Original Article

Reproducible porcine model for kidney allotransplantation of low weight miniature pig

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Background: Multiple porcine models have been established to study the mechanisms regarding kidney transplantation. With the development of xenotransplantation, the demand for a low weight miniature pig model has been increasing. A reliable and reproducible surgical technique to establish these models, and to address possible obstacles, has not been sufficiently defined in detail. The goal of the present study was to develop and optimize a low weight miniature pig porcine kidney transplantation model, including a comprehensive surgical description.

Methods: Eight male Bama miniature pigs (12–15 kg) were randomly chosen as kidney donors and, to facilitate investigation of the transplanted kidney, had undergone contralateral nephrectomy. The procured kidneys were perfused with iced saline then immediately cold stored in the University of Wisconsin preservation solution. The recipients were randomly allocated to left-to-right or right-to-right groups. Serum creatinine and urine volume were recorded post-transplantation, and the pigs underwent euthanasia at seven days post-transplantation.

Results: All eight pigs showed functioning grafts, immediately producing urine post-transplantation. The serum creatinine level increased the following transplantation gradually and reached a peak on the day of euthanasia. One renal artery thrombosis and one ureterovesical entrance stenosis were observed in the right-to-right group. No complications were observed in the left-to-right group.

Conclusions: We developed and optimized a reproducible porcine kidney transplantation model in the low weight miniature pig. Moreover, we addressed and emphasized critical points of the left-to-right transplantation surgery and detailed the anatomic techniques to avoid stenosis of blood vessels and prevent ureterovesical stricture.

Keywords: Porcine kidney allotransplantation model; vascular anastomosis; ureterovesical anastomosis

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Introduction

Kidney transplantation is well-accepted as the optimal choice to treat patients with end-stage renal failure, but because of a critical shortage of deceased human organs, a large number of patients die worldwide while they remain on transplant waiting lists (1).

In the United States, as of September 2019, over 80% of individuals on these lists were waiting for a kidney transplant (https://www. organdonor.gov). Xenotransplantation has been proposed as a potential solution to the organ shortage problem (2).

At present, with advances in genetic engineering of pigs over the past 30 years, the pig has been considered the most appropriate candidate for xenogeneic organ transplantation (3,4).

Numerous challenges had to be overcome for the pig to achieve preference as the best source for kidney transplantation. Initially, it was recognized that the kidney size, short development period, and physiological similarity to humans were all beneficial. Additionally, the general safety of its xenozoonosis, the deletion of expression of the three pig xenoantigens, and strong expression of one or more human complement- and coagulation-regulatory proteins could facilitate success in clinical organ transplantation (5).

There are two types of pigs used as sources of organs for transplantation into humans: domestic pigs and miniature pigs. Advantages of miniature pigs include excellent similarity to human anatomy, fewer blood types, and control or prevention of transmission of porcine endogenous retrovirus (PERVs) (5). Generally, most breeds of miniature pigs range from 23 to 91 kg. Moreover, considerable experience has been attained using miniature pigs as donors for xenotransplantation research (6).

Specifically relating to PERVs, a significant obstacle was solved using the CRISPR-Cas9 technique. Yang *et al.* reported the generation of pigs that carry PERVs inactivation, three-antigen knockout, and nine useful human transgenes, which might be the most suitable preclinical xenotransplantation model ever (7-10). Furthermore, the pig was selected from a species named the Bama miniature pig. This model must undergo animal experiments before being applied to xenotransplantation.

The xenotransplantation model was initially instituted using non-human primates, such as rhesus monkeys. The body cavity of the monkey is relatively small (less than 10 kg), lacking even enough abdominal space to receive a donor kidney from pigs, especially from high weight pigs. Therefore, there is great demand for low weight miniature pigs, at least in the research phase of xenotransplantation. However, most reports of porcine kidney transplantation have focused on high weight (more than 30 kg) miniature pigs (11,12).

Some reports have provided surgical techniques in xenotransplantation of miniature pigs (13,14), but no reports about the establishment of porcine kidney allotransplantation of low weight (less than 15 kg) miniature pigs have given detailed descriptions.

In the models reported previously, the donor pigs typically weighed 30–35 kg. With smaller pigs, the traditional end-to-end technique of vessel anastomosis might not be suitable because of the small vessel diameter and the end-to-end or side-to-side anastomosis method of ureterovesical anastomosis might be challenging and result in stricture.

In the present report, we performed a left-to-right method of kidney transplantation in order to solve the problem of short vessels by employing end-to-side anastomosis of both artery and vein. Moreover, to avoid the stenosis of anastomosis, we adopted a new method for ureterovesical anastomosis to prevent stricture, which was used previously in the kidney transplantation model of mice.

Overall, we described a reliable, reproducible surgical method for porcine kidney transplantation in low weight miniature pigs. The protocol detailed subsequently combined both feasibility and reliability with modifications specifically designed for a low weight miniature porcine kidney transplantation model, especially in pigs weighing less than 15 kg. The protocol can be used as a technique for further study of kidney xenotransplantation. We present the following article in accordance with the ARRIVE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1016/rc).

Methods

The detailed specifications of the materials for this section are located in supplemental materials (Table S1).

Animals

The animals used in the study were male Bama miniature pigs (12–15 kg) (*Table 1*). Eight male Bama miniature pigs were randomly chosen as kidney donors. The eight recipients were randomly allocated to left-to-right or right-

Table 1 Basic information of the male Bama miniature pigs

Group	Donor ID	Donor weight (kg)	Recipient ID	Recipient weight (kg)	Cold ischemia time (min)	Complications	Survival time (days)
Left-to-right	D1	12.5	R1	13.4	40	–	7
	D2	13.3	R2	14.5	48	–	7
	D3	13.6	R3	14.4	42	–	7
	D4	14.9	R4	15.6	42	–	7
Right-to-right	D5	12.6	R5	12.8	41	Artery occlusion	2
	D6	13.4	R6	13.9	43	–	7
	D7	14.3	R7	14.1	42	Ureterovesical anastomosis stenosis	7
	D8	13.5	R8	13.7	40	–	7

D, donor; R, recipient.

to-right groups.

The study was performed under a project license [No. 0102-1/6-12/7-ZX(X)-1] granted by the Animal Ethics Committee of Fuwai Hospital. All animal experiments were carried out in accordance with the National Institute of Health's Guidelines for the Care and Use of Laboratory Animals.

Kidney graft retrieval

Preoperative procedure

(I) House male Bama miniature pigs were raised in standard hardware for multiple week adjustment periods. To reduce the risk of infection, animals were given second-generation cephalosporin (e.g., cefuroxime). Pigs were fasted for 6 hours preoperatively to prevent aspiration.

(II) Premedication: atropine (0.04 mg/kg) intramuscularly, ketamine (20 mg/kg), and midazolam (0.3 mg/kg). Transfer pigs from the housing facilities to the operating room.

(III) Anesthesia induction: pig in the supine position. Preoxygenation with 1.4 L of oxygen with 5% isoflurane. Locally anesthetize vocal cords under direct laryngoscopy with 2% lidocaine, then intubate with 6.5 mm endotracheal tube (*Figure 1A*).

(IV) Maintenance of anesthesia: reduce isoflurane to 2.5%. Set tidal volume to 10–15 mL/kg body weight and ventilator to 14–16 breaths/minute. Pulse oximetry monitors heart rate and blood oxygen saturation. Confirm safe depth of anesthesia by the decreased pulse of less than 150 beats/minute and systolic blood pressure (BP) below 100 mmHg.

(V) Monitoring lines: cervical skin shave and povidone-iodine prepared and draped in a sterile manner. Seldinger technique for placement of internal jugular vein vascular catheter. Secure with sutures (*Figure 1B*).

(VI) Prophylactic antibiotics, antacid, fluid and pain management: metronidazole, 500 mg, 1 g of cefuroxime, and 20 mg of pantoprazole. During the operation, infuse 200 mL D5-Ringer's lactate solution, 1 mL of fentanyl intravenously continuously. Veterinary ointment to the eyes.

Surgical procedure

Kidney harvest (using the left kidney as an example)

(I) After standard sterile prep and drape, midline 20 cm abdominal incision. Insert retractor, displace small and large intestines to the right and protect with wet gauze.

(II) Mobilize the left kidney and the ureter from retroperitoneal soft tissue using cautery (*Figure 1C*), with specific care not to cause thermal injury to the ureter.

(III) Identify and dissect the left renal vein and artery using cautery as necessary, carrying the dissection to the inferior vena cava (IVC) and aorta (*Figure 1D*).

(IV) Further, expose the IVC and aorta for an additional 1 cm around the origins of the left renal vein and artery.

(V) Next, with the exposed ureter, follow it down to and expose the ureterovesical junction. Take a patch of

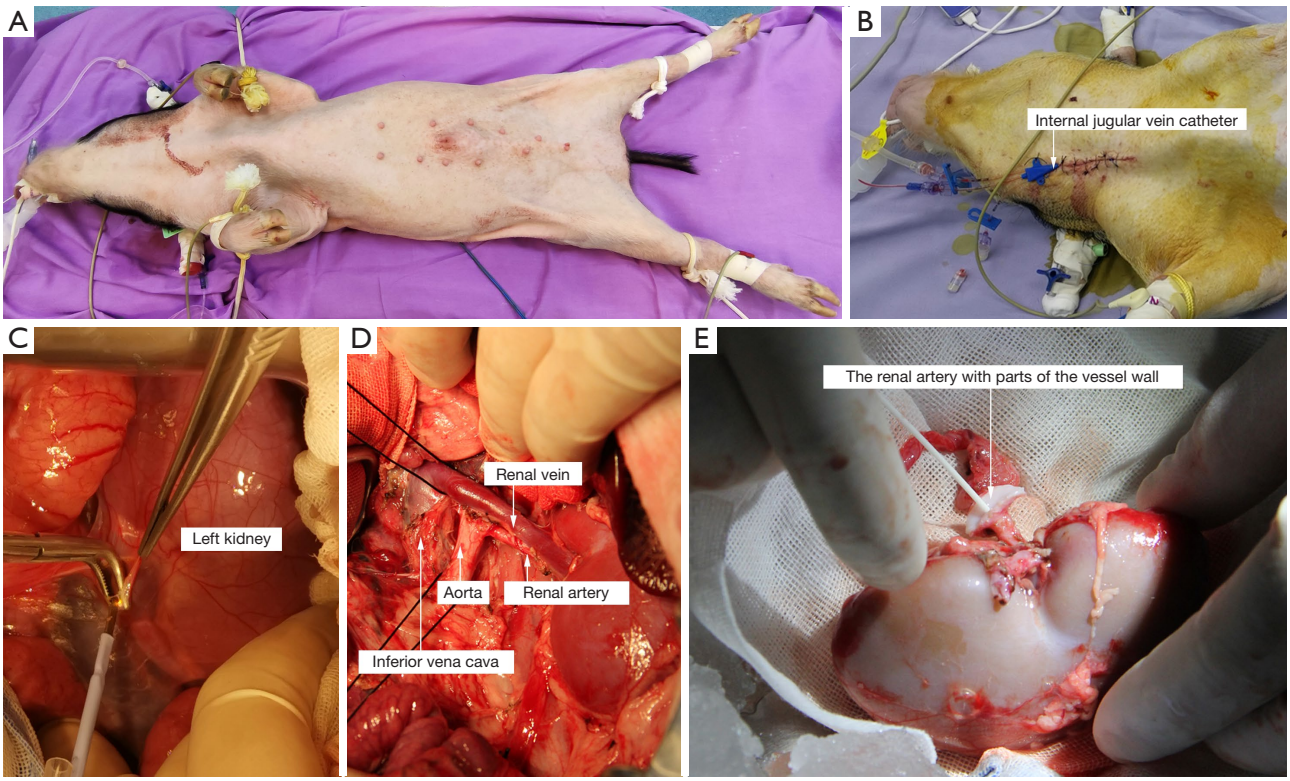

Figure 1 Preoperative procedures and surgical procedures of the kidney harvest. (A) Animal preparation. (B) Vascular catheterization. (C) Mobilization of left kidney. (D) Exposure of left renal vein and artery. (E) Cannulation of the renal artery and perfusion with iced saline.

bladder wall of about 1 cm all the way surrounding the ureter. Prepare a sterile organ bag with a bowl of ice.

(VI) Returning to the kidney, first, clamp the renal artery incorporating a patch of the aortic wall using a Satinsky clamp. Second, clamp the renal vein with a patch of the IVC wall using a Satinsky clamp. Next, for establishing a carrel patch, transect the renal artery closely adherent to the clamped aortic wall, and the renal vein closely adherent to the clamped IVC wall.

(VII) Remove the kidney graft to the back table where the renal artery is cannulated with a plastic sheath needle (18G) and flushed with ice-cold saline until the irrigating fluid turns clear. Store the kidney on ice until transplantation (*Figure 1E*).

(VIII) After the kidney graft retrieval, the heart of the pig was harvested by the other team for heart transplantation research, and the pig was then declared circulatory determination of death.

(IX) The harvest of the right kidney was similar to the previous description.

Kidney graft transplantation

Preoperative procedure

(I) Anesthetization and the internal jugular vein catheter placement are the same as preoperative procedure (II) to (VI) in "Kidney graft retrieval" section.

(II) Monitor arterial pressure with the placement of an intraarterial catheter in the marginal ear artery.

Surgical procedure

(I) After satisfactory sterile prep and drape, perform a 20 cm midline abdominal incision and place the abdominal retractor. Displace the gut to the left side to permit access to the right kidney. Cover the gut with wet gauze.

(II) Mobilize the right kidney and the ureter from surrounding retroperitoneal soft tissue using cautery (*Figure 2A*).

(III) Identify and dissect the right renal vein and artery to their junctions with the IVC and aorta using cautery as necessary.

(IV) Further expose the IVC and the aorta.

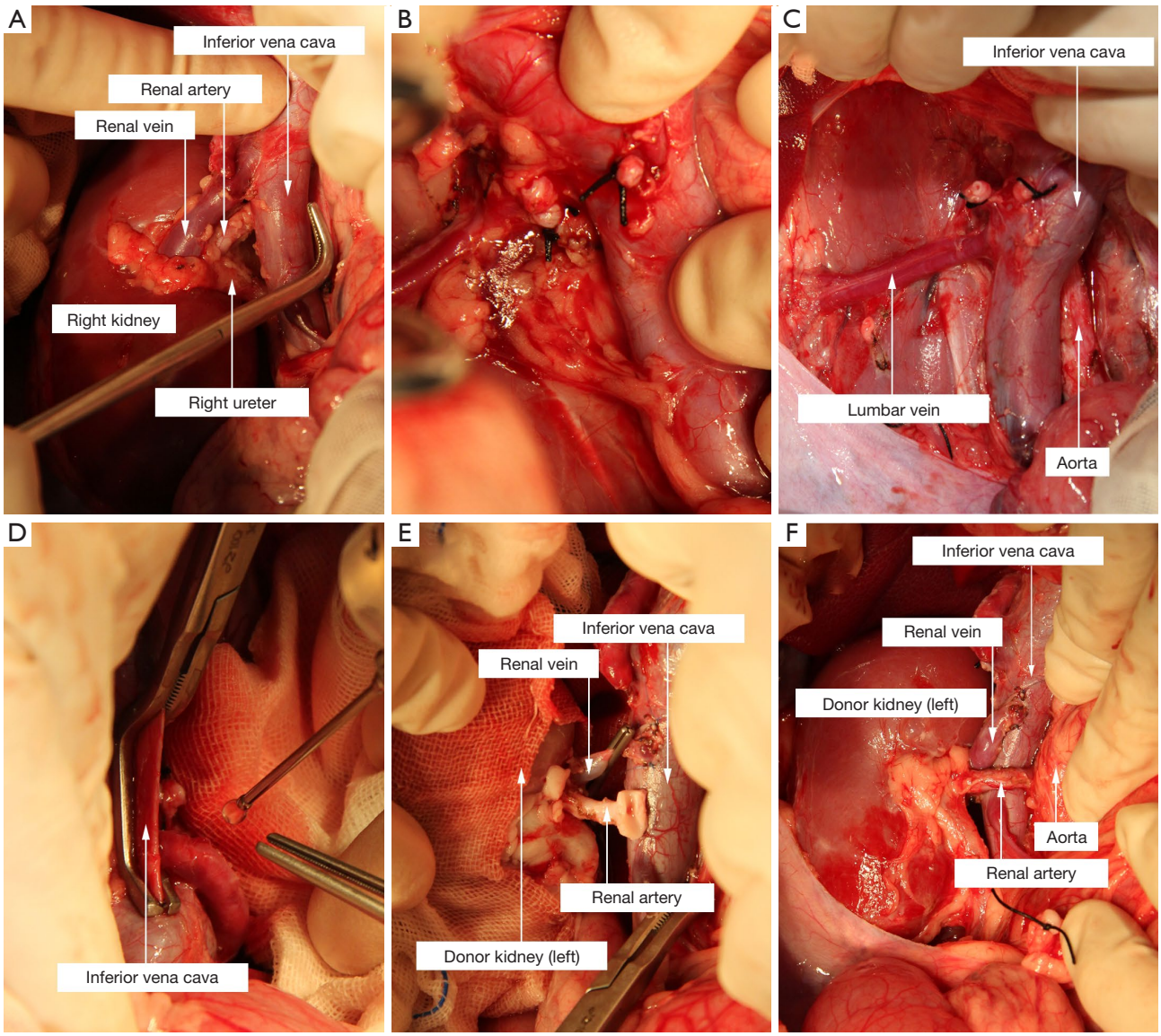

Figure 2 Nephrectomy procedure for recipient's kidney and vascular anastomosis. (A) Exposure, right renal vein and artery. (B) Transection renal artery and vein. (C) Control of lumbar vein. (D) Venous anastomosis. (E) Arterial anastomosis. (F) View of graft renal hilum.

(V) Next, follow the ureter down to the ureterovesical junction, then ligate (silk, 3-0) and transect the ureter distally.

(VI) Sequentially clamp the renal artery and renal vein using vascular clamps. Transect the artery and vein, leaving a stump of the artery to ligate and remove the kidney (*Figure 2B*). Note to take care of the lumbar vein (*Figure 2C*).

(VII) Transport the preserved kidney graft with the ice bag to the right abdominal cavity.

(VIII) Venous anastomosis (*Figure 2D*):

(i) Control the IVC utilizing a vascular clamp and using a 15 blade, make a 0.5-cm incision in the IVC that approximates the size of the renal vein carrel patch diameter. Use potts scissors to extend the incision as necessary.

(ii) Position the renal graft into the surgical field near the IVC. Place 2, 7-0 double-armed sutures at the cranial and caudal corners of the renal vein and the IVC carrel patch.

(iii) Approximate the kidney to the IVC, then tie the upper corner. Beginning with the posterior vein walls, perform a running stitch of IVC and renal vein carrel patch from cranial to caudal corners. After completing the suturing of the posterior walls, utilize the opposite stitch of the cranial tied suture to finish the stitch of the anterior walls. Tie the stitches at the caudal corner. Before the final tie, inject 0.5 mL saline with heparin to inspect for leak and prevent thrombin clot before complete closure of the anastomosis.

(iv) Place an atraumatic bulldog clamp on the renal vein and open the vascular clamp on the IVC. Check the anastomosis for a leak.

(IX) Arterial anastomosis (*Figure 2E,2F*):

(i) Apply the vascular clamp to the aorta completely. Use a 15 blade to make a small slit cut, approximately the length of the renal artery diameter. Secure a clean opening with a 3.5-mm round arterial punch.

(ii) Use a single 7-0 Prolene stitch to perform the arterial anastomosis, proceeding in like manner to the renal vein carrel patch anastomosis. Assure that the arterial endothelium is included in each stitch to prevent dissection. Maintain the systolic pressure of at least 90 mmHg with a constant infusion of norepinephrine. Inject 0.3 mL saline with heparin to inspect the leak and avoid thrombin clot before complete closure of the anastomosis.

(iii) Place an atraumatic bulldog clamp on the renal artery and slowly open the vascular clamp. Check the anastomoses for bleeding points.

(iv) Remove the bag and ice from around the kidney. Open the venous bulldog clamp followed by the arterial bulldog clamp. After reperfusion, urine production should begin promptly.

(X) Ureteral anastomosis:

(i) Make a full-thickness incision of the anterior bladder wall. Using curved forceps as a guide, make an incision about 1 cm from the ureterovesical junction of the recipient as an entry point for the donor ureter and cuff of the bladder wall to be introduced.

(ii) Draw the ureter retroperitoneally down to and into the bladder through the incision near the ureterovesical junction of the recipient.

(iii) Suture the cuff of the residual donor bladder wall to the inner wall of the recipient's bladder using 6-0 Prolene. Suture the serosa of the ureter to the serosa of the bladder using 6-0 Prolene. Intubate a 4.8-F double J stent with one end in the bladder and the other threaded up the ureter to prevent stenosis (*Figure 3A*). Close the entrance incision using 6-0 Prolene (*Figure 3B,3C*). The bladder mucosa was sutured in proximity to the ureterovesical anastomosis with an interrupted 6-0 Prolene suture to perform a tunnel to avoid reflux.

(iv) Place a 12-F Foley catheter into the bladder through the incision in the anterior wall of the bladder (*Figure 3D*) and inflate the balloon. Close the bladder incision using 6-0 Prolene. Bring out the other end of the Foley catheter through a separate incision in the lower abdomen.

(v) Assure the ureter is positioned retroperitoneally and close the peritoneal over the front side of the kidney to avoid displacement (*Figure 3E*).

(vi) After satisfactory hemostasis, remove the wet gauze covering the bowel and place the bowel back to the abdominal cavity. Close the abdominal wall with monofil one stitch and the skin with 3-0 silk stitches (*Figure 3F*).

(vii) Maintain the systolic pressure of at least 90 mmHg with intravenous injection (i.v.) norepinephrine drip.

(viii) Resect the contralateral (left) kidney. Position the bowel to the right and repeat the surgical procedure (II) to (VI) in "Kidney graft transplantation" section. Assure the left renal vessel closures at the aorta and IVC and ligation of the distal ureter. Check for bleeding and close the abdomen.

Postoperative procedure

(I) After abdomen closure, use a heating pad and electric blanket to keep the pig warm. Monitor BP and urine volume.

(II) Discontinue the norepinephrine and the ventilator. After extubation, closely monitor the pig until it can drink on its own. Maintain surveillance until the pig regains consciousness and can keep sternal recumbency. Until fully recovered, do not allow the

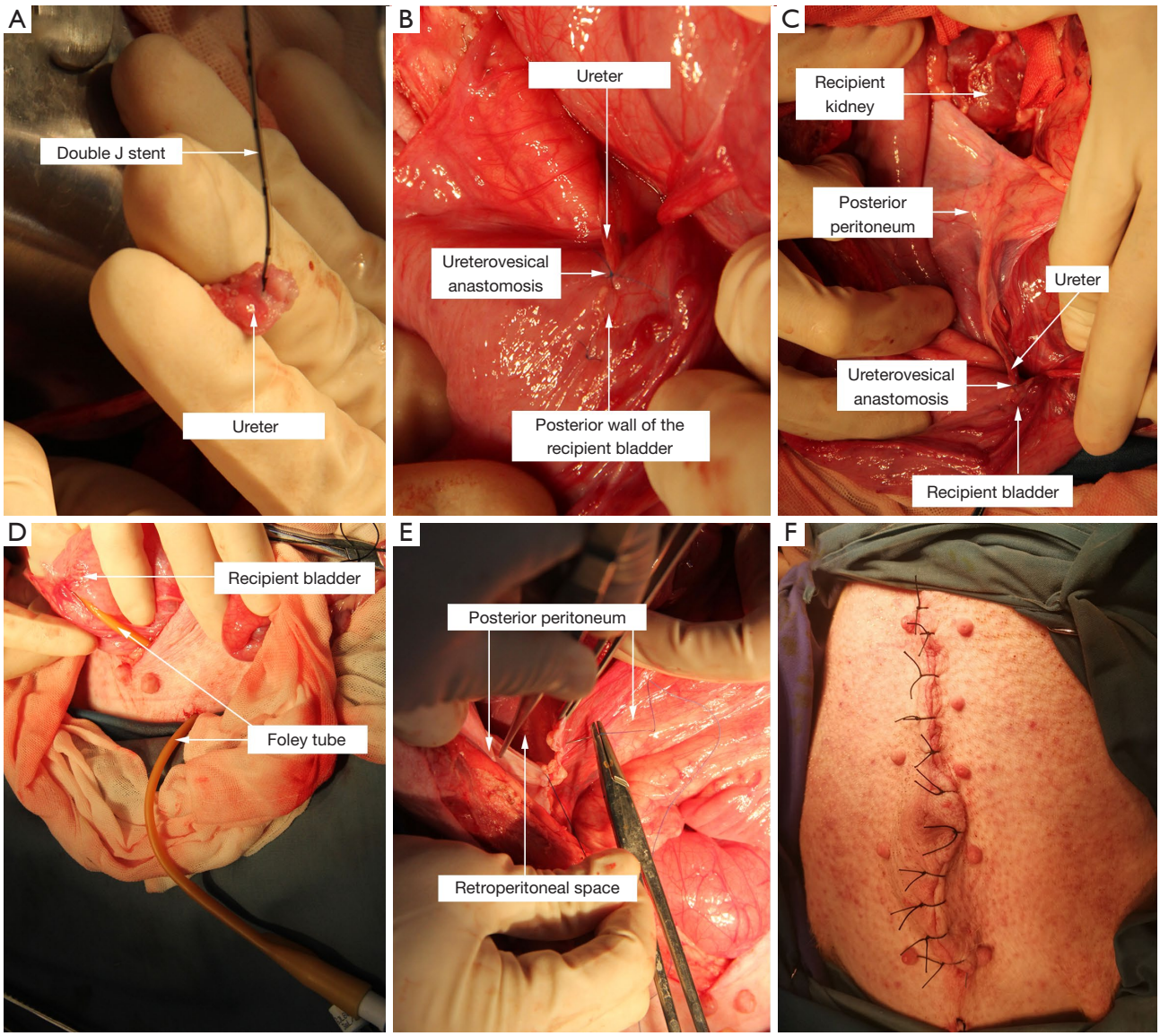

Figure 3 Ureteral anastomosis and subsequent operation. (A) Placement 4.8-F double J stent. (B) Ureteral anastomosis. (C) Retroperitoneal location of ureter. (D) Placement 12-F Foley tube into the bladder through the incision, anterior bladder wall. (E) Peritoneal closure. (F) Incision closure.

surgically treated pigs with other healthy animals.

(III) The pig should be positioned prone and allowed to recuperate in its housing facilities with close monitoring. Collect blood gas samples through the jugular vein catheter every 12 hours. Supply maintenance Ringer's lactate and use 0.3 mg buprenorphine for analgesia.

(IV) Postsurgical follow-up:

(i) For pain control, use 0.3 mg buprenorphine intravenously every 8 hours. Following the single dose of intraoperative antibiotics, if signs of infection appear, use cefuroxime 1 g i.v. twice a day until clinical improvement. Give Ringer's lactate until the pigs drink sufficient water on their own.

(ii) Collect venous blood samples and urine samples every 12 hours to assess the health and kidney function. Renal function and renal perfusion

were assessed daily by ultrasound.

(iii) On postoperative day 7, perform euthanasia. Perform the induction and maintenance of anesthesia as described previously (preoperative procedure (II) to (IV) in "Kidney graft retrieval" section). After collecting the kidney tissue samples, inject 1.5 mg/kg potassium chloride (KCl) solution intravenously to induce cardiac arrest under deep anesthesia.

Results

Comparison of the results from both groups have been documented with follow-up of 7 days until euthanasia, including monitoring kidney function with serum creatinine, blood urea nitrogen (BUN), potassium, kidney perfusion, and overall status with daily ultrasound. The mean times for graft retrieval for the left and right kidneys were 14.5 and 13.6 min, respectively. Because the renal artery and vein were transected only after mobilization and complete dissection of the kidney and vessels, the warm ischemia time was within 1 min. After complete perfusion, the kidney was transplanted as soon as possible with a mean cold ischemia time of 42.3 min. The study was intended to develop an acute rejection model, so we did not administer immunosuppression.

We completed four right-to-right and four left-to-right operations. From a surgical technical perspective, two postsurgical complications occurred. One stenotic ureterovesical anastomosis was identified in the right-to-right group. The hydronephrosis was identified by ultrasound on postoperative day 2 (*Figure 4A*). It was the first surgical procedure of our experiment, and we had not placed a Double J stent. The rescue operation was performed, the pig recovered well (*Figure 4B*) but experienced an additional diuretic phase following the rescue operation. We encountered one case of arteriovenous thrombosis in our study, and the pig died on postoperative day 2. When we used the right-to-right method, the course of the right renal artery was anterior to the IVC, which could have resulted in it being twisted and partially blocked by the IVC when the pig returned to the prone position (*Figure 4C,4D*). The data of the two pigs that suffered complications were excluded.

All remaining pigs maintained excellent clinical condition during the short follow-up. The serum creatinine and BUN values reached a peak on day 7 following surgery in both groups. The potassium level increased gradually but was in the safe zone on day 7. The urine volume decreased gradually and reached approximately 50 mL/h on day 7 (*Figure 5*).

Discussion

This study of low weight miniature porcine kidney transplantation model has excellent value for xenotransplantation. It is crucial to achieve reproducible, technically precise xenotransplantation success as gene-modified pigs are both high-priced, and the entire process consumes considerable time and effort.

Kirkman *et al.* were the first to report the miniature porcine model in kidney transplantation in 1979 (15). As emphasized previously, most porcine models used now have utilized high weight pigs that are less demanding for the vascular anastomoses (11,12,16-18).

The anatomic characteristics of low weight miniature pigs were notably different, particularly when the weight was reduced from 35 to 15 kg. From our observations, the diameter radius of the low weight miniature pig artery ranges from 1.2–1.6 mm, much narrower than that of a high weight pig. For vessels this small, end-to-end anastomosis is unreliable and not appropriate. Similarly, a ureteral radius of 1.0–1.2 mm in low weight miniature pigs almost certainly would yield an increased frequency of stenosis if end-to-end or side-to-side anastomoses were performed.

To ensure success in establishing a low weight miniature porcine kidney transplantation model, we have identified several critical steps in our protocol to minimize complications. First, we found in previous mice/rat kidney transplantation models that the renal arteries and veins were so thin that end-to-end anastomoses would result in a higher probability of anastomotic stenosis and thrombosis. To remedy this situation, we included a patch of either the aorta and IVC vessel wall as a patch graft at the time of kidney graft retrieval. This modification allowed us to maximize the length of vessels and avoid damage to the graft artery. Budgeon *et al.* reported that a carrel patch technique could reduce the risk of thrombosis and leakage by displacing the suture line away from the entrance to the renal artery (19). Carrel *et al.* and Mazzucchi *et al.* also arrived at a similar conclusion (20,21).

Second, to ensure an unobstructed ureter, we harvested the ureter with a patch of the bladder wall to help secure the ureterovesical junction intact. Using this method, the full length of the ureter remained intact. A bladder patch makes it more convenient and facilitates clear recognition for

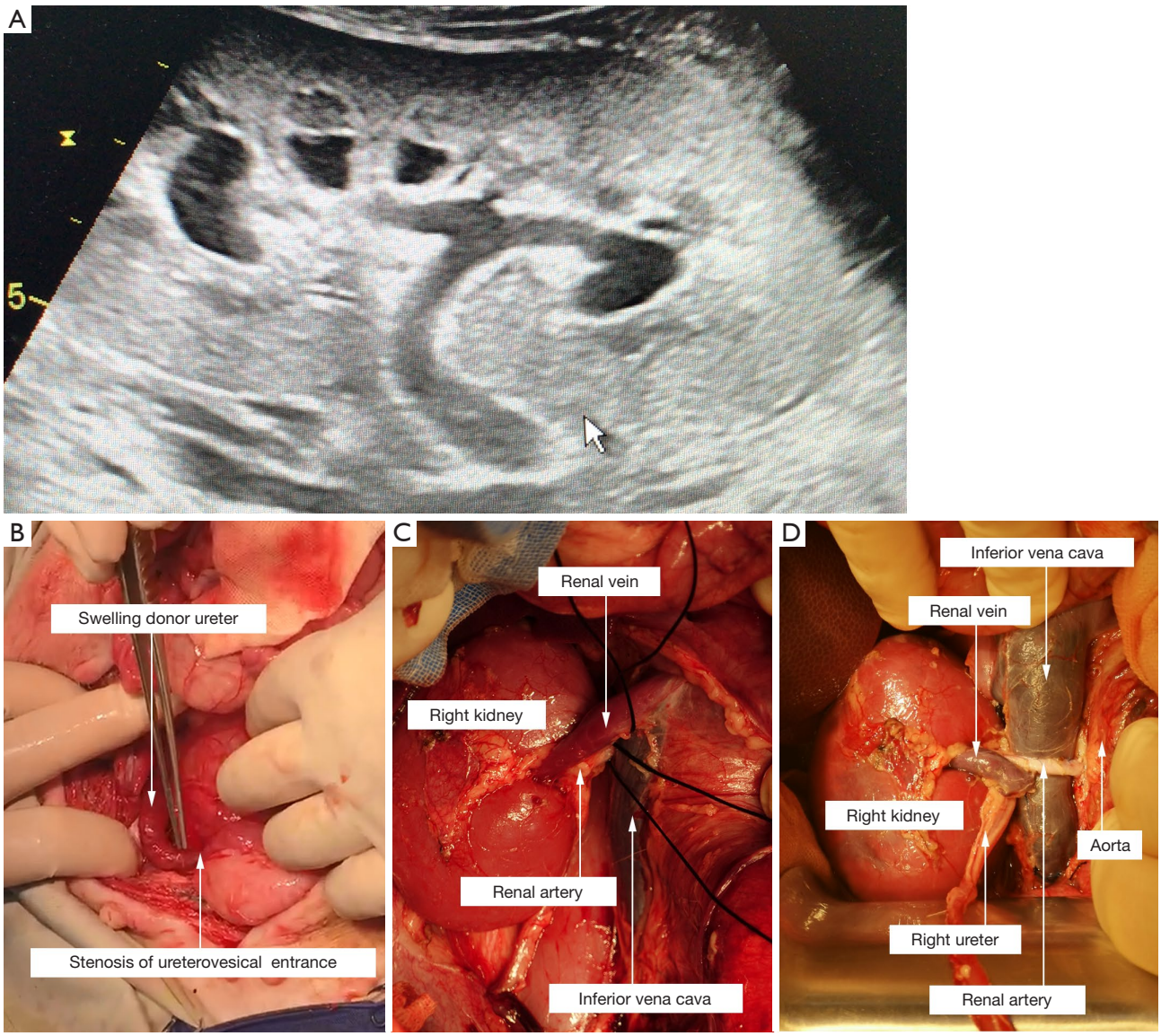

Figure 4 Postoperative complications: 2 cases. (A) Hydronephrosis demonstrated by ultrasound exam. (B) Stenosis, ureterovesical entrance. (C) Harvesting, right kidney. (D) Artery overriding IVC, suspicious partial blockage of IVC. IVC, inferior vena cava.

suturing the end of the ureter, reduces the tension on the anastomosis, and prevents the distal ureter from retracting from the recipient's bladder.

Additionally, because of the small diameter of the ureter, a double J stent was utilized to ensure smooth drainage. As noted previously, the only case in which we had not placed a double J stent developed ureterovesical anastomotic stenosis. This initial plan not to place a double J stent was based on our previous surgical experience with mice and rat kidney transplantation models, and we had not needed long-term follow-up. Subsequent to the single anastomotic stenosis, pediatric ureteral stents (4.8 F) were utilized. The advantages of a bladder patch (22) and ureteral stents (23-25) have been previously reported.

In the case of arteriovenous thrombosis, we found a dramatic deterioration in renal function in this animal postoperatively, with ultrasound implicating the renal artery and vein thrombosis with resultant reduced renal perfusion. The pig died the day after surgery, and the autopsy revealed emboli even in the IVC. We attributed the arterial and

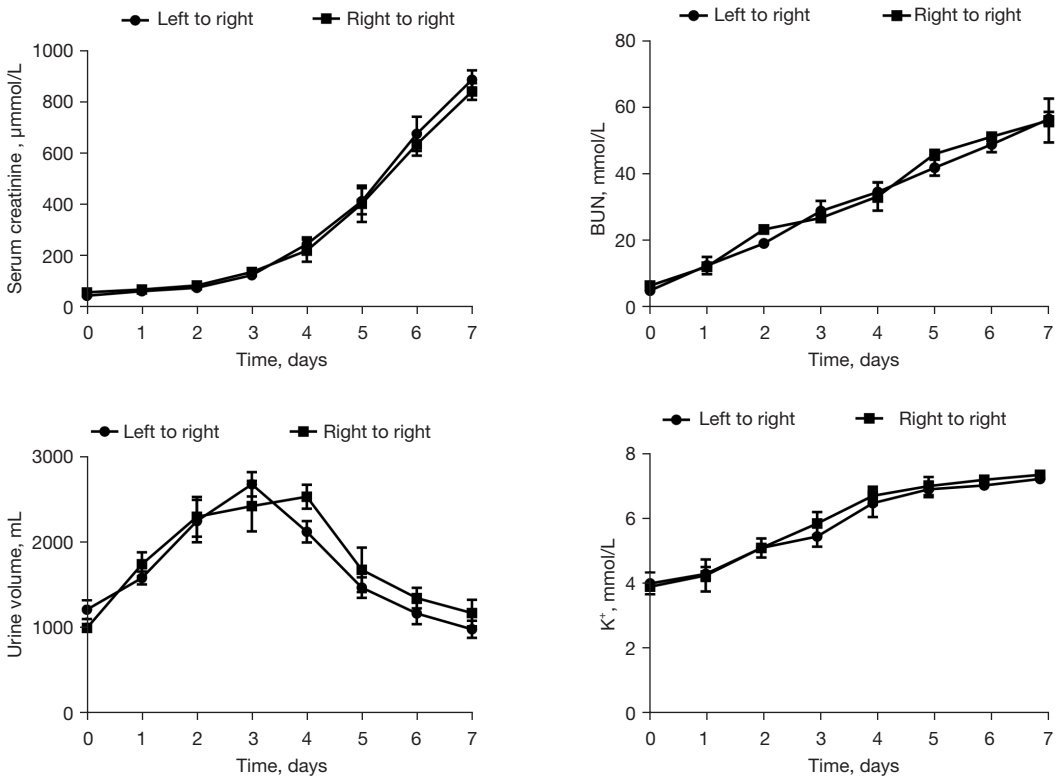

Figure 5 Trends: serum creatinine, BUN, urine volume, and K^+ level. BUN, blood urea nitrogen.

venous thromboses to the anterior-posterior relationship of the vessels. In right-to-right transplantation, the renal artery was sutured anterior to the vena cava, but this caused the renal artery and vein to form a twisted angle. This angle resulted in the renal artery being functionally shorter, putting it under higher tension with reduced perfusion and ultimately an increased likelihood of thrombosis (*Figure 4C*,*4D*). In the left-to-right group, the renal artery was located anterior to the vein after left-right reversal, which retained the vessel length needed for suturing and avoided the risk of compression.

Our principal aim was to explore and validate surgical techniques for the miniature pigs; anastomotic stenosis, vessel thrombosis, and urinary tract obstruction were the critical postoperative monitoring criteria. So, no effort was made to match donors and recipients, and no immunosuppressive agents were administrated. The renal function of pigs deteriorated, and acute rejection occurred within one week. Longer periods of observation were unnecessary for the assessment of surgical techniques, so euthanasia was performed at this time.

Although renal ischemia-reperfusion injury (IRI) also causes a rise in serum creatinine following renal transplantation and would be diagnosed as delayed graft function (DGF), we minimized ischemia time to obviate the probability of DGF. Kidney graft retrieval and the corresponding recipient surgery were initiated simultaneously. To ensure consistent ischemia time for left and right kidneys, each donor provided only a unilateral kidney.

There were limitations to the research. First, the high cost of animals limited the number we could include in this study. Second, the microsurgical technique necessary to gain competence for anastomosis requires considerable practice. In our center, an experienced micro-surgeon necessitated 5–8 cases to master the technique. However, after adequate practice, the surgery could be completed in 2 hours.

In conclusion, we developed and optimized a reproducible porcine kidney transplantation model in a low weight miniature pig that provides a relatively inexpensive model for xenotransplantation.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1016/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1016/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1016/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed under a project license [No. 0102-1/6-12/7-ZX(X)-1] granted by the Animal Ethics Committee of Fuwai Hospital. All animal experiments were carried out in accordance with the National Institute of Health's Guidelines for the Care and Use of Laboratory Animals.

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Supplementary

Table S1 The detailed specifications of the materials in the operation

Name of material/equipment	Company	Catalog number
0.9% saline	Wuhan Prosai Company	EY-C1178
Aortic punches	B. Braun Co., Ltd.	FB202R
Atropine	China Resources Double-crane Pharmaceutical Co., Ltd.	H11020766
Buprenorphine hydrochloride injection	Tianjin Pharmaceutical Research Institute Pharmaceutical Co., Ltd.	H12020275
Cefuroxime	GlaxoSmithKline Manufacturing S.p.A	H20181034
Double J stent	Boston Scientific Corporation	M0061752520
Heparin	Beijing Saisheng Pharmaceutical Co., Ltd.	H11020362
Ketamine	Fujian Gutian Pharmaceutical Co., Ltd.	H35020148
Metronidazole	Beijing Kai Technology Co., Ltd.	H11022489
Midazolam	Jenahexal Pharma GmbH	H20080453
Monofil	Covidien LLC	CL-915
Norepinephrine bitartrate injection	Tianjin Pharmaceutical Research Institute Pharmaceutical Co., Ltd.	H12020275
Pantoprazole	Takeda GmbH Production site Singen	H20160486
Prolene	ETHICON	8708H
Ringer's lactate	Otsuka Pharmaceutical Co., Ltd.	H12020009
Silk thread (3-0)	ETHICON	SA84G
UW solution	The University of Wisconsin	–

Co., Ltd., company limited.

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