



A step forward toward establishing a novel preclinical porcine model to study ischemia/reperfusion-induced acute and chronic kidney injuries

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Ischemic or ischemia/reperfusion injury (IRI) is the most frequently encountered type of acute kidney injury (AKI) clinically (1). It can be induced by transplantation, trauma, burns, sepsis, cardiac/thoracic surgeries and lower limb ischemia/reperfusion (IR) (1-3). There is no specific treatment for AKI. The current treatments are largely based on removing or reversing underlying causes and supportive care for managing volume and electrolyte balances. If these treatments fail, the renal replacement therapy is the only the United States Food and Drug Administration (FDA)-approved therapy. A considerable portion of patients with AKI progresses to chronic kidney disease (CKD) due to malrecovery and maladaptation, which severely increases the health care cost and compromises the quality of patients' lives (4). Further, AKI is associated with high mortality in hospitals and after discharge (5,6). Many reasons contribute to the current lack of effective therapeutics for AKI. The lack of a good preclinical model is one of them. While animal models will probably never accurately replicate the complexity of human diseases at least socially and environmentally, a good animal model will certainly help translate the results generated from the model into clinical practice.

In A. D. 162 Romans dissected pigs to gain a greater understanding of human anatomy and physiology. This is perhaps the earliest record for humans to use pigs in

biomedical research (7). Pigs and humans have similar physical sizes. Inflammation plays a pivotal role in the pathogenesis of AKI and CKD. Pigs share similar intralobular lymphatics and more than 80% of immune parameters with humans (8-10). Innate immunity is a predominant force driving progression of AKI. In humans neutrophils are the most abundant type of granulocytes and account for 40% to 70% of all white blood cells. They are also the most abundant component of innate immunity infiltrating the kidney immediately after IRI and inflicting damages by secreting cytotoxic compounds (11). Similar to humans' blood, pigs' peripheral blood is rich in neutrophils that make up 50% to 70% of white blood cells. They are also indispensable in triggering AKI. Swine kidneys are pyramidal and multi-lobular with vascular structures comparable to human kidneys (12). As a matter of fact, the anatomy of the swine kidney is more similar to humans than that of non-human primates (13). Use of pigs would draw fewer ethical concerns than use of non-human primates. Pigs have similar renal blood flow rate, resistance index, pulsatility index, and systolic/diastolic index as humans (14). Moreover, pigs and humans share similar renal function analytes such as creatinine, blood urea nitrogen (BUN) and anion secretion (8,9,15). The triple knockouts and selected transgenic porcine models from the National Swine Resource and Research Center (NSRRC) have

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facilitated translational research (16). Many pig antibodies, cytokines and detection kits are available nowadays. Some antibodies against human and mouse proteins have cross-reactivity with swine antigens. The anti ERK1/2 (Catalog # 9102) and ERK1/2 (Catalog# 9101) from the Cell Signaling Technology are two examples. The proximity to the human immunology, physical size, physiology and renal anatomy and increasing availability of research tools have made swine more and more popular subjects in the AKI research (1). Huang *et al.* recently published a review specifically for porcine models of AKI (17). This review summarized the current procedures to inflict acute IRI in the porcine kidney. It can be induced by bilateral or unilateral ischemia with closing the artery only, the artery and vein, or the whole renal pedicle through laparoscopic or open surgery. Unilateral ischemia is often accompanied with contralateral nephrectomy (17). With these models, a wealth of knowledge of the AKI pathophysiology has been generated and dozens of therapeutics have been tested (1,17). However, the high costs of the animals and animal housing, challenging surgical procedures and increasingly complicated animal welfare guidelines often discourage the frequent use of pigs in the AKI as well as CKD research.

To circumvent these disadvantages, Kinoshita *et al.* recently described a novel model of IRI in the kidney by inducing ischemia for 120 minutes in the left kidney and 60 minutes in the right kidney of a pig (18). The pigs survived and were followed for three months. The investigators withdrew blood separately from each kidney vein, performed wedge biopsy for each kidney cortex at the Day 0 and 7 after surgery and examined fibrosis respectively in each kidney at the end of study. Although only two pigs were used, which did not allow drawing any valid conclusions, the idea is worth noting and exploring further. Firstly, this model could provide two-fold data from histological, molecular, biochemical and immunological analyses of each kidney, thus halving the number of pigs needed for some types of studies and complying with three “R” principles (reduction, refinement and replacement) of animal welfare. Secondly, this model facilitates the comparisons of the results from two different ischemic times, since the two kidneys from the same pig are considered almost equal. The authors also noticed some limitations associated with the model. For examples, it is difficult to dissect the contributions from each kidney if the peripheral blood is analyzed. It is also difficult to rule out the possible ischemic preconditioning effect of the left kidney on the right kidney.

IR-induced AKI can progress to CKD, although this

type of CKD is less prevalent than hypertension- and diabetes-induced CKD. There have been only a few swine models for I/R-induced AKI/CKD, because a vast majority of I/R-induced AKI was not followed long enough to allow the development of CKD. I/R-induced AKI/CKD were demonstrated by embolization or partial ligation of renal arteries of the remnant kidney with contralateral nephrectomy in pigs (19,20). However, Kinoshita and his colleagues’ model is the first model this author has seen that has two kidneys present, a step closer to clinical scenarios (18). Moreover, the fibrotic area in the kidney subjected to 120 minutes ischemia is approximately double that in the 60 minutes ischemia kidney. This observation, albeit a very small sample size, raises an intriguing question as to whether the renal intrinsic factors play a dominant role, whereas the roles of pre-renal factors are moderate in developing fibrosis.

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Footnote

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References

1. Packialakshmi B, Stewart IJ, Burmeister DM, et al. Large animal models for translational research in acute kidney injury. *Ren Fail* 2020;42:1042-58.
2. Chopra TA, Brooks CH, Okusa MD. Acute Kidney Injury Prevention. *Contrib Nephrol* 2016;187:9-23.
3. Packialakshmi B, Stewart IJ, Burmeister DM, et al. Tourniquet-induced lower limb ischemia/reperfusion reduces mitochondrial function by decreasing mitochondrial biogenesis in acute kidney injury in mice. *Physiol Rep* 2022;10:e15181.
4. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;371:58-66.
5. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;16:3365-70.
6. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 2010;21:345-52.
7. Nutton V. Portraits of science. Logic, learning, and experimental medicine. *Science* 2002;295:800-1.
8. Meurens F, Summerfield A, Nauwynck H, et al. The pig: a model for human infectious diseases. *Trends Microbiol* 2012;20:50-7.
9. Dawson HD, Smith AD, Chen C, et al. An in-depth comparison of the porcine, murine and human inflammasomes; lessons from the porcine genome and transcriptome. *Vet Microbiol* 2017;202:2-15.
10. Pabst R. The pig as a model for immunology research. *Cell Tissue Res* 2020;380:287-304.
11. Lever JM, Hull TD, Boddu R, et al. Resident macrophages reprogram toward a developmental state after acute kidney injury. *JCI Insight* 2019. [Epub ahead of print].
12. Giraud S, Favreau F, Chatauret N, et al. Contribution of large pig for renal ischemia-reperfusion and transplantation studies: the preclinical model. *J Biomed Biotechnol* 2011;2011:532127.
13. Swindle MM, Makin A, Herron AJ, et al. Swine as models in biomedical research and toxicology testing. *Vet Pathol* 2012;49:344-56.
14. Aleksiewicz R, Lutnicki K, Bojarski M, et al. Haemodynamics Imaging of Swine Segmental Kidney Artery Using Duplex Doppler Technique. *J Vet Res* 2019;63:259-65.
15. Dhondt L, Croubels S, De Paepe P, et al. Conventional Pig as Animal Model for Human Renal Drug Excretion Processes: Unravelling the Porcine Renal Function by Use of a Cocktail of Exogenous Markers. *Front Pharmacol* 2020;11:883.
16. Eksler B, Rigotti P, Gridelli B, et al. Xenotransplantation of solid organs in the pig-to-primate model. *Transpl Immunol* 2009;21:87-92.
17. Huang J, Bayliss G, Zhuang S. Porcine models of acute kidney injury. *Am J Physiol Renal Physiol* 2021;320:F1030-44.
18. Kinoshita Y, Shirakawa K, Sano M, et al. Development of a novel porcine ischemia/reperfusion model inducing different ischemia times in bilateral kidneys-effects of hydrogen gas inhalation. *Transl Androl Urol* 2022;11:430-8.
19. Misra S, Gordon JD, Fu AA, et al. The porcine remnant kidney model of chronic renal insufficiency. *J Surg Res* 2006;135:370-9.
20. Sheu JJ, Ali HEE, Cheng BC, et al. Extracorporeal shock wave treatment attenuated left ventricular dysfunction and remodeling in mini-pig with cardiorenal syndrome. *Oncotarget* 2017;8:54747-63.

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