated with SAE.[9,99] It has been reported that patients with higher spleen/liver volume ratios >0.5 demonstrate increased likelihood of response to SAE for ascites.[9,99–101] SAL and/or splenectomy are more definitive approaches that apply similar physiological principles, although they are not our preferred options.

Outflow management

Outflow augmentation

Outflow augmentation is equally critical, albeit somewhat easier conceptually, as truly maximising the outflow is optimal. Intraoperatively, this is usually achieved with strategies such as venoplasty and venous reconstruction in LDLT, or careful single-cuff anastomoses using the piggyback-approach in DDLT.

LDLT: For left-sided grafts, inclusion of the middle HV is optimal (referring to a complete LLG rather than an extended left lateral segment) to improve the venous drainage of segments IVA/B. As described first by Suehiro *et al.*, in cases where the middle/left HV share a common orifice but have a short, combined trunk, a septoplasty is performed to widen the outflow.[76] Although not commonly required, if multiple venous orifices are present, a common venous outflow can be made with a large cadaveric outflow patch employed to create a very wide and technically feasible anastomosis, although others have suggested this more complex approach may not always be necessary.[76,102–104] Division of the recipient left phrenic vein is critical at this juncture to enable free mobilisation of the recipient HV/IVC juncture. This will prevent inadvertent anastomotic narrowing, which can cause outflow obstruction (Fig. 6).[76,105]

For right lobe grafts, right HV (RHV) venous patch-plasty techniques have been described by both Eastern and Western teams, which are added surrounding a downward incision in the RHV. An interposition graft can then be placed on the back table, with drainage of the V5 and V8 branches into the RHV patch-plasty to create a single large-orifice outflow. Alternatively, after reperfusion, the V5/8 graft can also be reconstructed into the recipient left/middle HV confluence. This technique was described by Lee *et al.* in 2003 and Ito *et al.* in 2004 to manage right lobe congestion, and refined by Fujiki *et al.* within the simultaneous context of PIM (Fig. 6).[106–108]

DDLT: Surgical management of hepatic outflow in DDLT is somewhat less complex, but critical, as inadequate graft outflow can lead to congestion and graft loss. There are generally two methods of venous outflow for DDLT: caval replacement, in which the entire retrohepatic IVC is replaced by the donor IVC, or piggyback, in which the recipient short HVs are individually ligated and the recipient IVC is left *in situ.* In this latter approach, the donor infrahepatic IVC is closed, and either the recipient and donor suprahepatic vena cava are respectively anastomosed (traditional piggyback), or the donor suprahepatic IVC is connected to the recipient retrohepatic IVC (side-to-side cavo-cavostomy).[109,110] Generally, there has not been a robust demonstration of the superiority of any of these approaches, with the piggyback technique generally reducing implantation time, but also being technically more challenging than caval replacement (also known as bi-caval or caval interposition).[111–114] The critical principles involve ensuring wide and unobstructed outflow without potential twisting or narrowing of the IVC outflow connection(s).

Outflow obstruction

Hepatic venous outflow obstruction is a unique problem and should be considered on a spectrum relative to the size, selection, and position of the liver graft. While outflow augmentation is generally critical in partial liver transplant, obstruction can occur with both partial and whole liver approaches. Obstruction may appear clinically with or without elevated liver function tests, new or worsened post-LT ascites, and even haemodynamic compromise and graft loss. Indeed, outflow obstruction is potentially under-recognised and should be considered in any case of graft dysfunction or ascites, and occasionally in the case of persistent pleural effusion. Assessment should be undertaken urgently with LVUS, possibly cross-sectional imaging, and/or IR-guided venogram.

In LDLT, the Kyoto group has reported that LLG may carry a greater risk of outflow obstruction, though not all published data concurs with this sentiment.[76,115,116] In DDLT, piggyback and caval replacement may both be associated with outflow obstruction, and it is not clear whether one might better obviate this complication.[117] For example, Widmer *et al.* performed a comparison of classical piggyback and caval replacement in the UK, demonstrating no clear difference in the UK cohort.[113]

Postoperative management of suspected outflow obstruction is usually assessed by urgent IR-guided venogram. IR-guided IVC/HV stenting with expandable metal stents can alleviate outflow obstruction and/or venous stenosis and can spare a highly morbid re-operation.[118–120] The Kyoto group described the assessment for hepatic venous outflow obstruction using computational fluid dynamics, which could even potentially spare diagnostic IR procedures and allow for tailored interventions.[121] However, we emphasise that any degree of stenosis particularly early post-operatively can lead to graft and recipient loss, which thus should prompt a re-operation if it is suspected and/or persistent.[121]

Re-operation should of course relieve stenosis and/or twisting/torsion when present; these are the two most common causes.[122] When such a simple fix is not available, more complex techniques must be pursued. Lerut *et al.*, among others, described a rescue side-to-side cavo-cavostomy to relieve outflow obstruction after piggyback approaches. This can be performed either by re-doing the anastomosis with a conventional abdominal approach (Merenda *et al.*, Lerut *et al.*) or using a superior, intra-venous approach for stapler positioning (Tong *et al.*).[123–126]

Discussion, future directions, and limitations of current evidence

This work reviews the mechanisms for hepatic haemodynamic regulation in the setting of liver transplantation, with a focus on how portal hyper- and hypoperfusion can be managed. Ultimately, this is intended to support the expanded use of both LDLT and DDLT grafts, maximise the longevity of transplanted grafts, and improve outcomes of

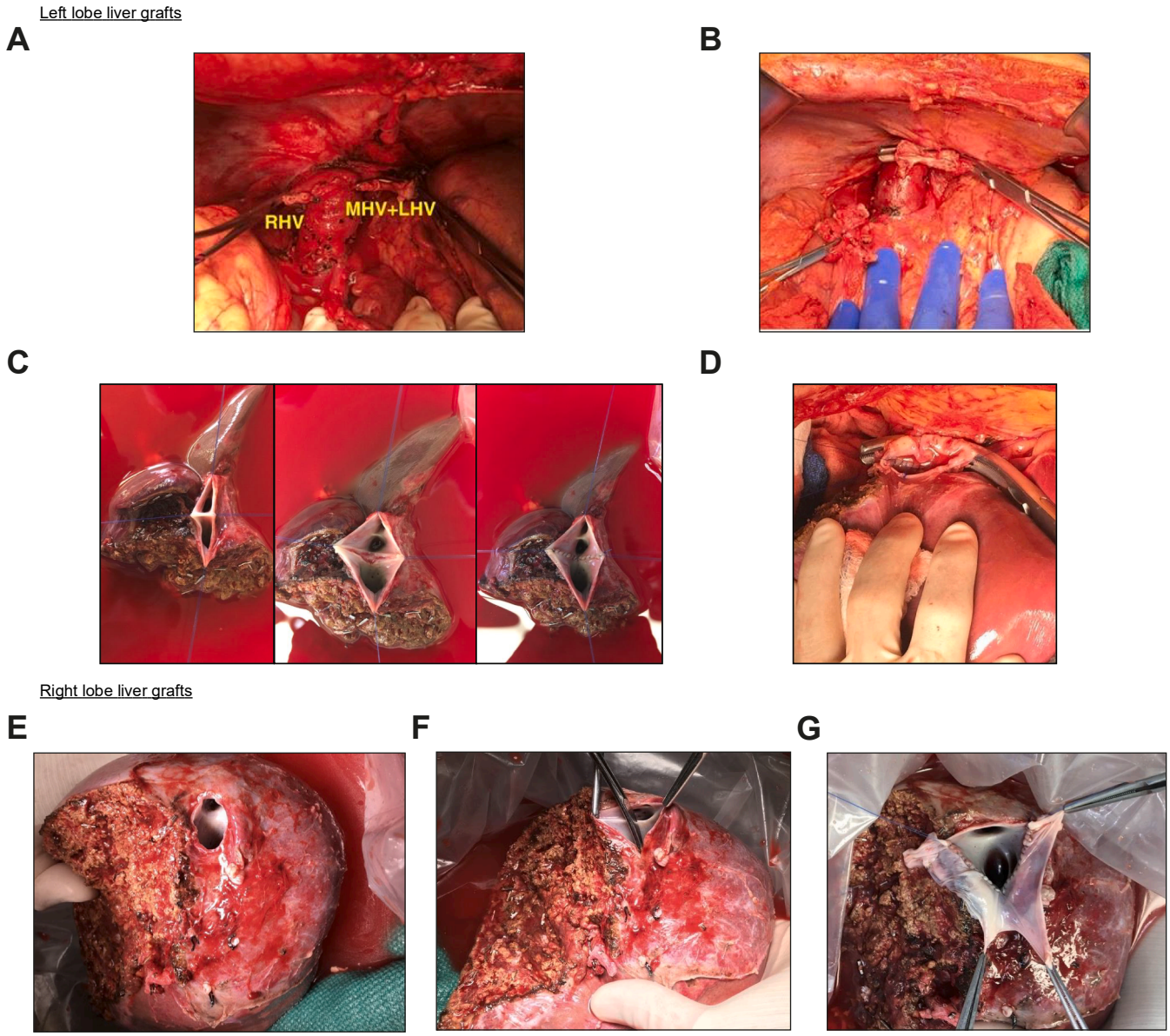

Fig. 6. Approaches to outflow augmentation in left and right lobe liver grafts. Note that phrenic vein ligation is routinely performed as described. Reprinted with permission from Fujiki *et al.* 2022.[76] LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein.

transplantation. This is particularly critical in addressing the supply-demand mismatch that has historically led to significant waiting list mortality.[127–130] The most critical concepts from this review include the mechanisms underlying SFSS, the concept of FGS in LDLT, and the applications of these concepts to management of relative graft inflow and outflow during transplantation.

Other relevant changes are also helping address both access to transplant and post-transplant outcomes. One example is machine perfusion, which has revolutionised transplantation.[131–136] Both normothermic machine perfusion and HOPE have been shown to mitigate ischaemia-reperfusion injury and post-reperfusion syndrome, which may impact post-transplant haemodynamics, although at present this has not been well studied.[137–139] Machine perfusion might also directly affect the graft itself via the described interplay between haemodynamics and graft regeneration. Further, machine perfusion is also being investigated for DD-SLT and LDLT, which might impact the need for PIM.[39,85,86,140] Another critical development is the rise of robotic approaches, particularly in LDLT. This has been most robustly described by the Riyadh group and has led to improvements for both the donor and recipient.[141–143] Robotic implantation has also been described, which may impact graft haemodynamics, though this is not clearly linked. Ongoing developments in LDLT approaches, particularly to PIM, continue to arise from Eastern centres, including in Korea and Japan, who are undoubtedly leaders in this space.[58,73,144–146] This includes an investigation of the impact of low GRWR grafts on cancer recurrence, which is an interesting topic that warrants future investigations.[145,146]

It is also critical to understand the limitations of the current evidence, which are numerous. Many protocols and

approaches are described as definitive, including those of the authors', but there has never been a prospective and/or randomised assessment of approaches, and thus each should be viewed as a recommendation. There are no standard or widely accepted thresholds for PIM, and indeed different groups even use different assessment tools to guide PIM. The described comparisons between PIM techniques are based on intuition and retrospective series, and there are no robust comparisons of when PIM should be performed, or which technique(s) are optimal. Not only the application of flow modulation, but also the timing is proposed as critical; however, true guiding data on the timing of modulation (*e.g.* splenectomy before or after reperfusion) is generally lacking. Outflow augmentation is proposed for all grafts in some series, but there is no prospective data supporting the benefits of this approach. FGS is proposed as a conceptual framework, but at present this cannot be quantified. Thus, the interplay between recipient, donor and technical factors is subject to the surgical team's judgment and is not yet scientifically assessable. Research on SFSS is challenging, given the relative rarity of this outcome, and future studies might help define a more frequent outcome to facilitate ongoing discovery.

Conclusions

An understanding of complex hepatic vascular regulation is essential to optimise liver graft function in transplantation. We review mechanisms of such regulation, and strategies to deal with relevant problems encountered in both partial and whole liver transplantation. This may help surgeons and hepatologists as they strive for improved access to transplantation across the world. The relationship between PV and HA flow is mediated by the HABR, which in turn mediates SFSS secondary to portal hyperperfusion. This understanding has led to multiple strategies from across the globe for PIM. It is equally crucial to maximise graft venous outflow to ensure graft function. These venous modifications in turn mediate HA flow. Much ongoing research is needed to solidify haemodynamic management strategies in both living and deceased donor liver transplant, and to assess the impacts of recent technological advances on such approaches.

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Abbreviations

DDLT, deceased donor liver transplant; DD-SLT, deceased donor split-liver transplant; FGS, functional graft size; GRWR, graft-to-recipient weight ratio; HA, hepatic artery; HABR, hepatic artery buffer response; HOPE, hypothermic oxygenated perfusion; HPCS, hemi-portocaval shunt; IR, interventional radiology; IVC, inferior vena cava; LDLT, living donor liver transplant; LHV, left hepatic vein; LLG, left lobe liver graft; LT, liver transplant; LVUS, liver vascular ultrasound; PIM, portal inflow modulation; PV, portal vein; PVF, portal vein flow; PVP, portal vein pressure; RHV, right hepatic vein; RI, resistive index; SAE, splenic artery embolisation; SAL, splenic artery ligation; SFSS, small-for-size syndrome; SLT, split liver transplant.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

The study was conceptualized and conducted under the direction of TDU and LC. Data collection and analysis was performed by TDU, CJW, and LC. Manuscript drafting was performed by TDU, LC and CJW. Critical manuscript review was performed by all authors.

Supplementary data

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