Intestinal/Multivisceral Transplantation 25

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25.1 The Embryological Basis of Multivisceral/Small Bowel Transplantation

The grape of the abdominal coelomic organs can be divided from the embryological point of view into three portions: the *foregut* (stomach and duodenum) with the glandular annexes (liver and pancreas), the *midgut* (small bowel and right colon), and the *hindgut* (left colon and rectum). The foregut has an arterial supply provided by the celiac axis; the midgut is vascularized from the superior mesenteric artery (SMA) and the hindgut from the inferior mesenteric artery (IMA). The foregut with the pancreas and the midgut share the same venous outflow through the superior mesenteric vein (SMV) and portal vein, while the hindgut has two venous outflows: the inferior mesenteric vein and the hemorrhoidal venous system. The liver, which is connected to the foregut and midgut by the portal vein and the biliary system, presents a unique double vascular supply which comes from the celiac axis and the portal vein and a single outflow into the inferior vena cava through the hepatic veins.

Transplant of the foregut with the liver has been performed for what was defined as a "cluster transplant" [1], but despite providing some useful information for the development of intestinal transplantation, it will not be discussed here. Transplantation of the hindgut has never been performed due to the complexity of the venous outflow reconstruction and the possible complications secondary to denervation of the rectum. In this chapter we will concentrate primarily on the technical aspects (see also Chap. 24) of transplantation of the midgut (isolated intestinal

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transplant) alone or in combination with the foregut and liver (multivisceral transplantation) or midgut and foregut alone without the liver (modified multivisceral transplantation).

25.2 Nomenclature

Since the initial experience in intestinal transplantation [2], several combinations of the hepato-gastro-enteric systems have been proposed and utilized to treat irreversible failure of the small bowel or small bowel and liver. Recently, Abu-Elmagd et al. [3] published details of three main types of intestinal/multivisceral transplant based on the frequency with which they have been adopted clinically.

Type I is the intestinal transplant which considers the transplant of the small bowel alone or transplantation of the small bowel en bloc with the colon and/or the pancreas.

Type II is the liver-intestine transplant which refers to the transplantation of the liver with the small bowel without the stomach-duodenum and pancreas, where the liver is kept in continuity with the midgut just by the portal vein. This type of graft requires the preservation of the stomach-duodenum and pancreas of the recipient, providing an anastomosis between the native portal vein to the graft portal vein or to the recipient inferior vena cava. Also in this combination, the donor graft can include the right colon.

Type III is the multivisceral graft transplant, which can be *full* when the gastroenteric system together with the liver and pancreas is transplanted en bloc or *modified* when the stomach-duodenum-pancreas and intestine are transplanted en bloc without the donor liver. In particular cases this modified multivisceral transplant has been performed maintaining also the native pancreaticoduodenal complex and the spleen (Fig. 25.1).

25.3 Graft Types and Indications

The use of the three main types of intestinal graft has changed over time, depending on the experience of the surgical team and the change in indications for intestinal transplantation. A paper published in 2009 examined the shifting of graft types over time in a large cohort (500 patients) of intestinal transplants performed over an 18-year period [4]. Dividing the 18-year experience in intestinal/multivisceral transplantation into three eras, Era I (1990–1994), Era II (1995–2001), and Era III (2001–2008), the indications rose from 35 % in Era I to 46 % in Era III for isolated intestinal transplants and from 20 % in Era I to 34 % in Era III for multivisceral transplantation. On the contrary, liver-intestinal transplants (type II) decreased from 45 % (Era I) to 20 % (Era III) with prevalent indications in pediatric patients. The polarization of the intestinal grafts in isolated intestine and multivisceral transplant reflects an almost international attitude and is due to early referrals of irreversible intestinal failure patients to transplant centers (isolated intestinal transplants) and the technical complexity of the liver-intestinal transplant compared to multivisceral transplantation.

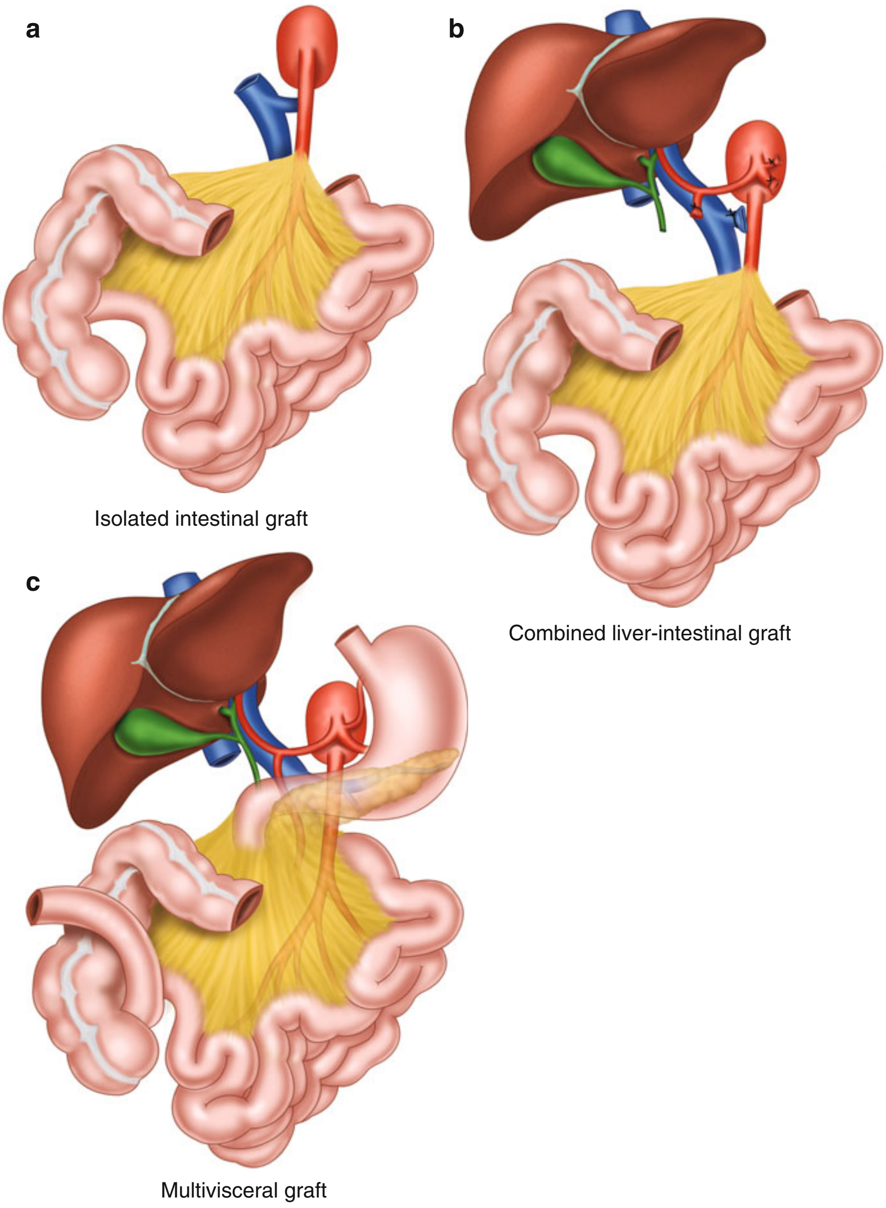


Fig. 25.1 Graft types: (**a**) isolated intestinal graft; (**b**) combined liver-intestinal graft; (**c**) multivisceral graft

25.4 Isolated Small Bowel Transplantation

The main indication for the transplant of the isolated midgut is any intestinal irreversible failure with normal liver function and no necessity to replace the stomach and the duodenum secondary to anatomical damage or dysmotility of these two organs. A variety of diseases can be treated with this transplant in adults and children: congenital or acquired anatomical shortening of the small bowel, diffuse dysmotility or congenital intestinal villi dysfunction, and desmoid tumors (see also Chap. 24). The small bowel can be transplanted alone or in continuity with the right colon to provide better absorption; in a few patients, the intestinal graft was transplanted with preservation of the enteric nervous ganglia, but no data exist on the outcome of ganglia preservation. The isolated intestinal graft can be transplanted reducing its size in the case of a small residual abdominal cavity, and of course it can be a perfect type of graft if there is an indication for living related transplantation, particularly from adult to child.

25.4.1 Recipient Procedure

After careful laparotomy, a total enterectomy of the recipient's residual small bowel is performed, if needed. The small bowel graft with or without the right colon can be revascularized orthotopically or heterotopically. In the first case, the SMA is anastomosed end-to-end to the recipient's SMA with 7-0 Prolene, and the same is done with the SMV of the donor and recipient. In the case of previous recipient SMA disease, the arterial inflow should be obtained with an interposition arterial graft from the recipient aorta and then with an anastomosis between the donor SMA and the arterial graft (Fig. 25.2). An orthotopical variant of the venous outflow is to anastomose the donor superior mesenteric vein end-to-side to the recipient portal

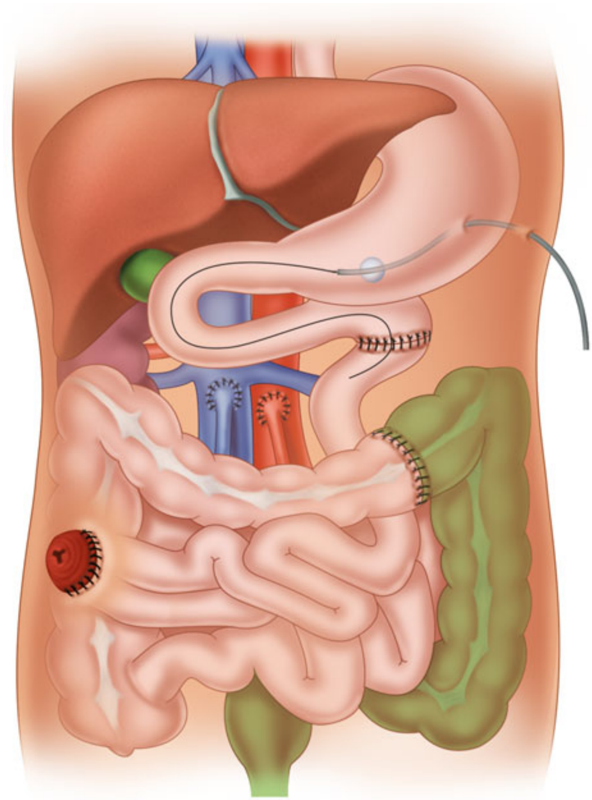


Fig. 25.2 Isolated intestine transplant (From Bozzetti et al. [18], with permission)

vein. This procedure is sometimes more difficult than the others and requires an extended mobilization of the recipient's pancreas and duodenum and exposure of the portal vein without damaging the recipient bile duct [5].

In the case of difficult dissection of the superior mesenteric vein or previous thrombosis of the recipient SMV and if the surgeon does not want to perform an orthotopic SMV reconstruction with the portal vein as described previously, a heterotopic revascularization of the intestinal graft can be performed (Fig. 25.3). In this case, after the enterectomy of the residual intestine, the surgeon should expose the anterior and lateral walls of the infrarenal aorta and inferior vena cava. After partial clamping of the aorta and IVC, an arterial graft and a venous graft from the donor are anastomosed end-to-side to the recipient's large abdominal vessels. Finally, first the donor SMA is anastomosed to the arterial graft followed by the anastomosis between the donor SMV and the vein graft. It should be emphasized that the heterotopical revascularization of the intestinal allograft facilitates its implantation. However, special attention should be paid to avoid kinking of the artery and vein by excessive length of the two vessels.

At the time of the initial clinical experience in small bowel transplantation, there was concern about possible native liver dysfunction in using this heterotopical venous reconstruction. Later, it was observed that reconstruction of the donor superior mesenteric vein into the systemic circulation did not cause any liver dysfunction and could be considered as effective as direct reconstruction into the portal venous system [6].

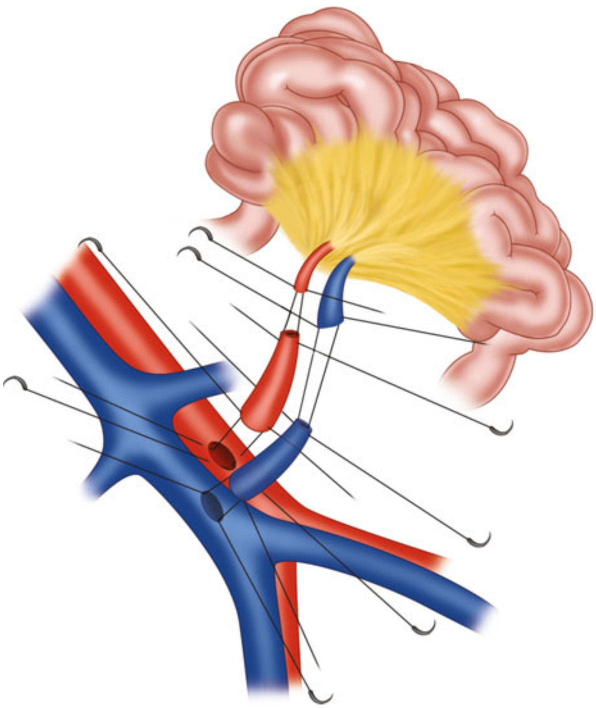


Fig. 25.3 Eterotopic revascularization of the intestinal graft

Tzakis et al. [7] first described the inclusion of the right colon in the isolated small bowel transplant graft. The supposed advantage of including the right colon was to improve the electrolytes and water absorption by the graft. Initial concerns were the possible increase in rejection of the colon segment and the subsequent increase in mortality rates of the recipients. In the first review of the results of such composite grafts done by the *International Intestinal Transplant Registry* in 2007, patients transplanted with isolated intestine together with the colon showed a significantly lower requirement of i.v. fluids or parenteral nutrition early and later after transplantation. Furthermore, no significant differences were reported in terms of mortality or rejection when intestine plus colon was compared to small bowel graft alone.

Once the graft has been revascularized and hemostasis obtained, the intestinal continuity is reconstructed proximally with the fourth portion of the duodenum or the stomach of the recipient. Distally the small bowel or the right colon is reconstructed with the remaining left colon or sigmoid colon. In some conditions, an endorectal pull-through with sphincter preservation and rectal mucosectomy is indicated. This quite difficult procedure can be indicated in cases of multiple juvenile polyposis extended into the rectum or in the case of Hirschsprung's disease with diffuse dysmotility extended from the rectum to the jejunum [7]. After bowel reconstruction, the surgery ends with the feature of the terminal ileostomy, having first placed an enteric feeding tube into the intestinal allograft. The distal stoma is necessary in order to obtain easy access to the intestinal allograft for intestinal biopsy and endoscopy. Some centers also advocate creating a proximal stoma to improve the immunological monitoring of the graft also for enteral nutrition. Of course, depending on personal choices, it is better to remember that stomas need to be closed at some time, and stoma closure is not without complications in such patients. The distal stoma is without question an extreme need for immunological monitoring; for differential diagnosis during the follow-up endoscopies, it is important to observe the bowel mucosa and perform biopsies of the allograft intestine and of the native bowel. Nutrition of the allograft can be obtained placing a transgastrostomy feeding tube long enough to reach the lumen of the allograft intestine.

25.5 Combined Liver-Intestine Transplantation

This composite graft, together with isolated intestinal transplantation, was one of the first models of intestinal transplant performed. The principal indications consist of irreversible intestinal failure combined with cholestatic cirrhosis with portal hypertension. The main patient population which may require this type of allograft is pediatric. The combination of a liver-intestine allograft invariably requires the sparing of the native stomach-pancreas and duodenum with preservation of their vascular supply through the native celiac axis and superior mesenteric artery and providing the venous outflow through a portacaval shunt to be performed before vascular anastomosis of the composite graft. Due to the fact that this type of allograft was used more often in children, several kinds of reduced size grafts have been performed.

25.5.1 Recipient Procedure

After removal of the residual small bowel and colon, the total native hepatectomy is performed with the piggyback technique. After the dissection of the native bile duct, the hepatic artery is cut distal to the gastroduodenal artery. The portal vein is clamped and cut up into the hilum. At this point, with the liver devascularized, the native proximal portal vein is anastomosed to the native inferior vena cava in end-to-side fashion with running sutures and unclamped to avoid congestion of the native gastro-pancreatic-duodenal bloc. After complete mobilization of the native liver, hepatectomy is performed after clamping of the hepatic vein confluence.

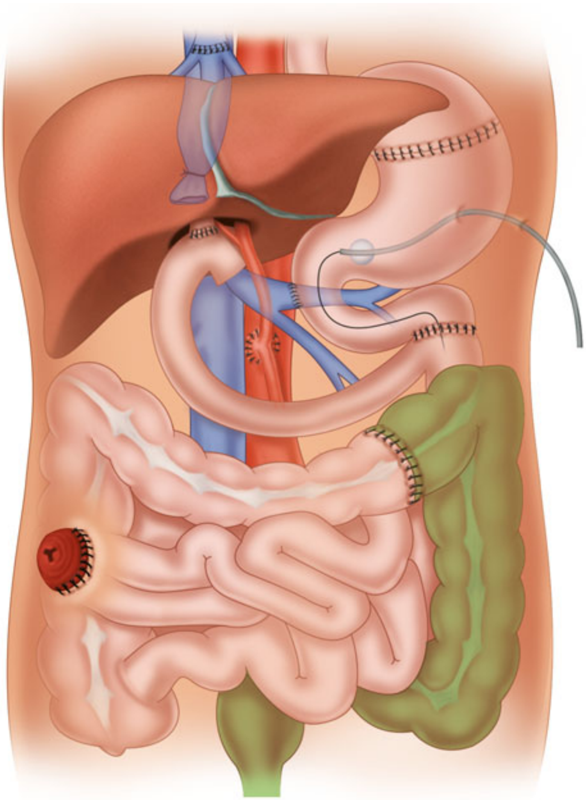
The liver-intestine allograft is then placed on the surgical field, and the first arterial reconstruction is performed. This can be done anastomosing the donor aortic patch on the anterior wall of the recipient's infrarenal aorta or, more easily, anastomosing first a segment of the donor's thoracic aorta end-to-side to the anterior wall of the infra-renal recipient aorta, followed by the anastomosis of the aortic carrel patch including the takeoff of the donor celiac axis and SMA to the aorta conduit in end-to-end fashion with running sutures. There are two main pitfalls in this kind of arterial reconstruction: (a) if the aortic patch around the donor SMA is too short, the inferior wall of the aorta conduit may partially close the takeoff of the SMA; (b) if the aortic conduit is too long, this can kink, producing a critical arterial flow to the SMA or both SMA and celiac axis.

After completion of the arterial reconstruction, the liver is put in place in the right sub-diaphragmatic space, and the venous outflow is reconstructed, anastomosing the donor inferior caval vein to the confluence of the recipient's hepatic veins. Only at this point is the liver-intestine allograft reperfused through the arterial reconstruction. Once complete hemostasis has been obtained, the intestinal continuity is performed, anastomosing first the proximal donor jejunal loop to the donor bile duct, followed by the anastomosis between the native fourth portion of the duodenum to the allograft jejunum and, finally, by the anastomosis between the native colon and the allograft last ileal loop just proximally to the segment of donor ileum which can be exteriorized for the temporary ileostomy (Fig. 25.4). A jejunal feeding tube is placed through a gastrostomy and pushed into the allograft jejunum through the duodenal-jejunal anastomosis.

25.5.2 Pitfalls of the Liver-Intestine Transplant Technique

Besides the arterial pitfalls described before which are rare but possible, there are two other major pitfalls in this procedure which we should be aware of. The first and the most frequent is the biliary tract reconstruction. Biliary complications secondary to the biliary-jejunal anastomosis are similar in rate to what one should expect after roux-en-Y biliary reconstruction in pediatric liver transplantation. The major concern is that in over-immunosuppressed patients, like intestinal transplant patients, this can become a life-threatening complication if not diagnosed promptly.

Fig. 25.4 Combined liver-intestine transplantation (From Bozzetti et al. [18], with permission)



The second pitfall is due to the absence of supporting tissue around the donor's portal vein/superior mesenteric vein conduit which, after total pancreatectomy, can become too long and prone to kinking and portal vein thrombosis.

In order to avoid these two possible complications, such as biliary stricture/leakage or portal vein kinking, several modifications to the original technique as described previously have been proposed.

Initially, the group from Omaha proposed performing (at the back table) a subtotal donor pancreatectomy, leaving the donor duodenum and the head of the pancreas in continuity with the donor bile duct, thereby avoiding biliary reconstruction and leaving some pancreatic tissue anterior to the donor portal vein. Although it is true that this method avoided two possible complications, a different one was described following this modification: a pancreatic fistula from the suture of the pancreatic remnant. The natural evolution of the in any case brilliant idea of the Omaha group was the one proposed later by the Miami group, which considered transplanting the entire donor pancreas and duodenum in continuity with the donor liver and small bowel. With this latest evolution of the liver-intestine allograft transplantation, the recipient will end the transplant with two pancreata, no biliary anastomosis, and less chance of portal vein kinking. No evidence of dangerous hypoglycemic episodes had been reported with the presence of two functioning pancreata.

25.5.3 Allograft Size Reduction

The presence of size discrepancies between donor and recipient may sometimes require graft size reduction in order to accomplish the full or partial closure of the abdominal cavity. The allograft size reduction can be obtained by reducing the liver, the small bowel, or both.

The liver reduction can be obtained with resection of the left lobe, transplanting the right trisegmental liver allograft or transplanting the left lateral segment after considerable reduction of the liver allograft [8].

The small bowel can be reduced by resecting the mid jejunum, avoiding deleterious functional loss of the transplanted bowel. The two graft reductions can be combined in the case of large size discrepancies.

Abdominal wall transplantation has been described to solve this frequent problem of size (see Chaps. 26 and 27).

25.6 Multivisceral Transplantation

Multivisceral abdominal transplantation with the liver was first described in dogs by Starzl in 1960 [9]. It was the first type of intestinal transplant performed clinically, and centers performing multivisceral transplantation nowadays substantially adopt the same surgical technique as then [10]. There are several indications for performing a multivisceral transplantation, schematically: any kind of irreversible intestinal failure which causes irreversible liver failure and where the need to remove the stomach and the pancreas is due either to extension of the disease to these upper abdominal organs or because of vascular damage to the celiac axis and/or the superior mesenteric artery. *Short bowel syndrome with liver failure* and complete *splanchnic venous thrombosis* are the main stems of the various diseases that can be treated with a multivisceral transplantation. *Gardner's syndrome with desmoid tumors* in the mesenteric root infiltrating the visceral arteries is another well-accepted indication for multivisceral transplantation. There are also several hollow visceral myopathies or neuropathies that can benefit from a multivisceral transplant sparing the native liver (see also Chap. 24).

25.6.1 Recipient Procedure

25.6.1.1 Full Multivisceral Graft

The surgical procedure in candidate recipients for a full multivisceral graft (with the liver) is quite simple, requiring the resection of all the remaining bowel, a total gastrectomy combined with total pancreatectomy, and a total hepatectomy with piggyback technique. Despite the easy principles of the pre-implant phase of the procedure, the surgery can sometimes be severely complicated by the presence of portal vein collaterals with bleeding from portal hypertension in patients who have often undergone previous multiple surgery and have dense vascularized adhesions. In order to decrease the risk of large amounts of blood loss, several strategies have been adopted. One possibility is to perform a transfemoral arterial embolization of the celiac axis and superior mesenteric artery once the donor surgeon has given assurance of the organs' quality. Another way is to start, after laparotomy, with dissection of the recipient's gastroesophageal junction. After the stomach has been mobilized from the esophagus and the left lobe of the liver mobilized and rotated to the right, the retro-gastric space is open, and the surgeon can attempt to clamp the celiac axis from above. The successful dearterialization of the stomach, pancreas, spleen, and liver can permit a relatively bloodless mobilization of the spleen and pancreas so as to obtain a left access to the proximal trunk of the superior mesenteric artery which can then also be clamped. Once control of the main arteries has been achieved, the final dissection of the stomach, pancreas, and remaining small bowel can be easily performed, leaving the proximal trunk of the celiac axis and superior mesenteric artery clamped. At this point, the hepatectomy with piggyback technique can be completed, leaving a clamp on the hepatic vein confluence.

25.6.1.2 Modified Multivisceral Graft

In patients where the liver is not required, the important step of the demolition part of the procedure is the isolation and sparing of the entire hepatic artery. Once the bile duct has been cut, the proper hepatic artery is visualized and followed proximally. The right gastric artery, the gastroduodenal artery, and all the pancreatic arterial branches arising from the hepatic artery are cut between ligatures. The hepatic artery is followed as far as its origin from the celiac axis. After the left gastric artery has been cut between ligatures, the splenic artery is carefully dissected just at its emergence from the celiac axis and cut between ligatures. The ligature on the proximal stump of the splenic artery is reinforced with a stitch. At this point, the stomach is cut at the level of the cardias. The spleen and distal pancreas are mobilized from left to right, and a Kocher maneuver of the duodenum and head of the pancreas is performed. The proximal trunk of the superior mesenteric artery is visualized and is clamped and cut. With the entire gastro-pancreatic-intestinal bloc in the surgeon's hands, the portal vein is clamped distally toward the liver and cut as low toward the superior mesenteric vein as possible, obtaining a good length of portal vein which can be useful if the donor portal vein should be too short.

25.6.1.3 Vascular Reconstruction (Full Multivisceral and Modified Multivisceral Graft)

Once perfect hemostasis has been obtained, the arterial reconstruction of the multivisceral graft must be done first. Several kinds of arterial reconstructions have been described, all of them suggesting, in one way or another, the need to keep the takeoff of the celiac axis and superior mesenteric artery together and the use of the donor aorta. The infrarenal donor abdominal aorta can be anastomosed directly to the recipient infrarenal or supraceliac aorta end-to-side. The same kind of aortic-aortic anastomosis can be performed using first a segment of the donor thoracic aorta as an aortic conduit. The open end of the donor abdominal aorta with the celiac axis and superior mesenteric artery can be closed with a patch of donor aorta to avoid slipping of the ligature or, even worse, dissection of the aortic intima [11]. Girlanda

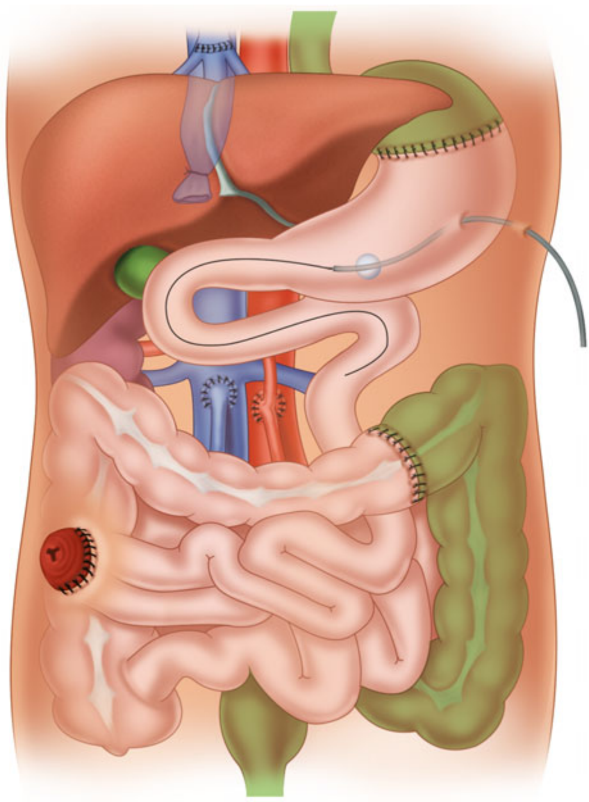


Fig. 25.5 Multivisceral transplantation (From Bozzetti et al. [18], with permission)

et al. [12] have also described other methods of rearterialization of a multivisceral graft in the case of multiple visceral arterial anomalies [12].

The venous outflow is usually performed anastomosing the suprahepatic donor inferior vena cava to the confluence of the recipient's hepatic veins (Fig. 25.5). Sometimes, the donor suprahepatic cava is anastomosed in piggyback to the recipient retrohepatic inferior vena cava if there is discrepancy between the donor inferior caval vein and the recipient hepatic vein confluence.

The only difference in the vascular reconstruction of the *modified multivisceral graft* lies in the reconstruction of the venous outflow of the graft which is done by anastomosing the two portal veins end-to-end (Fig. 25.6). In a large cohort of 100 consecutive multivisceral transplants performed at the University of Miami, the arterial reconstruction was principally performed with an anastomosis to the recipient infrarenal aorta with an interposed aortic conduit. The venous outflow was always with a portal-vein-to-portal-vein anastomosis in patients receiving a *modified multivisceral graft*. In more than two-thirds of recipients receiving a *full multivisceral graft*, the venous outflow was obtained with an anastomosis between the donor suprahepatic vena cava to the hepatic vein confluence of the recipient [13].

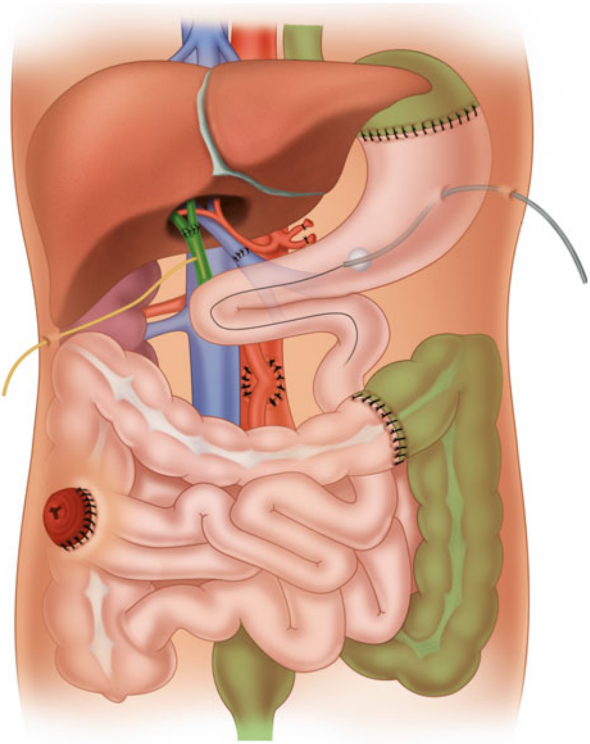


Fig. 25.6 Modified multivisceral transplantation (From Bozzetti et al. [18], with permission)

25.6.1.4 Intestinal Reconstruction

Gastrointestinal continuity is achieved by performing first an esophagogastric anastomosis and completed with the anastomosis between the donor intestine and the native colon just proximally to the end ileostomy. In the case of a *modified multivisceral* transplantation, a biliary reconstruction is required. This is usually achieved with a duct-to-duct biliary anastomosis over a T-tube. Because of the inevitable intestinal organ denervation, a pyloroplasty is performed for gastric drainage.

25.6.1.5 Technical Variants

Some further modifications of the *modified multivisceral transplant* have been proposed for different reasons. In 2007, Matsumoto proposed performing a multivisceral transplant sparing not only the liver but also the native pancreas and spleen in the recipient [14]. Others proposed the same type of multivisceral transplant, preserving only the native spleen but with a total pancreaticoduodenectomy of the recipient [15]. According to the authors who proposed the preservation of the native spleen and pancreas, the advantages of this procedure are the decreased risk of infection and/or posttransplant lymphoproliferative disease. The preservation of the native pancreas and the presence at the end of the transplant of two functioning pancreata can increase the islet cell mass, thus reducing the risk of posttransplant diabetes.

25.7 Special Issues in Intestinal/MV Transplantation

25.7.1 To Spleen or Not to Spleen

Recently several centers have suggested including the donor spleen in the case of *liver-intestine* type or *multivisceral type* transplantation. Technically speaking, there are no particular issues except for the fact that extreme care should be taken to avoid tearing the splenic capsule and rotation of the spleen around the axis of the splenic artery and vein. The primary objective of including the spleen in such types of intestinal transplants is to improve the recipient's defense against infections by avoiding the asplenic state; a secondary aim is the possibility of reducing rejection by increasing the mass of immunocompetent cells of donor origin according to the expansion-deleting leukocytes theory for tolerance induction in solid organ transplantation. However, despite a few reported cases and some spleens having to be taken out secondary to surgical complications, some patients who underwent intestinal transplantation with the donor spleen developed severe immune hemolysis.

In a series published by the Miami group in 2009, the authors concluded that including the spleen in multivisceral transplantation can be performed without significantly increasing the risk of graft-versus-host-disease [16]. However, the allogeneic spleen seems to have a modest protective effect on small bowel rejection, and autoimmune hemolysis is a concern, and this issue definitely requires further investigation.

25.7.2 The Kidney

Renal failure is one of the most frequent long-term complications after intestinal transplantation. High levels of immunosuppression for a longer time need antifungal therapy, and dehydration from enteric losses before and after transplant, in the case of graft dysfunction, is the main reason why a higher rate of patients develops chronic renal failure after small bowel transplantation. This complication becomes almost inevitable in patients who undergo retransplantation of the small bowel. For this small group of patients, associating a kidney transplant at the same time as the intestinal transplantation has been advocated. The kidney graft can be classically transplanted eterotopically in the right lower abdominal quadrant or alternatively, in the case of multivisceral transplantation, en bloc with the multivisceral graft, keeping the renal artery in continuity with the abdominal aorta and the visceral vessels. The renal vein in this case can be reconstructed end-to-side to the inferior caval vein of the recipient before the outflow reconstruction of the multivisceral graft. The reconstruction of the donor's ureter will be done with the usual technique, attaching it to the recipient's bladder or alternatively, if too short, to the recipient's ureter [17].

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