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Hemodynamic interaction between portal vein and hepatic artery flow in small-for-size split liver transplantation

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Abstract In split-liver transplantation, the entire portal flow is redirected through relatively small-for-size grafts. It has been postulated that excessive portal blood flow leads to graft injury. In order to elucidate the mechanisms of this injury, we studied the hemodynamic interactions between portal vein- and hepatic artery flow in an experimental model in pigs. Six whole pig liver grafts were implanted in Group 1 ($n=6$) and six whole liver grafts were split into right and left grafts and transplanted to Groups 2 ($n=6$) and 3 ($n=6$), respectively. The graft-to-recipient liver volume ratio was 1:1, 2:3 and 1:3 in Groups 1, 2 and 3, respectively. Portal vein- and hepatic artery flows were measured with an ultrasonic flow meter at 60,120 and 180min after graft reperfusion. Portal vein pressure was also recorded at the same time intervals. Graft function was assessed at 3,6h and 12h, and morphological changes at 12h after reperfusion. Following reperfusion, portal vein flow showed an inverse relationship to graft size, while hepatic artery flow was reduced proportionately to graft size. The difference was significant among the three groups ($P<0.05$). Portal vein pressure was significantly higher in group 3, compared to groups 1 and 2 ($P<0.05$). Hepatic artery buffer response was significantly higher in Group 3, compared to Groups 1 and 2 in relation to pre-occlusion values ($P<0.05$). Split-liver transplantation, when resulting in small-for-size grafts, is associated with portal hypertension, diminished arterial flow, and graft dysfunction. Arterial flow impairment appears to be related to increased portal vein flow.

Keywords Hepatic artery flow · Portal vein flow · Small-for-size grafts · Split-liver transplantation · Morphological changes

Introduction

Split-liver transplantation has been introduced to expand the donor pool, bridging the gap between supply and demand by fashioning two transplantable grafts from one liver, so benefitting two patients [2, 16]. Splitting of the liver for transplantation for two adults may, however, result in small-for-size-grafts. Life-sustaining functions may be jeopardized either by an inadequate quantity of liver parenchyma or by intrahepatic hemodynamic alterations potentially injurious to the graft [6, 14, 15]. Experimental and clinical studies have demonstrated that hepatic artery flow is mainly regulated by portal vein flow; increased portal vein flow decreasing hepatic artery flow [5, 9, 17]. We tested the hypothesis that in split-liver transplantation, the relative increase of portal vein flow during the reperfusion period may have a detrimental effect on hepatic arterial flow.

Materials and methods

Liver procurement

This study complies with the "Principles of laboratory animal care" (NIH publication No. 86–23, revised 1985) and the requirements of the Athens University Animal Ethics Committee. Twelve young Landrace pigs weighing 25–30kg were used as donors. Following an overnight fast, anesthesia was induced via an ear vein. Endotracheal ventilation was secured. The technique of liver retrieval has been described elsewhere [8]. The graft was perfused with 1000ml of University of Wisconsin (UW) solution via the infrarenal aorta and superior mesenteric vein (SMV). The liver was harvested with the whole length of the inferior vena cava (IVC) and was stored in UW solution at 4°C. Six livers were used as whole grafts for Group 1, and six were split into right- and left grafts for transplantation in Groups 2 and 3, respectively.

Bench surgery – graft splitting

The liver was prepared, and the anatomy of the hepatic veins was identified. The structures of the porta hepatis were dissected. The radicals of the portal vein (PV), hepatic artery (HA), and divisions of the common bile duct were identified. The main trunk of the HA, PV, and common bile duct (CBD) were allocated to the right graft. Our objective was to create two transplantable grafts. The left lateral segment of the liver was assigned as the left-, and the rest as the right graft. In pigs, the main artery of the left lateral segment branches off from the right gastric artery, thus, the right gastric artery was used as the inflow vessel for the left liver graft (Fig. 1). The branches of the PV and CBD leading to the left lateral segment were divided. The orifice of the left hepatic vein (LHV), which constitutes the main outflow of the left graft, determined the transection line of the parenchyma, which was marked on the liver surface at a point between the middle hepatic vein (MHV) and the LHV and ending close to the divided hilar structures separating the two grafts. The splitting of the liver was carried out by means of sharp transection. Hemostasis on the cut surfaces of the grafts was secured by suturing each individual radical with 5–0 prolene sutures. The right graft, having its own IVC, was ready for implantation. For the left grafts, a new IVC was fashioned from the stored extra IVC; the orifice of the right renal vein was anastomosed to the orifice of the LHV of the left graft, thus creating a new IVC. The left graft was ready for implantation in standard orthotopic fashion. Splitting was carried out with the graft submerged in cold UW and was completed in 90 ± 20min.

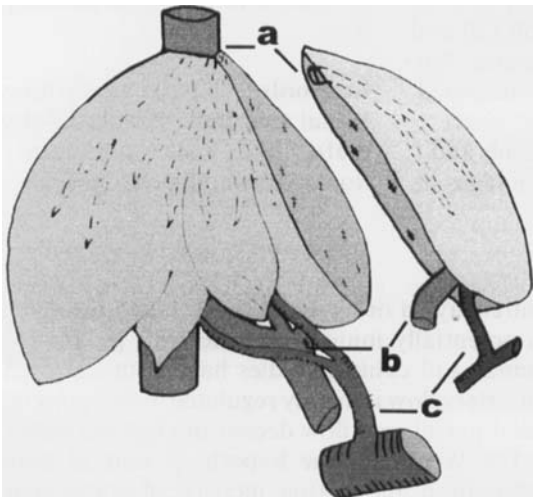

Fig. 1. Splitting of the porcine graft and division points of the left hepatic vein (*a*), portal vein branch (*b*) and hepatic artery (*c*). For clarity, the bile ducts have been subtracted

Engraftment

Eighteen young, white Lardrace pigs weighing 25–30kg were used as recipients, and six were assigned to each of Groups 1, 2, and 3. Following a 24-h fasting period, 10mg/kg ketamine and 0.5mg/kg of Diazepam were given intramuscularly. A suitable ear vein allowed intravenous access. General anesthesia was induced with a bolus dose of thiopental sodium 5mg/kg and continued at a maintenance dose of 1mg/kg as soon as the trachea was intubated. Analgesia was provided with Fentanyl 5mg/kg per h, and muscle relaxation with pancuronium bromide at a loading dose of 0.1mg/kg, followed by a continuous infusion of 0.3mg/kg per h. The animals were ventilated with O_2 in air mixtures of FiO_2 (60%). Isoflurane was added at concentrations of 0.8–1.5%. Tidal volume and frequency of ventilation were adjusted to maintain end-tidal CO_2 at approximately 30mm Hg. The left carotid artery was cannulated. The left jugular vein was catheterized and a balloon-tipped Swan-Ganz catheter (5.5 Fr, Abott, USA) was placed into the pulmonary artery.

The whole-, right-, and left grafts were transplanted in standard orthotopic fashion into Groups 1, 2, and 3, respectively. Heparin was administered at 1mg/kg of body weight. During the anhepatic phase, a passive portojugular bypass was routinely used. IVC anastomoses were completed with 5–0 polypropylene sutures, and portal vein anastomoses with 6–0 polypropylene sutures, leaving a growth factor of 30%. The arterial anastomoses were completed with interrupted 7–0 and 8–0 polypropylene sutures for the right and left grafts, respectively. Biliary drainage was achieved with end-to-side hepaticojejunostomy with 6–0 polydioxanone sutures (PDS).

Measurements

Hemodynamic monitoring included mean arterial pressure (MAP) in mm Hg, mean pulmonary arterial pressure (MPAP) in mm Hg, central venous pressure (CVP) in mm Hg, pulmonary capillary pressure (PCW) in mm Hg, and cardiac output (CO). Portal vein pressure (PVP) in mm Hg was recorded by placing a 14 G catheter in the recipient portal vein and connecting it to a multi-channel data-recording unit (Siemens SC 6002 SMS, Danvers, Mass). Blood flow in the portal vein and the hepatic artery was measured with precalibrated perivascular ultrasonic flow cuffs using an ultrasonic flowmeter (Transonic System, New York, model 72011), which incorporates a non-occlusive zero facility. Measurements were taken at 60-, 120-, and 180min after graft reperfusion. Hepatic arterial buffer response (HABR) was studied 180min after reperfusion, when the animals were hemodynamically stable. Specifically, the portal vein was occluded for 30s, and the hepatic artery flow was estimated.

Blood samples for liver function tests were collected at 3,6- and 12h after reperfusion. Liver biopsies were taken 12h after reperfusion and examined under light microscopy with hematoxylin-eosin staining. Experiments were ended 12h after reperfusion, when all animals were killed with a lethal dose of pentothal.

Statistical analysis

Data were analyzed with the Mann-Whitney test and one-way analysis of variance (ANOVA) where appropriate. A value of $P < 0.05$ was set as statistically significant.

Results

The graft-to-recipient liver volume ratios were 1:1, 2:3, and 1:3 in Groups 1, 2, and 3, respectively. Following reperfusion, portal vein flow (mean ± SD) at 60-, 120-, and 180min, respectively, was 0.60 ± 0.04, 0.62 ± 0.04, and 0.65 ± 0.05ml/g per min in Group 1; 0.71 ± 0.04, 0.68 ± 0.04, and 0.70 ± 0.05ml/g per min in Group 2; and 1.02 ± 0.05, 1.01 ± 0.04, and 1.04 ± 0.05ml/g per min in Group 3 (Fig. 2). There was a significant difference among all groups at all time points ($P < 0.05$).

Hepatic artery flow (mean ± SD) at 60-, 120-, and 180min, respectively, was 0.32 ± 0.06, 0.34 ± 0.05, and 0.37 ± 0.04ml/g per min in Group 1; 0.22 ± 0.01, 0.24 ± 0.03, and 0.26 ± 0.03ml/g per min in Group 2; and 0.13 ± 0.01, 0.14 ± 0.02, and 0.20 ± 0.03ml/g per min in Group 3. (Fig. 3). Again, there was a significant difference among the three groups at all time points ($P < 0.05$).

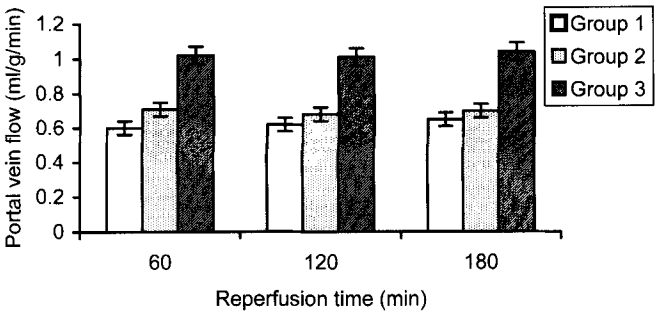

Fig. 2. Effects of liver-graft size on portal vein flow (mean ± SD). Group 1 underwent standard orthotopic liver transplantation, and groups 2 and 3 underwent split-liver transplantation. The graft-to-recipient liver volume ratio was 1:1, 2:3 and 1:3 in groups 1, 2, and 3, respectively. The increase in portal vein flow was inversely proportionate to graft size. The difference was significant among the three groups at all time points ($P < 0.05$)

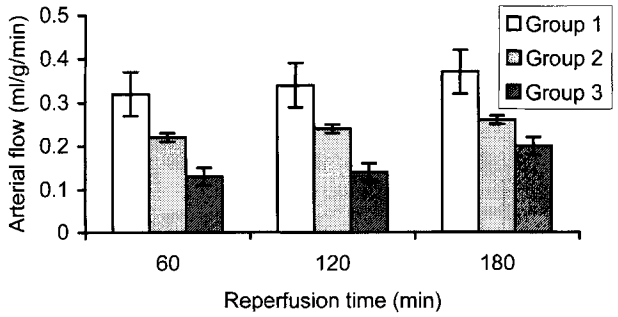

Fig. 3. Effects of liver-graft size on hepatic arterial flow (mean ± SD). Group 1 underwent standard orthotopic liver transplantation, and groups 2 and 3 underwent split-liver transplantation. The graft-to-recipient liver volume ratio was 1:1, 2:3, and 1:3, in groups 1, 2 and 3 respectively. The decrease in hepatic arterial flow was proportional to graft size. The difference was significant among all three groups at all time points ($P < 0.05$)

Portal vein pressure (mean ± SD) at 60-, 120-, and 180min was 6.1 ± 0.6, 6 ± 0.3, and 5.8 ± 0.2mmHg in Group 1; 5.8 ± 0.5, 5.6 ± 0.7, and 7.8 ± 0.6mm Hg in Group 2; and 11 ± 1.1, 11.5 ± 1.2, and 15.4 ± 1.3mm Hg in Group 3 (Fig. 4). The changes in Group 3 compared significantly ($P < 0.05$) to Groups 1 and 2at each time point.

HABR 180min after reperfusion showed an elevation of the arterial flow (mean ± SD) from 0.37 ± 0.03 to 0.44 ± 0.02ml/g per min in Group 1; from 0.26 ± 0.03 to 0.32 0.03ml/g per min in Group 2; and from 0.20 ± 0.02 to 0.28 ± 0.04ml/g per min in Group 3 (Fig. 5). Changes were significant in all three groups compared to the pre-occlusion values ($P < 0.05$). Arterial buffer response was significantly higher in Group 3, compared to Groups 2 and 1 (40 ± 10% elevation in Group 3, vs 25 ± 10% in Group 2, and 20 ± 8% in Group 1) in relation to pre-

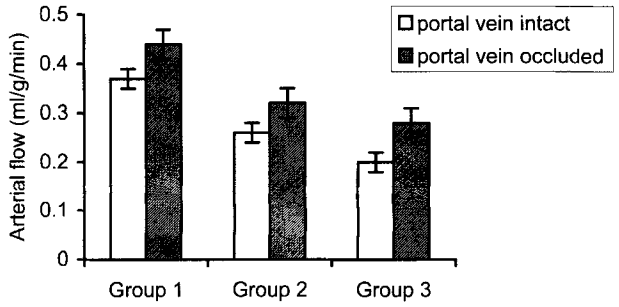

Fig. 4. Hepatic arterial buffer response in relation to graft size (mean ± SD). Group 1 underwent standard orthotopic liver transplantation, and groups 2 and 3 underwent split-liver transplantation. The graft-to-recipient liver volume ratio was 1:1, 2:3, and 1:3 in groups 1, 2, and 3, respectively. The recorded HABR in relation to pre-occlusion values in group 3 was higher than that in groups 1 and 2 ($P < 0.05$). However, even with the portal vein occluded, arterial flow remained significantly reduced in groups 2 and 3 compared with group 1 ($P < 0.05$)

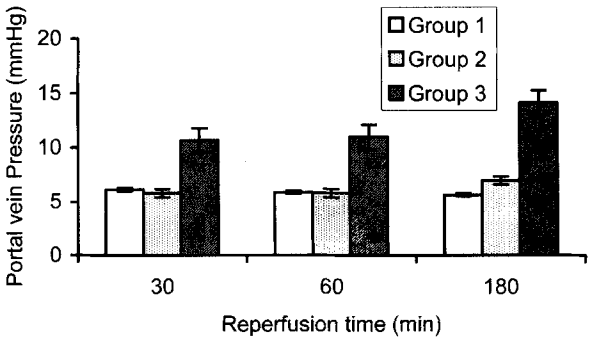

Fig. 5. Portal vein pressure in relation to graft size (mean ± SD). Group 1 underwent standard orthotopic liver transplantation and groups 2 and 3 underwent split-liver transplantation. The graft-to-recipient volume ratio was 1:1, 2:3, and 1:3 in groups 1, 2, and 3, respectively. The portal vein pressure was significantly higher in group 3 than in groups 1 and 2 at all time points ($P < 0.05$)

occlusion values ($P < 0.05$) (Fig. 5). However, even with the portal vein occluded, arterial flow remained significantly reduced in Groups 2 and 3 compared to Group 1 (0.28 ± 0.04, and 0.32 ± 0.03, vs 0.44 ± 0.02ml/g per min) ($P < 0.05$).

Liver function showed significant deterioration in group 3 compared to the other two groups. At 12h after reperfusion AST was 134.0 ± 45.6 in group 1, 153.0 ± 55.5 in group 2, and 483.7 ± 149.4 in group 3 ($P < 0.05$) group 3, vs groups 1 and 2) (Fig. 6). INR was 2.1 ± 0.3 in group 1, 2.6 ± 0.4 in group 2, and 5.7 ± 0.1 in group 3. ($P < 0.05$ group 3 vs groups 1 and 2) (Fig. 7).

Histology of liver biopsies taken at 12h following reperfusion in Groups 1 and 2 showed normal features. By contrast, venous dilation, perivenular congestion, and sinusoidal dilation were pronounced in Group 3. In the congested areas, erythrocytes were observed in Disse's spaces intermingled with the cells of the liver plates. Hepatocytes presented cloudy swelling, hydropic changes and vacuolar degeneration.

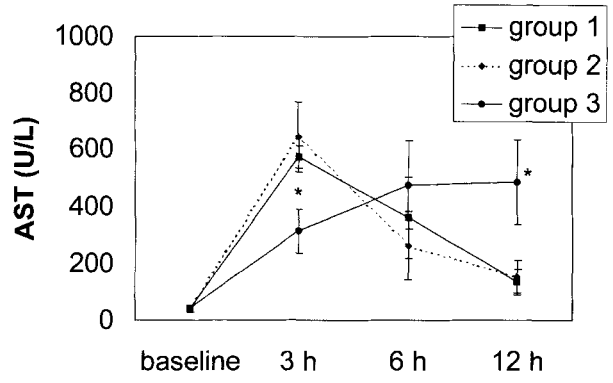

Fig. 6. Serum levels of aspartate transferase (*AST*) in the three groups. The graft-to-recipient volume ratio was 1:1, 2:3, and 1:3 in groups 1, 2 and 3, respectively. AST increased significantly in group 3, compared with groups 1 and 2, 12 h following reperfusion ($P < 0.005$)

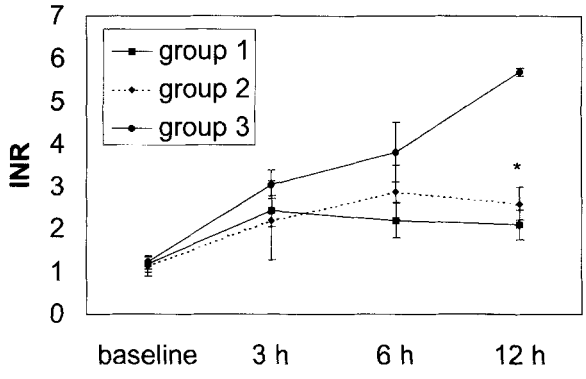

Fig. 7. International normalized ratio (*INR*) following reperfusion in the three groups. The graft-to-recipient volume ratio was 1:1, 2:3, and 1:3 in groups 1, 2, and 3 respectively. INR was significantly higher in group 3 than in groups 1 and 2 at 12 h following reperfusion ($P < 0.05$)

Discussion

Split-liver transplantation constitutes the most advanced technique aimed at expanding the limited donor pool. This innovative procedure provides two grafts from one donor liver [2, 16]. However, when the grafts are mismatched to the recipient's size, a variety of postoperative problems may ensue [6, 9, 14].

We found that portal flow to the split grafts (Groups 2 and 3) showed an inverse relationship to graft size. By contrast, arterial flow decreased disproportionately to graft size; 3h after reperfusion, arterial flow was reduced by 30% and 48% in the right and left grafts, respectively, compared to whole graft arterial flow. A similar haemodynamic pattern of hepatic blood flow has been observed in living related liver transplantations, where size disparity between graft and native liver is the rule. These haemodynamic changes can partly be attributed to the hepatic artery responding to increased portal flow in a reciprocal manner in order to keep the total blood inflow within acceptable limits [8, 9, 12].

The hepatic arterial system ends at the sinusoidal capillaries of the portal vein system: this anatomical interrelationship may be the reason for the proportionate reduction of arterial flow in small-for-size grafts, where sinusoidal resistance is increased due to a relatively high portal vein flow [6]. In such circumstances, hepatic artery flow has to overcome the transformed, usually low-resistance sinusoidal system, into a high-resistance capillary bed [6, 9]. Our study demonstrates that portal vein pressure was persistently elevated in pigs that received grafts weighing approximately 30% of the standard liver. Compensatory mechanisms involved in the autoregulation of portal vein- and hepatic artery flow appear to be incapacitated in grafts under a critical graft-to-standard-liver-volume ratio, at least during the early post-transplant period. Liver grafts of 30% of the standard liver volume are prone to functional failure, with a mechanism of injury that is still unknown. We have shown that decreased arterial flow induced by the excessive portal flow and direct damages inflicted to sinusoidal lining cells by portal hypertension are detrimental. Our findings are in accordance with those of Man et al. [11] who demonstrated the detrimental role of portal hypertension in small-for-size liver grafts in an experimental model in rats. Severe sinusoidal congestion, as demonstrated in our study, is compatible with portal hypertension and diminished arterial flow observed only in grafts weighing 30% of the recipient liver [11]. Flow injury to sinusoidal endothelial cells and activation of Kupffer's cells has been described after extended liver resections in rats [14]. The

immunological component of high portal inflow injury is characterized by the release of a number of cytokines, which trigger an inflammatory response to the host, resulting in graft failure [5, 17]. During the early postoperative period in human liver transplantation, hepatic artery flow is only 10% of the total liver flow [6, 9, 14] and may be further diminished by the coexistence of warm ischemic injury, acute rejection, and poor arterial reconstruction technique [2, 15, 16]. Therefore, small-for-size grafts are more vulnerable to graft failure secondary to ischemic injuries or even hepatic artery thrombosis, than size-matched or full grafts [12, 15].

We have also found that the HABR response remains intact, as in human liver transplantation [9]. We have documented for the first time that the arterial buffer response shows an inverse relationship to graft size. Lautt has proposed the adenosine washout hypothesis to explain the arterial buffer response phenomenon [10]. According to this theory, a constant release of adenosine among the hepatic arterioles and portal venules keeps the balance between the two liver inflows. Elevation of portal flow washes out more adenosine (a vasodilator substance), resulting in hepatic arteriole vasoconstriction and a reduction in arterial flow. The reduction in portal vein flow induces the adverse effect. This hypothesis has been supported by experimental data [4]. It should however be noted, that in small-for-size grafts, even with the portal vein occluded, arterial flow does not reach the same levels observed in whole grafts when the portal vein is not occluded. Most probably, independent factors unrelated to portal vein flow are also implicated in the diminished arterial flow in small grafts. Hickman et al. [7] have demonstrated that in approximately 50% of reduced pig-liver grafts, hepatic arterial flow values remain depressed to 50–60% of the baseline values, and plasma norepinephrine are up to 20-fold higher, 3h after reperfusion. By contrast, in whole liver grafts, arterial flow and plasma norepinephrine levels returned to near normal 2h after reperfusion. Norepinephrine should be considered as a substantial contributing factor to diminished arterial flow in small-for-size grafts since it is the reason why portal vein occlusion fails to completely reverse arterial flow impairment, compared to intact grafts at 3h after reperfusion [3].

Our experiment shows that during the early postoperative period, the arterial inflow in small-for-size liver grafts (as in split livers for two adult recipients) operates under high resistance and remains decreased, compared to size-matched grafts. This diminished arterial flow predisposes to graft ischemic injury and hepatic artery thrombosis [1, 6, 15]. Preventive intervention should be directed at measures to decrease portal hypertension by modifying the portal vein flow.

It has been shown in adult-to-adult living donor liver transplantation that the liver promptly regenerates within 14 days to near-normal volume, with restoration of the altered portal hemodynamics during the same period [11]. If the sub-optimal volume grafts were protected by some therapeutic intervention during the first postoperative period, reperfusion damages may be ameliorated.

Although in humans, successful transplantation of extra-small grafts, less than 30% of the standard liver volume, from living donors has been reported [13], grafts of 40 to 30% of the standard liver volume should be considered marginal. In pigs, grafts of 30% of standard liver volume are complicated with severe reperfusion injury and functional failure (Figs. 6, 7). This is most probably due to lack of any portosystemic collateral circulation, which lessens the impact of the high portal flow to the grafts and eliminates the development of severe portal hypertension.

The recognition of the altered hemodynamics of arterial and portal flow in small-for-size grafts following splitting of one liver for transplantation in two adults warrants increased attentiveness. Every effort for a timely diagnosis should be made in order to treat postoperative problems that may ensue. A further study is currently underway to test whether the decrease of portal vein flow confers any protection on small-for-size grafts. In conclusion, split-liver transplantation, when resulting in small-for-size grafts may be associated with portal hypertension, diminished arterial flow, and graft dysfunction. Arterial flow impairment appears to be related to increased portal vein flow and intrahepatic portal hypertension. The graft volume determines the magnitude of the intrahepatic haemodynamic changes and the ensuing reperfusion damages.

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