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Pig Kidney Transplantation: An Up-To-Date Guideline

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Key Words
Pig · Kidney · Transplantation

Abstract
Background: Swine and human beings have many aspects in common that make swine a well-characterized large animal model for kidney transplantation (KTx). However, pigs have some peculiar anatomical characteristics that standardized techniques must adapt to. The aim of this study was to prepare an up-to-date guideline for porcine KTx. ***Methods:*** To achieve this goal, we performed a Medline search using the terminology 'kidney' or 'renal' and 'transplantation' and 'pig' or 'swine' or 'porcine'. We found over 1,300 published articles since 1963. Only 13 studies focused on the surgical aspect. Furthermore, we reviewed related books and articles about swine anatomical characteristics and surgery. Finally, our experimental experiences of KTx during the last few decades were added to this collection. ***Results:*** Proper hosting, fasting, anesthesia, medical therapy and monitoring can prevent postoperative complications. Explantation with a Carrel patch of the aorta facilitates the implantation and prevents future stenosis. Native nephrectomy makes the follow-up of the implanted organ more precise. KTx in the infrarenal fossa via end-to-side anastomosis to the aorta and inferior vena cava followed by ureteroureterostomy are the recommended options for KTx in pigs compared to other possible methods. ***Conclusion:*** Pigs, with respect to their characterizations, constitute one of the best large animal models for KTx. Preoperative preparations are as important as the intra- and postoperative management. Using the most adaptable methods of surgery with respect to the specific anatomical characteristics of pigs can prevent undermining the studies and avoid preventable complications and pitfalls.

Introduction

Experimental studies have been used for a long time in different fields of medicine. However, in surgery, finding the best animal model, with the most similar physiology and anatomy to human beings, has always been a challenging issue [1, 2]. Pigs, with respect to their characteristics, constitute one of the best animal model for surgical studies, especially for kidney transplantation (KTx) [3–6]. Many studies on porcine models in the field of KTx have been performed during the last few years with different subcategories (procurement [7], cold storage [8], ischemia/reperfusion injury [9], preservation solution [10], graft function [11], rejection [12], immunosuppression [13], xenotransplantation [14] and urology [15]). Although all of them have performed KTx on the porcine

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Table 1. Experimental studies in pig KTx with a surgical point of view

Author	Year	Language	Focus	Type of study
Golby et al. [6]	1971	English	Kidney transplantation	Guideline
Calne et al. [35]	1972	English	Kidney transplantation	Guideline
Nerstrom et al. [20]	1972	English	Kidney transplantation	Guideline
Mazzoni et al. [36]	1972	English	Kidney transplantation	Experimental (n = 23)
Kierfeld et al. [42]	1973	English	Kidney transplantation	Experimental (n = 16)
Yanaga et al. [44]	1991	English	Kidney transplantation	Guideline
Pennington [25]	1992	English	Kidney transplantation	Guideline
Wang et al. [37]	2003	English	Kidney transplantation	Experimental (n = 10)
Zonta et al. [17]	2003	Italian	Urological anastomosis	Experimental (n = 24)
Zonta et al. [39]	2005	English	Urological anastomosis	Experimental (n = 30)
Swindle [45]	2007	English	Kidney transplantation	Guideline
Bestard Vallejo et al. [16]	2008	Spanish	Kidney transplantation	Experimental (n = 25)
Jochmans et al. [33]	2009	English	Kidney transplantation	Experimental (n = 11)

model, there are no guidelines about 'how we do it', especially for the surgical aspects. The few available studies are neither up to date nor focused on the surgical point of view and most of them are not written in English [16–20]. The aim of this study is to prepare an up-to-date guideline for performing porcine KTx.

Methods

In order to achieve our goals, we performed a Medline search using the terminology 'kidney' or 'renal' and 'transplantation' and 'pig' or 'swine' or 'porcine'. We found over 1,300 published articles since 1963. However, only a few of them (13 studies) focused on the surgical aspects (table 1). Furthermore, we reviewed related books and articles about anatomical characteristics and surgery in swine. Finally, our experimental experiences of porcine KTx during the last few decades were added to this collection.

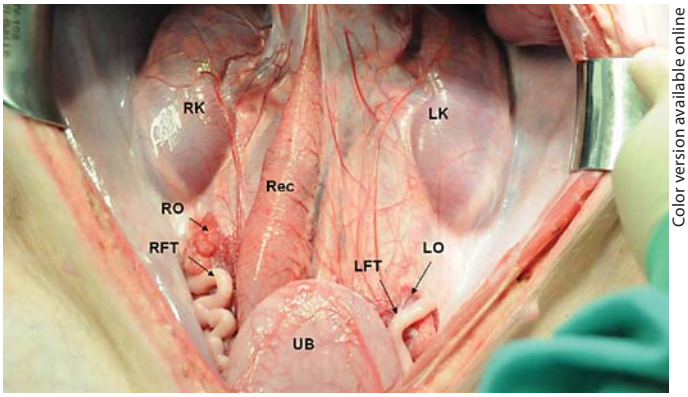

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Fig. 1. The urinary system of the pig. RK = Right kidney; LK = left kidney; Rec = rectum; RO = right ovarian; LO = left ovarian; RFT = right fallopian tube; LFT = left fallopian tube; UB = urine bladder.

Results

Pig as an Animal Model

KTx-Related Anatomical Characteristics of the Pig

The kidneys of the pig are more like those of human beings in anatomy and function than those of most other animal species. The average weight of a kidney in a 30-kg pig is approximately 150 g without a significant difference between the left and right kidneys [21] (fig. 1). The adrenal glands are located near the cranial poles of both kidneys and the right gland is intimately associated with the wall of the postcava. The renal artery and vein, which are almost always only 1 per kidney, divide into two craniocaudal branches close to the renal hilus [22–28] (fig. 2). The division of the left renal vein is more medial than the division of the right renal vein. This can lead the surgeon to the wrong idea of two separate renal veins. The ureters extend craniocaudally to the dorsolateral aspect of the neck of the urinary bladder (fig. 2, 3). The segmental lumbar arteries are relatively small in pigs, originating almost as a single branch from the aorta, and are divided after 3–4 mm [29].

Advantages

Pigs are not pets, have relatively low costs and are in many aspects more similar to humans than dogs, cats,

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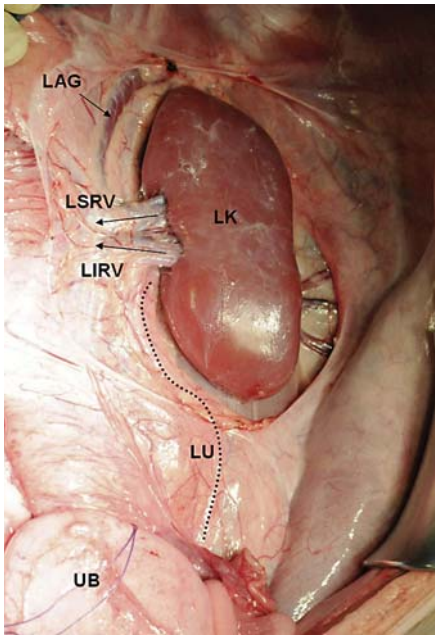

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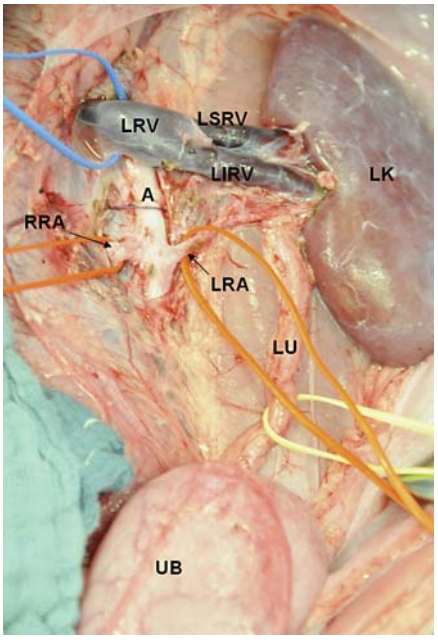

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Fig. 2. The left kidney of the pig after opening the retropritoneal cavity. LAG = Left adrenal gland; LK = left kidney; LSRV = left superior renal vein; LIRV = left inferior renal vein; LU = left ureter (….), UB = urine bladder.

Fig. 3. View of the left kidney of the pig after vascular and uretral preparation. LRV = Left renal vein; LSRV = left superior renal vein; LIRV = left inferior renal vein; A = aorta; LK = left kidney; RRA = right renal artery; LRA = left renal artery; LU = left ureter; UB = urine bladder.

or rodents. There is a long background of scientific investigation of pigs, which serves as a basis for further investigation. The urinary system of swine is similar to that of human beings in many ways, especially in anatomy (fig. 1) and function. Pigs weighing 30 kg are the easiest size for use in renal transplantation studies [22, 25, 30]. At this size, there is enough abdominal place for a KTx without endangering the success due to technical limitations. Furthermore, the transport and management of the animals at this size is more feasible, especially considering their rapid growth for the follow-up time.

Drawbacks

Commercial breeds of pigs reach a large size very quickly. They can suffer from malignant hyperthermia, cardiac irritability, peptic ulceration and small-bowel obstruction. Hyperthermia can be handled with dantrolene (3.5 mg/kg). Cardiac arrhythmias can be avoided by limiting stress during the induction of anesthesia, using tranquilizers and dissociative agents, or administrating prophylactic antiarrhythmics. It is also helpful to keep swine well oxygenated during induction of anesthesia. Peptic ulceration is preventable via proper management using histamine blockers in stressful situations. Postoperative small-bowel obstruction is only an occasional problem causing death in less than 5% of animals [4, 21, 25, 31].

Preoperative Preparations and Anesthesia

Preoperative preparations for animals include allowing them to become accustomed to the environment for at least 2 days, fasting for 8–12 h with free access to water and application of a narcotic protocol. Our premedication protocol includes: azaperone 4–8 mg/kg i.m., midazolam 0.5–0.7 mg/kg i.m. and ketamine 11–33 mg/kg i.m.; thereafter induction: midazolam 0.5–0.7 mg/kg i.v., ketamine 11–33 mg/kg i.v. and atropine 0.04 mg/kg i.v., followed by endotracheal intubation. Pressure-controlled ventilation can be done in a half-closed system [our protocol; ventilation parameters: frequency (11/min); volume (10–15 ml/kg); O_2 (0.5–1.0 l/min); air (1.5–2.0 l/min) or N_2O (1.5–2.0 l/min), and isoflurane (1.45–2.04%) with end-tidal CO_2 of 35–45 mm Hg] [21, 31–33]. A urinary catheter can be placed in female pigs in order to monitor postoperative urine production. Since the urinary duct in pigs, especially in males, has many folds, it is better to avoid catheterization. A percutaneous transcystic catheter can be used instead.

Cardiovascular and Hemodynamic Monitoring

Intravenous administration, blood sampling and cardiocirculatory measurements (central venous pressure and mean arterial pressure) can be performed using an inserted 16-gauge catheter via the internal jugular vein and common carotid artery (fig. 4).

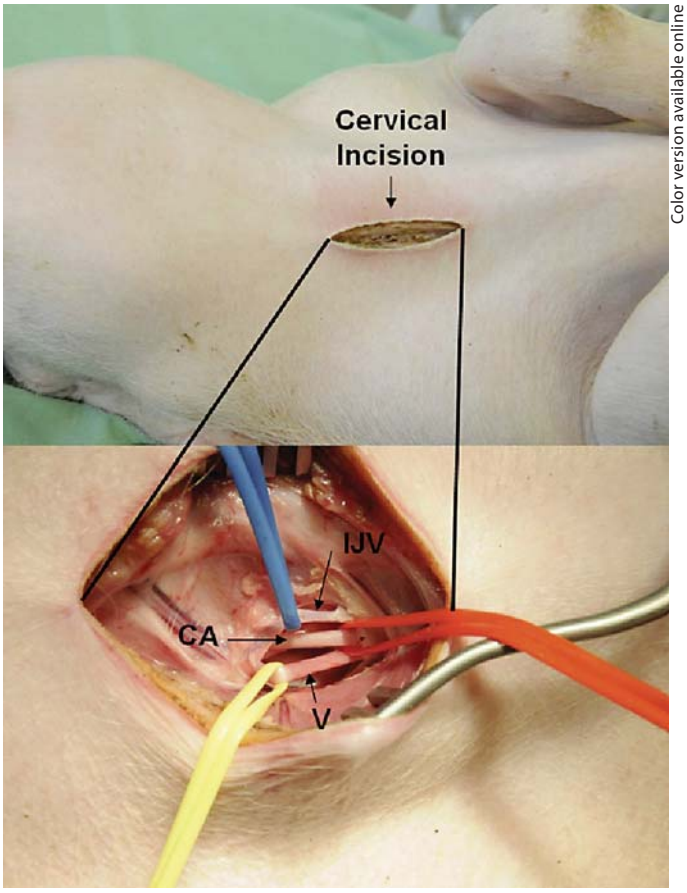

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Fig. 4. Cervical incision and preparation in the carotid sheet of the pig. CA = Carotid artery; V = vagus nerve; IJV = internal jugular vein.

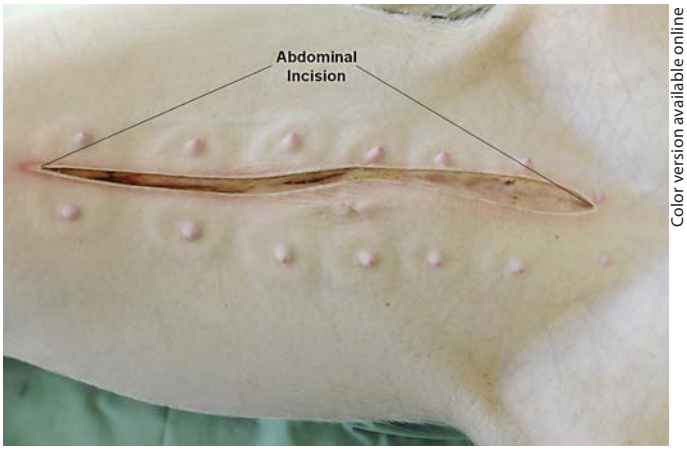

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Fig. 5. Abdominal midline incision in the pig for multiorgan procurement.

Explantation

Kidneys can be explanted through a multiorgan procurement approach which may be used to reduce the number of laboratory animals [7] or kidney-focused methods. In kidney-focused methods, cross-over donation and autotransplantation can also reduce the number of laboratory animals. The explantation can be performed through laparoscopy or laparotomy. There are two options for the laparotomy approach: full-length midline abdominal intraperitoneal incision and lateral extraperitoneal incision. The midline incision is preferred because of the increased surgical exposure. Female pigs are preferred for surgery because of the ease of making midline incision [22, 25, 30] (fig. 5). However, by choosing only female pigs, there is a risk for bias, since female kidneys have been shown to be more resistant to ischemia/reperfusion injury [34]. In male pigs, the skin incision below the umbilicus is in echelon inside or outside the nipple line and curved laterally at the level of the penis to avoid penis lesions [6, 20, 25, 35]. The flank approach may be preferred if the donor is expected to survive the experiment, especially if a future reimplantation procedure with a midline approach is anticipated. In this case, a decision has to be made concerning which kidney is to be explanted. For the left kidney, the renal artery will be shorter and the renal vein longer. For the right kidney, the opposite is true, and the adrenal gland is closely associated with the junction of the renal vein and vena cava. If using a flank approach, the left kidney is usually the kidney of choice for removal. In this method, assistance is necessary to retract the peritoneum and contained viscera away from the kidney vessels which are dissected free.

After mobilization and preparation of the perirenal tissue, the vessels are dissected gently (fig. 2, 3). Papaverine solution (2.5%) can be dabbed on the renal artery to reduce its spasm level [35]. Mobilization of the adrenal gland and division of its vein from the renal vein between ligatures may be necessary to obtain full exposure of the latter. The aorta can be prepared for canulation 3 cm inferior to the renal artery (fig. 6). Disruption of the lymphatic vessels is common in this level which should be avoided if possible. The disrupted vessels or sacs can be ligated. Ligation and division of the lateral lumbar arteries at this time is necessary, if the donor is sacrificed. Diuresis should be established at this time with Ringer's lactate (1,500–2,000 ml), mannitol (1 mg/kg) and furosemide (1–2 mg/kg). Since young pigs are prone to renal spasm, phenoxybenzamine (2 mg/kg) can be administered only when the donor is supposed to be sacrificed, otherwise it can cause hypotension.

After heparinization (200 IU/kg), the aorta (or iliac artery) is cross-clamped below the renal artery and the preservation catheter is inserted. It is important to control the possibly available lower pole arteries of the kidney, which seldom exist in pigs. The preservation solution is infused with a control pressure. The aorta is cross-clamped above the renal artery and renal veins are cut close to the vena cava for washing out. The onset time of the renal ischemia is noted. A Carrel patch of the aorta, which enhances the implantation, can be removed together with the orifice of the renal artery (fig. 7). When a reciprocal transplant is planned, the defect in the aorta, from which the Carrel patch is taken, can be used for anastomosing the Carrel patch of the reciprocal kidney graft. Otherwise, when the donor should survive, the defect in the aorta can be closed with a small patch [6, 25, 35]. If the kidneys are procured en bloc (fig. 8), they are divided during the back table by splitting the aorta and the inferior vena cava longitudinally.

Although pigs with a weight of 30 kg do not have a complex vascular net in the golden triangle, ischemic necrosis is a risk. It is important to remove the ureter with as much periureteral tissue as possible in order to retain its blood supply and as long as possible to make various ureteral anastomosis feasible (fig. 7). Dividing the ureter obliquely at the pelviureteral junction has also been mentioned in the literature [6], which is not recommended because of the difficult anastomosis.

Preservation and Cooling

The renal arteries and veins are trimmed and the allografts are packed in a sterile bag and stored at 4°C for variable periods according to decided protocols. Some investigators indicate that cold perfusion would worsen and increase the renal artery spasm. They believe that, in the case of direct implantation after explantation, there is no need to preserve the organ since a warm ischemia time of 30–40 min does not damage the kidney enough to cause dysfunction [25]. However, for storage for such a short period of time, cold Ringer's lactate with or without 5,000 IU/l of heparin, 125 mg/l of methylprednisolone, and 25 g/l of mannitol is enough. Otherwise, preservation solutions such as histidine-tryptophan-ketoglutarate or University of Wisconsin solution can be used.

Back Table

Arteries, veins and the ureter should be checked before implantation. This can be performed through washing the lumens with normal saline or preservation solutions. Tearings and perforations can be sutured. A vascular patch can also be used in the case of large lacerations. If there is no aortic patch available, arterioplasty can be performed in order to reduce the future risk of stenosis. Regarding the anatomy of the renal veins, which was mentioned previously, preparation of the left renal vein is necessary and will be discussed in the implantation part.

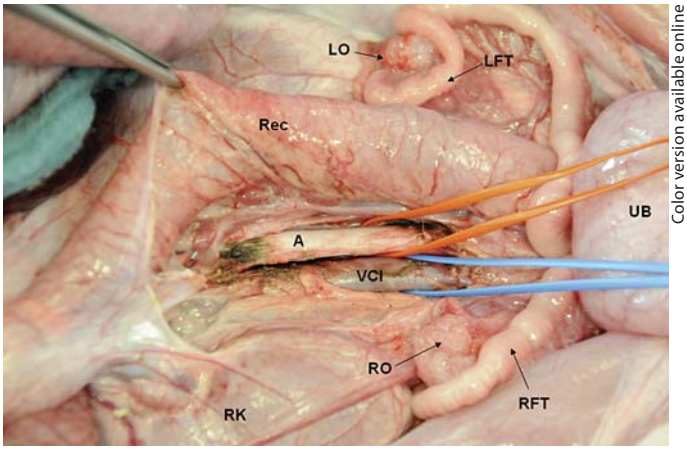

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Fig. 6. Preparation of the infrarenal aorta and the infrahepatic vena cava inferior of the pig in order to be cannulated for perfusion with preservation solution. LO = Left ovarian; LFT = left fallopian tube; Rec = rectum; A = aorta; VCI = vena cava inferior; UB = urine bladder; RK = right kidney; RO = right ovarian; RFT = right fallopian tube.

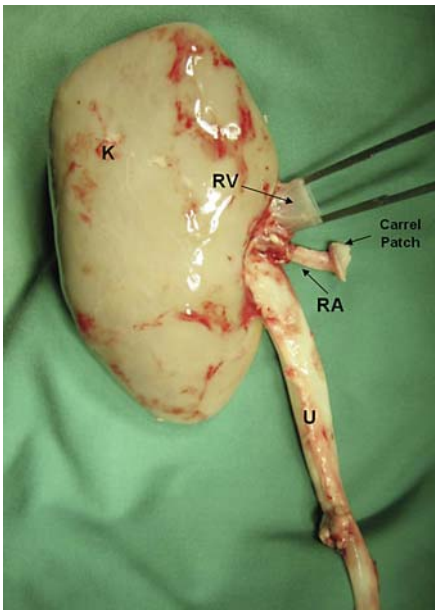

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Fig. 7. A porcine kidney after procurement and explantation. K = Kidney; RV = renal vein; RA = renal artery; U = ureter.

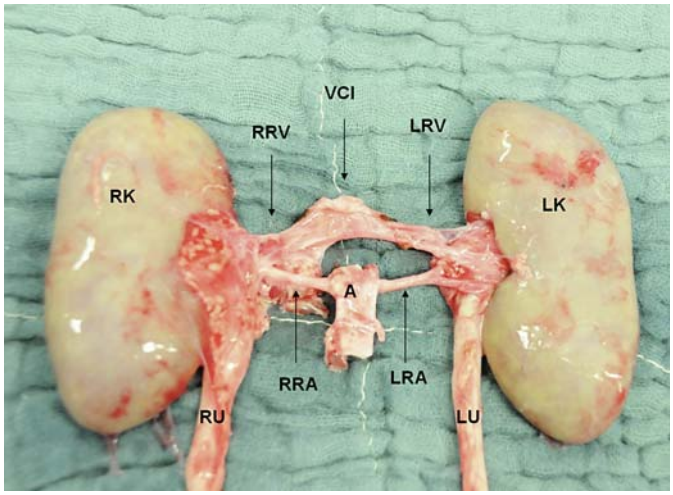

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Fig. 8. En-bloc explantation of porcine kidneys with the trunk of aorta and inferior vena cava. VCI = Vena cava inferior; RRV = right renal vein; LRV = left renal vein; RK = right kidney; LK = left kidney; A = aorta; RRA = right renal artery; LRA = left renal artery; RU = right ureter; LU = left ureter.

Native Nephrectomy

The recipients can undergo native nephrectomy before KTx. It prepares the proper space for orthotopic implantation and gives a better opportunity to evaluate the function of implanted organs. Through avoiding the urine production from native kidneys, the function of the transplanted kidney can be better followed, specifically through laboratory values. Native nephrectomy can be performed before, between and after KTx. There is no evaluation in the literature about the time of nephrectomy. We perform intraoperative native nephrectomy because animals go under anesthesia only once and do not suffer from the complications of a previous operation.

Implantation

For implantation the pig undergoes the same preoperative anesthesia and cardiovascular procedures which were mentioned in the explantation. After administration of an antibiotic (for example enrofloxacin 2.5 mg/kg) and under continuous induction of a narcotic analgetic (for example fentanyl 8 μg/kg/h) as well as balanced electrolyte solution (40 ml/kg), laparotomy will be performed. The site of implantation should be prepared while avoiding disruption of the lymphatic vessels as much as possible (fig. 6). Disrupted lymphatic vessels should be ligated or cauterized. KTx can be performed in pigs orthotopically or heterotopically. Using the orthotopic technique, the renal artery of the donor, with or without the Carrel patch, is anastomosed to the aorta of the recipient. This technique is more reliable and preferable because of the reduced risk of arterial thrombosis as a consequence of a larger arterial anastomosis lumen in comparison to the heterotopic method [17, 20, 25]. The possible complications of this technique are leaks at ureteral anastomosis, paraplegia from spinal cord ischemia and lymph leakage from the interaortocaval lymph ducts. Using the heterotopic technique, the donor's renal artery is anastomosed to the end or side of the iliac artery. This method is more difficult for inexperienced surgeons and results in a higher rate of arterial thrombosis (up to 50%) [25] due to the narrow diameter of the iliac artery (3–4 mm) as well as its spasms. Furthermore, a higher rate of morbidity due to ileus can be seen in this model, which prevents it from being used as a chronic disease model. The rate of spinal cord ischemia and ureteral anastomosis leakage is lower in this method as a consequence of less dissection required around the aorta and minimized length of implanted ureter [25, 36, 37].

Vascular Anastomosis

The venous anastomosis is first constructed end to side (to the inferior vena cava or iliac vein) or end to end (to the renal vein or iliac vein) with 5-0 or 6-0 Prolene [6, 35, 38]. Here, two stay sutures can simplify suturing and help to make the suture line more visible. In implantation of the left kidney, since the bifurcation of the superior and inferior renal veins is too far from the hilus of the kidney, it is better to divide the renal veins and anastomose them separately or make a common ostium at the site of anastomosis (fig. 9). Concerning the anatomical division of the porcine renal veins (craniocaudal instead of anteroposterior), sacrificing of one of the renal veins is not recommended. Anastomosis of the left renal vein before the bifurcation is not recommended either because the renal vein would be too long and the possibility of kinking would be increased. A similar arterial anastomosis is then performed through an end-to-side (to the aorta or common iliac artery) or end-to-end (to the remnant renal artery of the recipient) method with a continuous single layer of everting 6-0 or 7-0 atraumatic Prolene [6, 35, 38] sutures. Prior to finishing the anastomosis, it is necessary to prevent air and clot embolism. This can be performed through flushing the lumen with heparinized saline (10 IU/ml) and removing the air from the anastomosis ostium. For air removal, the clamp on the aorta or common iliac artery can be opened for a short time while the last suture of the anastomosis has not been performed. In this step, it is important that the blood flow does not enter the organ, which can be pre-

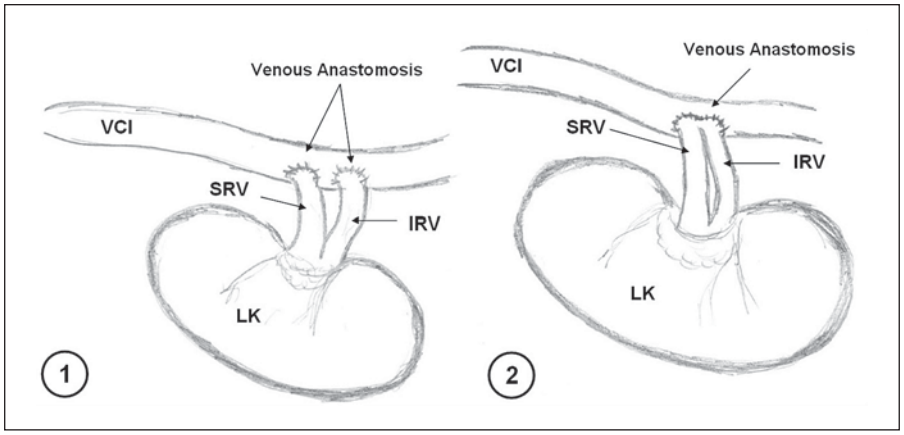

Fig. 9. Different types of venous anastomosis of the porcine kidney: (1) separate anastomosis of the superior and inferior renal vein, (2) one common ostium anastomosis of the superior and inferior renal vein. VCI = Vena cava inferior; LK = left kidney; SRV = superior renal vein; IRV = inferior renal vein.

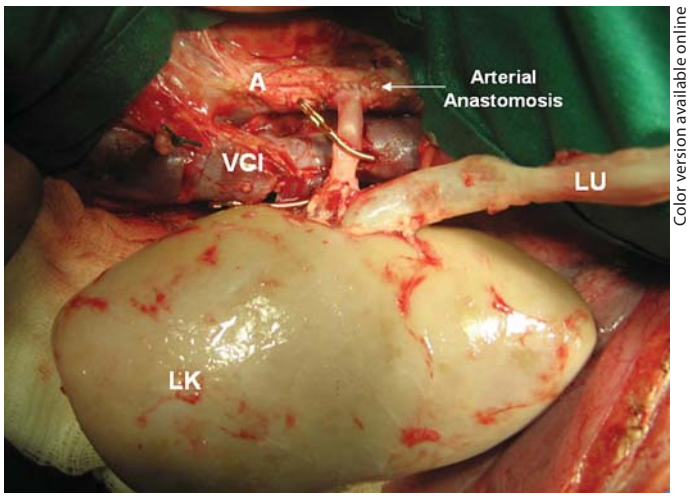

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Fig. 10. Anastomosis of the porcine left kidney in its right infrarenal fossa. LK = Left kidney; VCI = vena cava inferior; A = aorta; LU = left ureter.

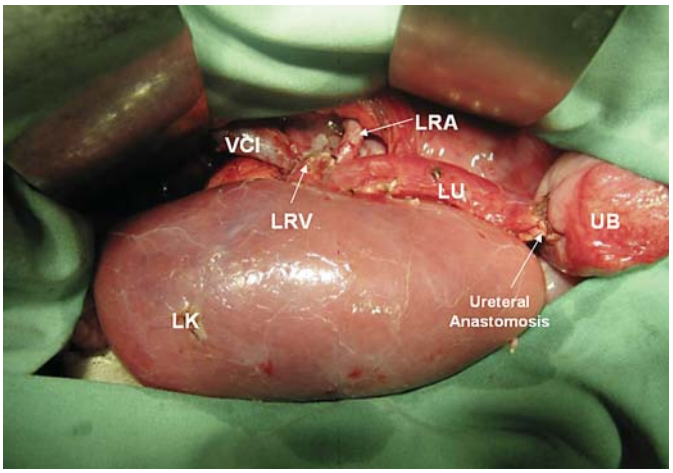

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Fig. 11. Implanted porcine kidney after reperfusion and ureteral anastomosis. LK = Left kidney; VCI = vena cava inferior; LRV = left renal vein; LRA = left renal artery; LU = left ureter; UB = urine bladder.

vented through a clamp as near as possible to the graft side of the anastomosis (fig. 10). To prevent renal artery thrombosis, it is also recommended to give aspirin (325 mg/day) for 3 days before implantation [25]. Following heparinization (200 IU/kg), when the venous and then the arterial clamps are removed, the renal ischemic time ends. Additional stitches may be required to control hemorrhage but usually packing with gauze swabs while the ureteral anastomosis is sutured is enough [33]. Cord infarction and hind limb paralysis (5.3%) [6] may happen as a consequence of spinal cord ischemia from ligation of lumbar arteries, total occlusion of the suprarenal aorta, hypotension and inadequate anticoagulation.

Ureteral Anastomosis

The pigs' ureter has a narrow caliber and fragile mucosa which is susceptible to edema during surgical management. These represent challenging aspects for surgeons who have to manage the KTx [39]. The middle and distal segments of the ureter receive blood from the common iliac artery and its branches. Ischemic necrosis is a risk if long segments of donor ureters are used [6]. The methods which have been performed in a swine model can be divided into three major groups: (1) ureterocalicostomy [40], (2) ureteroureterostomy [41] and (3) ureterocystostomy [42]. Ureterocystostomy has been performed through Lich-Gregoir and Leadbetter-Politano

methods in pigs. The Lich-Gregoir technique is our method of choice. It is made with continuous 4-0 or 5-0 Polydioxanone sutures (fig. 11). A variation of the Leadbetter-Politano method has also been studied by Zonta et al. [39] in a porcine model. They believe their new direct method results in a lower complication rate in comparison to the Lich-Gregoir and Leadbetter-Politano methods in a porcine model (10 vs. 40% in Leadbetter-Politano and 60% in Lich-Gregoir).

Histopathological Analysis

Biopsies should be taken in the pig kidney as far peripheral as possible, ideally through the calyceal fornix [43]. Punctures in the cranial infundibulum are dangerous because it is encircled by the ventral and dorsal branches of the cranial division of the renal artery (fig. 10) [22]. Direct puncture in the renal pelvis may result more often in a vascular complication than a transparenchymal calyceal approach because the posterior artery may be injured.

Postoperative Management

Zero or one long-term absorbable suture is suitable for closure of the abdominal wall, and an absorbable 3-0 suture is used in a subcuticular pattern to close the skin. The cervical wound is closed with 3-0 Dexon. The arterial as well as central venous lines are secured to the skin with 2-0 silk sutures and capped after flushing with heparinized saline solution. Postoperatively, the animal is warmed by a heat lamp, extubated when fully awake, and then returned to the cage. To prevent cannibalization, the animals should be housed separately until recovered from surgery. Immediately after transplantation, the animal can have free access to food and water. Crystalloid fluids, analgesic, antithrombotic, stress ulcer prophylactic and immunosuppressive medical therapy can be administered depending on the study protocol [44, 45].

Rejection

Unselected domestic swine differ greatly in their response to renal allograft. Rejection is absent in as many as 25% of the recipients. Matches can be found when the immunogenetics are carefully controlled, as in swine leukocyte antigen-matched swine. Rejection can be seen histologically by the 3rd postoperative day, chemically by the 4th postoperative day and as death from renal failure which happens at about the 10th or 11th postoperative day, and can be documented after the native kidneys are removed [25].

Conclusion

The anatomical and physiological similarities of pigs have made this species an optimal animal model for experimental studies of KTx. Concerning the numerous numbers of experimental studies on KTx, an up-to-date guideline for this issue can help avoid preventable complications and pitfalls. Preoperative preparation is as important as the intra- and postoperative managements. Using the most adaptable methods of surgery with respect to the specific anatomical characteristics of pigs can prevent undermining the studies.

Disclosure Statement

The authors declare that they have no competing interests.

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