Chronic remote ischemic conditioning in patients with mild hypertension in the absence of antihypertensive medication: a multicenter, randomized, double-blind, proof-of-concept clinical trial

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Abstract

Background: Exploratory studies have shown that remote ischemic conditioning (RIC) may lower blood pressure (BP). In this multicenter, randomized, double-blind, parallel-controlled trial, we aimed to investigate the safety and efficacy of BP-lowering via RIC in patients with mild hypertension.

Methods: Patients with an office BP of 130/80—160/100 mmHg and a 24-hour average BP ≥125/75 mmHg not on antihypertensive medication were recruited. After a 1-week compliance screening phase, the participants were randomly assigned in a 1:1 ratio to RIC or sham RIC treatment twice a day for 4 weeks. The primary efficacy outcome was the change in the 24-hour average systolic BP from baseline to 4 weeks. The secondary efficacy outcomes included changes in the 24-hour average diastolic BP, daytime and nighttime average BP, office BP, and 24-hour average heart rate. Safety events were assessed during the intervention period.

Results: Between June 2021 and July 2022, 95 participants were randomly allocated to the RIC (n=49) and sham RIC (n=46) groups. In the intention-to-treat analysis, the reduction in the 24-hour average systolic BP was significantly greater in the RIC group (-4.6±9.5 vs. -0.9±6.8 mmHg; baseline-adjusted between-group mean difference: 3.6 mmHg; 95% confidence interval: -6.9 to -0.3 mmHg, adjusted P=0.035). The reduction in the 24-hour average diastolic BP (baseline-adjusted between-group mean difference: -2.7 mmHg, P=0.009), daytime average diastolic BP (-2.6 mmHg, P=0.025), night-time average diastolic BP (-2.6 mmHg, P=0.027), and office systolic/diastolic BP (-7.4/-5.2 mmHg, P<0.001) were also significantly greater in the RIC group than the sham RIC group. However, the changes in the daytime/nighttime average systolic BP and 24-hour average heart rate were not significantly different between the groups (each P≥0.05). The per-protocol analysis yielded similar results. No major adverse events were reported in both groups.

Conclusions: RIC is safe in patients with mild hypertension and may lower BP in the absence of antihypertensive medications. However, the effects of RIC on clinical outcomes in these patients requires further investigation.

Key words: hypertension, remote ischemic conditioning, blood pressure lowering

Non-standard Abbreviations and Acronyms

BP, blood pressure

CI, confidence interval

ITT, intention to treat

OR, odds ratio

PP, per protocol

RIC, remote ischemic conditioning

NO, nitric oxide

ET-1, endothelin-1

Ang-II, angiotensin II

TNF-α, tumor necrosis factor-alpha

IL-1β, interleukin-1 beta

IL-10, interleukin-10

IL-6, interleukin-6

VEGF, vascular endothelial-derived growth factor

SDF-1α, stromal-derived factor-1α

Introduction

Despite the availability of numerous pharmacological and non-pharmacological antihypertensive strategies, hypertension remains uncontrolled in many patients for various reasons (such as poor adherence, financial costs, and the lack of time)[4, 5], which leads to poor health outcomes and increased healthcare costs. Therefore, the search for new and cost-effective antihypertensive approaches to manage hypertension is of great importance.

Remote ischemic conditioning (RIC) is a non-pharmacological strategy that can trigger endogenous protective effects on remote organs via repetitive transient limb ischemia/reperfusion using pneumatic cuffs.[6] It has been well explored in ischemic cardiocerebrovascular diseases from experimental to clinical studies and has been demonstrated to benefit patients with acute ischemic stroke.[7-12] Previous studies have also found that multiple mechanisms (including humoral, neural, and immune pathways) may be involved in the protective effects of RIC.[6, 7, 13-15] Theoretically, the protective mechanisms of RIC may also be beneficial in hypertension via multiple pathways, thereby leading to a decline in blood pressure (BP).[16] In addition, many patients with mild hypertension have no clinical symptoms and prefer non-pharmacological therapy over lifelong pharmacological therapy, and RIC is a simple and low-cost non-pharmacological therapy. Therefore, the antihypertensive efficacy of RIC for hypertension is worth exploring.

Intriguingly, the relationship between RIC and BP has gradually gained attention since the first case report by Medias *et al.,*[17] the findings of which are consistent with our observed findings of studies of RIC in patients with ischemic cerebrovascular disease and clinical practice. To explore the underlying mechanisms and BP-lowering effects of RIC, our group investigated RIC in spontaneously hypertensive rats and found that 6-week RIC reduced the mean BP by 15 mmHg and ameliorated vascular remodeling through inflammatory regulation.[18] Further pilot clinical trials exploring the BP-lowering effects of RIC in patients with mild hypertension showed that chronic RIC performed for 4 weeks reduced 24-hour average systolic BP by 5–8 mmHg.[19, 20] The BP-lowering effects of RIC urgently need to be confirmed by rigorously designed clinical trials. In this multicenter, randomized, double-blind clinical trial, we aimed to explore the safety and efficacy of RIC in patients with mild hypertension who were not taking antihypertensive drugs.

Methods

Study Design

This was a multi-center, randomized, double-blind, parallel-controlled, proof-of-concept trial. To evaluate whether chronic RIC has a BP-lowering effect in patients with mild hypertension, participants were recruited from three centers in China between June 2021 and July 2022 and randomly assigned to receive RIC or sham RIC for 4 weeks. This study was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University (No. [2018]049), and written informed consent was obtained from all participants. The trial was registered at *www.clinicaltrials.gov* (unique identifier: NCT04915313).

Participants

The inclusion criteria of participants in this trial were as follows: 1) age 50–80 years, 2) office systolic/diastolic BP between 130/80 mmHg and 160/100 mmHg and 24-hour average systolic/diastolic BP ≥125/75 mmHg,[21] 3) no history of taking antihypertensive drugs or having discontinued antihypertensive drugs for at least one month before randomization, 4) no intention to receive any other antihypertensive therapies during the 4-week study period, 5) written informed consent obtained from the subjects or their legally authorized representatives.

The exclusion criteria included: 1) known or suspected secondary hypertension; 2) contraindications for RIC or sham RIC, such as vascular injury, soft tissue injury, fractures, infection, or known peripheral vascular disease in either arms; 3) history of hemostatic disorders, systemic bleeding, or thrombocytopenia; 4) atrial fibrillation or other severe arrhythmias, such as severe bradycardia, third-degree atrioventricular block, or ventricular tachycardia; 5) previous myocardial infarction or stroke; 6) severe or unstable medical conditions, such as severe hepatic dysfunction (defined as alanine aminotransferase or aspartate transaminase 2 times greater than the upper limit of normal), severe renal dysfunction (defined as serum creatinine 1.5 times greater than the upper limit of normal), severe heart failure (New York Heart Association class III and IV), respiratory failure, malignant tumors, or autoimmune diseases; 7) participation in other clinical trials simultaneously; and 8) participants who were not suitable for this trial for other reasons as determined by the researchers.

Screening and Randomization

The screening process for the participants in this study is summarized in Supplementary Figure S1. Trained investigators used a simple questionnaire and office BP

measurements to initially screen potential participants. The potential participants who provided informed consent were further checked for BP eligibility (both office and 24-hour ambulatory BP) and against other inclusion and exclusion criteria, while complete baseline data were collected. These eligible participants were then invited to the second screening, namely 1-week compliance screening. In this compliance screening period, participants were required to complete sham RIC twice a day for one week, and only those who completed sham RIC more than 12 times proceeded to randomization.

Participants who successfully completed the 1-week compliance screening phase were randomly assigned in a 1:1 ratio to the RIC and sham RIC groups. Randomization was stratified by center using block randomization, with a block size of four. The computer-generated randomization sequence was managed by a designated staff member, who was not engaged in participant recruitment and follow-up, and was solely accessible for treatment allocation. Investigators who were responsible for enrollment numbered participants sequentially and obtained the corresponding treatment device for each participant from the staff who managed the randomization code. The appearance of the device for RIC or sham RIC was identical to ensure that the study personnel were blinded to the treatment assignment. All patients and investigators responsible for patient enrollment, follow-up, and assessment of treatment outcomes were blinded to the randomized allocation.

Interventions and Follow-up (4 weeks)

Immediately after completing the 1-week compliance screening phase, participants with good compliance were randomly allocated to the RIC and sham RIC groups and received RIC or sham RIC twice daily for 4 weeks, respectively. All participants were asked to complete all the prescribed treatments for RIC or sham RIC. All participants were required to maintain their previous lifestyle (including sleep duration, smoking, drinking, exercise, and salt intake) and not add any antihypertensive drugs during the 4-week study period unless their BP surpassed 180/110 mmHg which was confirmed within 24 hours.

The RIC protocol included five cycles of bilateral upper arms with 5-minute inflation to 200 mmHg and 5-minute deflation alternately using an automated device, whereas the sham RIC protocol included five cycles of bilateral upper arms with 5-minute inflation to 60 mmHg and 5-minute deflation alternately.[7, 10] The RIC and sham procedures were performed using an electronic auto-control device (Xuanyitong, Beijing Renqiao, China).

All participants were followed up weekly by telephone to record the actual number of treatment sessions of RIC or sham RIC, to remind them to continue with the treatment, and to record any addition of drugs and major changes to the previous lifestyle until they completed the 4-week follow-up examination.

BP Measurement

Office BP was measured at baseline and 4 weeks post-randomization. At the baseline survey visit, the appropriate arm of each participant for BP measures was selected and used for subsequent follow-up visits. For each visit, attempts were made to measure the patient's office BP within the same approximate timeframe of the day (i.e., morning: 9 to 12 am, afternoon:1 to 4 pm). Participants were requested not to drink coffee, alcohol, smoke, or exercise within 30 minutes before BP measurements, they were also asked to empty their bladder before BP measurement. Office BP was measured three times consecutively, 1 minute apart, using a digital automatic BP monitor (HEM-907, OMRON, Japan) after the patient rested in the sitting position for more than 5 minutes, and the last two readings were averaged for analysis. Patients with baseline office BP of 130/80-139/89 mmHg were defined as stage 1 hypertension and ≥ 140/90 mmHg as stage 2 hypertension.

Ambulatory BP measurements were performed at baseline and 4 weeks post-randomization using an ambulatory BP monitor (ABPM-05, Meditech, Hungary). The cuff was placed on the same arm in each visit. Ambulatory BP was measured every 30 minutes during the daytime (06:00–21:59) and every 60 minutes during the nighttime (22:00–05:59). Repeated ambulatory BP measurements were required if the number of 24-hour readings was less than 70% of the expected readings.

Outcomes and Follow-up

Efficacy Outcomes

The primary efficacy outcome was the change in the 24-hour average systolic BP assessed on the basis of ambulatory BP measurements from baseline to 4 weeks. The secondary efficacy outcomes included changes in the 1) 24-hour average diastolic BP, 2) daytime average systolic/diastolic BP, 3) nighttime average systolic/diastolic BP, 4) office systolic/diastolic BP, and 5) 24-hour average heart rate from baseline to 4 weeks. We also assessed the proportion of patients who had a decrease of greater than 5 mmHg in the 24-hour average systolic BP.

Safety Outcomes

The safety outcomes included 1) hypertension crisis (BP elevation >180/120 mmHg

associated with new or worsening target organ damage)[21] within the 4-week intervention period; 2) hypotensive emergency (BP <100/60 mmHg)[22] within the 4-week intervention period; 3) a composite cardiocerebrovascular endpoint (myocardial infarction, acute heart failure, stroke, and transient ischemic attack) within the 4-week intervention period; and 4) any objective signs of tissue or neurovascular injury resulting from RIC and sham RIC (such as skin petechiae, palpation for tenderness in the upper arms, local edema, and skin breakage). Any suspicious adverse events associated with RIC or sham RIC procedure were reported to the investigators.

Exploratory outcomes

To explore the potential mechanisms underlying the benefits of RIC on mild hypertension, we set some exploratory outcomes according to several previous studies, [16] namely, the changes in plasma biomarkers of nitric oxide (NO), endothelin-1 (ET-1), angiotensin II (Ang-II), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-10 (IL-10), interleukin-6 (IL-6), vascular endothelial-derived growth factor (VEGF), and stromal-derived factor-1α (SDF-1α) from baseline to 4 weeks. Methods about blood sample collection and biomarkers testing can be seen in the supplementary methods.

Sample Size Estimation and Statistical Analysis

To detect a mean difference of 5 mmHg in the 24-hour average systolic BP reduction at 4 weeks between the RIC and sham RIC groups and a standard deviation of the BP reduction of 8 mmHg (ensuring a power of 80% at a 2-sided α-level of 0.05 and assuming 10% of missing data on the primary outcome), we planned to randomize 92 participants in a 1:1 ratio in this trial (sample size calculated using PASS 15 software). The effect size was estimated based on data from previous pilot clinical trials.[19, 20] The study by Gao *et al.* [19] reported that the between-group mean difference in 24-hour average SBP reduction was 8 mmHg, the standard deviation of SBP reduction was 8 mmHg, while the study by Tong *et al.* [20] reported that 30-day daily RIC treatment led to a reduction in 24-hour average SBP by 5 mmHg. Therefore, in order to ensure enough sample size, the final sample size estimation of this study was conservatively based on a 5 mmHg of between-group difference in 24-hour average SBP and a standard deviation of the BP reduction of 8 mmHg.

Primary analyses were performed on data corresponding to the intention-to-treat (ITT) population. For the ITT population, patients with missing data at 4 weeks were assigned

their baseline values for statistical analyses. The secondary analyses followed the per-protocol (PP) principle. The PP population excluded patients who were ineligible for inclusion after randomization, did not complete ≥ 80% of the prescribed RIC or sham RIC, or did not complete the 4-week follow-up in this trial.

The Shapiro–Wilk test was used to assess the distribution of continuous data. Normally distributed variables are expressed as mean ± standard deviation, non-normality distributed variables are expressed as medians (interquartile ranges). Between-group differences were analyzed using the unpaired t-test or Mann–Whitney U test, respectively. In addition, analysis of covariance was also employed to adjust for baseline measurements to assess the treatment effect (including BP, heart rate, and plasma biomarkers). Categorical variables are expressed as counts (percentages). Their between-group differences were analyzed using the chi-squared test. Odds ratios (*ORs*) and 95% confidence intervals (*CIs*) were also calculated. The supplementary statistical analysis documented the methods used in exploring different response patterns and their potential factors in the BP change of participants following RIC treatment.

All data were analyzed using SPSS (version 25.0), and two-sided *P*-values <0.05 were considered significant.

Results

A total of 515 patients with potential mild hypertension were screened between June 2021 and July 2022. Of them, 109 were eligible for this study and invited to undergo the compliance screening phase; 95 (87.2%) completed the 1-week compliance screening phase and were randomly allocated to the RIC (n = 49) and sham RIC (n = 46) groups. Of these randomly assigned participants, 86 (90.5%, 44 in the RIC group and 42 in the sham RIC group) completed the entire PP trial, four were found ineligible for inclusion after randomization [4.2%; three in the RIC group (two with severe obstructive sleep apnea and one who discontinued antihypertensive drugs no more than one month prior) and one in the sham RIC group with hyperthyroidism], one (1.1%) did not complete >80% of the prescribed treatment in the RIC group, and four (4.2%; one in the RIC group and three in the sham RIC group) were lost at the 4-week follow-up (Figure 1).

Baseline Characteristics

The baseline characteristics of the RIC and sham RIC groups based on the ITT analysis are summarized in Table 1. There were no significant differences in age (60.6 ± 7.6 vs.

62.5 ± 8.2 years, $P = 0.247$), the proportion of males (44.9 vs. 50%, $P = 0.629$), or body mass index (25.3 ± 3.3 vs. 25.9 ± 4.3 Kg/m^2, $P = 0.426$) between the RIC and sham RIC groups. Smoking habits, alcohol consumption, the presence of diabetes, the presence of hyperlipidemia, exercise habits, salt intake, mild hepatic dysfunction, and 10-year risks of atherosclerotic cardiovascular disease were also similar between the two groups. At baseline, the 24-hour average systolic BP was 134.5 ± 8.9 mmHg in the RIC group and 134.6 ± 9.2 mmHg in the sham RIC group with no significant difference ($P = 0.968$). Besides, the 24-hour average diastolic BP, daytime average systolic/diastolic BP, nighttime average systolic/diastolic BP, office systolic/diastolic BP, stage of hypertension, and 24-hour average heart rate were balanced at baseline between the two groups. PP analysis showed similar baseline characteristics between the two groups as well (Supplementary Table S1).

Ambulatory and Office BP

Table 2 and Figure 2 display the BP at 4 weeks and BP changes from baseline to 4 weeks in the ITT population. Regarding the primary endpoint, there was a greater reduction in the 24-hour average systolic BP in the RIC group compared with that in the sham RIC group (-4.6 ± 9.5 vs. -0.9 ± 6.8 mmHg; between-group mean difference, -3.6 mmHg; 95% *CI*, -6.9 to -0.2 mmHg; $P = 0.038$). The baseline-adjusted between-group mean difference was -3.6 mmHg (-6.9 to -0.3 mmHg, adjusted P=0.035). In addition, more patients had a reduction of greater than 5 mmHg in the 24-hour average systolic BP in the RIC group than the sham RIC group (51.0% vs. 23.9%, P=0.006). The PP analysis (Supplementary Table S2) showed similar results, wherein the 24-hour average systolic BP reduced -5.9 ± 8.6 mmHg in the RIC group and -0.7 ± 6.7 mmHg in the sham RIC group [between-group mean difference: -5.3 mmHg (-8.6 to -1.9 mmHg, $P = 0.002$); baseline-adjusted between-group mean difference: -5.2 mmHg (-8.5 to -1.9 mmHg, adjusted P =0.002)], and the proportion of patients who had a reduction of greater than 5 mmHg in the 24-hour average systolic BP was 56.8% in the RIC group and 23.8% in the sham RIC group ($P = 0.002$).

The reductions in other secondary BP endpoints in the ITT analysis were also significantly greater in the RIC group than in the sham RIC group, including the 24-hour average diastolic BP (-3.3 ± 5.4 vs. -0.6 ± 4.2 mmHg; between-group mean difference, -2.7 mmHg; $P = 0.008$), daytime average diastolic BP (-2.9 ± 5.7 vs. -0.3 ± 5.4 mmHg; between-group mean difference, -2.6 mmHg; $P = 0.025$), night-time average diastolic BP (-3.9 ± 6.2 vs. -1.5 ± 5.4 mmHg; between-group mean difference,

-2.4 mmHg; $P = 0.048$), office systolic BP (-8.8 ± 9.0 vs. -1.1 ± 6.5 mmHg; between-group mean difference, -7.7 mmHg; $P < 0.001$), and office diastolic BP (-5.6 ± 6.9 vs. -0.3 ± 5.4 mmHg; between-group mean difference, -5.3mmHg; $P < 0.001$). The baseline-adjusted between-group mean differences were similar to the above. However, there were no significant between-group mean differences in the changes of daytime average systolic BP ($P = 0.085$), nighttime average systolic BP ($P = 0.110$), and 24-hour average heart rate ($P = 0.781$). PP analysis also showed similar results for the secondary BP endpoints (Supplementary Table S2).

Different response patterns in BP change of patients following RIC treatment and the exploratory outcomes regarding the potential mechanisms underlying the hypotensive benefits of RIC on mild hypertension were displayed in supplementary results.

Safety Outcomes

The patients who underwent the study intervention were included in the safety analysis (Table 3). During the compliance screening phase, no subjects experienced adverse events. Three subjects (6%) in the RIC group reported skin petechiae, and no patients in the sham RIC group reported adverse events. No difference in adverse events was found between the two groups ($P = 0.243$, Table 3). Despite the adverse events in the RIC groups being related to the intervention, none of the patients experienced severe adverse events.

Discussion

In this multicenter, randomized, double-blind, proof-of-concept trial, we found that in patients with mild hypertension, a 4-week treatment of RIC significantly reduced both ambulatory and office BP. RIC was well-tolerated and did not result in any major adverse events.

Previous exploratory studies have shown that RIC may reduce BP.[23] For example, a series of self-experimentation by Medias, a normotensive or prehypertensive person, showed that both acute bouts of RIC and repeated RIC have a hypotensive effect, and the BP-lowering effect of repeated RIC persists 5–10 d after treatment cessation.[17, 24, 25] In addition, Tong *et al.* reported that repeated RIC could result in a BP reduction in patients with mild hypertension.[20] However, no consensus has been reached about the effects of RIC on BP because of limited evidence. The results of this study may provide important evidence, showing that repeated RIC treatment may result in a BP reduction in patients with hypertension. Importantly, no major adverse events were reported after

4 weeks of treatment.

The BP-lowering effect of RIC is comparable to the BP-lowering effect of lifestyle modifications, as shown in previous clinical trials.[21, 26-31] Previous studies have shown that exercise training reduces the 24-hour average systolic/diastolic BP by 5.4/3.0 mmHg,[28] and the Dietary Approaches to Stop Hypertension diet decreases the 24-hour average systolic/diastolic BP by 3.5/2.9 mmHg,[31] compared with the reduction in the control group. In this trial, we found that the 24-hour average systolic/diastolic BP reduced by 3.6/2.7 mmHg in the ITT analysis and 5.3/3.5 mmHg in the PP analysis after 4 weeks of treatment with RIC compared with the reduction in the control group. In addition, the reduction in office BP was also greater in the RIC group, with a net reduction of 7.7/5.3 mmHg compared with the sham RIC control group.

As a novel potential antihypertensive therapy, RIC has two advantages: 1) it is safe in clinical settings[9, 32] and can be used without the concern of severe adverse events, even in elderly patients or patients with concomitant diseases; and 2) it is easy to apply and can provide more flexibility for patients because it can be performed anywhere at the patients' convenience [e.g., RIC can be used during leisure activities (while watching television or browsing the Internet), meetings, or professional work]. In addition, RIC has been shown to improve exercise performance.[33] Therefore, a combination of RIC and exercise or other lifestyle modifications may enhance the BP-lowering effects.

The clinical benefits of the observed reduction in BP with RIC must still be discussed. A previous large-population study has shown a continuous log-linear association between cardiovascular risk and BP in patients with BP greater than 115/75 mmHg.[34] In addition, the benefits of BP-lowering treatment in the context of cardiovascular risk are well established. The results of a recent meta-analysis exploring the BP-lowering effect on cardiovascular events and death showed that each reduction of 10 mmHg in systolic BP was associated with 20% and 13% lower risks of cardiovascular events and all-cause mortality, respectively.[35] If we extrapolate from this estimation on a log-linear scale, the net reduction (3.6 mmHg) in the 24-hour average systolic BP by RIC would decrease the risk of cardiovascular events by 7.2% and the risk of all-cause mortality by 4.7%.

The underlying mechanisms for the hypotensive benefits of RIC remain to be clarified. It seems likely that multifactorial mediated the BP-lowering effect of RIC.[16] Our previous animal experiment has shown that RIC decreased plasma proinflammatory factors (TNF-α and IL-1β) and increased anti-inflammatory factors (IL-10) in

spontaneously hypertensive rats, which might be responsible for BP reduction.[18] In this study, we tested the inflammatory factors including TNF-a, IL-1β, IL-10, and IL-6, however, none of them have a significant difference between the RIC and sham RIC groups. Besides, some previous studies also reported that RIC increased plasma NO and inhibited the synthesis of ET-1.[36-38] They are important vasoconstrictor or diastole factors and may be candidates for the mechanism of the hypotensive effect of RIC. In this study, we did not observe a similar change trend of NO and ET-1. Other potential biomarkers including Ang-II, SDF-1α, and VEGF also were not significantly different between the two groups. The large individual differences between human beings may be the reason that leads to the inconsistency between the results of the biomarkers change of RIC observed in this study and in previous studies. Plasma proteomics may be helpful in screening interesting plasma proteins responsible for reduced blood pressure of RIC and clarifying the mechanisms, which need to be further explored.

Our study has some limitations. First, considering the potential impact of coronavirus disease 2019, this study only recruited a relatively small number of participants from three centers in the same area (Beijing, China), which may have caused bias and limited the generalizability of the findings. Second, the RIC protocol used in this study was pragmatic and has been used in previously published studies,[7, 39] but the optimal protocol of RIC for lowering BP remains unclear and must be explored, especially a less RIC frequency (once every three to four days). Third, the compliance screening by sham RIC procedure before randomization explored in this study may cause unblinding because this approach may not be truly blinded for those participants that were allocated to the RIC group, which may provide a reference for future research on chronic RIC. In addition, this study only investigated the BP-lowering effects of chronic RIC in mild hypertension who were not on antihypertensive medication, whether it has beneficial effects on other hypertensive conditions (such as hypertension with antihypertensive medication or resistant hypertension) and has long-term clinical benefits by reducing cardiovascular events for hypertension requires further investigations. An ongoing pilot study that exploring the effects of chronic RIC on resistant hypertension may help to answer some of the questions (registered at *www.clinicaltrials.gov* with NCT05426707). In addition, the underlying mechanisms involved in the BP-lowering effects of RIC require further investigation.

Conclusions

In conclusion, in patients with mild hypertension who do not take antihypertensive drugs, 4 weeks of treatment with RIC appears to be safe and well tolerated, and it could significantly reduce both ambulatory and office BP. Further studies are required to confirm these findings and explore the underlying mechanisms involved.

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Disclosures

The patent of the RIC device (patent no. ZL200820123637.X) used in this study belongs to Xuanwu Hospital Capital Medical University.

Supplemental Materials:

Table S1 Baseline characteristics of the PP population

Table S2 BP at 4-week and BP changes from baseline to 4 weeks in the PP population

Figure S1 Screening process of participants

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Table 1 Baseline characteristics of the ITT population

Variables	RIC group (n = 49)	Sham-RIC group (n = 46)	*P* value
Age, years	60.6±7.6	62.5±8.2	0.247
Male, n (%)	22(44.9%)	23(50.0%)	0.629
Body mass index, kg/m^2	25.3±3.3	25.9±4.3	0.426
Smoker, n (%)	17(34.7%)	12(26.1%)	0.363
Alcohol intake, n (%)	15(30.6%)	12(26.1%)	0.625
Diabetes, n (%)	6(12.2%)	4(8.7%)	0.741
On antidiabetic treatment, n (%)	5(10.2%)	1(2.2%)	0.108
Hyperlipidemia, n (%)	30(61.2%)	30(65.2%)	0.687
On lipid-lowering therapy, n (%)	8(16.3%)	5(10.9%)	0.439
Met the standard recommendation for exercise, n (%)	35(71.4%)	35(76.1%)	0.606
Salt intake, n (%)			0.998
1 beer bottle cap (≈ 6 g)	29(59.2%)	27(58.7%)	
2 beer bottle caps (≈ 12 g)	19(38.8%)	18(39.1%)	
3 or more beer bottle caps (≥18 g)	1(2.0%)	1(2.2%)	
Fasting plasma glucose, mmol/L	5.5±1.0	5.6±0.9	0.520
Serum total cholesterol, mmol/L	5.2±0.9	5.1±1.0	0.551
Serum triglycerides, mmol/L	1.3(1.0)	1.2(1.0)	0.704
Serum high-density lipoprotein cholesterol, mmol/L	1.4±0.4	1.3±0.3	0.395
Serum low-density lipoprotein cholesterol, mmol/L	2.9±0.8	3.0±0.8	0.690
Mild hepatic dysfunction, n (%)	4 (8.2%)	4 (8.7%)	1.000
10-Year Risks of Atherosclerotic	10.1±4.7	10.7±5.1	0.541
Cardiovascular Disease, n (%)			0.444
Low risk	10(20.4%)	6(13.0%)	
Medium risk	13(26.5%)	17(37.0%)	
High risk	26(53.1%)	23(50.0%)	
Stage 1 hypertension, n (%)	13(26.5%)	16(34.8%)	0.383
Stage 2 hypertension, n (%)	36(73.5%)	30(65.2%)	
24-hour average systolic BP, mmHg	134.5±8.9	134.6±9.2	0.968
24-hour average diastolic BP, mmHg	79.4±9.4	80.1±8.9	0.720
Daytime average systolic BP, mmHg	137.9±9.4	137.8±9.9	0.913
Daytime average diastolic BP, mmHg	82.2±9.8	82.8±9.5	0.730
Night-time average systolic BP, mmHg	127.9±11.2	129.0±11.4	0.615
Night-time average diastolic BP, mmHg	74.5±10.4	75.5±9.2	0.617
Office systolic BP, mmHg	144.0±7.6	142.6±8.6	0.395
Office diastolic BP, mmHg	86.2±9.7	85.6±8.2	0.727
24-hour average heart rate, bpm	70.9±7.7	70.4±7.2	0.734

ITT, intention-to-treat; RIC, remote ischemic conditioning; BP, blood pressure.

Table 2 BP at baseline and 4-week and BP changes from baseline to 4 weeks in the ITT population

	RIC group (n=49)			Sham RIC group (n=46)			Unadjusted[@] net difference (95% CI), RIC vs. Sham RIC	Unadjusted[@] *P* value	Adjusted[&] net difference (95% CI), RIC vs. Sham RIC	Adjusted[&] *P* value
	Baseline	4-week	Change in BP at 4-week	Baseline	4-week	Change in BP at 4-week				
24-hour average BP, mmHg										
Systolic BP	134.5±8.9	129.9±11.3	-4.6±9.5	134.6±9.2	133.5±10.8	-0.9±6.8	-3.6(-6.9 to -0.2)	0.038*	-3.6(-6.9 to -0.3)	0.035*
Diastolic BP	79.4±9.4	76.2±10.3	-3.3±5.4	80.1±8.9	79.5±10.2	-0.6±4.2	-2.7(-4.7 to -0.7)	0.008*	-2.7(-4.7 to -0.7)	0.009*
Daytime average BP, mmHg										
Systolic BP	137.9±9.4	133.9±12.2	-4.1±10.3	137.8±9.9	137.1±11.6	-0.6±8.8	-3.4(-7.3 to 0.5)	0.085	-3.4(-7.2 to 0.4)	0083
Diastolic BP	82.2±9.8	79.2±11.1	-2.9±5.7	82.8±9.5	82.5±10.8	-0.3±5.4	-2.6(-4.9 to -0.3)	0.025*	-2.6(-4.9 to -0.3)	0.025*
Night-time average BP, mmHg										
Systolic BP	127.9±11.2	122.7±11.5	-5.2±10.7	129.0±11.4	127.2±12.4	-1.8±9.7	-3.4(-7.5 to 0.8)	0.110	-3.8(-7.6 to 0.1)	0.055
Diastolic BP	74.5±10.4	70.6±9.2	-3.9±6.2	75.5±9.2	74.0±10.4	-1.5±5.4	-2.4(-4.8 to -0.1)	0.048*	-2.6(-4.9 to -0.3)	0.027*
Office BP, mmHg										
Systolic BP	144.0±7.6	135.2±9.9	-8.8±9.0	142.6±8.6	141.5±9.6	-1.1±6.5	-7.7(-10.9 to -4.5)	< 0.001*	-7.4(-10.5 to -4.2)	< 0.001*
Diastolic BP	86.2±9.7	80.7±10.8	-5.6±6.9	85.6±8.2	85.3±8.5	-0.3±5.4	-5.3(-7.8 to -2.7)	< 0.001*	-5.2(-7.7 to -2.7)	< 0.001*
24-hour average heart rate, bpm										
	70.9±7.7	69.5±6.9	-1.5±5.4	70.4±7.2	68.7±7.8	-1.8±5.6	0.3(-1.9 to 2.5)	0.781	0.5(-1.6 to 2.5)	0.661
Patients with a reduction greater than 5 mmHg in 24-hour average systolic BP										
		25(51.0%)			11(23.9%)		27.1% (6.1 to 45.1 %)	0.006*	/	/

* $P < 0.05$. @ Treatment difference and *P* value from unpaired t-test. & Treatment difference and P value from the analysis of covariance model.
ITT, intention-to-treat; RIC, remote ischemic conditioning; BP, blood pressure.

Table 3 Safety outcomes

Safety outcomes	Compliance screening (n=109)	Intervention phase	
		RIC group (n=49)	Sham RIC group (n=46)
Total adverse events	**0**	**3**	**0**
Hypertension crisis	0	0	0
Hypotensive emergency	0	0	0
Composite cardiovascular events	0	0	0
Skin petechiae	0	3	0
Palpation for tenderness	0	0	0
Edema	0	0	0
Skin breakage	0	0	0

RIC, remote ischemic conditioning.

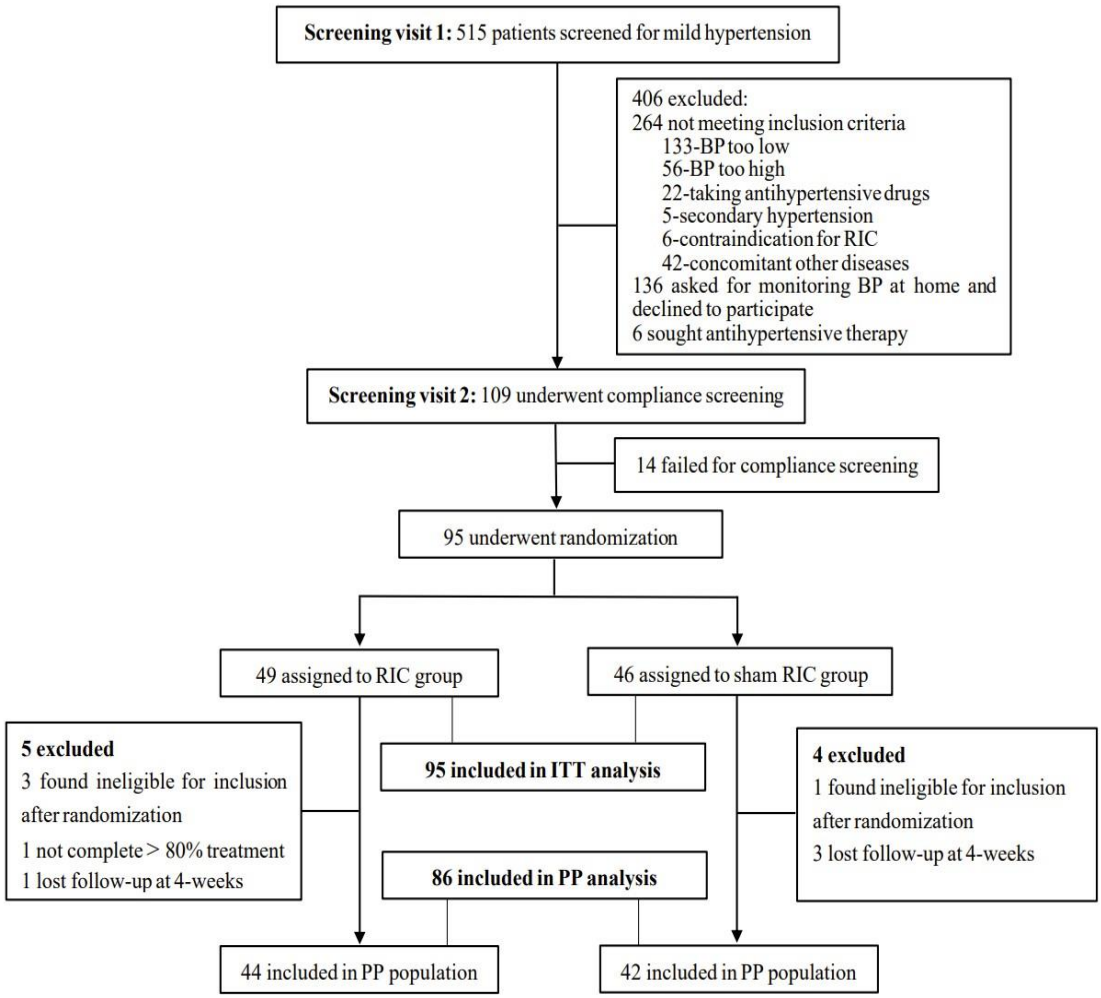

Figure 1 Flow chart of the actual screening and enrollment
BP, blood pressure; RIC, remote ischemic conditioning; ITT, intention-to-treat; PP, per protocol.

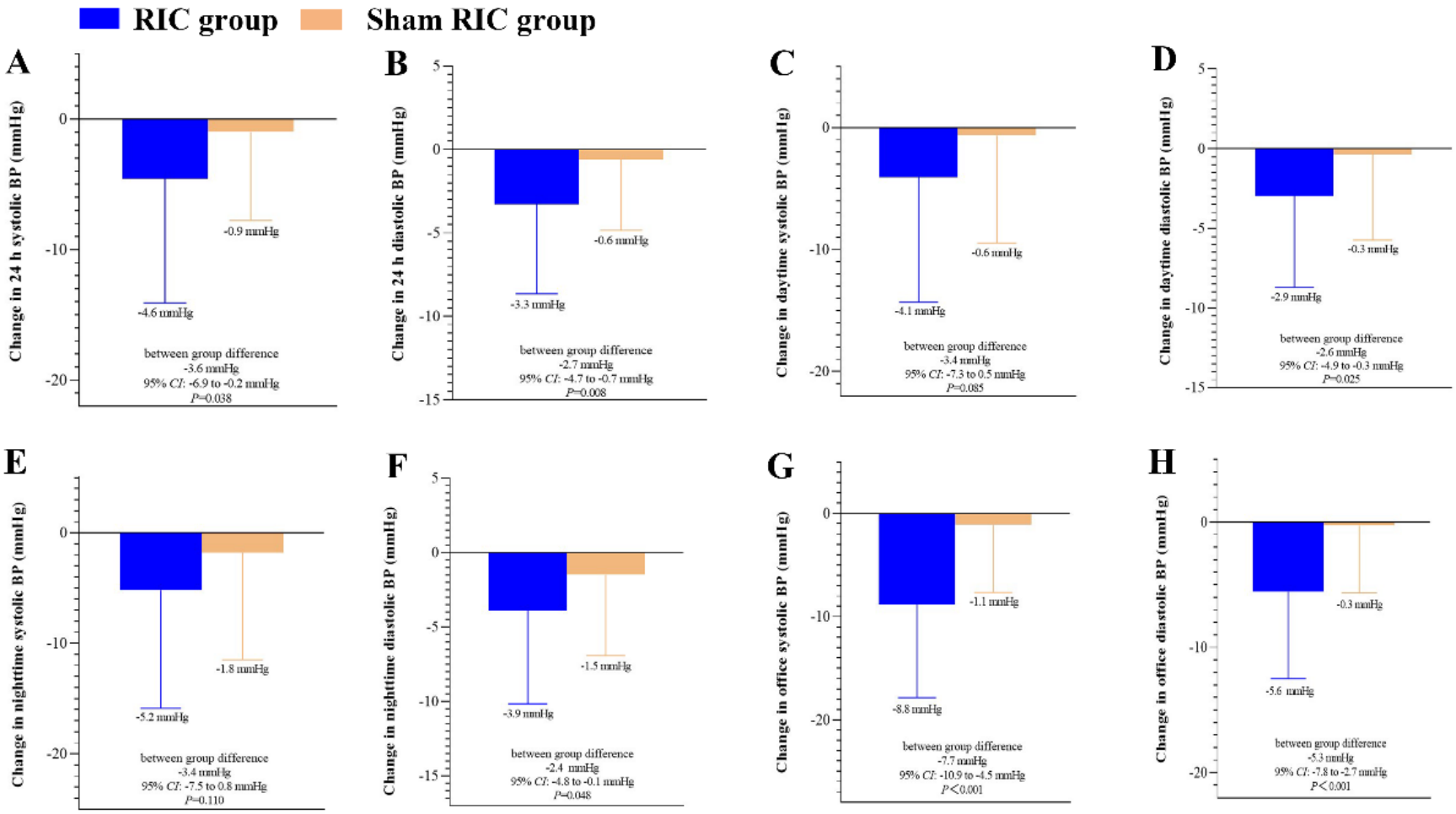

Figure 2 Change in ambulatory BP and office BP from baseline to 4 weeks in the ITT population
BP, blood pressure; RIC, remote ischemic conditioning; ITT, intention-to-treat.