Procurement for visceral organ transplantation: where to cannulate and how to perfuse?

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Procurement for visceral organ transplantation: where to cannulate and how to perfuse?

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Purpose of review
Despite significant improvements in visceral organ transplantation over the last few decades, some technical aspects of organ harvesting remain controversial. The purpose of this article is to review and summarize the latest literature on how to perfuse in multiorgan procurement.

Recent findings
Few prospective studies have analyzed and compared technical aspects of harvesting such as cannulation (aortic-only versus dual aortic and portal flush), flush rates and volumes as well as flush pressures (high pressure vs. gravity). However, these and most data available from additional retrospective and experimental studies do not clearly support one harvesting technique over another.

Summary
Currently, because of lack of superiority data, no clear guidelines exist on what cannulation techniques to apply during organ procurements in visceral organ transplantation. Additional prospective trials are needed to clarify these questions.

Keywords
donation after cardiac death, dual aortic and portal perfusion, organ procurement, single aortic perfusion

INTRODUCTION

Organ procurement for transplantation has significantly improved over the last decades and transformed a once emergent transplant procedure into a semi-elective procedure, allowing organ preservation over extended period of times and therefore organ sharing over long distances. However, there still currently exists no standardized technique that is used worldwide for organ procurement. Several technical variations exist for organ harvesting and decisions need to be taken in regards to choice of perfusion solutions, vascular access (cannulation) for flushing, as well as perfusion volumes, flows and pressures. All these variables have the potential to influence organ quality during procurement and long-term graft and patient survival. In this manuscript, we aimed at systematically review the literature in order to clarify whether one technique of organ harvesting is superior to another.

METHODS

Medline, PubMed and Cochrane Libraries were reviewed for publications including organ procurement, retrieval techniques and flush solutions. All study types on human and animal subjects were included in this review.

SINGLE AORTIC-ONLY FLUSH VS. DUAL AORTIC AND PORTAL VEIN FLUSH

There are two ways to cannulate for organ perfusion during harvesting: access the arterial system only through the infrarenal aortic or iliac artery cannulation (Fig. 1a); access both the arterial and venous systems by inserting the cannula in the infrarenal aorta or iliac artery and the inferior mesenteric vein (IMV) for the portal flush (Fig. 1b).

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KEY POINTS

- Although there are no clear data on its superiority, the aortic-only flush is a simple and fast technique to perfuse visceral organs during procurement. It remains unclear whether additional simultaneous portal perfusion may be deleterious to the pancreas.
- It may be advantageous to use a high-pressure flush during organ harvesting, as it mimics physiologic conditions and has been shown to increase graft survival, especially in liver procurements.
- Back-table aortic perfusion reduces the risk of ischemic type biliary injury during liver procurement.
- There currently is no consensus on the volume of flushing solution, but depending on the use of a low or high-viscosity solution, between 3 and 6 l are generally necessary to achieve appropriate organ perfusion.
- Low-viscosity solutions usually need a higher rinse volume (4–6 l) to achieve adequate flushing than high-viscosity solutions (3–4 l).
- Special considerations during organ harvesting include flushing during DCD procurement, split-liver transplantation, living donor, multivisceral and pediatric transplantation.

Surgical technique

Cadaveric organ procurement remains a complex procedure, despite many advances and efforts to standardize this operation. Here follows a description of organ procurement as performed in our center: The donor is placed in a supine position on the operating table. Perioperative antibiotics are given and a Time-Out is performed. The incision reaches from the pubic symphysis to the sternal notch as to gain access to both cavities, the chest and the abdomen. After incising the abdominal fascia, a retractor is put in place to provide sufficient exposure, in order to exclude pathological conditions such as malignancy, infectious or other disease processes that would preclude procurement.

Then, the liver is briefly evaluated for suitability of transplantation. The chest is then opened through a median sternotomy using a pneumatic saw and a self-retaining retractor is put in place. The abdominal dissection begins with a Cattel-Braash maneuver in order to expose the retroperitoneum and more specifically the inferior vena cava (IVC) and abdominal aorta. After preparation of both right and left common iliac arteries and the distal abdominal aorta, supraceliac aortic control is achieved by incising the left triangular ligament of the liver, dividing the superior part of the gastrohepatic ligament, retracting the left liver lobe laterally and exposing the aorta after dissecting through the right crus of the diaphragm. Three hundred units per kilogram of heparin are given and the left common iliac artery is ligated. The distal

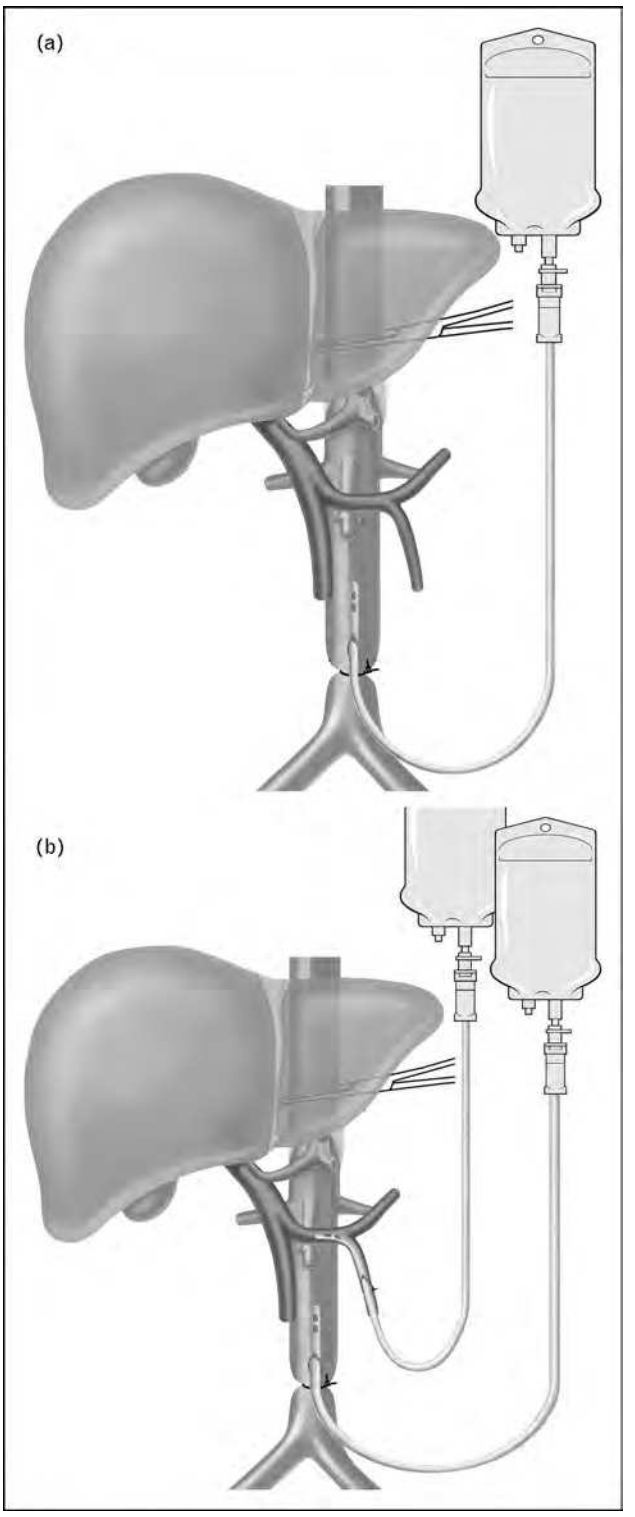

FIGURE 1. Schematic illustration of aortic-only (a) and dual aortic and portal vein perfusion (b) during multiorgan procurement.

part of the right common iliac artery is then ligated as well and a finger is used to hold pressure on the aorta, whereas an arteriotomy is performed proximal to the ligation. A 24-Fr cannula is then inserted into the aorta and secured in place with a heavy tie or umbilical tape. Care is taken not to advance the cannula to deep, and therefore impeding the flush to the renal vessels (Fig. 1). If the surgeon chooses to use the dual-perfusion technique, the IMV is exposed and also used for venous cannulation and portal flush using a 20-Fr cannula or smaller. In some centers, 'precooling' is performed through slow infusion in the IMV of a chilled isotonic saline solution with 5% dextrose for serum sodium levels less than 160 mEq/gl and 5% dextrose in free water for serum sodium levels greater than 160 mEq/gl [1]. Venting of the venous system is performed by incising the right atrium or the IVC below the renal veins. Sloshed ice is then placed in the abdominal cavity, and more specifically around the organs that are procured. Once cannulation is successfully performed and a good flush of the abdominal organs with infusion solution at 4°C is achieved, organ retrieval commences. Additional flushing of the liver and biliary structures through the common bile duct is usually performed on the back table at gravity pressure [2].

Single aortic-only vs. dual aortic and portal vein cannulation

Many transplant centers use the dual-flush technique in order to obtain maximal flow and most rapid cooling. However, as many organ procurements now also include pancreas explantations, the rational of perfusing the portal system with the same flow and pressure to the arterial system has been questioned. Additionally, a single-aortic-flush technique could potentially be faster and easier to perform.

Several studies have looked at the potential superiority of one flushing technique over the other. The first usage of the aortic-only perfusion only model was reported by Boillot *et al.* in 1993 and reported no detrimental effects of graft dysfunction in adults or pediatric transplantation using this procurement technique. Additionally, the authors also reported the rate of primary nongraft function and initial poor function as being similar to the ones observed with combined aortic and portal vein flush [3].

The only randomized prospective trial comparing dual aortic and portal perfusion (APP) versus aortic-only flush (APO), is a single-center study that randomized 20 patients in each arm. Donor parameters (age, body weight, liver function tests), surgical teams and ischemic times were similar in both groups. Although the perfusion took significantly longer to complete in the APO group (10.2 vs. 7.2 min), the liver temperature fell to its lowest level in a similar time (11.9 vs. 9.3 min). There was no primary graft nonfunction or graft arterial injury in either group and no difference in graft outcomes. The authors therefore concluded that the APO method produces equivalent result than the APP method and should be the preferred cannulation method because of its simplicity [4].

In the largest retrospective study to date, including 400 consecutive liver grafts, El-Rassi *et al.* aimed at detecting the effects of cadaveric liver retrieval without portal vein cooling on liver graft function and to identify risk factors for graft dysfunction using the aortic-only perfusion technique. Relevant parameters pertaining to the donor, recipient, graft and peri-operative variables were analyzed using univariate and multivariate models. The authors reported the rate of primary nonfunction and initial poor function of the liver grafts using the aortic-only flush as 0 and 9.5%, respectively, which is consistent with previous literature. They therefore concluded that effective liver perfusion occurs via the aorta and hepatic artery as well as via the portal vein, after the fluid transverses the intestinal bed. In addition, this study revealed that donor age, body mass index, blood pressure and vasopressors influenced graft function on univariate analysis using the aortic-only flush. Furthermore, prolonged anhepatic phase, transplantation duration and partial grafts influenced graft function as well. On multivariate analysis, the authors found a significant association between graft dysfunction and donor obesity as well as usage of partial grafts [5].

The second largest retrospective study comparing aortic-only cooling with classical aortic and portal cooling was published by de Ville de Gayet *et al.* One hundred sixty-three donor hepatectomies were performed consecutively over a 20-month period, of which 78 liver grafts were cooled via the APP method and 85 via the APO method. Overall graft and patient survival was not statistically different in both groups, except for the 3-month graft survival, which was significantly worse in the APP group (72 vs. 87%). In their subgroup multivariate analysis, comprising 140 cases, the authors found that low donor weight, donor hypernatremia and in-situ portal perfusion were determinants of higher postoperative ALT peaks. The authors therefore concluded that APO is at least as well tolerated as APP for organ procurement [6].

It has previously been postulated that there may exist a direct correlation between portal perfusion and poor outcome in pancreas procurement. Nghiem *et al.* studied the function of pancreatic

grafts harvested from six pancreas-liver donors and compared it with that of nine pancreas-alone donors. All donors had comparable physiological parameters. Pancreas and liver were flushed *in situ* with Collins solution and the portal vein was vented immediately. Pancreas-liver grafts received a significantly higher aortic flush volume than those in the other group. The authors found that recipients of pancreas-liver grafts had higher serum amylase and lipase as well as significantly lower levels of urine bicarbonate and pH than those in the pancreas-alone group [7].

Additionally, several case studies and comparative animal studies have also addressed the question of whether aortic perfusion only is as good as the dual aortic and portal perfusion technique. A brief summary of these studies can be found in Table 1 [4–6,8–11].

At our institution, we routinely perform the aortic cannulation technique (single cannulation or flush), as it represents an easy and rapid way to perfuse during organ harvesting and there are currently no available data suggesting inferiority of this approach. Although it has sporadically been suggested that portal flushing may alter pancreatic function during pancreas procurement, there currently exist no solid experimental or clinical data to support this theory.

PERFUSION PRESSURES, FLOW AND VOLUMES

As perfusion solution has a different temperature and viscosity than blood, surgeons perform a 'nonphysiologic' flush during organ procurement. Although most transplant surgeons will perfuse abdominal organs at a relatively low pressure (80–100 cmH_2O), some prefer to perfuse at a higher pressure of 150 mmHg using pneumatic compressions bags, especially when using the aortic-only perfusion technique.

In a randomized control trial, Tisone *et al.* looked at gravity perfusion (75–100 cmH_2O) vs. high-pressure (additional 100 mmHg) perfusion during organ procurement for kidneys. The first group comprised 25 patients and the second group 19 patients. All procurements occurred with University of Wisconsin solution and the dual cannulation and perfusion method (aortic and portal flush). The high-pressure group had the aortic cannula perfused with an additional 100 mmHg and the portal vein cannula by gravity. Immunosuppressive regiments and patient characteristics were similar in both groups. Primary endpoints of this study were donor creatinine, patient creatinine at time of discharge, primary nonfunction of the graft, early graft dysfunction and acute rejection. The authors found no statistically significant differences in any of these endpoints, although the incidence of acute rejection was higher in the high perfusion group (28 vs. 21%). Notably, the incidence of primary graft nonfunction was lower in the high-perfusion group (0 vs. 10.5%), but this did also not reach statistical significance. The authors therefore concluded that gravity perfusion pressure is as effective as high perfusion pressure [12].

The same group also published a randomized controlled trial comparing gravity to high-pressure perfusion for liver harvesting. Here again, all procurements occurred with University of Wisconsin solution and the dual cannulation and perfusion method (3000 ml aortic and 1000 ml portal flush). The first group comprised 45 donors and the second group 44 donors. The high-pressure group had the aortic cannula perfused with an additional 100 mmHg and the portal vein cannula by gravity. Donor and recipient characteristics as well as cold and warm ischemia times were similar between both groups. Primary endpoints of the study were graft function and survival, patient survival as well as primary nonfunction and initial poor function of

Table 1. Studies comparing aortic-only perfusion vs. aortic and portal vein perfusion

Authors	Study design	Number	Flush type	Outcome	Reference
Chui *et al.*	Randomized prospective	40 pts.	APO ($n=20$) vs. APP ($n=20$)	No PNF in either group, equivalent	[4]
El-Rassi *et al.*	Retrospective	400 pts.	APO	APO safe, PNF 0%, IPF 9.5%	[5]
De Ville de Goyet *et al.*	Retrospective	163 pts.	APO ($n=85$) vs. APP ($n=78$)	3-month graft survival worse in APP (72 vs. 87%)	[6]
Gabel *et al.*	Retrospective	44 pts.	APO ($n=22$) vs. APP ($n=22$)	3-month graft survival and PNF equivalent	[8]
Pinna *et al.*	Case series	55 pts.	APO ($n=38$) vs. APP ($n=17$)	No difference in graft survival	[9]
Filipponi *et al.*	Experimental	16 pigs	APO ($n=8$) vs. APP ($n=8$)	Graft survival similar, APP with higher AST	[10]
Bittard *et al.*	Experimental	18 rats	APO ($n=6$) vs. APP ($n=12$)	APO safe, liver ATP lower in APP	[11]

APO, aortic-only flush; APP, aortic and portal perfusion; AST: aspartate transaminase; APP, adenosine triphosphate; PNF, primary non-function.

the liver grafts. The authors found that high-pressure perfusion resulted in better early graft function (INR and aspartate transaminase) on postoperative day 5. and superior graft and patient survival at 1 month (89 vs. 75%). However, there was no difference in primary nonfunction and initial poor-function between both groups [13].

High-pressure portal perfusion is usually not recommended, as experimental animal data show that portal pressure above 15 mmHg and flow rates over 1 ml/g/min are deleterious to liver tissues [14].

Back-table arterial perfusion during liver procurement is routinely performed by most transplant centers. There is evidence that using high-pressure perfusion reduces the incidence of ischemic type biliary tract damage. Moench *et al.* hypothesized that insufficient perfusion of the biliary arterial vessels may be responsible for these types of lesions. The authors retrospectively analyzed 190 liver transplantations, of which 130 grafts were perfused by standard in-situ flush (including portal flush) only and 59 by additional high-pressure (150 mmHg) back-table ex-situ flush. All grafts were flushed with University of Wisconsin solution. Donor-related factors, recipient age, indication for transplantation, surgical technique, immunosuppression and ischemia time were similar in both groups. In the first group, 21 of 130 patients (16%) developed ischemic type biliary lesions while only one of 59 patients did in the second group. Additionally, multivariate analysis confirmed that back-table high-pressure flushing is a significant predictor of prevention for development of ischemic type biliary lesions [15,16].

The viscosity of a fluid is a measure of its resistance to gradual deformation by shear stress or tensile stress. According to the Hagen-Poiseuille equation, the volumetric flow rate is inversely proportionate to the dynamic fluid viscosity:

$$Q = \frac{\pi P r^4}{8 \eta l}$$

(Q = flow rate, P = pressure, r = radius, η = fluid viscosity, l = length of tubing).

The viscosity of the flush solution is therefore another important component that can influence flow and subsequently organ perfusion (Table 2). The five-fold higher viscosity of University of Wisconsin solution compared with Celsior results in a five-fold lower flow rate of University of Wisconsin solution at a given constant pressure. Although there are some reports suggesting that a low viscosity flush of organs correlates with better organ survival, especially in Donors after Cardiac Death procurements, as well as lower rates of biliary strictures, no good data exist in clinical practice and, therefore, high viscosity solutions such as the University of Wisconsin solution remain the gold standard for flushing during visceral organ procurement in many centers [14,17,18].

There currently exists no clear consensus on how much volume to use for organ perfusion. Several prospective randomized trials comparing low and high-viscosity solutions using the APP flushing method reported using higher volumes of low-viscosity solutions such as Celsior or histidine–tryptophan–ketoglutarate solution (HTK) when compared with high viscosity solutions such as the University of Wisconsin solution (low 4000–6000 vs. high 3000–4000 ml) [19–21]. At our institution, we usually infuse at least 4–6 l of a low viscosity perfusion solution (Institute George Lopez-1 solution) in order to achieve an adequate flush during organ retrieval. Often, the experienced surgeon can determine whether an adequate organ flush has occurred by examining the color and surface of the liver and intestines as well as clearance of the perfusion solution through venous venting.

Most data on flushing flow rates come from experimental studies. In a porcine model, histological evidence of graft edema and liver function tests were improved when liver grafts were perfused with a high aortic flow of 150 ml/min vs. a low flow of 50 ml/min [22]. In another experiment by Komokata *et al.*, porcine liver grafts were significantly less perfused and had poorer survival with flow rates of 10 vs. 30 or 50 ml/kg/min [23]. In most centers, including ours, flow rates average 50–100 ml/kg of perfusion solution [24].

Bile duct flushing is performed in most centers, on the back table with at least 20 ml of the same solution used for arterial and/or portal vein flushing [1].

Table 2. Dynamic viscosity of water and commonly used perfusion solutions at 4°C

Solution	Viscosity (cP)	Fold flow rate[a]
Water	1.57	0.64
Celsior	1.15	1.00
IGL-1	1.28	0.91
HTK	1.80	0.55
University of Wisconsin	5.70	0.20

cP, centipoise (1 cP = 0.001 Pa·s); HTK, histidine–tryptophan–ketoglutarate solution; IGL-1, Institute George Lopez-1 solution.
[a]flow rates referred to Celsior.

SPECIAL CONSIDERATIONS

Modified techniques of cannulation and perfusion have to be considered in special circumstances such

as donation-after-cardiac death (DCD) organs, living related grafts, in-situ and ex-situ splits, multivisceral and pediatric graft procurements.

Perfusions in donation-after-cardiac death procurements

DCD organ procurements represent a special challenge for the harvesting team, as cannulation of the aorta and organ perfusion in a minimal amount of time is of essence in order to minimize warm ischemia time. The aorta-only cannulation technique is used in this setting and some centers, including ours, additionally use a double balloon catheter to avoid losing time getting access to the supraceliac aorta. Additionally, a catheter is inserted in the IVC or iliac veins in order to vent the venous system. There have been many studies comparing which flush solution is superior for DCDs, including reports that HTK solution is associated with a reduced graft survival in liver transplantation [25].

As it remains unknown whether static cold storage is the ideal perfusion technique for DCDs, several groups are researching new preservation methods for experimental and clinical DCD transplantation. The most promising strategy is the use of machine perfusion [26]. This concept has been extensively investigated in experimental rodent and pig models either as normothermic or hypothermic oxygenated perfusion and has been tested in limited clinical trials [27–29,30▪▪,31▪▪,32]. Although the data are still preliminary, machine perfusion of donor DCD liver grafts before implantation may safely extend ischemia times and minimize ischemia-reperfusion injury in DCD organs. Hashimoto *et al*. described another strategy to reduce ischemic-type biliary strictures (ITBS) in DCD organs by infusing tissue plasminogen activator (TPA) in the donor hepatic artery of 22 grafts on the back table (0.5 mg per 100 g of the graft). Their rational for using TPA was that thrombus formation in the peribiliary microcirculation is a major factor in occurrence of ITBS. Although the authors found that only two of 22 recipients developed ITBS, 14 recipients developed excessive postreperfusion bleeding. This study concluded that TPA might be useful in prevention of ITBS for DCD donors, but that further studies are needed to confirm this hypothesis [33].

Perfusions in living donor procurement

Living Donor Liver Transplantation (LDLT) has emerged as an important option for many patients, particularly small pediatric patients and those adults that are at disadvantage by the current deceased donor allocation system. After the usual steps to dissect and separate the liver, the graft is removed and immediately flushed with cold preservation solution on the back-table through the portal vein. Formal hepatic arterial flush to preserve the liver graft is not recommended by most transplant centers because direct cannulation may injure the intima of the hepatic artery. A group from Taiwan recently described a new flush method for LDLT, which was in form of a retrograde arterial flush of the liver graft without arterial cannulation by flushing through the portal vein and simultaneously occluding hepatic venous outflow [34]. In a prospective randomized trial from the same group classic portal perfusion only was compared with portal perfusion plus retrograde arterial flush (RGAF). The results of this study showed significantly lower postoperative serum bilirubin until 3 weeks after transplantation and shorter postoperative hospital stay in the RGAF group [35▪].

Perfusion in in-situ and ex-situ split procurement

The most commonly used splitting technique in liver split procurements is the division into a left lateral sectoral graft (segments 2 and 3) for a child and a right trisegmental graft (segments 1 and 4–8) for an adult patient. Another splitting technique is the division in two full grafts (segments 1–4 and 5–8), which can both be used in adult recipients [36]. During the ex-situ splitting procedure, the liver is perfused in the usual fashion using the aortic-only or dual aortic and portal vein flush. The graft is then explanted and prepared as well as split on the back table at the recipient transplant center in ice-cold preservation solution. Additional flush through the hepatic artery is usually performed. During in-vivo splitting, the liver is dissected and prepared *in situ*. When the parenchymal transection is completed, two liver grafts are separated, each with its own vascular pedicles and venous drainage. At this time, the transected donor liver is perfused *in situ* using the single or dual-flush technique with preservation solution [37].

Perfusion in multivisceral procurement

The effect of flushing flow rate during multiple organ procurement on viability of the liver, pancreas, and intestine was investigated in porcine multivisceral transplantation by Komokata *et al*. Splanchnic organs were flushed *in situ* with 50 ml/kg University of Wisconsin solution via the aorta using a pump at a flow rate of 10, 30 or 50 ml/kg/min. Two-day survival was 17% in the 10 ml/kg/min group and 67% in other groups. The former group had inadequate flushing

out of the hepatic and intestinal grafts. At the flow rate of 30 ml/kg/min, the viability and integrity of all organs were well maintained. The authors concluded that the optimal flushing flow rate differs for each group [23]. There currently are no specific separate guidelines for multivisceral organ transplantation, although similar volumes, flush rates and pressure are used than in single or dual organ procurement [24].

Perfusion in pediatric transplantation

Pediatric organ procurement utilizes the same techniques as in adult procurements, but because of the rarity and small organ sizes, experienced procurement surgeons should be part of the explanting team. Infant donors are harvested using the APO technique, as the IMV is often too small to cannulate. After aortic cannulation, 500 IU/kg of heparin is infused and the flush is performed with a total volume of 50 ml/kg. In a 6-month infant that weighs 8 kg, the total infused solution volume therefore will comprise about 400 ml [1,38].

CONCLUSION

Owing to the overall scarcity of data comparing technical aspects of visceral organ procurement such as cannulation (aortic versus dual aortic and portal flush), flush rates, volumes and flush pressures, additional effort is necessary to design a large multicenter, randomized controlled trial to clarify the potential superiority of one technique over another, and more specifically, analyze the benefits of either cannulation site when procuring the pancreas for transplantation. Currently, both single and dual vascular cannulation can be recommended as effective methods for abdominal multiorgan procurement for transplantation.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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