Conditioning Medicine
www.conditionmed.org

ORIGINAL RESEARCH ARTICLE | OPEN ACCESS

The Effect of Remote Ischemic Conditioning on Blood Pressure control in patients with Chronic Kidney Disease: the ERIC-BP-CKD Pilot Study

Jason Chon Jun Choo[1], Jia Liang Kwek[1], Cynthia Ciwei Lim[1], Irene Yanjia Mok[1], Horng Ruey Chua[2,10], Yilin Jiang[3], Fei Gao[3,4], Kearney Jun Yao Tan[5], Gustavo Crespo-Avilan[3,6,7], Tazeen Hasan Jafar[1,8,9], Derek J Hausenloy[3,6,10,11,12]

Inadequately controlled hypertension in patients with chronic kidney disease accelerates progression of kidney dysfunction. Remote ischemic conditioning (RIC) using transient limb ischemia has been shown to protect the kidney and microvasculature in experimental and clinical studies. The ability to lower blood pressure in patients with CKD through application of daily chronic RIC (CRIC) is unknown. This study aimed to assess the feasibility and efficacy of lowering systolic blood pressure (SBP) in hypertensive CKD patients after administering 28 days of CRIC compared to sham. The study included stages one to four CKD patients with automated office blood pressure (AOBP) SBP >140mmHg on stable dose antihypertensives. Six patients were randomized to the CRIC treatment group and four to the control group, and treatments were performed daily for 28 days. AOBP and central aortic systolic blood pressure (CASP) readings were measured at baseline, day 28, and day 42. There were no differences in AOBP SBP or CASP between CRIC and control on either day 28 or 42. However, in the CRIC group, AOBP diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly decreased on day 28 when compared to control, and AOBP MAP remained significantly lower on day 42. Treatment adherence was excellent with completion of CRIC or control in 96% and 93% of participants, respectively. There were no adverse events reported. The application of 28 days of CRIC improved DBP and MAP but not SBP in this small proof of concept study. A larger study is necessary to confirm these findings.

Keywords: Remote ischemic conditioning, chronic kidney disease, hypertension

Introduction

Patients with chronic kidney disease (CKD) often have inadequately controlled hypertension (Lee et al., 2017), the presence of which is associated with more rapid progression of CKD and cardiovascular complications (Wan et al., 2019; Kim et al., 2020). As such, novel treatments are required to better control blood pressure and improve health outcomes in CKD. Remote ischemic conditioning (RIC) using transient limb ischemia/reperfusion has been shown to protect the kidney and microvasculature in experimental and clinical studies. Daily episodes of RIC (termed chronic RIC [CRIC]) applied for 1 to 12 months have been shown to lower systemic blood pressure (SBP), prevent stroke, and reduce post-myocardial infarction left ventricular remodeling in experimental and clinical studies (Wei et al., 2011; Meng et al., 2012; Jones et al., 2014; Chong et al., 2019). In addition, CRIC applied daily for 28 days has been shown to reduce SBP in patients with chronic ischemic heart failure (Pryds et al., 2017). Whether CRIC can reduce SBP in hypertensive patients with CKD is not known. The primary objective of the ERIC-BP-CKD study was to assess

[1]Department of Renal Medicine, Singapore General Hospital, Singapore; Duke-NUS Medical School, Singapore.[2]Division of Nephrology, Department of Medicine, National University Hospital, Singapore.[3]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore.[4]Programme in Health Services & Systems Research, Duke-NUS Medical School, Singapore.[5]Clinical Trials and Research Centre, Singapore General Hospital.[6]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore.[7]Department of Biochemistry, Medical Faculty, Justus Liebig-University, Giessen, Germany.[8]Programme in Health Services & Systems Research, Duke-NUS Medical School, Singapore. [9]Duke Global Health Institute, Duke University, Durham, NC, USA. [10]Yong Loo Lin School of Medicine, National University of Singapore, Singapore. [11]The Hatter Cardiovascular Institute, University College London, London, United Kingdom.[12]Cardiovascular Research Center, College of Medical and Health Sciences, Asia University, Taiwan.
Correspondence should be addressed to Professor Derek J Hausenloy (derek.hausenloy@duke-nus.edu.sg).

the feasibility and efficacy of CRIC administered for 28 days on lowering SBP in patients with CKD and hypertension when compared to sham. The secondary objectives were to measure central aortic systolic pressures, proteinuria, and kidney function.

Materials and methods

This was a proof-of-concept, single-center, randomized, controlled, double-blinded trial (NCT03236350). Ethics approval was granted by the SingHealth Centralized Institutional Review Board (Reference 2016-2966). Study inclusion criteria included: participants aged ≥ 21 years with CKD stages 1 to 4; stable treatment for hypertension; and automated office blood pressure (Agarwal, 2017) (AOBP) systolic blood pressure (SBP) >140mmHg. Average AOBP readings were measured after patients had rested alone for 5 minutes, followed by a fully automated sequence of two readings over 5-minutes. Exclusion criteria included: polycystic kidney disease; atrial fibrillation; peripheral arterial disease of the arms, long-acting sulphonylurea, nicorandil, or anticoagulation treatment. Eligible participants were randomized to receive either CRIC treatment (comprising four 5-minute inflations/deflation of CellAegis autoRIC® device on the upper arm) or control (comprising four 5-minute sham inflations and deflations of CellAegis autoRIC® device on the upper arm) performed daily for 28 days. The control sham device provides the same sound and vibration as the active CellAegis autoRIC® device but with no inflation of the cuff. Adherence to CRIC based on completed days and treatment cycles were automatically captured by the autoRIC® device. Demographics and clinical data were collected at baseline, whereas serum creatinine (including calculated eGFR CKD-EPI), spot urine protein-creatinine ratio (UPCR), and serum inflammatory biomarkers were measured at baseline and on day 28. AOBP readings (Omron® HEM-907), central aortic systolic pressures (CASP) BPro® Intro(Williams et al., 2011) were measured at baseline, day 28 and day 42 (2 weeks after stopping CRIC or sham). Anti-hypertensives were not adjusted throughout the study period and no specific lifestyle modification advice was given.

Statistical analysis was performed using Stata version 16 (StataCorp, Texas). Categorical variables were presented as proportions and continuous variables summarized as medians with interquartile ranges (IQR). Baseline characteristics were compared using Pearson chi-square test or Fisher's exact test for categorical variables and Mann-Whitney U test for non-normally distributed continuous variables. Our primary analysis compared changes in SBP between the CRIC and control groups using the intention to treat approach for all randomly assigned participants. Wilcoxon signed rank test was used to compare between two time-points and Wilcoxon rank-sum test was used to compare between control and treatment groups. Generalized Estimation Equations (GEE) were used to compare control and treatment groups over time. All analyses were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Sixteen patients were screened with 6 screen failures due to AOBP criteria. Ten patients were recruited with 6 patients randomised to CRIC and four to control. One participant in the CRIC group withdrew consent after randomization. Baseline demographic and clinical characteristics are shown in Table 1. Adherence to treatment was excellent with completion of CRIC or sham control in 96% and 93% of participants, respectively.

There were no differences in AOBP SBP or CASP between CRIC and control after either 28 or 42 days (Table 2). However, in the CRIC group, AOBP diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly decreased after 28 days when compared to control, and AOBP MAP remained significantly lower after 42 days. In addition, GEE analysis of AOBP DBP comparing CRIC and control groups showed significant differences over time. Differences over time were not observed for GEE analyses of AOBP SBP and MAP. There were also no differences in spot UPCR, serum creatinine, eGFR CKD-EPI or inflammatory biomarkers (interleukin-1α, interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor- α) between CRIC and control groups at 28 days. No adverse events were detected in this study.

Discussion

In this proof-of-concept study, CRIC did not improve SBP control when compared to control treatment after 28 days, although there were significant reductions in DBP and MAP as measured via AOBP. The significance of this is uncertain in view of the small sample size. The lowest DBP was 60.0mmHg in the CRIC group (median baseline 74.5mmHg) after 28 days, which should not pose a safety issue considering that coronary artery filling is only affected at DBP levels <55mmHg. The overall reduction in MAP and DBP with CRIC warrants further investigation to understand if blood vessel compliance or cardiac output was temporarily altered. Interestingly, at day 42 (14 days after completion of CRIC), the MAP remained low signifying a potential legacy effect of CRIC. In addition, although RIC has anti-inflammatory benefits in vivo in animal models (Pearce et al., 2021), serum inflammatory biomarkers were not significantly different in our small cohort of patients. A larger study population would be necessary to validate these findings and confirm safety issues in terms of the observed reduction in DBP with CRIC.

Sources of Funding

This study was funded by the SingHealth Foundation research fund (SHF/CTG059/2016). DJH is supported by the Duke-NUS Signature Research Programme funded by the Ministry of Health, Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist-Senior Investigator scheme (NMRC/CSA-SI/0011/2017), Centre Grant (CGAug16M006), and Collaborative Centre Grant scheme (NMRC/CGAug16C006). This article is based upon work from COST Action EU-CARDIOPROTECTION CA16225 supported by COST (European Cooperation in Science and Technology).

Disclosure

All authors declare no potential conflict of interest that might be relevant to the contents of this article.

References

Agarwal R (2017) Implications of blood pressure measurement technique for implementation of systolic blood pressure intervention trial (SPRINT). J Am Heart Assoc 6.

Chong J, Bulluck H, Fw Ho A, Boisvert WA, Hausenloy DJ (2019) Chronic remote ischemic conditioning for cardiovascular protection. Cond Med 2:164-169.

Jones H, Hopkins N, Bailey TG, Green DJ, Cable NT, Thijssen DH (2014) Seven-day remote ischemic preconditioning improves local and systemic endothelial function and microcirculation in healthy humans. Am J Hypertens 27:918-925.

Kim YT, Chung HJ, Park BR, Kim YY, Lee JH, Kang DR, Kim J-Y, Lee MY, Lee JY (2020) Risk of cardiovascular disease and chronic kidney disease according to 2017 blood pressure categories in diabetes mellitus. Hypertension 76:766-775.

Lee S, Oh HJ, Lee E-K, Lee O, Ha E, Kim S-J, Kang D-H, Choi KB, Ryu D-R (2017) Blood pressure control during chronic kidney disease progression. American Journal of

Table 1. Baseline characteristics of study participants

	Overall		Control group		CRIC group		
	(n=10)		(n=4)		(n=6)		
	n (%) or median (IQR)		n (%) or median (IQR)		n (%) or median (IQR)		P-value
Age	68.0	(18.0)	68.0	(7.0)	70.0	(22.0)	0.669
Gender-Male	5	(50.0%)	1	(25.0%)	4	(66.7%)	0.524
Race							0.810
Chinese	6	(60.0%)	2	(50.0%)	4	(66.7%)	
Malay	2	(20.0%)	1	(25.0%)	1	(16.7%)	
Indian	1	(10.0%)	1	(25.0%)	0	(0.0%)	
Others	1	(10.0%)	0	(0.0%)	1	(16.7%)	
Duration of Diabetes Mellitus							1.000
Less than 10 years	3	(30.0%)	1	(25.0%)	2	(33.3%)	
More than 10 years	5	(50.0%	2	(50.0%)	3	(50.0%)	
Duration of Hypertension							1.000
Less than 10 years	2	(20.0%)	1	(25.0%)	1	(16.7%)	
More than 10 years	8	(80.0%)	3	(75.0%)	5	(83.3%)	
History of CVA	1	(10.0%)	0	(0.0%)	1	(16.7%)	1.000
History of IHD	2	(20.0%)	1	(25.0%)	1	(16.7%)	1.000
Cause of CKD							
Diabetic kidney disease	3	(30.0%)	1	(25.0%)	2	(33.3%)	1.000
BMI, kg/m^2	26.7	(8.3)	29.9	(6.0)	24.0	(6.4)	0.136
Baseline AOBP SBP, mmHg	148.5	(5.0)	150.0	(4.0)	146.5	(4.0)	0.163
Baseline AOBP DBP, mmHg	76.0	(18.0)	83.0	(20.0)	74.5	(17.0)	0.748
Baseline AOBP MAP, mmHg	100.2	(13.3)	104.8	(14.0)	98.8	(11.3)	0.831
Baseline CASP, mmHg	136.8	(8.0)	141.0	(8.5)	135.5	(15.5)	0.165
Baseline serum Creatinine, µmol/L	199.0	(122.0)	150.0	(84.0)	238.0	(131.0)	1.000
Baseline eGFR CKD-EPI, ml/min	26.0	(28.0)	33.0	(23.0)	24.0	(34.0)	0.915
Baseline UPCR, g/g	3.2	(3.7)	1.7	(2.1)	4.5	(2.1)	0.136
Completion Days, %	92.9	(7.1)	96.4	(13.6)	92.9	(3.6)	0.898
Completion Cycles, %	98.2	(4.5)	97.8	(10.8)	98.2	(2.7)	0.901

AOBP, automated office blood pressure; BMI, body mass index; CASP, central aortic systolic pressure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; IHD, ischemic heart disease; MAP, mean arterial pressure; SBP, systolic blood pressure; UPCR, urine protein-creatinine ratio.

Table 2. Comparisons over time between CRIC and Control groups

	Control group		Comparison over different time points	CRIC group		Comparison over different time points	CRIC vs. Control	GEE performed with unstructured correlation matrix (CRIC vs. Control) *Interaction with Time	
	(n=4)			(n=6)					
	Median (IQR)		P-value	Median (IQR)		P-value	P-value	Coef. of CRIC*Time	P-value
AOBP SBP								0.06	0.973
Day 28	140.0	(16.0)	0.144 [a]	137.0	(25.0)	0.104 [a]	0.807		
Day 42	145.5	(12.5)	0.715 [b]	145.0	(16.0)	0.585 [b]	0.807		
			0.068 [c]			0.345 [c]			
AOBP DBP								-1.05	0.020**
Day 28	82.0	(8.0)	0.713 [a]	65.0	(12.0)	0.041 [a,**]	0.219		
Day 42	80.5	(18.0)	0.708 [b]	73.0	(21.0)	0.104 [b]	0.712		
			0.715 [c]			0.500 [c]			
AOBP MAP								-0.72	0.144
Day 28	101.3	(10.7)	0.465 [a]	93.7	(11.7)	0.043 [a,**]	0.327		
Day 42	102.8	(10.2)	0.715 [b]	94.7	(14.3)	0.043 [b,**]	0.389		
			0.465 [c]			0.345 [c]			
CASP								2.35	0.114
Day 28	137.5	(14.5)	1.000 [a]	127.0	(23.0)	0.225 [a]	0.453		
Day 42	138.3	(8.0)	0.068 [b]	136.0	(11.5)	0.787 [b]	0.327		
			1.000 [c]			0.080 [c]			

AOBP, automated office blood pressure; CASP, central aortic systolic pressure; CKD; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.[a]Day 28 vs. Baseline; [b]Day 42 vs. Baseline; [c]Day 42 vs. Day 28; **P = < 0.05

Hypertension 30:610-616.

Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, Li G, Ren C, Luo Y, Ling F, Jia J, Hua Y, Wang X, Ding Y, Lo EH, Ji X (2012) Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology 79:1853-1861.

Pearce L, Davidson SM, Yellon DM (2021) Does remote ischaemic conditioning reduce inflammation? A focus on innate immunity and cytokine response. Basic Research in Cardiology 116:12.

Pryds K, Nielsen RR, Jorsal A, Hansen MS, Ringgaard S, Refsgaard J, Kim WY, Petersen AK, Bøtker HE, Schmidt MR (2017) Effect of long-term remote ischemic conditioning in patients with chronic ischemic heart failure. Basic Research in Cardiology 112.

Wan EYF, Yu EYT, Chin WY, Fong DYT, Choi EPH, Lam CLK (2019) Association of blood pressure and risk of cardiovascular and chronic kidney disease in Hong Kong hypertensive patients. Hypertension 74:331-340.

Wei M, Xin P, Li S, Tao J, Li Y, Li J, Liu M, Li J, Zhu W,

Redington AN (2011) Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction. Circ Res 108:1220-1225.

Williams B, Lacy PS, Yan P, Hwee CN, Liang C, Ting CM (2011) Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an n-point moving average method. J Am Coll Cardiol 57:951-961.