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学位論文の内容の要旨

専　攻	分子情報制御医学	部　門	生体情報学
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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		

（論文要旨）

Background

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, and is one of the most common complications of major cardiovascular surgery, percutaneous coronary intervention and kidney transplantation. We previously reported that Renal Ischemic Preconditioning (IPC), which consisted of multiple cycles of short ischemia and reperfusion of the renal artery and vein, created a resistance to renal ischemia/reperfusion injury. An experimental limitation of that study was that IPC of the renal artery and vein is not a realistic procedure in a clinical setting. To overcome this limitation, Remote IPC (RIPC) is performed at a site remote to the target organs, as an effective prophylactic strategy against ischemic organ damage. However, the outcomes of clinical studies examining the benefits of RIPC are not consistent. Therefore, the aim of the present study is to develop an experimental RIPC model against Renal Ischemia/Reperfusion (I/R)-induced AKI for the further evaluation of complexity observed in the clinical studies.

Several RIPC protocols did not against I/R-induced AKI in anesthetized Mice

We investigated the effects of seven different RIPC protocols on the right femoral artery and vein: 1) 4 cycles of 5min ischemia by using clamp followed by 5min reperfusion before 45min I/R; 2) 4 cycles of 5min ischemia followed by 5min reperfusion before 30min I/R; 3) 6 cycles of 4min ischemia followed by 4min reperfusion before 30min I/R; 4) same RIPC with 2), but prolonged recovery time between RIPC and I/R from 15min to 6hr; 5) same RIPC with 2), but RIPC with femoral vascular permanent occlusion; 6) used an ice pack instead of clamping the femoral artery and vein; 7) used isoflurane- anesthetized instead of pentobarbital-anesthetized. However, none of these protocols protected the kidney against I/R injury. In conclusion, RIPC of a direct clamping of femoral artery and vein gave no protection against renal I/R-induced injury in anesthetized mice.

Discussion

A limitation of the present study is that the mice were anesthetized. Two recent clinical trials reported that RIPC did not improve clinical outcomes in patients undergoing cardiac surgery, or coronary-artery bypass graft surgery. The former study was performed under total anesthesia with intravenous protocol, which might interfere with RIPC effects, while the later study was done under nonstandardized anesthetics. Therefore, anesthetics themselves, not a specific anesthetic drug, might limit the effects of RIPC. There might be difference on the sensitivity to RIPC between the species. RIPC to the hind-limb of rats has reported to demonstrate the protective effects. On the other hand, to our knowledge, there is no report showing the protective effect of RIPC against AKI in mice, and the current study showed that mice were

insensitive to the multiple protocols of RIPC. Since we previously showed that the marine kidney is sensitive to the ischemic preconditioning procedure on renal pedicle against I/R-induced AKI, the species difference between rats and mice may result from the extra-renal mechanism. The other possibility for why RIPC did not show its protective effect in the present study might be due to the detailed surgical procedure. Although we did not 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 thus still worth considering as a potential choice of prophylactic treatment against AKI because of its non-drug and non-invasive nature.

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（備考）論文要旨は，日本語で１，５００字以内にまとめてください。