報告番号	香大医博甲　第657号

様式１０７

学位論文審査の結果の要旨

平成　29　年　1　月　23　日

審査委員	主　査	平野勝也		
	副主査	村尾孝児		
	副主査	南野哲男		
願出者	専攻	分子情報制御医学	部門	生体情報学
	学籍番号	13D738	氏名	張　一凡
論文題目	Remote ischemic preconditioning of the femoral artery and vein does not protect against renal ischemia/reperfusion-induced injury in anesthetized mice			
学位論文の審査結果	(合格)　・　不合格　（該当するものを○で囲むこと。）			

〔　要　旨　〕

Acute Kidney Injury (AKI), which is diagnosed based on oliguria and/or a decrease in glomerular filtration rate, is associated with high morbidity and mortality. Recent studies have suggested that remote ischemic preconditioning (RIPC), which consisted of multiple cycles of short ischemia and reperfusion of the arm or leg, creates a resistance to renal ischemia/reperfusion injury. However, the outcomes of clinical studies examining the benefits of RIPC are not consistent. For the further evaluation of complexity observed in the clinical studies, we tried to develop an experimental RIPC model against renal ischemia/reperfusion (I/R)-induced AKI.

We investigated the effects of 7 different RIPC protocols on the right femoral artery and vein. However, none of these protocols protected the kidney against I/R injury. The neutral effect of RIPC is probably due to following reasons: 1) anesthetics might limit the effects of RIPC; 2) the difference on the sensitivity of RIPC between the species; 3) the detail surgical procedure. Although we didn't find any benefit of RIPC in animals under anesthesia, a common finding among both basic and clinical studies is that RIPC did not exaggerate or increase the risk of AKI. RIPC is still worth considering as a potential prophylactic treatment against AKI because of its non-drug and non-invasive nature.

上記発表に対し、以下の質疑応答が適切におこなわれた。

【質問 1】 Why don't you use rats for this experiment at first?

応答: In a previous paper of our lab in collaboration with Department of Nephrology, Dr. Nishioka and his colleagues found that IPC on renal artery and vein protected renal function against I/R-induced AKI via p21-dependent pathway. They used p21-KO mice to prove their hypothesis (Kidney Int. 2014). Our preliminary hypothesis was that RIPC protects kidney through similar mechanism, so we used mice first.

【質問 2】 How did you make sure RIPC procedure was successful?

応答: The RIPC is consist of short time I/R. We could observe that the hind limb turned white during ischemia, and returned to normal color after reperfusion, suggesting that the hind limb blood flow was occluded temporary.

【質問 3】 What's the possible molecule mechanism of the beneficial effect of RIPC?

応答: Clinical studies have suggested potential protective mechanisms responsible for RIPC, such as increased TIMP-2 and IGFBP7 which induce G1 cell-cycle arrest (JAMA. 2015), inhibition of GSK3β (Am J Kidney Dis. 2015), or activation of hypoxia-inducible factor 1 (Int J Clin Exp Pathol 2016).

【質問4】 Did you check the effect of RIPC in rats?

応答: We investigated 4 cycles of 5min ischemia and reperfusion RIPC protocol in 45min I/R-injury SD rats (6 weeks old). This RIPC could not protect kidney against AKI. But we haven't checked other protocols.

【質問 5】 What's the significance of your RIPC study for clinical use?

応答: In our present study, we speculated that anesthesia (Circ J 2015) and the detail RIPC procedure (Circ Res. 2014) may influence the effect of RIPC. Although we did not find any benefit of RIPC in animals under anesthesia, first a common finding is that RIPC did not increase the risk of AKI. RIPC is thus still worth considering as a potential prophylactic treatment against AKI because of its non-drug, non-invasive nature and low cost.

【質問 6】 Have you checked the effect of RIPC in other AKI model?

応答: No, we haven't. We only check I/R-induced AKI in mice. Recent report have suggested that RIPC prevents contrast induced-AKI, but not IR-AKI (Crit Care. 2016).

【質問 7】 Why did you clamp femoral vessel as RIPC protocol? Have you tried other places?

応答: No, we haven't tried RIPC at other places. We clamped femoral vessel as our RIPC protocol because other studies showed benefit of this RIPC protocol (Liver Transplantation, 2011 & Hepatology, 2014).

【質問 8】 In your study, you used blood urea nitrogen (BUN) as a biomarker of AKI. Did you check other biomarker like plasma creatinine?

応答: No, we only checked BUN at 24 after I/R-injury induction. Currently, there are several kinds of kidney injury biomarker, like neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), BUN, plasma creatinine and so on. However, we believe that BUN is a sensitive marker to confirm the severity of AKI.

【質問 9】 Did you compare the difference between IPC and RIPC in mice?

応答: In the current study, we have not perform IPC in AKI mice. But previous paper of our lab showed IPC protected renal function against I/R-induced AKI via p21-dependent pathway (Kidney Int. 2014). We used to think RIPC protects kidney against AKI by similar mechanism. Unfortunately, we failed to observe any benefit of RIPC in anesthetized mice.

【質問 10】 Why did you use an ice pack instead of a vascular clamp in RIPC procedure?

応答: The RIPC is like cycles of blood flow reduction and recovery, we used ice pack to reduce femoral blood flow. We could observe the bind limb turned write with ice pack and returned normal color with a hand wormer, just like we observed by using a vascular clamp.

掲載誌名	Journal of Urology and Nephrology Open Access 第 2 巻, 第 2 号		
(公表予定) 掲載年月	2016 年 5 月	出版社 (等) 名	Symbiosis Open Access

(備考) 要旨は, 1, 500字以内にまとめてください。