

Stable chronic hemodialysis porcine model via renal vein catheterization of the posterior vena cava

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Article

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Abstract

Chronic *in vivo* models for evaluating medical devices used in hemodialysis before clinical application remain limited. We aimed to establish a porcine model of end-stage renal disease (ESRD) for maintenance intermittent hemodialysis. Göttingen and Nippon Institute for Biological Science (NIBS) miniature pigs were used. Following bilateral nephrectomy, catheters for dialysis access were inserted into the jugular vein or posterior vena cava (PVC) through the right renal vein. Hemodialysis was performed three times weekly for up to 39 days. Body weight and laboratory parameters were evaluated during hemodialysis. Catheter and porcine survival were compared according to catheter position and body weight. Heavier pigs had significantly longer survival than lighter pigs. Postoperatively, all pigs gradually lost weight. While catheter patency was maintained, blood urea nitrogen, creatinine, and potassium levels remained controlled during hemodialysis. Catheter survival was significantly longer in pigs with catheters placed in the PVC through the right renal vein than in those with jugular-venous catheters. Complications in the jugular-vein group included fibrin-sheath formation, thrombotic catheter occlusion, and tricuspid-valve injury. Thus, heavier pigs undergoing hemodialysis with a catheter inserted into the PVC through the right renal vein may provide a suitable ESRD model for maintenance intermittent hemodialysis.

Introduction

Hemodialysis is an established treatment for patients with end-stage renal disease (ESRD) [1]. Despite advances in hemodialysis technology, outcomes among patients receiving maintenance hemodialysis remain poorer than those among healthy individuals and kidney transplant recipients [2–4]. Further improvements in hemodialysis outcomes require continued basic and clinical research. However, experimental research on chronic hemodialysis is challenging because establishing *in vivo* ESRD models that survive sufficiently long to undergo repeated maintenance hemodialysis remains difficult [5]. Although arteriovenous fistulas (AVF), grafts (AVG), and peritoneal dialysis (PD) access have been established in large-animal models, most studies have focused on access performance, including blood flow and stenosis, rather than long-term dialysis in animals with ESRD [6–10]. Similarly, temporary hemodialysis for acute renal failure (ARF) has been reported in dogs and cats [11], but few experimental systems support long-term hemodialysis in *in vivo* models of ESRD [5, 12].

Medical devices used for chronic hemodialysis, including dialysis catheters, dialyzers, and adsorbents, have therefore been evaluated primarily using *in vitro* experiments, simulations, or short-term *in vivo* studies [13–15]. Establishing a chronic hemodialysis model would enable *in vivo* evaluation of dialysis-related medical devices and physiological experiments that are difficult to perform using existing experimental systems. Such a model could also facilitate investigation of ESRD-associated complications, including ectopic calcification, cardiac hypertrophy, pulmonary oedema, and bone metabolism disorders.

Pigs share anatomical and physiological characteristics with humans and are sufficiently large to accommodate clinically relevant medical devices and procedures, making them suitable for translational and preclinical research [16]. For long-term hemodialysis in pigs, stable dialysis catheter patency is essential for reliable extracorporeal circulation [5]. However, dialysis catheters designed for human central venous access may not be anatomically suitable for miniature pigs, potentially resulting in size mismatch, thrombosis, and vascular injury, adhesions, and other catheter-related complications [17]. Accordingly, this study aimed to establish a miniature porcine ESRD model suitable for long-term intermittent hemodialysis by evaluating body weight and catheter insertion site and using catheter placement in the posterior vena cava (PVC) through the right vein during bilateral nephrectomy.

Results

Pig survival and postoperative changes in body weight

Pigs undergoing the dialysis model developed uremic symptoms accompanied by reduced appetite. When pigs were stratified by body weight using a 30-kg cutoff, survival was significantly longer in the higher-body-weight group than that in the lower-body-weight group (Fig. 1a). Postoperatively, all pigs showed gradual weight loss (Fig. 1b).

Laboratory parameters

While catheter patency was maintained, blood urea nitrogen, creatinine, and potassium levels remained controlled during dialysis (Fig. 2a–c). In contrast, hemoglobin concentrations progressively decreased and stabilized at 5–7 g/dL (Fig. 2d).

Catheter survival

Catheter survival was significantly longer in the renal vein group than that in the jugular vein group (Fig. 3). Among the catheter configurations evaluated, placement of a 12 Fr tunneled cuffed catheter (TCC) through the right renal vein in pigs weighing 30–40 kg showed the most favorable catheter patency (Supplementary Table S1).

Catheter-associated complications

In the jugular vein catheter group, complications included fibrin sheath formation with adhesion to the venous wall, catheter occlusion due to thrombosis, and pulmonary thromboembolism. Hematoxylin and eosin (HE) and phosphotungstic acid hematoxylin (PTAH) staining confirmed fibrin sheath formation around the catheter (Fig. 4a and b). Fibrotic tissue adhered the catheter to the venous wall. Fibrotic tissue also extended into the catheter lumen. In one pig, a catheter-associated thrombus filled the right

atrium, and the animal died (Fig. 5a and b). Tricuspid valve injury and prolapse associated with catheter-tip migration into the right atrium were also observed (Fig. 5c and d).

Discussion

Maintaining catheter patency is crucial in a porcine hemodialysis model, and preventing fibrin sheath formation is important for preserving catheter function [18]. Our data revealed that smaller catheters did not provide sufficient blood flow for hemodialysis, whereas larger catheters had greater contact with the venous wall, which could also reduce blood flow. Larger catheters may also adhere to the venous wall between hemodialysis sessions, contributing to catheter occlusion. Because cardiovascular dimensions vary with body size, catheter size should be selected according to the animal's body weight and the experimental conditions. Among the conditions evaluated, a 12-Fr catheter was suitable for insertion through the renal vein in pigs weighing 30–40 kg. Stable dialysis was maintained without catheter occlusion or the need for additional anticoagulation between hemodialysis sessions.

Long-term porcine dialysis models have rarely been reported. Yamamoto et al. performed continuous hemodialysis for up to two weeks using a catheter inserted into the jugular vein, achieving stable dialysis that permitted *in vivo* evaluation of a dialysis membrane [5].

Postoperative weight loss was observed in all pigs in the present study. Several pigs had reduced food intake and required nutritional support via gastrostomy, and inadequate control of uremia may have contributed to these findings [19].

Compared with an intra-abdominal approach, nephrectomy through a retroperitoneal lumbar oblique incision may reduce postoperative intestinal adhesions and oedema and facilitate earlier oral intake. Appropriate feed selection and gastrostomy tube placement may therefore help limit nutritional deterioration and loss of body mass associated with anuria and uremia. This model could provide a foundation for future kidney transplantation research and the development of novel blood-purification devices [16].

Catheters designed for clinical use in humans may not be anatomically suitable for miniature pigs. In clinical practice, the catheter tip inserted through the jugular vein is positioned near the entrance to the right atrium [20, 21]. In miniature pigs, however, jugular venous access may be challenging because of the relatively narrow vessel, difficulty inserting a 14-Fr catheter, the short distance between the jugular vein and heart, and the relatively spherical cardiac anatomy. These characteristics may have contributed to frequent fibrin sheath formation, while the small right atrium and high catheter-tip mobility may have promoted catheter migration and valve injury. In contrast, positioning the catheter tip in the PVC just below the diaphragm was associated with stable blood flow during hemodialysis. The renal vein catheterization group had fewer complications, particularly fibrin sheath formation, and required fewer catheter reinsertions.

Central venous stenosis or occlusion is a recognized complication of long-term indwelling catheters [22, 23]. In the renal vein catheter group, one miniature pig developed a protruding lesion in the venous wall (data not shown). Although the present model was limited to approximately one month, extending the duration of catheter placement may facilitate investigation of the mechanisms underlying venous stenosis [24].

For patients with ESRD who are unable to undergo kidney transplantation or PD and have limited AVF or AVG options, long-term indwelling catheters may be required for hemodialysis. However, recurrent infection, fibrin sheath formation, and progressive central venous occlusion can compromise long-term vascular access [22]. The porcine model developed in this study may therefore provide a platform for investigating alternative vascular-access strategies when conventional access is limited.

This study has several limitations. First, the surgical approach was developed empirically using a limited number of large animals, and the resulting groups were compared retrospectively. Furthermore, the observation period was limited to 39 days, whereas chronic disease pathophysiology requires longer follow-up. Extending survival will likely require optimization of ESA therapy and nutritional management.

In conclusion, we established an *in vivo* maintenance intermittent hemodialysis model. This model may provide a platform for improving dialysis catheters, developing blood-purification devices, optimizing dialysis protocols, and evaluating alternative vascular-access strategies.

Methods

Miniature pigs

Animal experiments involving miniature pigs were approved by the Jichi Medical University Animal Ethics Committee (authorization number 21–044) and conducted at the Center for Development of Advanced Medical Technology, and all experiments were performed in accordance with relevant guidelines and regulations. Male Göttingen miniature pigs aged 13 ± 2 months weighing 21.9–29.2 kg (25.2 ± 2.6 kg) and male Nippon Institute for Biological Science (NIBS) miniature pigs aged 13 ± 2 months weighing 31.7–38.5 kg (35.4 ± 1.9 kg) were housed individually in pens (1 m $\times$ 1.5 m) with a bedding area (0.5 m $\times$ 1 m). All pigs were maintained under controlled temperature ($25 \pm 2^\circ\text{C}$), humidity ($60 \pm 10\%$), and lighting conditions (12-h light/dark cycle). After 10 days of quarantine and acclimatization, Göttingen miniature pigs were fed 400 g of regular swine diet (NS, Oriental East Co., Ltd., Tokyo, Japan) once daily (10:00–12:00), whereas NIBS miniature pigs were fed 400 g of experimental swine diet (JMP, Marui Kogyo Co., Ltd., Nagano, Japan) once daily (10:00–12:00); all pigs had free access to tap water.

Bilateral nephrectomy

After sedation induced by intramuscular administration of atropine sulfate (0.02 mg/kg), medetomidine hydrochloride (0.06 mg/kg), and midazolam (0.3 mg/kg), miniature pigs were anesthetized with sevoflurane (2.0–5.0%) in oxygen (25–100%) delivered through an endotracheal tube. All procedures were performed under the anesthesia described above.

In the jugular vein catheter group, surgery pigs were placed in the supine position, and surgery was performed through a midline abdominal incision. The kidneys were assessed using an intra-abdominal incision. The ureters, renal veins, and renal arteries were ligated, and both kidneys were removed. After bilateral nephrectomy, the incision was closed, the pig was repositioned in the prone position, and a hemodialysis catheter was inserted into the right or left jugular vein after surgical cutdown and direct exposure of the vessel (Fig. 6a). Because direct percutaneous puncture was technically difficult owing to the tough porcine skin, a surgical cutdown was used to expose the vessel before puncture.

In the PVC-through-right-renal-vein group, nephrectomy was performed through a lumbar oblique incision. Following the removal of the right kidney, the right renal vein was secured using a 5 – 0 non-absorbable monofilament suture (Fig. 6b). A hemodialysis catheter was inserted directly into the right renal vein in the cranial direction and fixed with sutures (Fig. 6c). After insertion, the catheter was exteriorized through a subcutaneous tunnel to create a TCC (Fig. 6d). The position of the catheter tip was confirmed fluoroscopically. The catheter tip was positioned in the PVC near the diaphragm (Fig. 7a).

Hemodialysis

Bilateral nephrectomy and hemodialysis catheter placement were performed on day 0. On day 2, miniature pigs underwent hemodialysis while awake using a hemodialysis system (DBB-200Si, NIKKISO Co., Ltd., Osaka, Japan), dialyzers (FB-70ub, ECO, FB-110ub ECO, FB-130ub ECO, FB-150 ub ECO, Nipro, Osaka, Japan), dialysate (Kindaly AF-2, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan), and blood circuit sets (NV-D series, NIKKISO Co., Ltd.) three times weekly through day 39 (Fig. 7b). The dialysate contained sodium 140, potassium 2.0, calcium 3.0, magnesium 1.0, chloride 110, bicarbonate 30, acetate 8 mEq/L, and glucose 1.0 mg/dL, and its composition remained unchanged throughout the study. Dialysis conditions were a blood flow rate of 150 mL/min, a dialysate flow rate of 600 mL/min, and a duration of 4 h. Anticoagulation was achieved with nafamostat mesylate (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), administered by continuous injection at 30 mg/h during dialysis. After dialysis sessions, the miniature pigs received intravenous darbepoetin (30 µg; KISSEI Pharmaceutical Co., Ltd., Nagano, Japan) and saccharated ferric oxide (20 mg of Fesin; Nichi-Iko Pharmaceutical Co., Ltd.) twice weekly and famotidine (20 mg; Nichi-Iko Pharmaceutical Co., Ltd.) three times weekly.

Blood sampling and analyses

Blood samples were collected from the hemodialysis catheter at the initiation of recirculation dialysis for measurement of hematocrit, electrolytes (sodium, potassium, chloride, and ionized calcium), blood urea nitrogen, and creatinine using an iSTAT® system (Abbott, Illinois, USA).

Pig and catheter survival

The date of surgery was designated as day 0, and the date of animal death was recorded. For euthanasia, administer KCl (40 mEq) after sedation using the anesthesia protocol described above.

Pig survival time was defined as the interval from surgery to animal death. Catheter survival time was defined as the interval from catheter placement to death due resulting from complications or catheter-related complications.

Pathological evaluation

Removed catheters and fibrin sheaths were fixed in 10% formalin. After fixation, HE and PTAH staining were performed.

Statistical analyses

Quantitative data are expressed as the mean $\pm$ standard deviation unless otherwise stated. Differences among groups were evaluated using one-way analysis of variance (ANOVA). Dunnett's multiple comparisons test was used for comparisons with the control group. Survival curves were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Statistical analyses were performed using GraphPad Prism version 8.4.3.

Declarations

Additional Information

Competing Interests Statement:

The authors declare no competing interests.

Author Contribution

YI, MK, and DI conceived of and designed the experiments. TN, YI, HM, YH, KE, TO, SN, KM, and DI. TN, YI, HM, and YH analysed the data. TN, YI, HM, Wrote the paper, and TN, YI, and DI contributed reagents, materials, and analysis tools. Discussion: TN, YI, MK, and DI scores

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Data Availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1

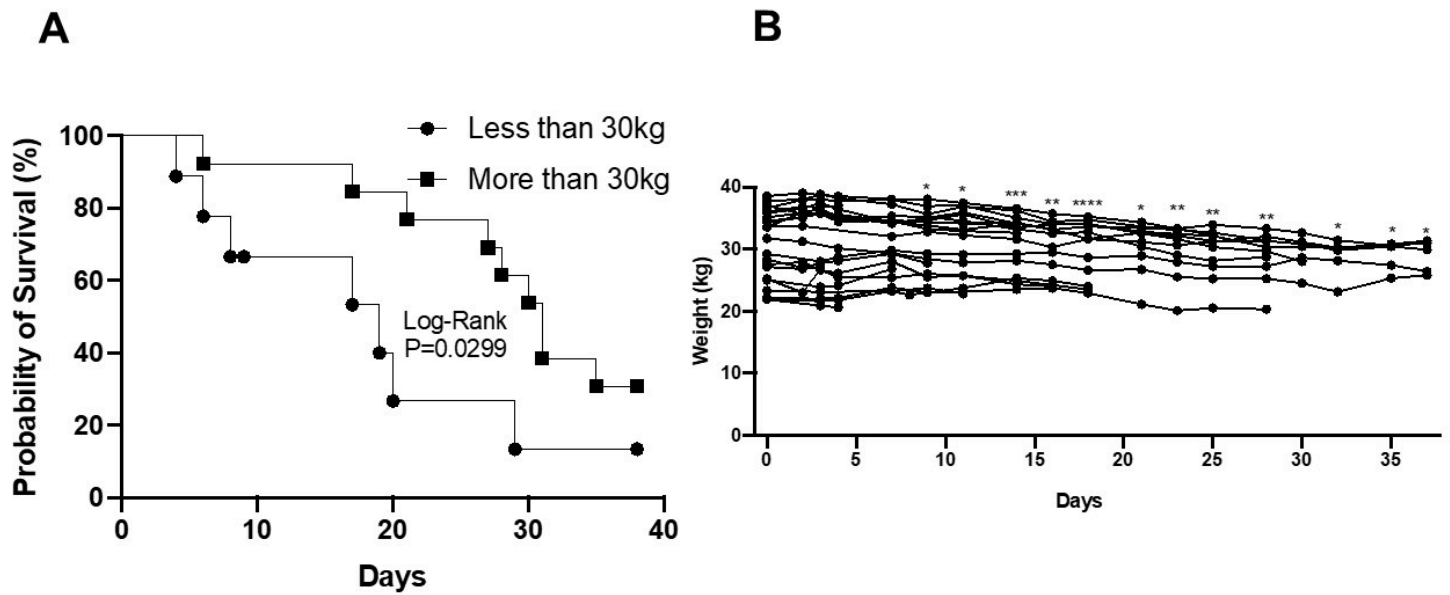


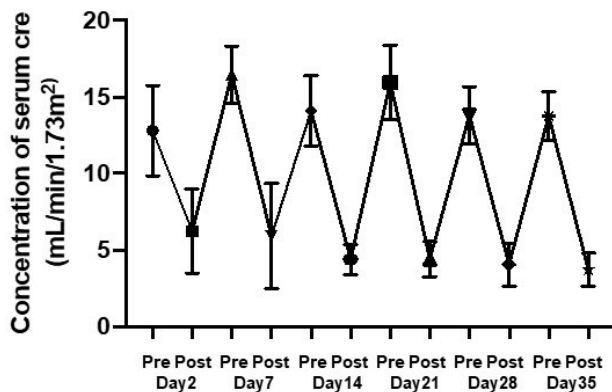
Figure 1

Pig survival and postoperative changes in body weight

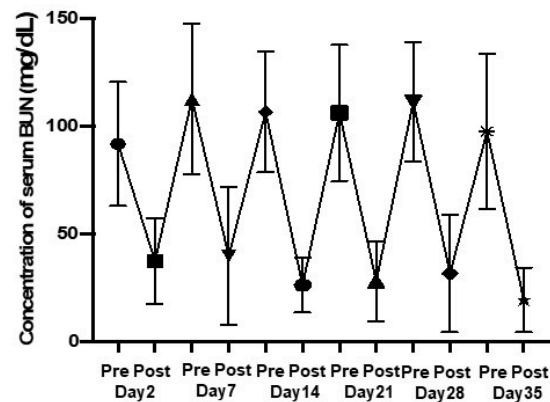
(a) Difference in pig survival between the higher- and lower-body-weight groups. **(b)** Changes in body weight after surgery. Bars represent the mean $\pm$ SD. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. P values were generated using one-way ANOVA followed by Dunnett's multiple-comparisons test, with day 2 as the control.

Figure 2

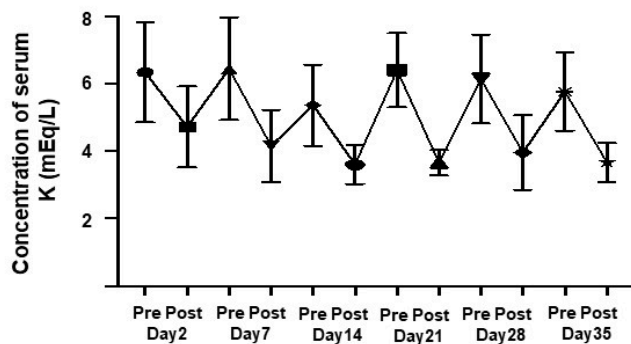
A



B



C



D

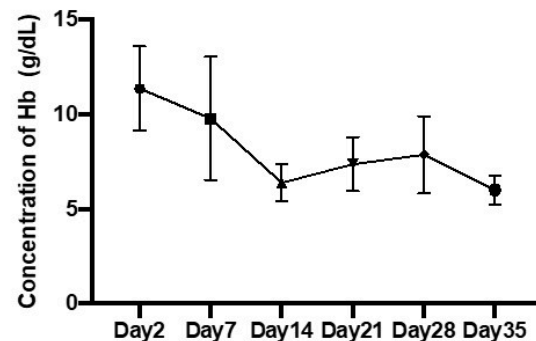


Figure 2

Laboratory parameters

(a) Creatinine concentrations before and after hemodialysis following surgery. **(b)** Blood urea nitrogen concentrations before and after hemodialysis following surgery. **(c)** Potassium concentrations before and after hemodialysis following surgery. **(d)** Hemoglobin concentrations before dialysis following surgery. Bars represent the mean $\pm$ SD.

Figure 3

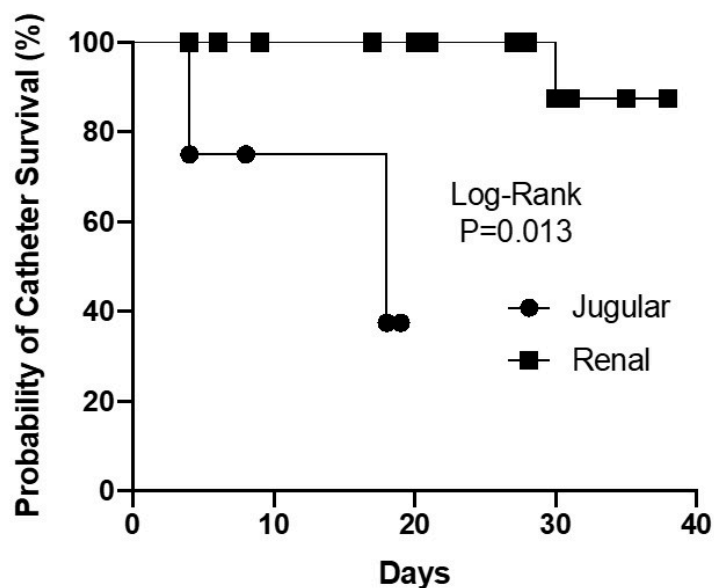


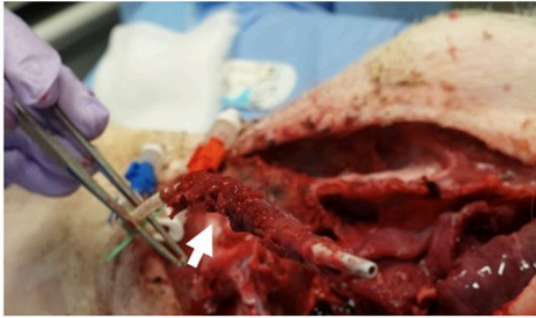
Figure 3

Catheter survival according to catheter placement site

Catheter survival in pigs with jugular vein catheters and those with catheters inserted directly into the posterior vena cava (PVC) through the right renal vein.

Figure 4

A



B

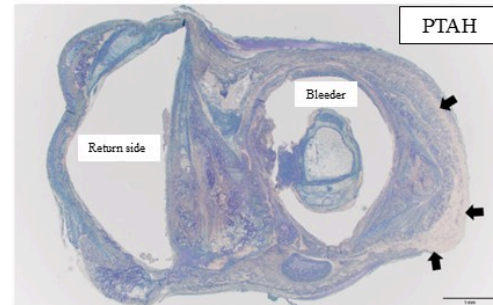
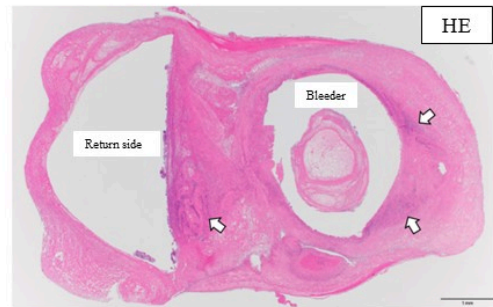


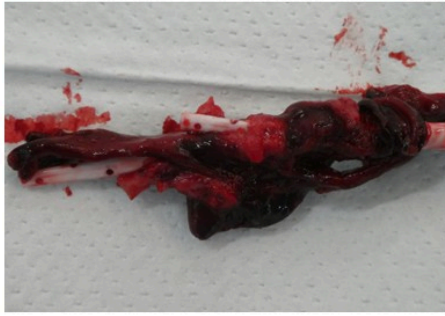
Figure 4

Fibrin sheath formation around the catheter

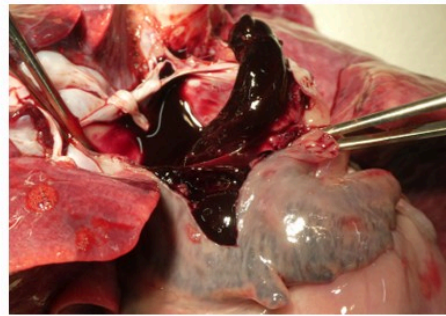
(a) Fibrin sheath formation around the catheter. **(b)** Hematoxylin and eosin (HE) and phosphotungstic acid hematoxylin (PTAH) staining of the fibrin sheath surrounding the catheter.

Figure 5

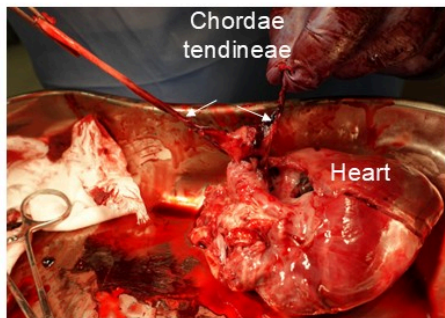
A



B



C



D

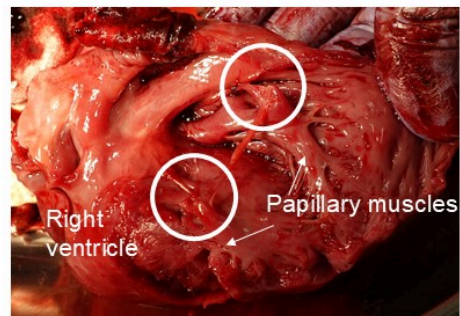


Figure 5

Catheter-associated complications in the jugular vein catheter group

(a) Catheter-associated thrombus. **(b)** A catheter-associated thrombus occupying the right atrium. **(C, D)** Catheter attachment to the chordae tendineae of the tricuspid valve, with tricuspid valve injury and prolapse associated with catheter-tip migration into the right atrium.

Figure 6

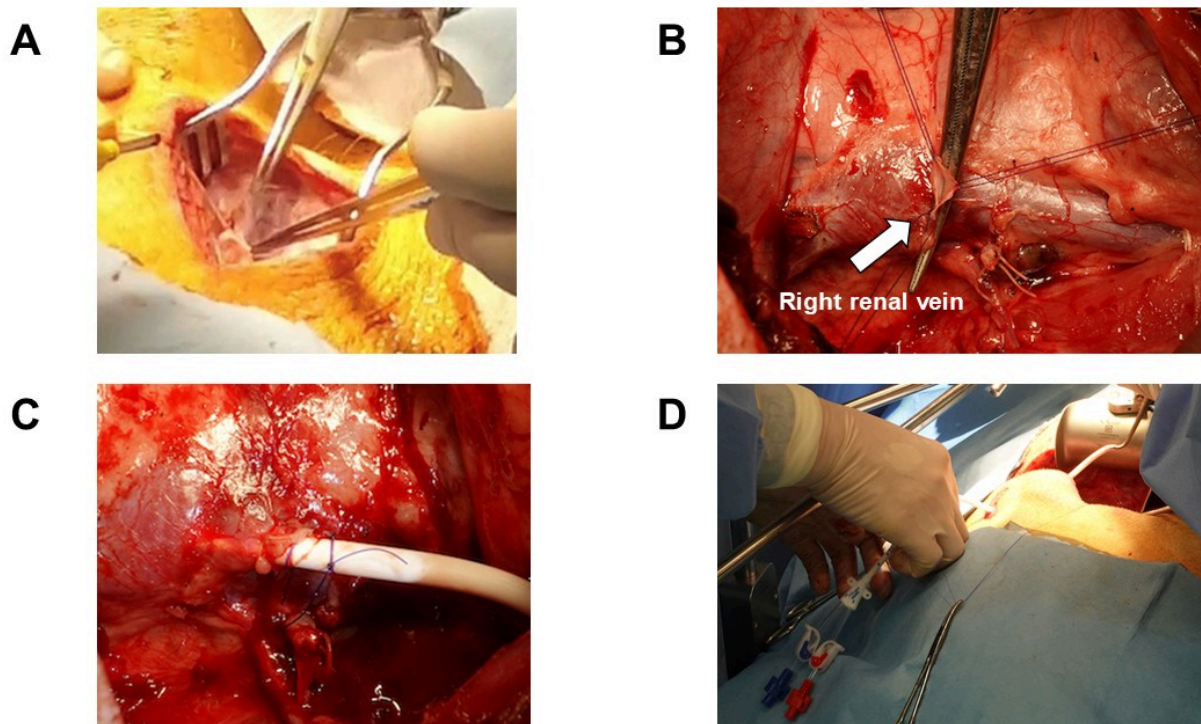


Figure 6

Catheter placement sites and catheter insertion procedures

(a) Insertion of a hemodialysis catheter into the left jugular vein. **(b)** The end of the right renal vein was secured with 5-0 nonabsorbable monofilament suture. **(c)** A hemodialysis catheter was inserted through the right renal vein into the posterior vena cava (PVC) in a cephalad direction. After confirming the catheter tip had reached the level of the hepatic vein, the right renal vein was sutured to secure the catheter. **(d)** After catheter insertion, the catheter was exteriorized through a subcutaneous tunnel.

Figure 7

A



B



Figure 7

(a) Three-dimensional computed tomography (3D-CT) showing the catheter tip near the level of the diaphragm in the posterior vena cava (PVC). **(b)** A pig undergoing hemodialysis with a catheter inserted into the PVC through the right renal vein.

Supplementary Files

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