Role of the renal sympathetic nervous system in mediating renal ischaemic injury-induced reductions in renal haemodynamic and excretory functions


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Summary

Aim: We investigated the role of renal sympathetic innervation in the deterioration of renal haemodynamic and excretory functions during the early post-ischaemic phase of renal ischaemia/reperfusion injury.

Methods: Anaesthetised male Sprague-Dawley rats were subjected to unilateral renal ischaemia by clamping the left renal artery for 30 min followed by reperfusion. Following acute renal denervation clearance experiments were performed. In a different set of experiments, the renal nerves were electrically stimulated at increasing frequencies and responses in renal blood flow and renal vascular resistance were recorded.

Results: Denervated post-ischaemic acute renal failure (ARF) rats showed higher urine flow rate, absolute and fractional sodium excretions, urinary sodium to urinary potassium, glomerular filtration rate and basal renal blood flow but lower basal renal vascular resistance (all p < 0.05 vs innervated ARF rats). Potassium excretion was significantly lower in denervated group as per fractional (p < 0.05 vs innervated ARF rats) but not absolute potassium excretion (p > 0.05 vs innervated ARF rats). The rise in mean arterial pressure and renal vasoconstrictor response to renal nerve stimulation were blunted in denervated ischaemic ARF rats (all p < 0.05 vs innervated ARF rats). Renal histopathology in denervated ARF rats manifested a significantly lower medullary congestion, inflammation and tubular injury compared to innervated counterparts (p < 0.05 vs innervated ARF rats).

Conclusions: The findings strongly suggest the involvement of renal sympathetic tone in the post-ischaemic events of ischaemic ARF, as the removal of its action to a degree ameliorated the post-ischaemic renal dysfunctions.

Key words: Ischaemic acute renal failure, acute renal denervation, renal nerve stimulation, renal sympathetic nerve, renal function, renal haemodynamics.

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INTRODUCTION

The kidneys are profusely innervated internal organs in which the renal adrenergic neurons supply all the segments of renal vasculature and are distributed throughout the renal cortex, outer stripe of the medulla, juxtamedullary region of the inner cortex and the renal tubules. These neurons exert major effects on various aspects of renal function, including renal haemodynamics, tubular sodium and water reabsorption, renin secretion and eventually arterial blood pressure. Accordingly, alterations in the renal sympathetic nerve activity can directly influence the functions of the innervated renal effector units and therefore may contribute to the pathophysiology of various disease states.

Norepinephrine injected into the renal artery of dogs resulted in an ischaemic type of acute renal failure in which there is a reduction in renal haemodynamics. Conversely, an ischaemic insult to the kidney has been reported to activate afferent renal nerve activity which then leads to a reflex activation of efferent renal sympathetic nerves.

Furthermore, renal sympathetic nerves and circulating catecholamines are believed to be involved in the development of the progressive renal tissue injury accompanying ischaemic acute renal failure. However, experimental evidence concerning the renal sympathetic nervous system and its contribution to the pathogenesis of ischaemia/reperfusion induced acute renal failure is confounding and warrants further investigation.

At present no effective treatment is available for the renal injury following ischaemia. In spite of a high mortality rate of 50%, most surviving patients are thought to recover full renal function. Restoration of renal function following episodes of ischaemic acute renal failure is attributable mainly to the ability of renal tissue to recover from sublethal or lethal cellular damage. Following acute renal failure, there may be incomplete recovery of renal function and in the long-term it may participate in the development of chronic and progressive renal dysfunctions. Because acute renal injury predisposes the kidney to the development...
of future complications, an understanding of the mechanism underlying the injury may allow novel therapeutic approaches to be developed.

Two experimental studies have provided evidence for the relationship between renal sympathetic nervous system and acute renal failure associated with ischaemia/reperfusion injury. Ogawa et al. demonstrated that renal denervation prior to the ischaemia attenuated the observed reduction in glomerular filtration rate after ischaemia/reperfusion.18 Similarly, Fuji et al. reported that renal denervation before the introduction of an ischaemic insult to the kidney partly counteracted the enhanced water and sodium excretions and alleviated the reduction in creatinine clearance in post-ischaemic animals.19 However, there has been less emphasis on the effect of renal denervation following the induction of ischaemic acute renal failure in rats. This was addressed in the present study by investigating the effect of renal denervation on renal dysfunctions and tissue injury during the early post-ischaemic phase of renal ischaemia/reperfusion injury. Over the same timeframe we investigated the responsiveness of the renal vasculature to direct electrical stimulation of the renal sympathetic nerves.

MATERIALS AND METHODS

Animals
Male Sprague-Dawley rats (250–350 g) were obtained from the Animal Care Facility, Universiti Sains Malaysia (USM), Penang, Malaysia. The animals were housed in standard cages with 12:12 h light-dark cycle and were fed ad libitum water and fed ad libitum. Animal care before and during the experimental procedures was conducted in accordance with the policies and guidelines of the Animal Ethics Committee, USM, Penang, Malaysia. All protocols employed had prior approval from the Animal Care and Use Committee, USM.

The animals were randomly divided into two groups. Group I was used to study the renal functional responses while group II was allocated for the renal haemodynamic study. Each group was further subdivided into four subgroups of five to seven animals each. These subgroups consisted of control innervated rats, control denervated rats and two groups subjected to ischaemia/reperfusion injury, one in which the renal nerves were left intact and one in which the kidney had been subjected to renal denervation.

Surgical preparation of animals
Rats were anaesthetised with sodium pentobarbitone (Nembutal; CAVE, France) at a dose of 60 mg/kg (i.p.) and body temperature was maintained at about 37°C by means of a thermostatically controlled pad. A tracheotomy (PE250; Portex, UK) was performed to provide a clear airway. A polyethylene catheter (PE50; Portex) was inserted into the left jugular vein to enable the administration of an intravenous (i.v.) maintenance infusion of saline (0.9% NaCl) at an infusion rate of 6 mL/h and to allow an intermittent arterial blood sample collection and direct measurement of mean arterial pressure using a pressure transducer (P23 ID Gould; Statham Instruments, UK) connected to a computerised data acquisition system (PowerLab; ADInstruments, Australia). A midline abdominal incision was performed to expose the left kidney and the renal artery. For the renal clearance study, the left ureter was cannulated (PE10; Portex) for collection of urine. Upon completion of the surgical preparation and before the induction of ischaemic renal failure and renal denervation, 2 mL of saline (i.v.) were given to the animal. Subsequently, the animal was left to stabilise for a period of 30–45 min prior to commencing the experimental protocols.

The renal ischaemic insult comprised occluding the left renal artery and vein with a non-traumatic clamp for a period of 30 min. At the end of the ischaemic period the clamp was released to allow reperfusion.20

Acute renal denervation of the left kidney was carried out at the beginning of the reperfusion phase of renal ischaemia/reperfusion injury. The procedure was performed by stripping the renal artery and vein out of its adventitia. All observable renal nerves passing from the celiac and aortico-renal ganglia to the kidney were carefully isolated, dissected and then cut. This was followed by coating the remaining tissue with a solution of 10% phenol in absolute alcohol.21–23 The effectiveness of this procedure has already been established in our previous study.21 In the control and untreated acute renal failure animals, the renal sympathetic nerves were left intact and the animals were allowed an equivalent time period (≈15 min) before commencing the experimental protocols.

In the renal haemodynamic study, a flowmeter probe (EP 100 series; Carolina Medical Instruments, USA) was attached to the isolated left renal artery. The probe was connected to a Square-Wave Electromagnetic Flowmeter (Carolina Medical Instruments) which was linked to a computerised data acquisition system (PowerLab; ADInstruments, Australia).

Experimental protocols
Following renal denervation the animals were subjected to one of the following protocols:

Protocol I
Six 20-min urine collections were performed to measure urine volume and subsequently calculate urine flow rate, glomerular filtration rate, absolute sodium excretion, fractional sodium excretion, absolute potassium excretion, fractional potassium excretion and glomerular filtration rate, respectively.

Protocol II
Basal renal blood flow and renal vascular resistance values were determined before commencing renal nerve stimulation experiment. The renal nerves were stimulated (Grass S 48 Stimulator; Grass Instruments, USA) at frequencies of 1, 2, 4, 6, 8, and 10 Hz, at 0.2 ms duration and 15 V for a period of 15 s in ascending then descending orders. The magnitudes of reduction in renal blood flow and changes in renal vascular resistance were recorded. At each frequency renal blood flow and renal vascular resistance were allowed to return to the baseline pre-stimulus values. In denervated animals the stimulation was carried at the distal cut end of the renal nerve from the left kidney hilus.22

At the end of the experiment, the animals were killed using an overdose of anaesthetic and the left kidney was removed and immediately cleared of connective tissue, blotted on tissue paper and preserved in 10% formalin solution for histological examination. Subsequently, the animals were disposed of in accordance with the guidelines of the Animal Ethics Committee, USM, Penang, Malaysia.

Biological samples and biochemical analyses
Urine samples were collected in microcentrifuge tubes (Eppendorf, Germany) and the volumes obtained were quantified gravimetrically. Blood samples were collected (0.5 mL) from the right carotid artery into a pre-cooled heparinised syringe, centrifuged (3000 rpm, 1 min) and the clear plasma was separated. The blood cells were resuspended in normal saline at an equal volume to the plasma obtained and reinfused into the animal immediately. Plasma and urine samples were stored at –4°C until assayed for sodium and potassium using flame photometry (Hitachi, Japan) and for creatinine by means of spectrophotometry (Hitachi).

Histopathological study of renal tissue
Excised left kidneys were processed for light microscopic observation according to standard procedures. The tissues were fixed in 10% formalin before being processed using Citidel 1000 histokinette (Shandon Scientific, UK). After processing, the tissues were embedded in paraffin with Histo- Center II-N (Barnstead/Thermolyne, USA) and sectioned to a thickness of
Renal functional responses in control innervated (C-INN), control denervated (C-DNX), ischaemic acute renal failure innervated (ARF-INN), and ischaemic acute renal failure denervated (ARF-DNX) Sprague-Dawley rats. (A) Urine flow rate (UV), (B) absolute sodium excretion (UNaV), (C) fractional sodium excretion (FSNa), (D) absolute potassium excretion (UKV), (E) fractional potassium excretion (FPK), (F) urinary sodium to urinary potassium ratio (UNa/UK) and (G) glomerular filtration rate (GFR). Data presented as mean ± SEM. The statistical analysis of the data was performed using one- and two-way ANOVA followed by Bonferroni-Dunn all means post-hoc test. The differences between the means were considered significant at 5% level. All statistical analysis was performed using SUPERANOVA statistical package (Abacus, USA).

RESULTS
General observations

Body weights of the rats were similar in all four groups (control innervated group: 288 ± 5 g, control denervated group: 270 ± 6 g, ischaemic acute renal failure innervated group: 290 ± 7 g and ischaemic acute renal failure denervated group: 285 ± 10 g).

Acute effects of ischaemic injury and renal denervation on renal function

Fig. 1 presents the data from the four groups of rats subjected to the functional studies. Renal function of rats subjected to 30 min ischaemia showed a marked deterioration when measured during the reperfusion phase. As compared to the control innervated group not subjected to the renal ischaemia challenge, post-ischaemia rats with an intact renal innervation manifested a significantly higher (all p < 0.05) urine flow rate (Fig. 1A), sodium (Fig. 1B,C) and potassium excretions (Fig. 1D,E), both in absolute and as a fraction of the filtered load. There were no significant (p > 0.05) alterations in the urinary sodium to urinary potassium ratio (Fig. 1F) in either experimental ascending and descending orders. Changes in renal blood flow were expressed as percentage decrease from the baseline values calculated at the beginning of the administration of each stimulation frequency used. All data are the average values calculated from individual animals and are given as mean ± SEM. The statistical analysis of the data was performed using one- and two-way ANOVA followed by Bonferroni-Dunn all means post-hoc test. The differences between the means were considered significant at 5% level. All statistical analysis was performed using SUPERANOVA statistical package (Abacus, USA).
In non-ischaemic rats, there was a significantly higher urine flow rate, absolute sodium excretion, fractional sodium excretion, absolute potassium excretion, fractional potassium excretion, urinary sodium to urinary potassium ratio and glomerular filtration rate (Fig. 1A–G) following renal denervation (all \( p < 0.05 \)) compared to ischaemic renal failure rats with intact renal nerves. In contrast to these observations, renal denervation in post-ischaemic animals did not significantly alter absolute potassium excretion (all \( p > 0.05 \) ) (Fig. 1D), but it did significantly lower fractional potassium excretion (all \( p < 0.05 \) ) (Fig. 1E) as compared to innervated littersmates. In the early reperfusion phase, glomerular filtration rate (Fig. 1G) was significantly higher (all \( p < 0.05 \) ) in acute renal failure rats subjected to acute renal denervation compared to innervated ischaemic acute renal failure group. No significant differences were observed in urine flow rate, absolute sodium excretion, fractional potassium excretion and urinary sodium to urinary potassium ratio between denervated ischaemic renal failure rats and the denervated control group (Fig. 1A–F). However, fractional sodium excretion was significantly higher (all \( p < 0.05 \) ) in denervated rats subjected to ischaemia/reperfusion as compared to denervated control group (Fig. 1C). Mean values for absolute potassium excretion and glomerular filtration rate, on the other hand, were significantly lower (all \( p < 0.05 \) ) in denervated post-ischaemic animals when compared to denervated control counterparts (Fig. 1D,G).

**Acute effects of ischaemic injury and renal denervation on haemodynamic responses**

The effects of post-ischaemic treatment with renal denervation on the renal haemodynamics alterations induced by 30 min ischaemia are shown in Fig. 2 and 3. Innervated post-ischaemic rats had a significantly higher (all \( p < 0.05 \) ) mean arterial pressure (Fig. 2A) as compared to the control innervated group. Higher baseline renal vascular resistance (Fig. 2B) and concomitantly lower basal renal blood flow (Fig. 2C) were also observed in innervated acute renal failure (all \( p < 0.05 \) vs control innervated group).

Removal of renal sympathetic innervation in non-ischaemic rats did not significantly alter mean arterial pressure, baseline renal vascular resistance and baseline renal blood flow as compared to control innervated group. In contrast, renal denervation in ischaemic renal failure animals resulted in a significantly lower mean arterial pressure (Fig. 2A), lower basal renal vascular resistance (Fig. 2B) and concurrently higher basal renal blood flow (Fig. 2C) as compared to innervated rats subjected to renal ischaemia/reperfusion challenge (all \( p < 0.05 \) ).

Direct electrical stimulation of the renal sympathetic nerves resulted in frequency-related increases in renal vascular resistance and simultaneous frequency-dependent reduction in renal blood flow in all experimental groups. However, the overall increase in renal vascular resistance and mean percentage reduction in renal blood flow were significantly lower (all \( p < 0.05 \) ) in ischaemic renal failure rats with intact renal nerves as compared to the control counterparts (Fig. 3A,B).

In both control and ischaemic renal failure rats, there was a marked attenuation in the renal vasoconstrictor responses to direct electrical stimulation of the renal nerve following removal of the renal sympathetic tone by denervation. Such an effect was reflected by significantly lower renal vascular resistance (Fig. 3A) and hence a lower overall mean percentage drop in renal blood flow (Fig. 3B) in response to renal nerve stimulation (all \( p < 0.05 \) vs respective innervated groups).
renal denervation is performed during the acute phase of reperfusion injury.

Ogawa and colleagues reported that renal denervation before the ischemic period attenuated the reduction in glomerular filtration rate after ischemia/reperfusion challenge.18 Fujii et al. indicated that renal denervation before the application of an ischemic insult to the kidney counteracted the enhanced water and sodium excretions and alleviated renal dysfunctions in post-ischemic animals.19 These findings support the view that renal sympathetic nerve activity is directly related to the impact on renal function in the period of ischemic injury. However, the effects of renal denervation on the post-ischemic events of ischemia/reperfusion induced acute renal failure have been largely unexplored. This was addressed in the present study in an attempt to further clarify the role of renal sympathetic nervous system in the deterioration of renal hemodynamic and excretory functions during the early post-ischemic phase of renal ischemia/reperfusion injury.

In the setting of the innervated group, there was a robust and sustained diuresis, natriuresis and kaliuresis in the post-ischemic period, which could be attributed to impaired urinary concentrating ability through, at least in part, ATP depletion and/or backleak of filtrate across the damaged proximal and distal tubular epithelia and/or osmotic diuresis due to profound solutes loss. The observed excretory responses to renal ischemia/reperfusion have been reported in previous studies18–20 and reaffirmed the effectiveness of the model in this experimental setting. Our study extended previous findings to show that potassium excretion was raised and as a consequence there was an absence of any statistically significant difference in urinary sodium to urinary potassium ratio in the early post-ischemic phase. Together, these observations would confirm that enhanced salt excretion was primarily due to impaired tubular functions following renal ischemia. This was to a degree supported by the histological evaluation of the post-ischemic kidneys.

The findings of the present study where renal denervation took place in the post-ischemic time frame did not parallel those reported when renal denervation was performed before the induction of renal ischemia/reperfusion injury. It was evident that acute renal denervation in the post-ischemic period measurably enhanced sodium and water excretions but conversely attenuated the excretion of potassium. Abundant experimental evidence indicates that enhanced salt excretion was primarily due to impaired tubular functions following renal ischemia. This was to a degree supported by the histological evaluation of the post-ischemic kidneys.

Acute effects of ischemic injury and renal denervation on renal histopathological examination

Histopathological examination of renal tissues obtained from innervated ischemic renal failure rats revealed the presence of marked medullary congestion and inflammation of the outer zone inner stripe of the medulla, together with evident tubular injury in the medullary outer zone outer stripe (p < 0.05 vs innervated control group). In the group subjected to renal denervation, the presence of these lesions was significantly lower (p < 0.05 vs innervated ischemic renal failure group); yet, it was not completely abolished (p < 0.05 vs innervated or denervated control groups). Typical photographs are shown in Fig. 4.

DISCUSSION

Renal sympatho-excitation is believed to be involved in the development of ischemic acute renal failure.19 Using a rat model of ischemic acute renal failure, herein we report that several manifestations of renal function, hemodynamics and structure can be substantially alleviated when renal denervation is performed during the acute phase of reperfusion injury.

Fig. 3 Renal nerve stimulation (RNS) responses in control innervated (C-INN), control denervated (C-DNX), ischemic acute renal failure innervated (ARF-INN), and ischemic acute renal failure denervated (ARF-DNX) Sprague-Dawley rats. (A) Effect on renal vascular resistance (RVR). (B) Effect on percentage reduction in renal blood flow (RBF). Data presented as mean ± SEM (n = 57). Data were analysed by two-way ANOVA followed by Bonferroni-Dunn all means post-hoc test. *p < 0.05: significant difference between C-INN and C-DNX groups. **p < 0.05: significant difference between ARF-INN and C-INN groups. ***p < 0.05: significant difference between ARF-INN and ARF-DNX groups.

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cantly higher levels compared to ischaemic acute renal failure animals with intact renal innervation.

The ability of renal denervation to counteract the enhanced kaliuretic responses in the early reperfusion phase of renal ischaemia/reperfusion injury remains unclear. Potassium is freely filterable at the glomerulus and most of the filtered load is reabsorbed by the tubules. However, the cortical collecting duct can secrete potassium and contribute to changes in its excretion at this tubular segment.30 The secretion of potassium is accompanied by sodium reabsorption at the cortical collecting duct, a process which is predominantly controlled and influenced by the action of the hormone aldosterone.30 Thus, one possible mechanism behind the observed changes in sodium, potassium and water excretions is the denervation-induced suppression of renin-angiotensin-aldosterone system (RAAS) and its impact on modulation of water and electrolyte reabsorption and secretion along the cortical collecting ducts. The latter view was supported by the observation that the urinary sodium to urinary potassium ratio, an indirect renal functional marker of aldosterone action on the collecting tubules whose value is inversely proportional to plasma aldosterone level,23,31,32 was significantly higher in denervated acute renal failure rats as compared to innervated counterparts. In other words, loss of renal neural input could have resulted initially in enhanced excretions of sodium and water and therefore augmented the diuretic and natriuretic responses, and thereafter active reabsorption of potassium which opposed the decreased proximal tubular reabsorption could have developed.

The reduction in glomerular filtration rate in the early post-ischaemic phase of renal ischaemia/reperfusion injury was most likely attributable to increased renal vascular resistance and consequent reduction in renal blood flow following renal ischaemia. A similar pattern of change in glomerular filtration rate and renal blood flow was observed in earlier studies using this model18–20,33,34 and further supported the reliability and reproducibility of this animal model of acute renal failure. A further possible contributory factor underlying this reduction in glomerular filtration rate was the marked interstitial congestion, as was evident in the histopathological assessment of ischaemic renal tissues, which would be consistent with increased renal vascular resistance. Renal denervation showed a considerably beneficial effect in ameliorating glomerular filtration rate, renal vascular resistance, renal blood flow and tissue injury which would further indicate a role for the overactive sympathetic nervous system in this pathophysiological state.

The current study provided further evidence that the renal vasoconstrictor response to electrical stimulation of renal nerves, as reflected by the percentage of reduction in renal blood flow and changes in renal vascular resistance, was noticeably decreased after reperfusion following 30 min ischaemia. These findings suggested that both the ischaemia itself and the reperfusion period activated the renal sympathetic nervous system and augmented norepinephrine release from nerve terminals. It is known that hyperactive sympathetic nervous system and prolonged exposure to catecholamines can contribute to dampening of adrenergic receptor responsiveness to endogenous as well as

Fig. 4 Light microscopy of renal tissue (5 μm) from (A) control innervated (C-INN), (B) control denervated (C-DNX), (C) ischaemic acute renal failure innervated (ARF-INN) and (D) ischaemic acute renal failure denervated (ARF-DNX) Sprague-Dawley rats. Arrows indicate damage to the tubular structure (H&E staining). (E) Histopathological change/grade. Each column and bar represents the mean ± SEM (n = 5–7). Grades: no damage (0), mild (1), moderate (2), severe (3), very severe (4). Data were analysed by one-way ANOVA followed by Bonferroni-Dunn all means post-hoc test.

**p < 0.05: significant difference between ARF-INN and C-INN groups.
†p < 0.05: significant difference between ARF-INN and ARF-DNX groups.
‡p < 0.05: significant difference between ARF-DNX and C-DNX groups.
exogenous adrenergic vasoconstrictor stimuli, a phenomenon which is known as desensitisation. Desensitisation is a very complex process that triggers a number of inter-related yet distinct mechanisms occurring at the receptor level to turn off the receptor-mediated signal transduction pathway.35 Receptor desensitisation may occur within seconds to minutes of agonist stimulation, and is generally considered to result from either sequestration of the receptors so that they are unavailable for interaction with the ligand, down-regulation of the receptors or inability of the receptor to couple to G-protein due to receptor phosphorylation.36,37 Accordingly, it is likely that endogenous norepinephrine released by renal sympathetic nerve endings and increased renal vascular resistance played an important role in the development of ischaemia/reperfusion induced acute renal failure and, moreover, contributed to the reduction in renal blood flow and simultaneous increase in mean arterial pressure during the reperfusion phase in our study. Furthermore, desensitisation of α1-adrenoceptors by renal sympathetic nervous system activation may have contributed to the observed reduction in the renal vasoconstrictor responses to renal nerve stimulation as this subtype plays the major role in regulation of renal vascular tone.38-40 On the other hand, the ameliorative effects of renal denervation on renal function, haemodynamics and structure were unlikely to be due to an effect other than that of renal denervation-induced reduction in renal sympathetic outflow, since a significant drop in the renal vasoconstrictor response to direct electrical stimulation of the renal nerves was observed when the stimulation was performed in denervated animals. The latter effect indicated the effectiveness of this procedure in establishing a sufficient level of peripheral sympatho-inhibition in the diseased animals. Together, these findings suggest that pathogenesis of ischaemic acute renal failure is mediated at least partly by presynaptic enhanced noradrenergic neurotransmission and possible action on postsynaptic α1-adrenoceptors. This, to a degree, explains the attenuation in sodium and water excretions observed by Fujii and co-workers when they performed renal denervation prior to the induction of ischaemia/reperfusion19 while an enhancement in these responses was observed in our study when renal denervation was carried out immediately after renal ischaemia. This would further suggest that possible post-synaptic effect of norepinephrine and established tubular injury tend to abrogate the renoprotective effect of renal denervation on sodium and water excretions.

In summary, data from these experiments support the view that the renal sympathetic nerves are involved in the pathogenesis of ischaemic acute renal failure. An enhanced impact of the renal sympathetic nerves on excretory function is an early consequence of renal ischaemia/reperfusion injury. Renal denervation immediately after ischaemic injury considerably improves the pattern of renal dysfunctions post-ischaemia; however, this manoeuvre incompletely resolves these dysfunctions insofar as the diuresis and natriuresis in the reperfusion phase of renal ischaemia/reperfusion persist. The observed renal functional and haemodynamic responses to acute renal denervation in ischaemic renal failure rats are mostly likely attributable to the reduction in the activation of RAAS.

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