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Mini-review

Scorpion venoms, kidney and potassium

Jaruboot Angsanakul, Visith Sitprija*

Queen Saovabha Memorial Institute, 1871 Rama 4 Road, Bangkok 10330, Thailand

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ABSTRACT

Scorpion venoms cause renal injury by the interaction of renal ischemia due to intense renal vasoconstriction and inflammatory reactions due to proinflammatory cytokines and mediators. Renal vasoconstriction is not only induced by catecholamine storm but also by angiotensin II and the direct action of venom on vascular ion channels. Increased aldosterone also contributes to hypertension. Blocking of renal tubular K channels decreases renal K excretion and increases serum K level which increases aldosterone release. Hyperaldosteronism increases K excretion mostly through ROMK2 and ROMK3 unblocked by the venom. The presence of angiotensin converting enzyme inhibitor in some scorpion species can increase serum K. Therefore, there are both K increasing and K decreasing effects in renal K excretion. Serum K in scorpionism is the net result of the two opposing effects. Hyperkalemia is therefore inconsistent.

1. Introduction

There are thousands of scorpion species, but approximately 30 scorpion species are medically important. According to recent epidemiologic data, at least 1.2 million scorpion stings per year with more than 3000 deaths were reported (Chippaux and Goyffon, 2008). Of the 6 families of scorpions, only those in the families Buthidae and Hemiscorpiidae are of human hazards. Significant envenomations are due to Hemiscorpiidae family, genus Hemiscorpius, in the Middle East and family Buthidae which includes Mesobuthus and Hottentotta species in India, Leiurus species in the Middle East, Androctonus and Buthus species in North Africa, Tityus species in South America, Centruroides species in North America and Parabuthus species in South Africa. Scorpion envenoming produces both local and systemic symptoms. Local symptoms include pain, swelling, redness and heat. Lymphadenopathy may be observed. Systemic symptoms of autonomic nervous systemic involvement, developing within minutes or hours, consist of mydriasis, sweating, salivation, diarrhea, vomiting, priapism, sweating, hyperthermia, hypertension, hypotension, cardiac arrhythmias, myocarditis and pulmonary edema (Krishna Murthy, 2000; Yugandhar et al., 1999). These symptoms are attributed to the effects of the venom on ion channels and inflammatory reactions. Severe scorpion envenoming causes an autonomic storm which can result in multisystem organ failure and death (Gwee et al., 2002). It is interesting that, irrespective of different species of scorpions, clinical manifestations are similar with varying degrees of severity. Lethal fraction of venom from different species has similar effects on the autonomic nervous system. Hypertension is observed in over 80% in the victims of Indian red scorpion sting. Pulmonary edema is a frequent complication, and may overshadow the other manifestations. Insulin administration reverses hemodynamic changes and pulmonary edema. Scorpion envenoming increases the release of catecholamines, glucagon, liver enzymes, serum amylase, free fatty acid and cortisol. Serum triglyceride level is decreased. Unopposed α adrenergic stimulation suppresses insulin secretion. Several electrolyte disorders have been described. Hyperglycemia, hyperkalemia, hypokalemia, hypomagnesemia, hypermagnesemia, hypocalcemia, hyponatremia and acid-base

* Corresponding author. Tel.: +662 2526117; fax: +662 2540212.
E-mail addresses: visithstprj@yahoo.com, visith@redcross.or.th (V. Sitprija).

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disorder are common (Andrade et al., 2004; Ismail, 1995; Murthy et al., 1986; Osnaya-Romero et al., 2008). Renal failure can occur. Since scorpion venom modulates K channels, dyskalemia in scorpion envenoming is therefore interesting among other electrolyte changes. Both hyperkalemia and hypokalemia have been observed. Indeed, in the presence of renin-angiotensin activation, hypertension and hyperaldosteronism, hyperkalemia is paradoxical. Renal K secretion plays an important role in K homeostasis. Several types of K channels in renal tubules are modulated by scorpion toxin (Hebert et al., 2005; Lu and MacKinnon, 1997). Study of serum potassium in scorpion envenoming therefore attracts attention. Considering multiple causes of hypertension (Krishna Murthy, 2000) complicated by the presence of angiotensin converting enzyme inhibitor in the venom of some scorpion species (Longenecker et al., 1980; Meki et al., 1995; Zeng et al., 2012), mechanisms involved in renal dysfunction induced by the venom effects on vascular ion channels and dyskalemia caused by venom effects on renal tubular K channels deserve a brief review.

2. Pathophysiology

Components of scorpion venoms consist of phospholipase, sphingomyelinase, hyaluronidase, mucopolysaccharides, histamine, serotonin, acetylcholinesterase, proteases, protease inhibitors, polypeptides and proteins. Several peptides can potentiate endogenous peptides in the host. Symptomatology in the host is thus induced by the venom itself and by endogenous mediators generated by the host. The kidney and liver are the main routes of venom excretion. After envenoming the venom rapidly distributes to all tissues with highest concentration in the kidney (Ismail, 1995; Seyedian et al., 2012).

Scorpion venoms induce the release of proinflammatory and anti-inflammatory cytokines and vasoactive mediators which include IL-1β, IL-4, IL-6, IL-8, IL-10, TNFα, IFNγ, NO, PGE_2 and kinins (Petricevich, 2010). TNFα plays important roles in generating other proinflammatory cytokines, causing metabolic derangement and organ injury (Abdoon and Fatani, 2009; Petricevich, 2010). In addition,TNFα can form ion permeable channels on the cell membrane through insertion into the lipid layer (Kagan et al., 1992). Both classical and alternative pathways of complement system are activated (Bertazzi et al., 2003). Local and systemic reactions are effects of these proinflammatory cytokines as an innate immune response of the host and effects of the venom on ion channels. Systemic reactions are displayed as hemodynamic changes, metabolic alteration and autonomic nervous system involvement. Scorpion venom effects on ion channels play a key role in causing hemodynamic alteration and autonomic nervous symptoms. In a study by Arie-Saadia et al. (1996) using cultured cardiac cells, the venom of *Leiurus quinquestriatus* hebreus increased Ca uptake into cardiocytes. This was inhibited by nifedipine indicating Ca influx into cardiocytes and presumably vascular muscle cells through L type Ca channels. The Ca uptake by the sarcoplasmic reticulum could be due to activation of adrenoceptors. Slow inactivation of Na channels by scorpion venom would increase intracellular Na which increases Na–Ca exchange (NCX) resulting in increased cytosolic Ca (Maier and Hasenfuss, 2006). Closing of K channels by scorpion venom depolarizes vascular smooth muscle cells and open Ca channels. Increased cytosolic Ca causes vasoconstriction and hypertension. Combining both effects (NaScTx and KTx) would prolong the action potential. Ca efflux from sarcoplasmic reticulum also increases cytosolic Ca. Kurtoxin (*Parabuthus transvaalicus*) opens P type Ca channels (Sidach and Mintz, 2002). In autonomic neurons, slow inactivation of Na channels, closing of K channels and opening of Ca channels result in the release of neurotransmitters, both catecholamines and acetylcholine (Kongsamut et al., 1989; Serone and Angus, 1999 : Waterman, 1996). Therefore, both sympathetic and parasympathetic nervous systems are stimulated. Parasympathetic stimulation is of short duration, but sympathetic stimulation is prolonged. Hypertension with cardiovascular symptoms are therefore common along with gastrointestinal symptoms such as salivation, vomiting, diarrhea, increased gastric and pancreatic secretion representing both adrenergic and cholinergic effects (Ismail, 1995; Krishna Murthy, 2000). Renin-angiotensin system activation by catecholamines increases angiotensin II with secondary aldosterone release. Aldosterone causes hypervolemia through salt and water retention. Therefore, direct vascular effects of venom through ion channels, catecholamines, angiotensin II and aldosterone are responsible for hypertension. Hypotension is believed to be attributed to catecholamine depletion with predominant effect of acetylcholine. Pulmonary edema caused by scorpion venom has been attributed to cardiac failure and increased vascular permeability due to venom (Krishna Murthy, 2000). Additionally, down regulation of Na–K ATPase at the basal border of the alveolar epithelial cell type II by endocytosis and surfactant deficiency result in decreased lung liquid clearance (Comellar et al., 2003). In man, pulmonary edema is observed several hours after the sting. In rats pulmonary edema can occur within one hour. Insulin increases alveolar fluid clearance through up-regulation of ENaC at the apical border of alveolar epithelial cells (Deng et al., 2012). It is also possible Na–K ATPase activity is increased by insulin.

3. Renal injury

Clinically, proteinuria, hematuria and hemoglobinuria can be manifested in scorpionism (Pipelzadeh et al., 2007). As in other animal toxins renal failure is also observed in scorpion envenoming (Sitprija and Sitprija, 2012), especially in the Middle East, South Asia, North Africa and Eastern Mediterranean region (Pipelzadeh et al., 2007; Viswanathan and Prabhu, 2011). Renal ischemia, attributed to renal vasoconstriction due to catecholamine storm, renin angiotensin activation and perhaps direct toxin effect on ion channels are responsible for the development of renal injury. In an isolated renal perfusion study, *Tityus serrulatus* venom increased renal vascular resistance and decreased glomerular filtration rate indicating direct vasoconstriction effect of the venom on vascular ion channels (De Sousa Alves et al., 2005). The venom possibly closes K channels, activates Na channels and open Ca channels. Ischemia itself can activate inflammatory

reaction which further enhances ischemia (Granger, 2006; Zhang et al., 2003). Venom enzymes and secondary effects of the venom, due to proinflammatory cytokine and mediators, such as intravascular hemolysis, hemoglobinuria, disseminated intravascular coagulation, rhabdomyolysis, myoglobinuria, complement activation and free radicals further contribute importantly to renal injury (Krishna Murthy, 2000; Sitprija and Sitprija, 2012). Whether or not the venom has direct injury to the kidney remains to be studied. Fig. 1 summarizes the mechanism responsible for acute kidney injury by scorpion venom. Clinically, renal failure is catabolic and often oliguric. Clinical pictures do not differ from AKI due to other animal toxins (Sitprija, 2008). Hemoglobinuria, thrombocytopenia, disseminated intravascular coagulation, hematuria and jaundice due to hemolysis and liver injury have been reported (Ismail, 1995; Krishna Murthy, 2000). Hemolytic uremic syndrome has been observed (Valavi and Ansari, 2008). Renal pathological changes include tubular necrosis, cellular infiltration of renal interstitium, glomerular mesangial hypercellularity, vasculitis and thrombotic microangiopathy (Dehghani et al., 2012; Heidarpour et al., 2012; Sitprija and Sitprija, 2012). Patchy cortical necrosis has been observed. Despite a variety of renal pathological changes described, acute renal failure in scorpion envenoming is not common when compared with that observed in snake bite. The other toxin components in the venom may have counteracting effects on renal hemodynamic changes. The presence of angiotensin converting enzyme inhibitor (ACEI) or bradykinin potentiating peptide (BPP) in certain scorpion species may provide protective effect against acute kidney injury. It has been shown that ACEI prevented the decrease in renal blood flow and glomerular filtration rate in dogs envenomated with Russell's viper venom (Chaiyabutr and Sitprija, 1999). Mesobuthus (Zeng et al., 2012), Buthus (Meki et al., 1995) and Centruroides species (Longenecker et al., 1980) are scorpions reported to have ACEI. It is also possible that natriuretic peptides with glomerular filtration and renal blood flow increasing effects may be present in some scorpion venoms, and these peptides may protect renal injury.

4. Toxin and renal epithelial K channels

Among ion channels in renal tubules, perhaps only K channels are modulated by scorpion toxins (Hebert et al., 2005). These K channels include voltage gated K channels (Kv), ROMK (Kir1.1) and Ca activated K channels (Kca). Among the 3 classes of K channel blocking toxins (KTx), (αKTx, βKTx and γKTx), most toxins are αKTx (Mouhat et al., 2008). Scorpion αKTx targets Kv especially which are widely distributed in many cell types including kidney (cortex, outer and inner medulla). The channels are regulated through phosphorylation by serum-glucocorticoid kinase (SGK). A number of scorpion toxins inhibit Kv1.1, Kv1.2, Kv1.3, Kv1.6, Kv1.7 and Kv1.10 in the renal tubule. Kv plays an important role in K secretion and creates positive potential in the tubular lumen for transportation of cation. Table 1 shows K channels in renal tubular cells affected by venoms from various scorpion species which include voltage gated K channel (Kv), ROMK (Kir 1.1) and Ca activated K channel (Kca) (Coetzee et al., 1999; Dhawan et al., 2003; Gati et al., 2012; Grissmer et al., 1994; Hebert et al., 2005; Hopkins, 1998; Koschak et al., 1998; Lewis and Garcia, 2003; Lu and MacKinnon, 1997; More et al., 2005; Mouhat et al., 2008; Peter et al., 2001; Restrepo-Angulo et al., 2010; Rochat et al., 1998).

ROMK is low conductance and inward rectifying K channel that secretes K through the apical border of distal nephrons including medullary and cortical thick ascending

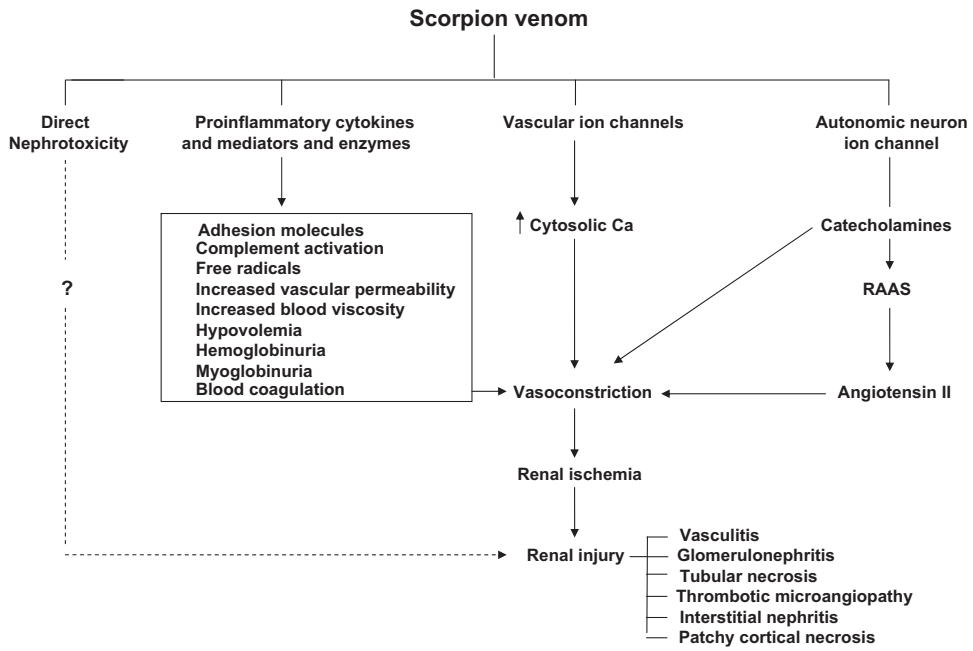

Fig. 1. Diagram showing renal injury caused by scorpion venom. RAAS: renin angiotensin aldosterone system.

Table 1
Scorpion toxins and renal K channels.

Scorpion toxins	Kv1.1	Kv1.2	Kv1.3	Kv1.6	Kv1.7	Kv1.10	ROMK1 (Kir 1.1a)	Maxi-K (Kca 1.1)	SK (Kca 2.1–2.3)	References
Maurotoxin (MTX) (*Scorpio maurus palmatus*)	↓	↓	↓							Rochat et al., 1998
Kaliotoxin (KTX) (*Androctonus mauritanicus*)	↓	↓	↓					↓		Gati et al., 2012; Grissmer et al., 1994, Hebert et al., 2005; Mouhat et al., 2008
Tityustoxin (*Tityus serrulatus*)		↓								Hopkins, 1998
Charybdotoxin (ChTX) (*Leiurus quinquestriatus*)	↓	↓	↓	↓		↓	↓	↓		Gati et al., 2012; Hebert et al., 2005, Lu and MacKinnon, 1997; Mouhat et al., 2008
OSK1 (*Orthochirus scrobiculosus*)	↓	↓	↓						↓	Mouhat et al., 2008; Restrepo-Angulo et al., 2010
Toxin (*Pandinus imperator*)			↓							Peter et al., 2001
Hongotoxin-1 (*Centruroides limbatus*)			↓	↓						Coetzee et al., 1999; Koschak et al., 1998
Iberiotoxin (IbTX) (Mesobuthus tumulus)								↓		Gati et al., 2012
Margotoxin (MgTX) (*Centruroides margaritatus*)	↓	↓	↓	↓						Lewis and Garcia, 2003; Mouhat et al., 2008; Coetzee et al., 1999
BTK_2 (*Buthus tamulus*)	↓									Dhawan et al., 2003
Noxiustoxin (NTX) (*Centruroides noxius*)	↓		↓		↓					Mouhat et al., 2008
Toxin (*Palamneus gravimanus*)	↓									More et al., 2005

Kv: voltage gated K channel; Kca: calcium activated K channel.

limb of Henle loop, distal convoluted tubule, cortical collecting duct and outer medullary collecting duct. ROMK2 (Kir1.1b) and ROMK3 (Kir1.1c) provide the pathway for apical K recycling which is important for supplying luminal K for Na–K–2Cl cotransport through NKCC2 in the thick ascending limb of Henle's loop. ROMK1 (Kir1.1a) is present only in the cortical and outer medullary collecting duct (Wang and Hebert, 2000). A high K intake and aldosterone increase the number of ROMK. As apical K channel, ROMK contributes to positive lumen potential for paracellular transport of Mg and Ca from luminal to basolateral border. Charybdotoxin from *Leiurus quinquestriatus* inhibits ROMK1 through electrostatic forces between the positive charges on the venom molecule and negative charges in the outer-mouth of K channel (Lu and MacKinnon, 1997). ROMK2 and ROMK3 are spared from scorpion venom effect.

Ca activated K channels (Kca) with both high conductance (Maxi-K or BK, Kca1.1) and low conductance (SK) are present in the distal nephron. Kca channels are modulated by intracellular Ca. Increased intracellular Ca opens and polarizes Kca channels and reduces cellular Ca influx through closing of Ca channel. Decreased intracellular Ca closes Kca channels (Jackson, 2000). Maxi-K or BK channels (Kca1.1) are activated by voltage, wall tension and intracellular Ca and Mg (Bailey et al., 2006). In the renal tubule Maxi-K channels are identified in distal nephron including principle and intercalated cells in cortical collecting duct and late distal tubule. Kca is inhibited by charybdotoxin, iberiotoxin (*Mesobuthus tamulus*), kaliotoxin (*Androctonus mauritanicus*) and OSK1 (*Orthochirus scrobiculosus*) (Table 1). Maxi-K channels are upregulated by high urine flow rate and high K intake. Maxi-K shares with ROMK in K secretion in the renal tubules. Maxi-K is inhibited by charybdotoxin, iberiotoxin and kaliotoxin (Hebert et al., 2005). OSK1 inhibits low conductance Kca (SK) (Restrepo-Angulo et al., 2010). In mice deletion of Maxi-K channels caused hyperkalemia which stimulates the release of aldosterone causing hypertension (Grimm et al., 2009). Hypertension can also result from opening of L-type Ca channels caused by blocking of Maxi-K (Wu and Marx, 2010). This can be another mechanism of hypertension in scorpionism.

Several scorpion toxins inhibit K channels. The decrease in urinary K excretion would depend upon the number and degree of K channel inhibited by toxin and the degree of toxin inhibition. In this respect, charybdotoxin inhibiting Kv1.1, Kv1.2, Kv1.3, Kv1.6, Kv1.10, ROMK and Maxi-K would theoretically decrease urinary K excretion at a greater degree than other scorpion toxins. Injection of *Leiurus quinquestriatus* venom to rabbits caused elevation of serum K, but urinary K was not studied (Andrade et al., 2004). Elevation of serum K has been observed in rats following envenomation of *Androctonus crassicanda* (Ozkan et al., 2008), closely related to *Androctonus mauritanicus* with kaliotoxin which blocks several K channels (Table 1). Data on K intake and urinary K were not available. Hyperkalemia would be observed with high K intake, another factor to be considered. In a study in rat, Buthus venom injection decreased urinary Na and K excretion. This was later followed by increased urinary K (Ismail et al., 1978). The urinary electrolyte data could reflect the effect of hypotension and shock. Due to interaction between K transport and Mg and Ca transport in the distal tubules, inhibition of Kv channel would decrease Mg and Ca reabsortpion resulting in hypomagnesemia and hypocalcemia. For example, Kv1.1 is expressed in the kidney colocalizing with TRPM6 which transports Mg along the luminal membrane of distal convoluted tubule. Efflux of K from the luminal border of distal convoluted tubule creates lumen positivity which favors Mg reabsorption in the lumen of distal tubules. Deletion mutation of Kv1.1 in a hereditary disease can cause hypermagnesuria and hypomagnesemia (Glaudemans et al., 2009). Urine Mg and Ca are expected to be increased. On the assumption that this mechanism operates in scorpion envenoming hypomagnesemia and hypocalcemia can be explained on this basis.

Increased aldosterone secretion in scorpion envenoming is mediated by several mechanisms (Gueron et al., 1992). In addition to the effect of hyperkalemia which stimulate aldosterone release (Giebisch and Windhager, 2009a), renin-angiotensin activation through angiotensin II (AII) stimulates adrenal cortex to release aldosterone (Giebisch and Windhager, 2009b). Through binding with beta adrenergic receptor generation of cAMP increases PKA which stimulates Na–K ATPase resulting in cellular K influx and decreased serum K (Clausen, 1983). Aldosterone increases Na reabsorption through ENaC and increases K excretion through ROMK. The effect counters K excretion inhibition of scorpion toxin. Therefore, although charybdotoxin inhibits ROMK1, ROMK2 and ROMK3 spared from inhibition can serve to increase K excretion by increased aldosterone as a counter mechanism.

The presence of angiotensin converting enzyme inhibitors (ACEI) or bradykinin potentiating peptide (BPP) in scorpion venom inhibits angiotensin II generation and aldosterone secretion. Venoms from *Centruroides sculpturatus*, *Buthus occitanus* and *Mesobuthus martensii* Karsh contain ACEI or BPP (Longenecker et al., 1980; Meki et al., 1995; Zeng et al., 2012). Decreased plasma aldosterone would enhance the inhibitory effect on K excretion of scorpion venom. Interestingly, atrial natriuretic peptides (ANP) have been identified in the victim of *Androctonus australis* garzonii envenoming (Soualmia et al., 2008). This is not specific but represents the normal host response. Natriuretic peptide (ANP) is released by IL-6 in response to increased wall stress of cardiac atria (Witthaut, 2004). ANP would counteract renin-angiotensin activation and its sequence effects including decreased aldosterone.

At the clinical level, hypokalemia, hyperkalemia, hypermagnesemia, hypomagnesemia, hyponatremia and hypocalcemia have been described in scorpion envenoming (Krishna Murthy, 2000). To our knowledge urinary electrolyte data in human reports are lacking. In a few instances the causes were obvious. For example, hyperkalemia and hypermagnesemia were due to metabolic acidosis and acute renal failure. Hypokalemia was due to diarrhea and metabolic alkalosis resulted from vomiting. In many instances the cause was not known due to lack of data. Excluding acute renal failure, metabolic acidosis and gastrointestinal disturbances, the serum K level is the net result of serum K increasing effect of inhibition of renal tubular K channels, and decreased aldosterone by ACEI and

ANP and the serum K lowering effect of increased aldosterone through AII, and catecholamine through activation of Na–K ATPase.

5. Conclusion

Renal dysfunction by scorpion toxins is caused by renal ischemia induced by intense renal vasoconstriction due to catecholamines, angiotensin II and effects of venom on vascular ion channels. Effects of proinflammatory cytokines, venom enzymes and inflammatory reactions are equally important contributions to the development of acute renal injury. Serum electrolyte changes in scorpionism can be nonspecific secondary to either gastrointestinal disturbance caused by parasympathetic stimulation or acute renal failure. However, the specific effect of scorpion venom on inhibition of K transport of renal tubular K secretory channels (Kv, ROMK and Kca) can cause K retention and hyperkalemia which stimulates aldosterone secretion. Hyperaldosteronism as a secondary effect of the venom through the host response stimulates K secretion by ROMK2 and ROMK3 spared from venom inhibition and causes hypokalemia. The venom effects thus counteract each other and the serum K is the net result of the two effects taking also in consideration K intake and the presence of ACEI in some scorpion species. Hyperkalemia in scorpion envenoming is therefore inconsistent. Scorpionism is a good lesson for exercise in renal physiology.

Ethical statement

No ethical issue.

Conflict of interest statement

There is no conflict of interest for this work.

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