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Feasibility of Laparoscopic Combined Para-Orthotopic Pancreas and Orthotopic Kidney Transplantation: Initial Research with a Pig Model

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the feasibility of laparoscopic combined para-orthotopic pancreas and orthotopic kidney transplantation in a pig model.

Material/Methods: Twelve white female pigs, (4–5 months old, weight range 40–45 kg) were used as donors and recipients, and 6 laparoscopic-combined pancreas and kidney transplantations were performed. After bilateral nephrectomy, the pancreatic artery and vein were anastomosed to the right renal artery and vein, respectively, and the pancreatic fluid was diverted to the duodenum or jejunum. The renal artery and vein were anastomosed to the left renal artery and vein, respectively. The ureter (or kidney pelvis) was anastomosed to the left native ureter (or kidney pelvis). The data of the operations were recorded, and grafts were inspected at autopsy.

Results: Four of the 6 recipient pigs underwent the entire procedure. The duodenum-to-duodenum anastomosis was unfinished in 1 case, and both the duodenum-to-duodenum and renal pelvis-to-pelvis anastomoses were left unperformed in another case. The mean recipient operative time was 429±43 minutes. The mean venous and arterial anastomotic times were 69±15 minutes and 37±18 minutes, respectively, for pancreas transplantation and 56±09 minutes and 42±06 minutes, respectively, for kidney transplantation. The time for renal pelvis-to-pelvis anastomosis was 56±13 minutes and for duodenum-to-duodenum anastomosis was 90±13 minutes. The mean blood loss for recipient pigs was 98±35 mL. An immediate viable blood supply was seen in the 4 pancreatic grafts and in the 5 kidney grafts during the operation by the appearance of a bright red color after revascularization. Five pancreatic grafts had autopsy-proven reliable artery anastomoses and 4 reliable vein anastomoses. All 6 kidney grafts had autopsy-proven reliable artery anastomoses; however, 1 had a vein anastomotic stricture.

Conclusions: Our study showed that laparoscopic-combined para-orthotopic pancreas and orthotopic kidney transplantation in pigs is surgically possible.


MeSH Keywords: Animal Experimentation • Kidney Transplantation • Laparoscopy • Pancreas Transplantation

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Background

Combined pancreas and kidney transplantation is an ideal therapeutic treatment option for patients suffering from diabetes mellitus with end-stage renal disease [1–3]. Because the pancreas is located deep in the abdominal cavity, open surgery for orthotopic pancreatic transplantation is a challenge. Engraftment of a pancreas allograft into the iliac fossa by open surgery is the dominant technique in clinical practice worldwide. With heterotopic pancreatic transplantation in the iliac fossa, the external drainage of the pancreatic juice is commonly diverted to the bladder or lower intestine, where it is associated with many complications; this also affects the long-term survival of the transplanted pancreas. Pancreas transplantation has undergone many years of development; nevertheless, the effects and rates of pancreas transplantations are not as ideal as those of kidney and liver transplantation [4]. In China, pancreatic transplantation has been restricted to a few centers, with decreasing numbers of transplantations performed. Internationally, one of the main hurdles to expansion of pancreas transplantation are problems related to the surgery itself [4–7]. Efforts to decrease the postoperative complications of pancreas transplantation have been made by some surgical teams, endeavoring to elevate the position of anastomoses of the pancreatic vessels (to the common iliac artery or vena cava or portal vein) and intestinal canal (to the proximal jejunum or the duodenum) with good outcomes [7,8]. Open surgery for kidney transplantation is a common technique and is used by almost all surgical teams with a high rate of success; however, there remain some limitations, and there remains room for kidney transplantation to develop. On the basis of a preliminary study of laparoscopic orthotopic kidney transplantation [9,10], we initiated study of laparoscopic pancreatic high-position (para-orthotopic) combined laparoscopic orthotopic kidney transplantation. The pancreatic artery and vein are anastomosed to the right renal artery and vein, respectively, and the pancreatic fluid is diverted to the duodenum or jejunum. The renal artery and vein are anastomosed to the left renal artery and vein, respectively. The kidney pelvis (or ureter) is anastomosed to left native kidney pelvis (or ureter). The transplanted pancreas and kidney are close to their physiological positions. Herein, we report the results of the initial study of laparoscopic combined para-orthotopic pancreas and orthotopic kidney transplantation with a pig model.

Material and Methods

Twelve white female pigs, 4–5 months old, weight 40–45 kg, were used in the study. The animal experiments in this study were approved by the animal ethics committee of Beijing Chaoyang Hospital. Transfer of the pigs into the laboratory occurred 24 hours prior to surgery and fasting was enforced

12 hours before the operation. Animals were premedicated with intramuscular ketamine (10 mg/kg) and atropine (10 µg/kg). General anesthesia was induced with intravenous fentanyl (10 µg/kg) and anesthesia was maintained with isoflurane (1–5%).

Donor operation

After anesthesia was successfully induced, a large cross-anterior abdominal incision was made. The proximal and distal duodenum were ligated and transected. The hepatic artery and common bile duct were ligated and divided. The bilateral renal arteries and veins were isolated. The spleen was mobilized, and the spleen artery and vein were ligated near the spleen. The upper and lower margins of the pancreatic tail were freed of their mesenteric attachments. The body of the pancreas was isolated. Heparin was intravenously injected to obtain systemic heparinization with a dosage of 200 IU/kg. An abdominal aorta cannula was placed at sites inferior to the superior mesenteric artery. The abdominal aorta was blocked at the site up to the celiac artery. The portal vein near the pancreas was cut open. Then, *in situ* perfusion was made through the cannula. The perfusion was stopped when the pancreas and kidneys became cool and pale and effluent from the opening of the portal vein was clear. The aorta and the inferior vena cava were divided and transected at the sites up to the celiac artery and low to the superior mesenteric artery. Finally, the pancreatic graft was eviscerated en bloc, along with a length of 7–10 cm of duodenum and spleen and kidneys. Then, the bilateral kidneys were separated, and one of them was selected for the donor kidney. The left or right common iliac artery and internal and external iliac arteries were removed for later angioplasty use.

Artery angioplasty and vein “beltization” technique

In the bench operation, the organs were separated carefully. Donor pancreas and kidney angioplasty were conducted. Three styles of pancreatic artery angioplasty were used: the superior mesenteric artery anastomosed to the celiac artery stem, a Y-shaped iliac arterial graft (the common iliac artery and internal and external iliac arteries) anastomosed to the celiac artery and superior mesenteric artery, or the aorta was tailored and sutured properly with the 2 openings of the celiac and superior mesenteric arteries. Venous effluent is provided by the portal vein or the splenic vein. The splenic vein and renal vein were approached using the “beltization” technique, in which a 5-0 Prolene thread was used to suture the vein wall circumferentially along its margin with a 2-mm interval between each stitch. After the last suture, a knot was made expanding the vessel wall, making the opening of the vein open, clear, and durable (Figures 1, 2).

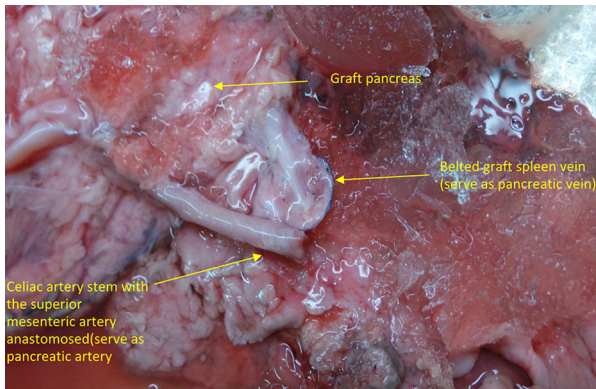


Figure 1. Beltization technique using 5-0 Prolene thread to suture the vein wall circumferentially along its margin with a 2-mm interval between each stitch. The angioplasty and portal vein beltization finished for the pancreas.

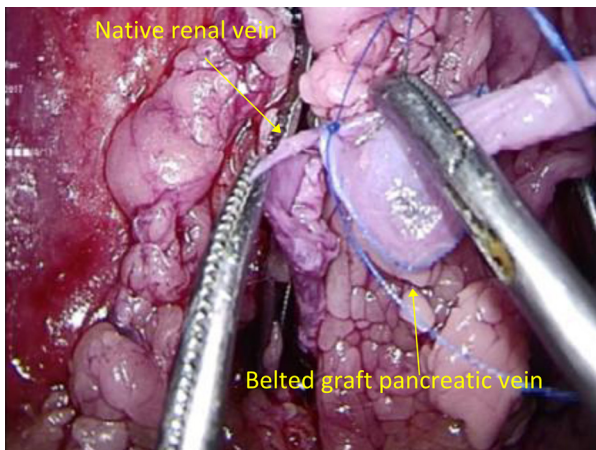


Figure 2. Beltization of the vein wall circumferentially along its margin with Prolene thread, expanding the vessel wall and making the opening of the vein open and clear and durable for anastomosis.

Cooling device

A silicon tube formed the cooling device: a silicon tube cage (Patented in RP China, Patent No. z12014 2 0820782.9) was used in the study. As we reported in our previous study [9], based on the general anatomic size of the pig kidney or pancreas, to find a model, such as a bottle, the silicon tube surrounded the model and extended spirally and then was fixed by several parallel banding threads to form a cage-like device. The kidney or pancreas could be positioned within the cage. Circulating, near-freezing ice water was continuously infused into one end of the tube and effused from the other end in order for the apparatus to completely envelope the kidney and induce hypothermia (Figure 3).

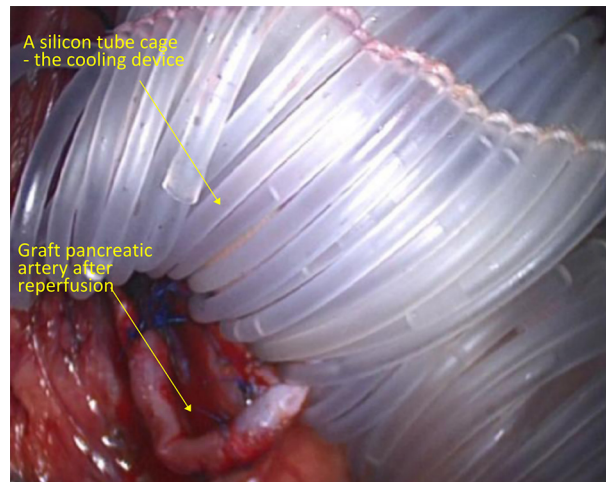


Figure 3. The silicon tube extended spirally and then was fixed by several parallel banding threads to form a cage-like device. Circulating, near-freezing ice water was continuously infused into one end of the tube and effused from the other end in order for the apparatus to completely envelope the pancreas or kidney and induce hypothermia during laparoscopic anastomosis.

Recipient operation

After anesthesia was induced, with supine position, a 15-cm abdominal midline incision was made. The recipient's bilateral kidneys were removed via extraperitoneal approach by open procedure, having the artery and vein clamped with bulldogs or titanium clips, and having vessels prepared for later anastomosis.

Repositioning the animal to the left lateral decubitus position, the graft pancreas with the cooling device was introduced through the incision. With similar techniques for laparoscopic orthotopic kidney transplantation as those previously reported [9,10], the pancreatic vein was end-to-end anastomosed to the native right renal vein, and the pancreatic artery was anastomosed end-to-end to the native renal artery with nonabsorbable 5-0 sutures. Then, repositioning the animal accordingly to the right lateral position, the allograft renal artery and vein were anastomosed to the left renal artery and vein, respectively, with a kidney pelvis-to-pelvis (or pelvis-to-ureter, or ureter-to-ureter) anastomosis laparoscopically through the retroperitoneal route. Repositioning the animal supine again, through the midline incision, the abdominal cavity was reopened, and the right posterior peritoneum near the transplanted pancreas was cut open to form a window to allow in the duodenum graft. Then, the donor duodenum-to-recipient duodenum or proximal jejunum end-to-side anastomosis was performed. Finally, the abdominal wound was closed, and the laparoscopic-combined para-orthotopic pancreas and orthotopic kidney operations were finished. During vessel anastomosis,

Table 1. The observation data of the laparoscopic combined pancreas and kidney transplant operation for the recipient pigs.

Cases number	Donor kidney	Pancreas angioplasty		Cold ischemic time (min)			Anastomotic time (min)					Transplant-operation time (min)	Blood lose	Blood supply		Anastomoses					
		Artery	Vein	P	K	PV	PA	KV	KA	PP	DD (DJ)			P	K	PV	PA	KV	KA		
1	L	Y-shaped graft	Portal V	240	405	75	45	56	38	47		435	100	Purple	Pink	S					
2	L	SMA to CA	Portal V	215	375	95	33	55	50			350	150	Pink	Purple					S	
3	R	SMA to CA	Splenic V	245	305	54	45	70	35	62	90	460	80	Pail	Pink	S	S				
4	L	Aorta with Two openings	Splenic V	220	390	55	5	48	45	75	108	475	130	Pink	Pink						
5	L	Y-shaped graft	Portal V	235	398	65	40	45	35	45	85	420	50	Pink	Pink						
6	L	Aorta with two openings	Splenic V	196	355	68	35	65	46	50	75	435	80	Pink	Pink						
Mean±				225±	371±	69±	37±	56±	42±	56±	90±	429±	98±								
SD				18	35	15	18	09	06	13	13	43	35								

L – left; R – right; SMA – superior mesenteric artery; CA – celiac artery; Portal V – portal vein; Splenic V – splenic vein; P – pancreas; K – kidney; PV – pancreas vein; PA – pancreas artery; KV – kidney vein; KA – kidney artery; PP – pelvis to pelvis anastomosis; DD – duodenum to duodenum anastomosis; DJ – duodenum to jejunum anastomosis; S – stricture.

hypothermia was induced by the device circulating ice water. After anastomosis was finished, for each organ, the disposable devices were cut and removed from the animal's body. The "quiet needle holder" technique meant that we did not button up any clip time of the needle holder during vessel anastomosis, and 2.8-mm laparoscopic instruments were used for vessel anastomoses. At the end of the operations, the animals were sacrificed by sodium pentobarbital overdose, and then, autopsies were performed.

Results

Six cases of laparoscopic-combined pancreas and kidney transplantation were performed, and 4 of the 6 underwent the entire procedure. The duodenum-to-duodenum anastomosis was unfinished in 1 case, and both the duodenum-to-duodenum anastomosis and kidney pelvis-to-pelvis anastomosis were left unperformed in another case because of work-time limitations. The observation data of the laparoscopic-combined pancreas and kidney transplant operation for the recipient pigs are shown in Table 1. The mean combined pancreas and kidney transplant operative time was 429±43 minutes. Cold ischemia time for the pancreas was 225±18 minutes and it was 371±35 minutes for kidneys. The mean venous and arterial anastomotic times were 69±15 minutes and 37±18 minutes, respectively,

for pancreas transplantation and 56±09 minutes and 42±06 minutes, respectively, for kidney transplantation. The time for kidney pelvis-to-pelvis anastomosis was 56±13 minutes and for duodenum-to-duodenum anastomosis it was 90±13 minutes. The mean blood loss for recipient pigs was 98±35 mL. An immediately viable blood supply was seen in the 4 pancreatic grafts and the 5 kidney grafts during the operation by the appearance of a bright red color after revascularization. Five pancreatic grafts had autopsy-proven reliable artery anastomoses, as did 4 out of 6 vein anastomoses. All 6 kidney grafts had autopsy-proven reliable artery anastomoses, and 1 vein anastomotic stricture was proven by specimen inspection (Figures 4–8). From the third case on, microscopy pathologic examinations were performed in grafts, confirming macroscopic inspections. Histopathologic examination demonstrated near normal renal architecture in 4 of the allografts (Figure 9). Pancreases with reliable artery and vein anastomoses had clear lobular structures, integrated interlobular ducts and acini under light microscope. The structures of islet cells remained intact, showing no apparent signs of immediate ischemia-reperfusion injury, with near complete restoration of the vasculature and recovery of organs after transplantation. Pancreases with artery and vein thrombi had pancreatic edema and great loss of acinar tissue with swelling of acinar cells, blurred lobular structure and autolysis of membranous structures (Figure 10).

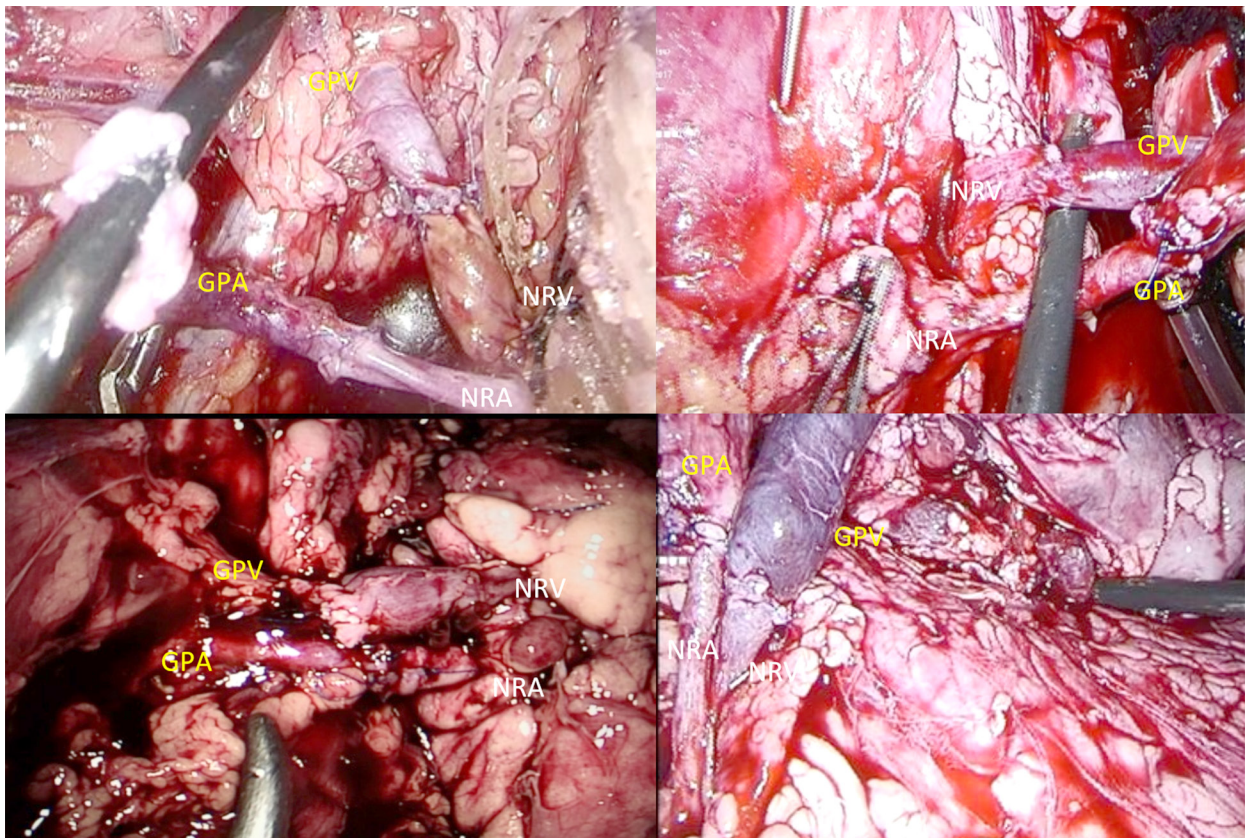


Figure 4. Pancreatic grafts had reliable artery and vein anastomoses that are shown in the screenshots. GPV – graft pancreatic vein; GPA – graft pancreatic artery; NRV – native renal vein; NRA – native renal artery.

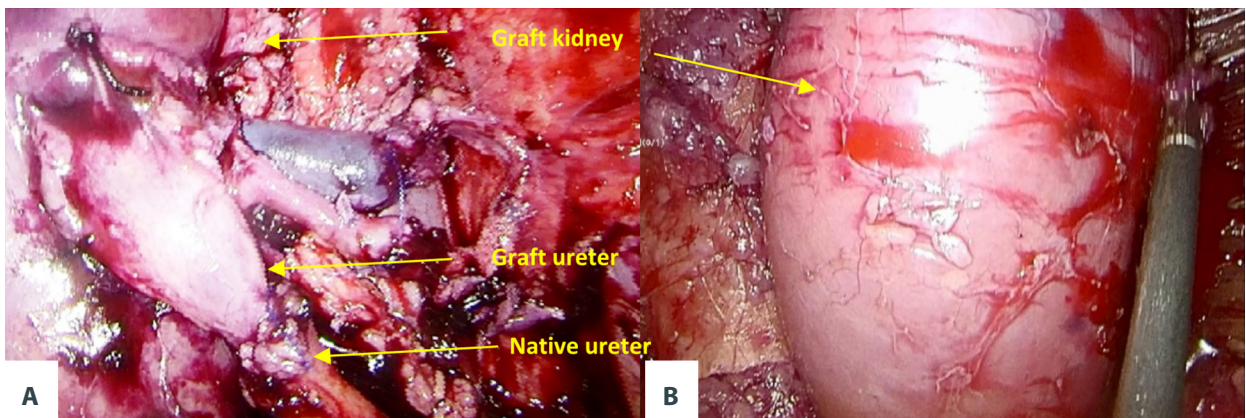


Figure 5. (A, B) A viable blood supply was seen in the kidney grafts during the operation by the appearance of a bright red color after revascularization. (A) The kidney artery and vein are anastomosed to the left renal artery and vein, the ureter is anastomosed to left native ureter.

Discussion

Pancreas transplant recipients continue to suffer high surgical morbidity, and there are problems with conventional strategies for pancreas transplant operations [6,7,11,12]. The primary complication related to pancreatic graft loss is technical failure. Recent reports of pancreas transplantation outcomes

show a 5–10% graft failure rate due to thrombosis [7]. Technical failure is reported mainly due to vascular thrombosis (50%), pancreatitis (20%), infection (18%), fistulas (6.5%), and hemorrhage (2.4%) [13].

For pancreas transplantation, we have to manage both endocrine and exocrine drainage. Initially, the most common

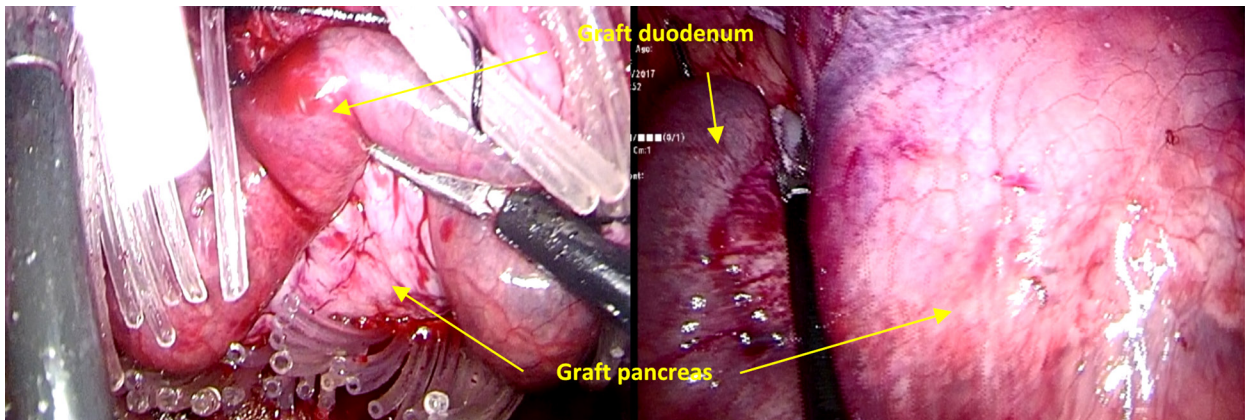


Figure 6. An immediate viable blood supply was seen in the pancreatic grafts with the duodenum during the operation by the appearance of a bright red color after revascularization.



Figure 7. Kidney grafts had autopsy-proven reliable artery, vein, and ureter anastomoses.

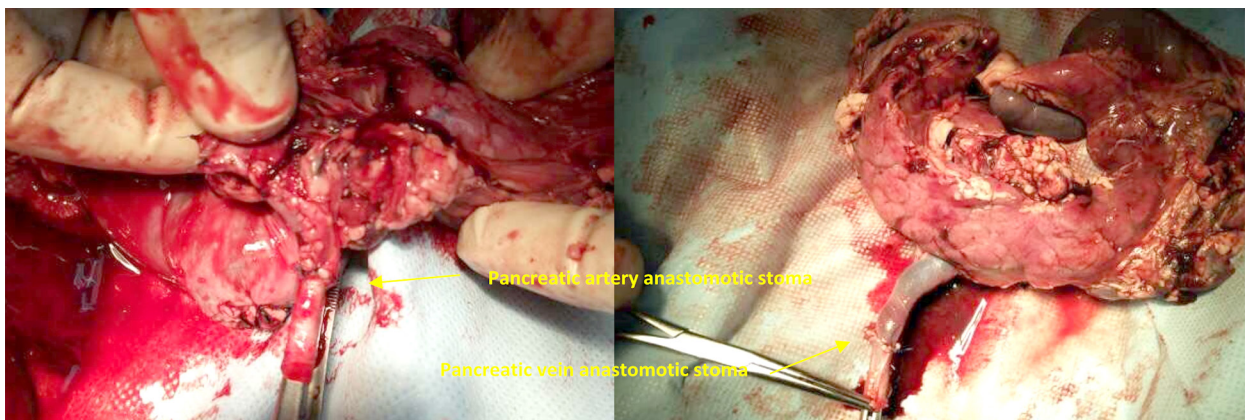


Figure 8. Pancreatic grafts had autopsy-proven reliable artery and vein anastomoses.

technique for the exocrine pancreas secretions was bladder drainage. However, because of the complications of a bladder-drained pancreas transplantation, including uterine reflux pancreatitis, significant metabolic acidosis, urinary tract infections, cystitis, and hematuria, the preferred exocrine drainage in pancreas transplantation has changed from bladder drainage to enteric drainage, where the donor duodenum is sewn to

the proximal jejunum, and the pancreatic artery and vein are anastomosed to the right iliac artery and vein, respectively [8]. We could imagine that when the pancreatic artery and vein are anastomosed to the right iliac artery and vein and the donor duodenum is sewn to the proximal jejunum, high tension may be imposed not only on the vessel anastomosis but also the enteric anastomosis. This is a possible explanation for vascular

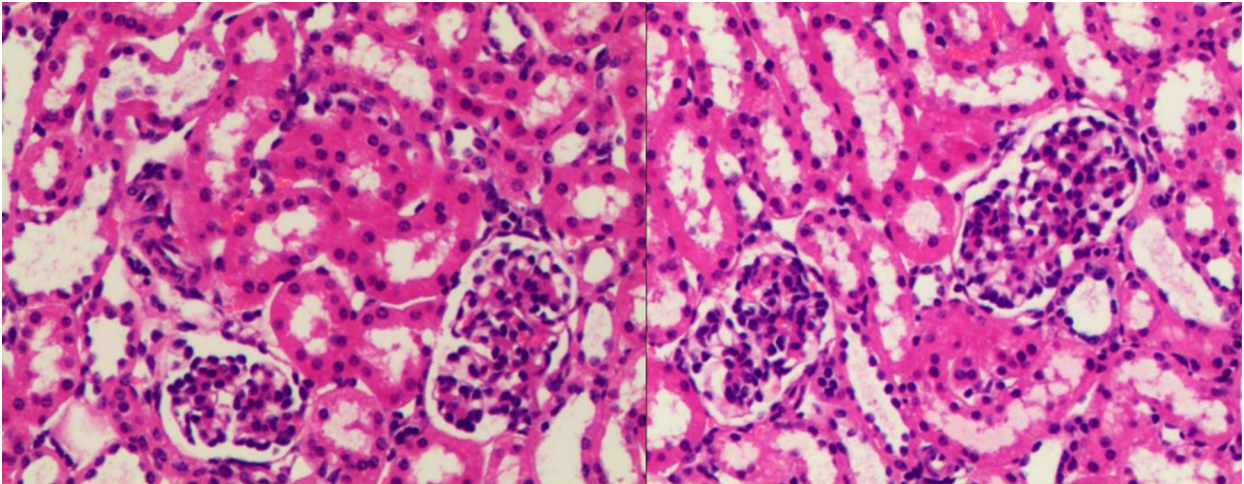


Figure 9. Histopathologic examination showed near normal renal architecture in the kidney allografts.

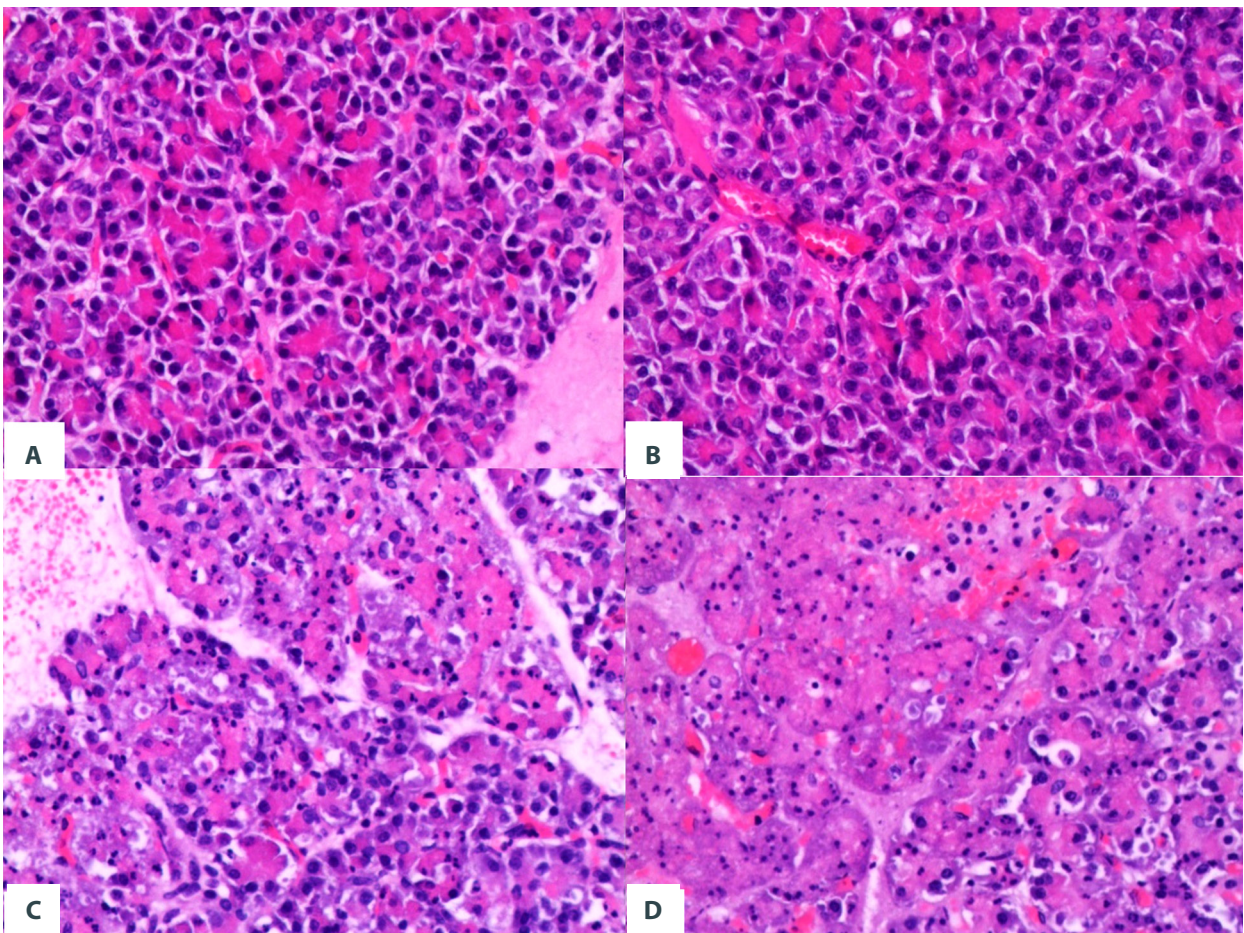


Figure 10. (A, B) Pancreases with reliable artery and vein anastomoses had clear lobular structures, integrated interlobular ducts and acini under light microscope. (C, D) Pancreases with artery and vein thrombi had pancreatic edema and great loss of acinar tissue with swelling of acinar cells, blurred lobular structure and autolysis of membranous structures.

thrombosis and enteric fistulas. Medfield et al. reported their experience with pancreas transplantation, in which the donor portal vein was anastomosed to the major branch of the recipient's superior mesenteric vein, the donor iliac artery was planted in the recipient iliac artery, and the donor duodenum was anastomosed to the recipient's small intestine [8]. Moreover, newer techniques for pancreas transplantation have been described in which the portal venous drainage and direct duodeno-duodenostomy were employed [11,14–16]. However, with the pancreatic artery anastomosed to the right external iliac artery, high tension on the vessels and enteric anastomosis may remain. Ryu et al. reported modified surgical techniques for pancreas transplantation in 11 patients, in which the donor duodenum was anastomosed to the recipient duodenum, the donor portal vein was anastomosed with the inferior vena cava with a diamond-shaped patch, and the Y-graft artery was anastomosed to the right common iliac artery of the recipient. They found that 1 recipient underwent postoperative bleeding at the duodenal anastomosis site, and 1 patient developed partial graft thrombosis [7].

In the present study, the transplanted pancreas and kidney are close to their physiological condition and anatomical position. Compared to open surgery, laparoscopic pancreas transplantation may be more tension-free for vessels anastomosis, and may permit “no touch” maneuvering of the organ. The silicon tube cage not only induced hypothermia but also protected the organs and provided operational assistance. Localizing a cooling scope with small dimensions could consequently lead to significant improvement in pancreas and kidney transplantation. The “quiet needle holder” technique and the 2.8-mm laparoscopic instruments, as well as beltization of the grafts vein facilitating anastomoses for vessel anastomoses were also important factors for the success of laparoscopic-combined pancreas and kidney transplantation. Laparoscopic orthotopic kidney transplantation was reported to be feasible in animal experiments [9,10,17]. Thus far, there have been no experiences of laparoscopic pancreas transplantation reported in the literature.

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Conclusions

The disadvantages were that the number of cases was small, and there was lack of pancreatic enzyme measurements, glucose level measurements, and kidney function examinations. Finally, we had no time for postoperative observations.

Our study has shown that laparoscopic-combined para-orthotopic pancreas and orthotopic kidney transplantation in pigs is surgically possible.

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