의학석사 학위논문

신장이식수술에서 신장이식 공여자에 시행한 원격 허혈 양상화가 수술 후 신기능에 미치는 영향

Effects of remote ischemic preconditioning on postoperative recovery of renal function in donors of living donor kidney transplantation

울 산 대 학 교 대 학 원

의 학 과

김 새 결

Effects of remote ischemic preconditioning on postoperative recovery of renal function in donors of living donor kidney transplantation

지 도 교 수 송 준 걸

이 논문을 의학석사학위 논문으로 제출함

2018년 6월

울 산 대 학 교 대 학 원

의 학 과

김 새 결

김새결의 의학석사학위 논문을 인준함

심사위원 신 원 정 인

심사위원 송 준 걸 인

심사위원 고 원 욱 인

울 산 대 학 교 대 학 원

2018 년 6 월

Abstract

Backgrounds: Remote ischemic preconditioning (RIPC) has been reported to protect renal function through anti-inflammatory reaction, but whether RIPC could reduce renal injury occurring in the residual kidney of living donor is not known. The purpose of this study is to evaluate effect of RIPC on recovery of postoperative residual renal function and long-term prognosis in living kidney donor.

Methods: We conducted a prospective, double-blind, randomized, controlled trial involving living kidney donors who were scheduled for elective kidney transplantation. RIPC was performed on the upper arm and compared with sham procedure. We compared the proportion of patients whose serum creatinine level was greater than the upper normal limit which is 1.4 mg/dL at the time of discharge. Serum creatinine and estimated glomerular filtration rate (eGFR) until a year after operation were measured. Multivariate logistic regression analysis was performed to find the predictors for elevated serum creatinine at discharge. In addition, we evaluate a predicting ability of cystatin C and search a cutoff value predicting serum creatinine level over 1.4 mg/dL at the time of discharge using receiver operating characteristic (ROC) curve analysis. The incidence of chronic kidney disease (CKD) at one year after operation was also measured.

Results: Between April 2016 and August 2017, 170 patients were included and randomized to each group (85 in the RIPC group and 85 in the control group). The proportion of patients whose serum creatinine level was greater than 1.4 mg/dL at the time of discharge was greater in the control group (17 patients [20%] vs. 6 patients [7.1%]; $p = 0.025$). Levels of postoperative serum creatinine were significantly greater in the control patients as compared with the RIPC group at postoperative day 2 and 3 (1.2 mg/dL, 95% confidence interval [CI] 0.9–1.5 vs. 1.0, 95% CI 0.9–1.2 and 1.3 ± 0.3 mg/dL vs 1.0 ± 0.2 mg/dL; $p = 0.009$ and $p < 0.001$, respectively). Levels of eGFR were significantly lower in control groups at postoperative day 3 (67.1 ± 13.0 ml/min/1.73m^2 vs 75.3 ± 12.6 ml/min/1.73m^2; $p = 0.018$). No

significant difference in the serum creatinine or eGFR was observed until a year post-surgically. The predictors of elevated serum creatinine at discharge are RIPC (Odd ratio [OR] 0.26, 95% CI 0.07–0.82; p = 0.029), Age (OR 0.89, 0.83–0.95; p < 0.001), eGFR (OR 0.95, 0.90–0.85; p < 0.001), postoperative cystatin C which was measured within 24 hours after operation (OR 1.84, 95% CI 1.24–2.85; p = 0.004). ROC analysis shows that the cut-off value of postoperative cystatin C predicting serum creatinine > 1.4 mg/dL at discharge was 0.9 mg/L and the area under the curve was 0.82 (sensitivity 95.7%, specificity 66.9%). There was no significant difference in the incidence of CKD at one year after operation (6 patients [7.1%] vs. 8 patients [9.4%]; p = 0.78).

Conclusion: RIPC is a helpful procedure to improve immediate postoperative renal function of kidney donors. In addition, postoperative cystatin C is useful diagnostic marker for prediction of renal injury.

Keywords: remote ischemic preconditioning, kidney donor, kidney transplantation, cystatin C

Table of contents

Tables and figures

Introduction

Kidney transplantation (KT) is considered as a treatment of choice to treat end-stage renal disease.[1] Although living donor KT has been widely performed because of greater graft survival rate than deceased donor, concerns about the residual renal function of donors has been raised.[2-5] Reduction of residual renal function of kidney donors has been considered due to structural damage and chronic inflammation caused by hyperfiltration of residual glomerulus and uremic toxin.[6,7] Renal damage due to hyperfiltration and inflammation was instantaneously developed after donor nephrectomy.[7,8]

Remote ischemic preconditioning (RIPC) has been derived from ischemic preconditioning technique and shown to reduce inflammation derived from ischemic reperfusion injury, inducing brief period of nonlethal ischemia at a distant site, producing systemic protection to ischemic reperfusion injury.[9] Therefore, it would be meaningful to investigate whether RIPC could reduce the inflammatory injury occurring in the residual kidney of living donor. Although studies reported the clinical benefits of RIPC, most were cardiovascular surgery studies.[10-12] In addition, previous reports on the effects of RIPC in renal transplantation showed that the results were largely inconsistent and were usually focused on the post-transplant function of the recipient.[13] There is no well-designed clinical trial about RIPC in KT donors.

Therefore, the purpose of this study is to evaluate effect of RIPC on recovery of postoperative residual renal function and long-term prognosis in patients undergoing donor nephrectomy. Also, we determined whether Cystatin C (CysC) measured during operation and immediate postoperative period can predict changes in renal function in kidney donors.

Methods

The study was approved by Asan Medical Center institutional review board (No.2015-1173). Informed consent was obtained before enrollment of the study.

Patient selection

Living kidney donor for elective kidney transplantation, aged between 20 to 60 years old was included. Factors which could affect kidney injury were excluded. Patients who had history of acute kidney injury, morbid obesity, liver cirrhosis, hypertension, diabetes mellitus, patient with hypoalbuminemia (< 3.0 g/dL), hypoproteinemia (< 6.0 g/dL), anemia (hemoglobin < 10.6 g/dL, hematocrit < 30%), low body weight (body mass index < 18 kg/m^2) were excluded.

The sample size was determined through the previous study.[14] It shows that average estimated glomerular filtration rate (eGFR) calculated by chronic kidney disease epidemiology collaboration (CKD-EPI) equation on 7 postoperative day was 55 mL/min/1.73m² (standard deviation 11 mL/min/1.73m²). The sample size was calculated based on the assumption that RIPC would increase the eGFR by 10%. Based on the formula for calculating the sample size,[15] the sample size required for each group to detect this difference was 75.999 with a power of 80% and a statistical significance level of $\alpha = 0.05$. Considering dropout rate of 10%, we aimed for a sample size of n = 85 per group.

A total of 170 patients were allocated into the control group or RIPC group in a 1:1 ratio. The randomization table was computer generated using R (version 2.13.1) by a trial administrator who was independent of all other aspects of the trial. One of the table delivered to anesthesiologist who was not involved in our study. Surgeon, patients, and the investigators involved in the surgery were blinded to randomization.

RIPC protocol and surgical procedures

General anesthesia was induced and maintained in all patients as a routine procedure in this

center as follows: anesthesia was induced with 4-5 mg/kg thiopental sodium and 0-50 μg fentanyl and maintained with desflurane and 50% oxygen in air with remifentanil target-controlled infusion. Muscle relaxation was achieved with 0.6 − 1.2 mg/kg rocuronium before intubation and for maintenance, bolus 10 − 20 mg of rocuronium injection as needed. All patients underwent nephrectomy with laparoscopic or hand-assisted laparoscopic surgery (HALS).

After intubation, a catheter was inserted to radial artery. When patient's vital sign was stable, independent anesthesiologist who are not relevant to this study performed RIPC after surgical positioning and before incision. In the RIPC group, RIPC consisting of three cycles of 5-min inflation of a blood pressure cuff to 200 mmHg to one upper arm followed by 5-min reperfusion with deflating the cuff was performed. In the control group, the cuff is placed in the upper arm, but the procedure such as increasing the pressure is not performed.

Data collection

Demographics and preoperative hemodynamic variables and laboratory finding including complete blood count, prothrombin time, activated partial thromboplastin time, BUN (blood urea nitrogen), serum creatinine, estimated glomerular filtration rate (eGFR) calculated by chronic kidney disease epidemiology collaboration (CKD-EPI) equation, total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), electrolyte, routine urinalysis with microscopic exam of patients were collected. During operation, Cystatin C was sampled from arterial catheter before RIPC and after reperfusion. In addition, Cystatin C was sampled within 24 hours after operation.

After operation, routine postoperative care was performed by transplantation team, we collected data including laboratory findings and vital sign until discharge. After discharge, patients followed up on an outpatient basis for 1 year, a laboratory test was performed at each visit.

Outcome measure

The primary outcome was to compare post-operative renal function, which is estimated by the proportion of patients whose serum creatinine level was greater than 1.4 mg/dL, the upper normal limit, at the time of discharge. We evaluate a predicting ability of cystatin C and search a cutoff value predicting serum creatinine level over 1.4 mg/dL at the time of discharge. Serum creatinine and eGFR after 1, 3, 6, 12 months of operation and the incidence of chronic kidney disease (CKD) which was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria were also measured.[16]

Statistical analysis

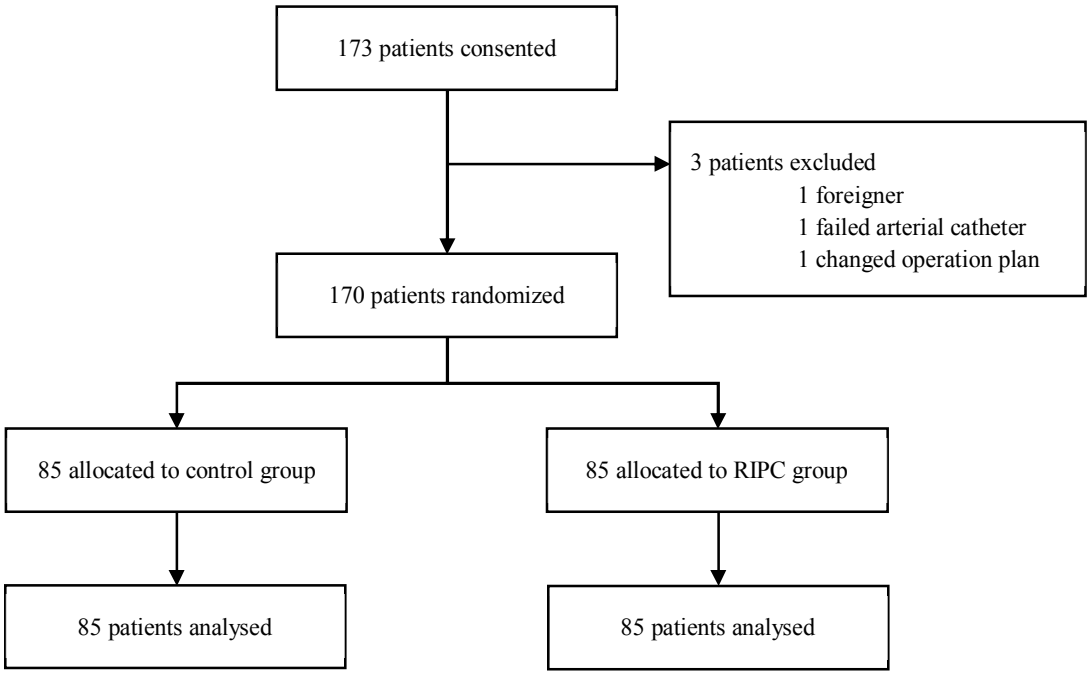
The data are presented as the means ± standard deviation (SD) or median ± 95% confidence interval (CI), as appropriate. The comparison of each group was performed using Pearson's chi-square or Fisher's exact test for categorical variables and student t-test for continuous variables. Risk factors for impaired kidney function were investigated using multivariate logistic regression analysis. SPSS version 21.0 for Windows were used for the statistical analyses. A value of $p < 0.05$ was considered as statistically significantly different.

Results

Study population and perioperative conditions

Between April 2016 and August 2017, 173 patients were consented for the trial. Excluding 3 patients, we enrolled 170 patients and 85 patients assigned to each group (Figure 1). As shown in Table 1, there was no difference in terms of age, weight, height, Body mass index and American Society of Anesthesiologists physical status classification (ASA_PS) class. The proportion of gender was significantly different between control and RIPC group (male gender, 54.1% vs. 45.9%, respectively; $p = 0.003$). Perioperative data are detailed in Table 2. In control group, serum creatinine of preoperative period was greater than control group (0.8 mg/dL, 95% CI 0.7–0.9 vs. 0.7 mg/dL, 95% CI, 0.6–0.8; $p = 0.005$) without clinical significance. Other perioperative variables did not significantly different between two groups.

Figure 1. Flow chart of the trial



Between April 2016 and August 2017, 173 patients were consented for the trial. Excluding 3 patients, we enrolled 170 patients and 85 patients assigned to each group and analysed.

Table 1. Demographics of donors

	Control (n = 85)	RIPC (n = 85)	p-value
Age, year	42.0 [33.0;49.0]	44.0 [37.0;51.0]	0.334
Male, n (%)	46 (54.1)	26 (45.9)	0.003
Weight, kg	63.8 [57.2;76.0]	61.4 [55.3;69.3]	0.106
Height, cm	165.5 [158.6;173.1]	162.0 [156.6;168.0]	0.049
BMI, kg/m^2	24.0 ± 2.8	23.7 ± 2.9	0.447
ASA_PS			1.000
1, n (%)	60 (70.6%)	59 (69.4%)	
2, n (%)	25 (29.4%)	26 (30.6%)	

Data are mean ± SD or median ± [95% CI], when appropriate. BMI, body mass index; ASA_PS, American Society of Anesthesiologists physical status classification

Table 2. Perioperative findings of donors

	Control (n = 85)	RIPC (n = 85)	p-value
Preoperative parameters			
Systolic blood pressure, mmHg	118.4 ± 14.1	116.7 ± 12.2	0.383
Diastolic blood pressure, mmHg	77.1 ± 10.2	76.9 ± 9.6	0.871
Heart rate	75.4 ± 11.9	74.0 ± 9.1	0.386
Hemoglobin, g/dl	14.0 ± 1.4	13.6 ± 1.3	0.043
BUN, mg/dL	13.0 [11.0;16.0]	12.0 [10.0;14.0]	0.018
Creatinine, mg/dL	0.8 [0.7; 0.9]	0.7 [0.6; 0.8]	0.005
eGFR, ml/min/1.73m^2	106.6 ± 11.1	106.8 ± 10.6	0.899
Total protein, g/dL	7.2 [6.9; 7.5]	7.1 [6.9; 7.4]	0.730
Albumin, g/dL	4.1 ± 0.3	4.0 ± 0.3	0.280
Total Bilirubin, mg/dL	0.5 [0.4; 0.8]	0.5 [0.4; 0.7]	0.398
AST, IU/L	19.0 [16.0;22.0]	18.0 [16.0;21.0]	0.483
ALT, IU/L	16.0 [12.0;25.0]	15.0 [12.0;19.0]	0.079
Sodium, mmol/L	140.0 [139.0;141.0]	140.0 [139.0;142.0]	0.834
Potassium, mmol/L	4.2 ± 0.4	4.2 ± 0.3	0.348
Chloride, mmol/L	102.8 ± 2.3	103.1 ± 2.1	0.385
Intraoperative parameters			
Operation time, min	212.0 [190.0–235.0]	205.0 [183.0–225.0]	0.090
Operation site (right), n (%)	34 (40.0)	36 (42.4)	0.876
Hartmann's solution, ml	600.0 [450.0–700.0]	600.0 [500.0–700.0]	0.313
Transfusion of RBC, n (%)	0 (0)	1 (1.2)	1.000
Plasma solution, ml	1302.1 ± 547.3	1205.9 ± 534.1	0.248
20% Mannitol, ml	160.0 [140.0;190.0]	150.0 [140.0;175.0]	0.334

Urine output, ml	270.0 [220.0;420.0]	290.0 [190.0;400.0]	0.365
Ischemic time	5.0 [3.0; 8.0]	4.0 [3.0; 6.0]	0.250
Vital sign of baseline			
Mean blood pressure, mmHg	76.0 [71.0;89.0]	78.0 [71.0;89.0]	0.630
Heart rate	67.6 ± 10.4	68.6 ± 11.3	0.545
Vital sign before intervention			
Mean blood pressure, mmHg	81.0 [73.0;92.0]	77.0 [71.0;87.0]	0.051
Heart rate	64.4 ± 10.4	65.6 ± 8.9	0.426
Vital sign after intervention			
Mean blood pressure, mmHg	84.2 ± 9.6	85.4 ± 12.8	0.507
Heart rate	65.0 [58.0;73.0]	66.0 [59.0;72.0]	0.792
Postop CysC, mg/L	0.9 ± 0.1	0.9 ± 0.2	0.389

Data are mean ± SD or median ± [95% CI], when appropriate. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC, red blood cell; Postop CysC, cystatin C measured within 24 hours after operation

Outcomes

The proportion of patients whose serum creatinine level was greater than 1.4 mg/dL at the time of discharge was greater in the control group (n = 17, 20% vs. n = 6, 7.1%; p = 0.025) (Figure 2). There was no difference in hospital stay between two groups (7 days, 95% CI 6–7 vs. 7days, 95% CI 7-8; p = 0.071).

The predictors of elevated serum creatinine at discharge determined by multivariate logistic regression analysis are shown in table 3. RIPC (Odd ratio[OR] 0.26, 95% CI 0.07–0.82; p = 0.029), Age (OR 0.89, 0.83–0.95; p < 0.001), eGFR (OR 0.95, 0.90–0.85; p < 0.001), postoperative CysC which was measured within 24 hours after operation (OR 1.84, 95% CI 1.24–2.85; p = 0.004) were associated with serum creatinine level greater than 1.4 mg/dL when discharge.

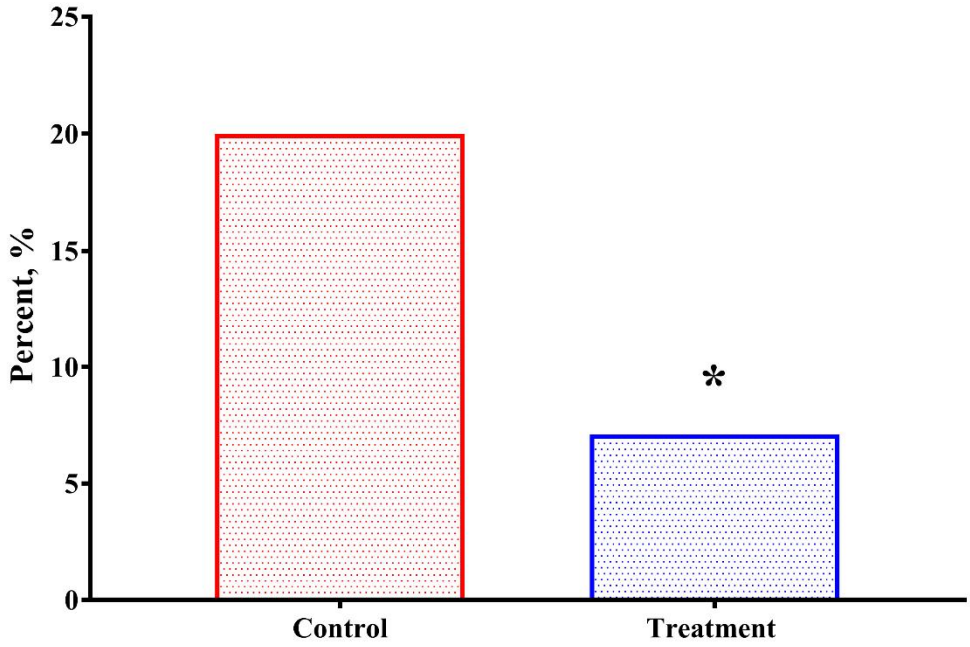
Levels of postoperative serum creatinine were significantly greater in the control patients as compared with the RIPC group at postoperative day (POD) 2 and 3 (1.2 mg/dL, 95% CI 0.9–1.5 vs. 1.0, 95% CI 0.9–1.2 and 1.3 ± 0.3 mg/dL vs 1.0 ± 0.2 mg/dL; p = 0.009 and p < 0.001, respectively). Levels of eGFR were significantly lower in control groups at POD 3 (67.1 ± 13.0 ml/min/1.73m^2 vs 75.3 ± 12.6 ml/min/1.73m^2; p = 0.018). No significant difference in the serum creatinine or eGFR at 1, 3, 6, 12 months post-surgically (Figure 3).

Receiver operating characteristic (ROC) curve analysis shows that the cut-off value of postoperative CysC predicting serum creatinine > 1.4 mg/dL at discharge was 0.9 mg/L and the area under the curve was 0.817 (Figure 4).

As shown in Table 4, using this cutoff value, the incidence of last serum creatinine > 1.4 mg/dL at discharge was significantly greater when postoperative CysC > 0.9 mg/L (n = 1, 1.1% vs. n = 22, 28.9%, n = 20, 22.5% vs. n = 49, 64.5%; p < 0.001, p < 0.001, respectively). Also, the cutoff value could predict renal function until 1 year postoperatively.

There was no significant difference in the incidence of CKD between control (n = 6, 7.1%) and RIPC group (n = 8, 9.4%) (p = 0.78). No patients with postoperative cystatin C ≤ 0.9 mg/L progressed to CKD.

Figure 2. Proportion of serum creatinine ≥ 1.4 mg/dL at the time of discharge



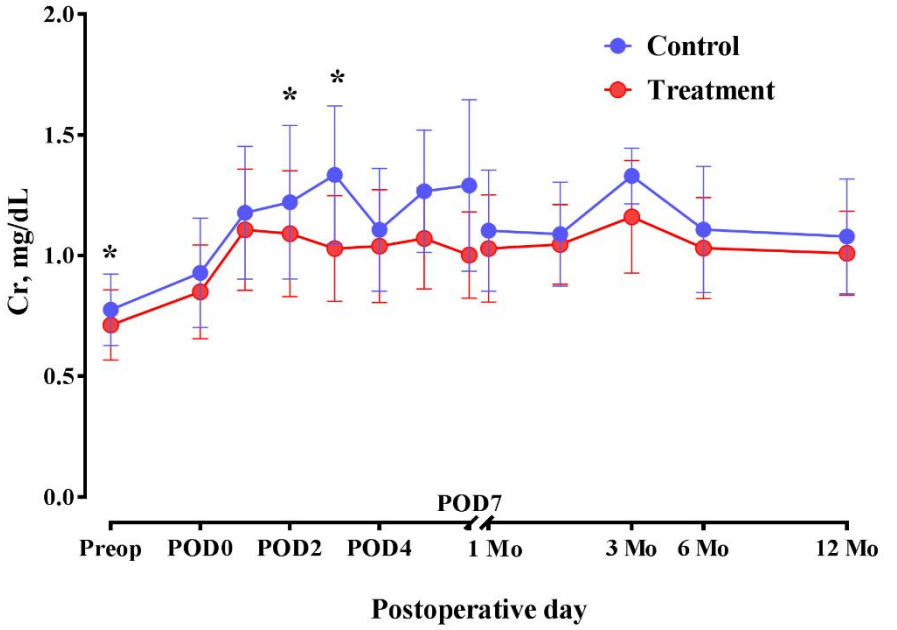
The proportion of patients whose serum creatinine level was greater than 1.4 mg/dL, the upper normal range, at the time of discharge was greater in the control group (n = 17, 20% vs. n = 6, 7.1%). *p < 0.05

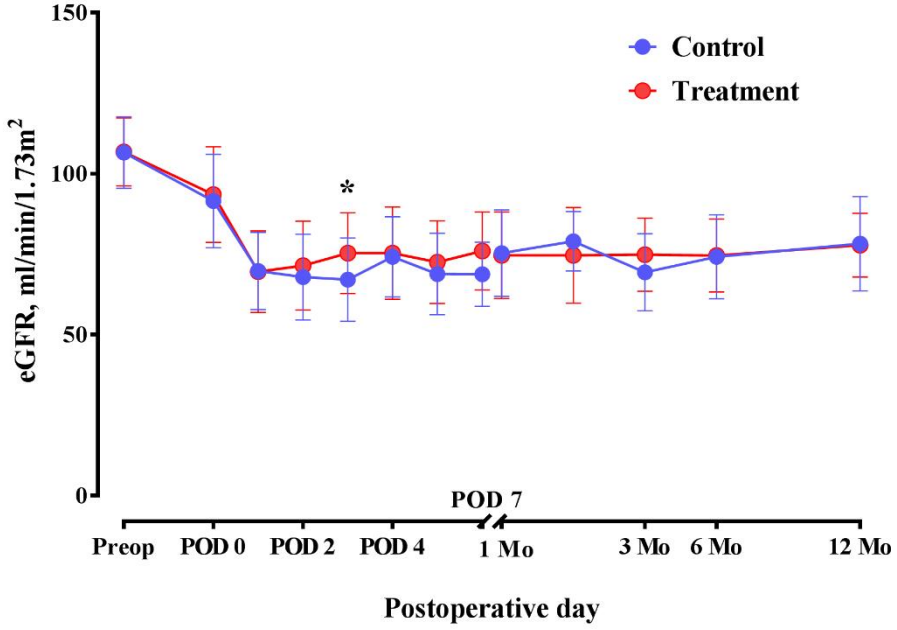
Table 3. Risk factor of serum creatinine > 1.4mg/dL at the time of discharge

	Univariate			Multivariate		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
RIPC	0.3	0.1 – 0.78	0.018	0.26	0.07 – 0.82	0.029
Age	0.95	0.91 – 0.99	0.022	0.89	0.83 – 0.95	< 0.001
ASA_PS	0.8	0.27 – 2.07	0.66			
Sex			0.991			
Body mass index	1.17	1.00 – 1.37	0.053			
Operation time	1.01	1.00 – 1.03	0.018			
Operation site	1.1	0.45 – 2.80	0.83			
Systolic blood pressure	1.03	1.00 – 1.07	0.067			
Albumin	2.56	0.52 – 13.04	0.249			
eGFR	0.95	0.91 – 0.99	0.011	0.95	0.90 – 0.85	< 0.001
Ischemic time	1.03	0.88 – 1.19	0.662			
Postop CysC, mg/L	1.91	1.39 – 2.75	< 0.001	1.84	1.24 – 2.85	0.004

RIPC, remote ischemic conditioning group; ASA_PS, American Society of Anesthesiologists physical status classification; eGFR, estimated glomerular filtration rate; Postop CysC, cystatin C measured within 24 hours after operation

Figure 2. Change of serum creatinine and eGFR

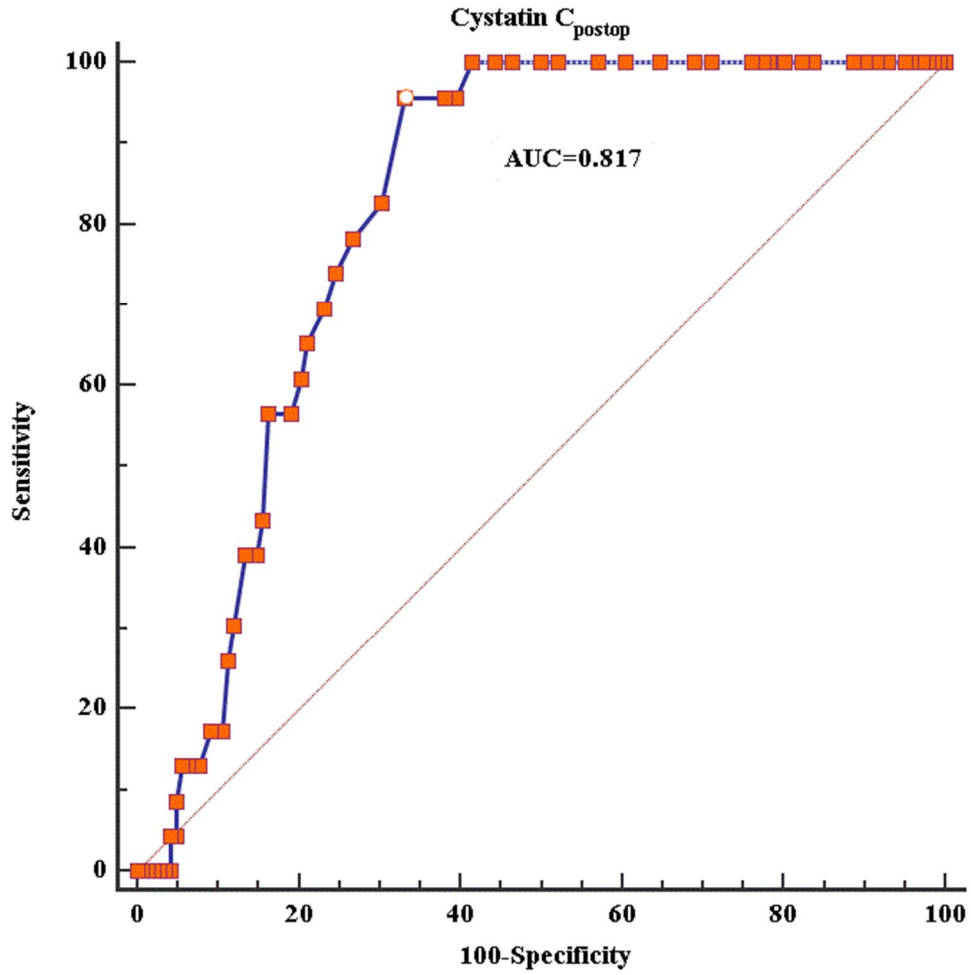




Levels of postoperative serum creatinine were significantly greater in the control patients as compared with the RIPC group at postoperative day (POD) 2 and 3 (1.2 mg/dL, 95% CI 0.9–1.5 vs. 1.0, 95% CI 0.9–1.2 and 1.3 ± 0.3 mg/dL vs 1.0 ± 0.2 mg/dL; $p = 0.009$ and $p < 0.001$, respectively). Levels of eGFR were significantly lower in control groups at POD 3 (67.1 ± 13.0 ml/min/1.73m^2 vs 75.3 ± 12.6 ml/min/1.73m^2; $p = 0.018$). No significant difference in the serum creatinine or eGFR at 1, 3, 6, 12 months post-surgically.

eGFR, estimated glomerular filtration rate; *$p < 0.05$

Figure 4. ROC curve for postoperative cystatin C level as predictors of last serum creatinine > 1.4 mg/dL



Receiver operating characteristic (ROC) curve analysis shows that the cut-off value of postoperative CysC predicting serum creatinine > 1.4 mg/dL at discharge was 0.9 mg/L and the area under the curve was 0.817.

Table 4. Clinical characteristics according to a cutoff value of 0.9 mg/L of cystatin C

	CysC ≤ 0.9 (n = 89)	CysC > 0.9 (n = 76)	p-value
Laboratory findings			
At POD 0			
Serum creatinine, mg/dL	0.8 ± 0.2	1.0 ± 0.2	< 0.001
eGFR, ml/min/1.73m^2	96.8 ± 14.1	86.7 ± 13.2	< 0.001
At POD 1 month			
Serum creatinine, mg/dL	1.0 ± 0.2	1.2 ± 0.2	< 0.001
eGFR, ml/min/1.73m^2	80.1 ± 12.6	68.9 ± 11.9	< 0.001
At POD 3 month			
Serum creatinine, mg/dL	1.2 ± 0.2	1.2 ± 0.2	0.109
eGFR, ml/min/1.73m^2	78.5 ± 17.7	71.7 ± 11.2	0.514
At POD 6 month			
Serum creatinine, mg/dL	0.9 ± 0.2	1.2 ± 0.2	< 0.001
eGFR, ml/min/1.73m^2	79.5 ± 11.3	70.1 ± 11.6	0.001
At POD 12month			
Creatinine, mg/dL	1.0 ± 0.2	1.1 ± 0.2	
eGFR, ml/min/1.73m^2	81.1 ± 10.6	74.9 ± 13.6	
Last serum creatinine > 1.4 mg/dL, n (%)	1 (1.1)	22 (28.9)	< 0.001
CKD	0 (0.0)	14 (15.7)	< 0.001

Data are mean ± SD or median ± [95% CI], when appropriate. POD, postoperative day; CKD,

chronic kidney disease

Discussion

This study demonstrates the clinical effects of RIPC in living donors undergoing kidney transplantation. RIPC attenuate the incidence of donors whose serum creatinine over 1.4 mg/dL at the time of discharge. In addition, postoperative CysC concentration is a useful early marker to detect residual renal function in kidney donors.

Although experimental animal studies have demonstrated the beneficial effect of RIPC, the protective effect of RIPC in human have yielded contradictory results. There are several studies suggesting the positive effect of RIPC on kidney and heart.[17-20] However, recent two prospective, large phase III trials show RIPC did not improve organ function and clinical outcome including complication or mortality.[21,22]

One of the reason for the negative effect of RIPC in these studies can be explained by anesthetics during maintenance of anesthesia. A majority of patients in these two studies was received propofol for maintenance. It has been shown that propofol can abrogates the protective effect of RIPC.[12,23,24] In our trial, we did not use propofol and found significant difference of renal function during day 2 and 3 after operation and at the time of discharge. However, there was no significant difference between the two groups were found at follow up period until a year. Recent meta-analysis which included 33 trials of RIPC involving a total of 5999 patients undergoing cardiac surgery shows no difference between two groups in clinical outcome including AKI, acute myocardial infarction and mortality. It reported significant reduction in area under the curve for myocardial biomarkers.[12] Considering recent study, RIPC may be beneficial to outcomes of postoperative period during hospitalization including biomarkers but may not have significant clinical outcomes in the long term. Longer observation is needed for long-term to identify the effect of the procedure.

It has been suggested that serum CysC has been superior to serum creatinine in most studies for early diagnosis of AKI. CysC detect AKI 12-24 hours earlier than serum creatinine and showed high predictive power for all-cause AKI with area under the ROC curve of 0.89 in meta-analysis involving 4247 adults.[25,26] Furthermore, in kidney donors, CysC is useful marker for detecting partial recovery of kidney function and progression to CKD.[14] In our study,

postoperative cystatin C level is the independent risk factor of serum creatinine over 1.4mg/dL when discharge in donors. The cut off value of 0.9 mg/L of cystatin C can predict residual renal function until a year postoperatively as well as renal function during hospitalization including the incidence of serum creatinine over 1.4 mg/dL when discharge.

Recently, KT donors have been concerned about lifelong risk. Although KT donors are very healthy person and no comorbidity, several studies suggest the increased risk of end-stage renal disease (ESRD) and preeclampsia in KT donors compared with selected control populations.[3,4,27,28] In addition, Kidney Disease: Improving Global Outcomes (KDIGO) workgroup offer guideline on evaluation and care of KT donors, which recommend considering individualized risk and benefit, methods to minimize risks, and need for post-donation follow up.[29] For this perspective, searching a modality to preserve residual renal function in kidney donor is important and our trial is meaningful in terms of investigating RIPC which may protect kidney function.

The limitation of our trial is the follow up of postoperative period is not completed. Until now, there was no significant difference between two groups in respect of serum creatinine, eGFR and the incidence of CKD. Considering the last kidney donors was enrolled in August 2017, more longer observation is needed in our cohort to determine the long-term effect of RIPC in KT. It would have been better to measure the inflammatory mediator and uremic toxin in the control and RIPC groups to identify physiologic change after RIPC. In addition, the protocol of RIPC varies from studies in terms of the timing, frequency and intensity, and there was no consensus in defining the most favorable protocol. Further study was needed to determine optimal ischemic insult for protecting ischemia-reperfusion injury.

Conclusion

RIPC is a helpful procedure to improve immediate postoperative renal function of kidney donors. In addition, postoperative cystatin C is useful diagnostic marker for prediction of renal injury. The cutoff value of 0.9 mg/L of cystatin C could predict renal dysfunction in kidney donors.

Reference

1. Suthanthiran M, Strom TB: Renal transplantation. N Engl J Med 1994; 331:365-76
2. Wolfe RA, Roys EC, Merion RM: Trends in organ donation and transplantation in the United States, 1999-2008. Am J Transplant 2010; 10:961-72
3. Mjoen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Oyen O, Reisaeter A, Pfeffer P, Jenssen T, Leivestad T, Line PD, Ovrehus M, Dale DO, Pihlstrom H, Holme I, Dekker FW, Holdaas H: Long-term risks for kidney donors. Kidney Int 2014; 86:162-7
4. Muzaale AD, Massie AB, Wang MC, Montgomery RA, McBride MA, Wainright JL, Segev DL: Risk of end-stage renal disease following live kidney donation. JAMA 2014; 311:579-86
5. O'Keeffe LM, Ramond A, Oliver-Williams C, Willeit P, Paige E, Trotter P, Evans J, Wadstrom J, Nicholson M, Collett D, Di Angelantonio E: Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. Ann Intern Med 2018; 168:276-84
6. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. J Am Soc Nephrol 2001; 12:1315-25
7. Rossi M, Campbell KL, Johnson DW, Stanton T, Haluska BA, Hawley CM, Dimeski G, McWhinney BC, Ungerer JP, Kaisar OM, Isbel NM: Uremic toxin development in living kidney donors: a longitudinal study. Transplantation 2014; 97:548-54
8. Hoogendijk-van den Akker JM, Warle MC, van Zuilen AD, Kloke HJ, Wever KE, d'Ancona FC, zdemir DM, Wetzels JF, Hoitsma AJ: Urinary biomarkers after donor nephrectomy. Transpl Int 2015; 28:544-52
9. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D: Remote ischemic conditioning. J Am Coll Cardiol 2015; 65:177-95
10. Yi B, Wang J, Yi D, Zhu Y, Jiang Y, Li Y, Mo S, Liu Y, Rong J: Remote Ischemic Preconditioning and Clinical Outcomes in On-Pump Coronary Artery Bypass Grafting: A Meta-Analysis of 14 Randomized Controlled Trials. Artif Organs 2017; 41:1173-82
11. Tan W, Zhang C, Liu J, Li X, Chen Y, Miao Q: Remote Ischemic Preconditioning has

a Cardioprotective Effect in Children in the Early Postoperative Phase: A Meta-Analysis of Randomized Controlled Trials. Pediatr Cardiol 2018; 39:617-26

12. Deferrari G, Bonanni A, Bruschi M, Alicino C, Signori A: Remote ischaemic preconditioning for renal and cardiac protection in adult patients undergoing cardiac surgery with cardiopulmonary bypass: systematic review and meta-analysis of randomized controlled trials. Nephrol Dial Transplant 2017; doi:10.1093/ndt/gfx210:gfx210-gfx
13. Veighey K, MacAllister R: Ischemic Conditioning in Kidney Transplantation. J Cardiovasc Pharmacol Ther 2017; 22:330-6
14. Bang JY, Kim SO, Kim SG, Song JG, Hwang GS: Cystatin-C is associated with partial recovery of kidney function and progression to chronic kidney disease in living kidney donors: Observational study. Medicine (Baltimore) 2017; 96:e6037
15. Sakpal TV: Sample size estimation in clinical trial. Perspect Clin Res 2010; 1:67-9
16. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 2013; 3:1-150
17. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price V, Tsagakis K, Neuhauser M, Peters J, Jakob H, Heusch G: Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. Lancet 2013; 382:597-604
18. MacAllister R, Clayton T, Knight R, Robertson S, Nicholas J, Motwani M, Veighey K: Efficacy and Mechanism Evaluation, REmote preconditioning for Protection Against Ischaemia-Reperfusion in renal transplantation (REPAIR): a multicentre, multinational, double-blind, factorial designed randomised controlled trial, NIHR Journals Library, 2015
19. Zarbock A, Schmidt C, Van Aken H, et al.: Effect of remote ischemic preconditioning

on kidney injury among high-risk patients undergoing cardiac surgery: A randomized clinical trial. JAMA 2015; 313:2133-41

20. Zarbock A, Kellum JA, Van Aken H, Schmidt C, Kullmar M, Rosenberger P, Martens S, Gorlich D, Meersch M: Long-term Effects of Remote Ischemic Preconditioning on Kidney Function in High-risk Cardiac Surgery Patients: Follow-up Results from the RenalRIP Trial. Anesthesiology 2017; 126:787-98

21. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM: Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. New Engl J Med 2015; 373:1408-17

22. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Böning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schön J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K: A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. New Engl J Med 2015; 373:1397-407

23. Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, Peters J: Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. Acta Anaesthesiol Scand 2012; 56:30-8

24. Zangrillo A, Musu M, Greco T, Di Prima AL, Matteazzi A, Testa V, Nardelli P, Febres D, Monaco F, Calabro MG, Ma J, Finco G, Landoni G: Additive Effect on Survival of Anaesthetic Cardiac Protection and Remote Ischemic Preconditioning in Cardiac Surgery: A Bayesian Network Meta-Analysis of Randomized Trials. PLoS One 2015; 10:e0134264

25. Herget-rosenThal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, Philipp T, Kribben A: Early detection of acute renal failure by serum cystatin C. Kidney Int 2004; 66:1115-22

26. Yong Z, Pei X, Zhu B, Yuan H, Zhao W: Predictive value of serum cystatin C for acute kidney injury in adults: a meta-analysis of prospective cohort trials. Sci Rep 2017; 7:41012

27. Reisaeter AV, Roislien J, Henriksen T, Irgens LM, Hartmann A: Pregnancy and birth after kidney donation: the Norwegian experience. Am J Transplant 2009; 9:820-4

28. Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, Hildebrand AM, Reese PP, Storsley L, Gill JS, Segev DL, Habbous S, Bugeja A, Knoll GA, Dipchand C, Monroy-Cuadros M, Lentine KL, Network D: Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med 2015; 372:124-33

29. Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, Gallon L, Garvey CA, Guleria S, Li PK-T: KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation 2017; 101:S7

Abstract (Korean)

서론: 원격 허혈 양상화는 항염증 작용을 통하여 신장 기능을 보호한다고 알려져 있으나, 이것이 신장 기증자에서 신장 손상을 줄일 수 있는지는 알려져 있지 않다. 본 연구의 목적은 생체 신장이식을 하는 기증자에서 원격 허혈 양상화를 시행하였을 때 수술 후 잔존 신기능의 회복과 장기 예후에 대한 효과를 평가하는 것이다.

연구대상 및 방법: 정례 신장이식수술이 예정되어 있는 신장 기증자를 대상으로 이중 맹검, 무작위 대조 연구를 시행하였다. 치료군에서는 상완에서 원격 허혈 양상화를 시행하였으며, 대조군에서는 상완에 압력계만 감고 원격 허혈 양상화를 시행하지 않았다. 치료군과 대조군에서 퇴원 시 혈청 크레아티닌 수치가 상한치(1.4 mg/dL) 이상인 환자 비율, 수술 후 1년까지의 혈청 크레아티닌 수치와 추정 사구체여과율, 만성 신질환의 발생율을 비교하였다. 다변량 로지스틱 회귀분석을 이용하여 퇴원 시 혈청 크레아티닌이 1.4 mg/dL를 넘는 경우를 예측할 수 있는 인자를 확인하였다. 또한 수신자 조작 특성 곡선 분석 (receiver operating characteristics curve analysis)을 통하여 퇴원 시 혈청 크레아티닌 수치를 1.4 mg/dL이상으로 예측할 수 있는 cystatin C의 결정치(cut off value)와 예측능을 탐색한다.

결과: 2016년 4월부터 2017년 8월까지 총 170명의 환자가 포함되어 원격 허혈 양상화 군(85 명) 또는 대조군(85 명)으로 무작위 추출되었다. 퇴원 시 혈청 크레아티닌 수치가 1.4 mg/dL 이상인 환자의 비율은 대조군에서 더 높았다(17 명[20 %] vs. 6 명[7.1 %]; p = 0.025). 수술 후 혈청 크레아티닌 수치는 수술 후 2 일과 3 일에 원격 허혈 양상화 군에 비해 대조군에서 유의하게 더 높았다(1.2 mg/dL, 95 % CI 0.9-1.5 vs. 1.0 mg/dL; p = 0.009, 95 % CI 0.9-1.2, 1.3 ± 0.3 mg/dL vs 1.0 ± 0.2 mg / dL; p < 0.001, 각각). 추정 사구체여과율은 수술 후 3 일째(67.1 ± 13.0 ml/min/1.73 m^2 vs. 75.3 ± 12.6 ml/min/1.73 m^2; p = 0.018) 대조군에서 유의하게 낮았다. 1, 3, 6, 12개월 째 혈청 크레아티닌이나 추정 사구체여과율에는 차이가 없었다. 다변량 로지스틱 회귀 분석에서 혈청 크레아티닌 상승의 예측 인자는 원격 허혈 양상화(Odd ratio [OR] 0.26, 95 % CI 0.07-0.82, p = 0.029), 연령(OR 0.89, 0.83-0.95, p < 0.001), 수술 후 24 시간 이내에 측정 한 추정 사구체여과율(OR 0.95, 0.90-0.85; p <

0.001), 수술 후 cystatin C(OR 1.84, 95 % CI 1.24-2.85, p = 0.004) 였다. 수신자 조작 특성 곡선 분석 결과, 퇴원 시 혈청 크레아티닌이 1.4 mg/dL보다 클 것으로 예측되는 수술 후 cystatin C의 결정치는 0.9 mg/L이었고, 곡선 아래 면적은 0.817이었다. 수술 1년 후의 만성 신질환의 발병률은 유의한 차이가 없었다(6 명[7.1%] vs. 8 명[9.4%]; p = 0.78).

결론: 원격 허혈 양상화는 생체 신장 기증자의 수술 직후 신기능을 향상시키는 데 도움이 되는 술기이다. 또한, 수술 후 cystatin C 수치는 신상 손상 예측에 유용한 진단 표지자이며, cystatin C의 결정치 0.9 mg/L는 생체 신장 기증자에서 신장 기능 저하 여부를 예측할 수 있다.

핵심어: 원격 허혈 양상화, 신장 기증자, 신장 이식, cystatin C