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Research Article

Acute Remote Ischemic Preconditioning Alters Autonomic Function, Corrected Left Ventricular Ejection Time, and Pulse Transit Time in Healthy Adults

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Abstract

Background: Remote ischemic preconditioning (RIPC) leads to systemic protective responses via neural, hormonal, and endothelial pathways, with autonomic modulation as a key mediator. While most studies focus on heart rate variability (HRV) and arterial stiffness, limited data exist on RIPC's acute effects on cardiac systolic timing and vascular pulse conduction. ***Objective***: To investigate the acute effects of RIPC on autonomic function, heart rate-corrected left ventricular ejection time (cLVET), and pulse transit time (PTT) in healthy adults. ***Methods***: Fifteen healthy young men completed RIPC and sham RNIPC protocols. RIPC involved four 5-min cycles of upper-arm cuff inflation to 230 mmHg followed by 5-min deflation; sham used 30 mmHg. Continuous ECG and digital pulse wave recordings were obtained before and after each intervention. HRV indices, PTT, PWV, and cLVET were derived from ECG-gated waveform analysis. ***Results***: Following RIPC, mean RR interval, SD1, pNN50, high-frequency power, and SD2 increased significantly, while systolic blood pressure decreased. PTT increased significantly, with a corresponding reduction in calculated PWV. In addition, cLVET decreased significantly after RIPC. In the sham RNIPC condition, no significant changes were observed in HRV indices, PTT/PWV, or cLVET, although systolic blood pressure also declined significantly. ***Conclusions***: Acute RIPC induced coordinated changes in autonomic and cardiovascular timing, including enhanced vagal HRV, prolonged PTT, reduced PWV, and shortened cLVET, suggesting cLVET and PTT as useful markers for short-term autonomic–cardiovascular responses in healthy adults.

Keywords: Corrected left ventricular ejection time; Heart rate variability; Pulse transit time; Remote ischemic preconditioning.

التكييف المسبق الحاد للإقفالة عن بعد يغير الوظيفة الذاتية، وتصحيح وقت إخراج البطين الأيسر، ووقت مرور النبض لدى البالغين الأصحاء

الخلاصة

الخلفية: التكييف الإقفاري عن بعد (RIPC) يؤدي إلى استجابات حماية جهازية عبر المسارات العصبية والهرمونية والبطانية، مع كون التعديل التلقائي وسيطا رئيسيا. بينما تركز معظم الدراسات على تباين معدل ضربات القلب (HRV) وتيبس الشرايين، هناك بيانات محدودة حول تأثيرات RIPC الحادDMة على توقيت القلب الانقباضي وتوصيل النبض الوعائي. **الهدف**: دراسة التأثيرات الحادة ل RIPC على وظيفة الجهاز الذاتي، ووقت إخراج البطين الأيسر المصحح بمعدل ضربات القلب (cLVET)، ووقت انتقال النبض (PTT) لدى البالغين الأصحاء. **الطرائق**: أكمل خمسة عشر شابا أصحاء بروتوكولات RIPC وRNIPC وهمية. تضمنت RIPC أربع دورات مدتها 5 دقائق من تضخم الكفة في الذراع العلوي حتى 230 ملم زئبق تلتها انكماش لمدة 5 دقائق؛ الوهمي استخدم 30 ملم زئبق. تم الحصول على تخطيط القلب المستمر وتسجيلات موجات النبض الرقمية قبل وبعد كل تدخل. تم اشتقاق مؤشرات PWV، PTT، HRV، وcLVET من تحليل الموجة المدعومة بنظام تخطيط القلب الكهربائي. **النتائج**: بعد RIPC، ارتفع متوسط فترة RR، SD1، pNN50، القدرة عالية التردد، وSD2 بشكل ملحوظ، بينما انخفض ضغط الدم الانقباضي. ارتفع PTT بشكل ملحوظ، مع انخفاض مماثل في PWV المحسوب. بالإضافة إلى ذلك، انخفض cLVET بشكل كبير بعد RIPC. في حالة RNIPC الوهمية، لم تلاحظ تغييرات ذات دلالة في مؤشرات PTT/PWV، HRV، أو cLVET، رغم أن ضغط الدم الانقباضي انخفض بشكل ملحوظ أيضا. **الاستنتاجات**: أدى اضطراب RIPC إلى تغييرات منسقة في توقيت العضلات الذاتية والقلبية الدموية، بما في ذلك زيادة معدل ضربات القلب المبهم، وطول فترة PTT، وانخفاض PWV، وتقصير cLVET، مما يشير إلى أن cLVET وPTT كمؤشرات مفيدة للاستجابات الذاتية والقلبية الوعائية قصيرة المدى لدى البالغين الأصحاء.

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INTRODUCTION

Remote ischemic preconditioning (RIPC) refers to the application of brief, non-injurious cycles of ischemia and reperfusion to a limb in order to confer protection against ischemia–reperfusion injury in distant organs and tissues [1]. Since its original description, RIPC has attracted considerable interest as a simple, non-invasive intervention capable of activating systemic cardioprotective and vasculoprotective pathways without directly exposing the target organ to ischemia [2]. The mechanisms underlying RIPC are complex and are thought to involve an integrated interaction among neural, humoral, and endothelial pathways. Among these, autonomic modulation has emerged as a key candidate mechanism [3]. Experimental evidence suggests that transient limb ischemia activates peripheral sensory afferents, which relay signals to central autonomic nuclei within the brainstem and thereby alter efferent autonomic outflow to the heart and peripheral vasculature [4].

Through this neurohumoral crosstalk, RIPC may influence not only tissue protection but also short-term cardiovascular regulation. Human studies provide support for this autonomic hypothesis. In particular, changes in heart rate variability (HRV) following RIPC have been interpreted as evidence of altered sympathovagal balance, although the available evidence suggests that these effects are more consistently observed after repeated rather than single-session RIPC exposure [5]. HRV is a valuable non-invasive index of autonomic modulation, but it does not fully characterize the downstream functional consequences of autonomic adjustments on cardiac mechanical performance and vascular pulse-wave transmission [5]. Two relevant physiological indices in this context are left ventricular ejection time (LVET) and pulse transit time (PTT). LVET represents the duration of blood ejection from the left ventricle into the aorta during systole and is considered a non-invasive marker of cardiac mechanical function and loading conditions [6]. Because autonomic activity can alter heart rate, myocardial contractility, and ventricular loading, LVET may provide useful insight into the mechanical expression of autonomic modulation. In general, LVET tends to shorten with tachycardia and heightened sympathetic drive, whereas longer ejection duration may be observed under conditions of lower heart rate and reduced cardiovascular stress [7]. Nevertheless, interpretation of LVET requires caution because it is influenced by heart rate and depends on accurate detection of ejection onset and termination [8]. PTT reflects the time required for the arterial pulse wave to travel from the heart to a peripheral recording site, commonly estimated from the interval between the electrocardiographic R wave and the onset of the peripheral pulse waveform. It is widely used as a non-invasive marker of arterial stiffness and short-term hemodynamic status [9]. In physiological terms, shorter PTT is generally associated with increased vascular stiffness and/or elevated blood pressure, whereas longer PTT is associated with greater arterial compliance and lower vascular load [10]. Because of its sensitivity to acute cardiovascular changes, PTT is often used to monitor short-term responses to autonomic and hemodynamic perturbations [11]. However, its measurement can be affected by signal quality, pulse-onset detection, and beat-to-beat blood pressure variability [10]. Despite growing interest in the autonomic and vascular consequences of RIPC, an important gap remains in literature. Most human studies have focused predominantly on HRV or on isolated vascular outcomes, whereas comparatively few have examined cardiac systolic timing and peripheral pulse-wave conduction within the same experimental framework. Consequently, the acute temporal interaction between autonomic regulation, cardiac mechanical function, and vascular impulse transmission following remote ischemic conditioning (RIPC) remains insufficiently understood, particularly in healthy adults. A more nuanced understanding of the physiological responses may help elucidate the underlying mechanisms while minimizing confounding factors associated with disease. Therefore, it is clear that left ventricular ejection time (LVET), pulse transition time (PTT), and heart rate variability (HRV) should be evaluated together. Accordingly, this study was designed to investigate the acute effects of RIPC on LVET and PTT, along with traditional HRV indices, in healthy adults. By integrating autonomic regulation with RIPC and vascular impulse transmission, this study aims to provide a more comprehensive characterization of the short-term cardiovascular responses resulting from RIPC.

METHODS

Study design and participants

This study employed a controlled within-subject experimental design to examine the immediate physiological responses to remote ischemic preconditioning (RIPC) compared with a sham remote non-ischemic preconditioning (RNIPC) protocol [12]. Healthy adult volunteers were recruited from the university population. The inclusion criteria required participants to have normal blood pressure, no history of cardiovascular, metabolic, or neurological disorders, non-smoking status, and no regular use of medications. Participants were additionally instructed to refrain from caffeine consumption, intense physical exercise, and heavy meals prior to the experimental session [13]. A total of fifteen healthy male participants (22.5 ± 3.7 years) completed both the RIPC and RNIPC sessions. All procedures followed the ethical standards of the institution and were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before participation in the study.

Data acquisition

Electrocardiogram (ECG) and digital pulse waveform (DPW) signals were acquired simultaneously using a PowerLab 26T multichannel data acquisition unit and recorded using LabChart Pro version 7.2 software at a sampling rate of 1 kHz (ADInstruments, Australia). Cardiac electrical activity was recorded using a standard ECG configuration (Lead II), while DPW signals were acquired from the terminal phalanx of the left middle finger using a strap-mounted piezoelectric pulse transducer. All signals were sampled at high frequency and digitally stored for subsequent analysis. Signal processing included appropriate filtering procedures to minimize motion distortions and high-frequency noise while preserving waveform integrity.

Experimental protocol

All experiments were conducted in a quiet, temperature-controlled laboratory environment (22–26 °C), with

participants resting in a semi-supine position. After an initial stabilization period of 10–15 minutes, baseline measurements of brachial blood pressure, heart rate, and a 5-minute simultaneous ECG and DPW recording were obtained before intermittent remote ischemic preconditioning [14]. Remote ischemic conditioning (RIPC) was then induced by placing a blood pressure cuff around the upper right arm and inflating it to 230 mmHg for 5 minutes, followed by 5 minutes of deflation. This process was repeated four times, as previously described [15]. Immediately after the fourth cycle, brachial artery blood pressure and heart rate were measured, and an electrocardiogram (ECG) and digital pulse wave (DPW) were recorded for another 5 minutes to determine the post-RIPC status. A sham control protocol was performed 4–6 weeks after the RIPC session. Baseline blood pressure, heart rate, ECG, and DPW were measured for 5 minutes before intermittent cuff inflation. The blood pressure cuff was then inflated to 30 mmHg for 5 minutes, a pressure insufficient to impede venous return, to simulate cuff inflation without significantly restricting blood flow, followed by 5 minutes of deflation. This low-pressure inflation-deflation sequence was repeated four times. Immediately after the fourth cycle, additional 5-minute blood pressure, heart rate, and ECG recordings were obtained, along with DPW recordings [16].

Heart rate variability analysis

ECG recordings were visually inspected to identify and exclude ectopic beats and artifacts. The cleaned R–R interval time series were analyzed using dedicated HRV software (Kubios HRV Standard software). Time-domain indices included mean RR interval and pNN50, while frequency-domain parameters included high-frequency (HF) and low-frequency (LF) power. Nonlinear heart rate dynamics were further assessed using Poincaré plot–derived indices SD1 and SD2. Hemodynamic parameters, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), were also recorded to complement the assessment of autonomic and cardiovascular responses [17].

Vascular stiffness and pulse wave–derived parameters

Pulse transit time (PTT) was defined as the interval between the ECG R wave and the peak of the first derivative of the digital pulse wave, corresponding to the 50% rise point of the DPW amplitude [18]. Pulse wave velocity (PWV) was calculated using the equation PWV = D/PTT, where D represents the arterial path length between the heart and the tip of the left middle finger, expressed in meters and estimated as 0.5 × body height [19]. PTT was expressed in seconds. Left ventricular ejection time (LVET) was determined from the foot of the DPW waveform to the dicrotic notch. These landmarks were identified using the "a" and "e" waves of the second derivative of the DPW signal [20]. LVET was further corrected for heart rate using the formula cLVET = LVET/√RR interval [21]. Final LVET values were calculated by averaging measurements across 20–30 cardiac cycles.

Ethical considerations

The study protocol was approved by the Department of Physiology, and all procedures were conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki (2013) for research involving human participants. The study was conducted between October 15, 2025, and February 15, 2026. All participants received a thorough explanation of the study procedures, potential risks, and expected benefits and provided written informed consent before participating. Participants' data were kept confidential throughout the study, and all data were anonymized before analysis.

Statistical analysis

All data are presented as mean ± standard deviation (SD). Differences between paired measurements were evaluated using the paired Student's t-test. Because this test assumes normally distributed data, the Kolmogorov–Smirnov test was applied to assess normality. When data did not satisfy the normality assumption required for parametric testing, the Wilcoxon matched-pairs signed-ranks test was used instead. The Kolmogorov–Smirnov and Wilcoxon matched-pairs signed-ranks tests were performed using GraphPad InStat software (version 3.06). The analyses compared baseline vs. post within each condition. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

Following experimental remote ischemic preconditioning (RIPC), several heart rate variability (HRV) indices changed in a direction consistent with enhanced parasympathetic modulation (Table 1).

Table 1: Heart rate variability (HRV) indices and blood pressure before and after remote ischemic preconditioning (RIPC) (n= 15)

HRV indices	Before RIPC	After RIPC	*p-value*
SBP (mm Hg)	126.4±9.7	121.3±10.5	0.03
DBP (mm Hg)	68.7±11.1	67.2±12.9	NS
Mean RR (ms)	856.47±83.13	905.2±101.4	0.004
SD1 (ms)	34.8±21.4	43.73±26.02	0.004
pNN50 (%)	25.97±23.75	34.78±24.83	0.015
HF (ms2)	1299.67±1694.42	1743.33±2001.1	0.021
SD2 (ms)	53.25±24.4	63.93±23.08	0.002
LF (ms2)	883.13±711.2	1278.03±888.59	NS

NN50%: Is the percentage of normal R-R intervals that differ by 50 ms. LF is the low frequency band power (0.04–0.15 Hz band). HF is the high frequency band power (0.15–0.4 Hz band). SD1 (Standard Deviation 1) on the Poincaré plot, i.e. it is the width of the plot (minor axis of the ellipse). SD2 (Standard Deviation 2) on the Poincaré plot, i.e. it is the length of the plot (major axis of the ellipse). Systolic, Diastolic blood pressure = SBP, DBP.

The mean RR interval increased significantly from 856.5 ± 83.1 ms to 905.2 ± 101.4 ms ($p< 0.004$), SD1 increased from 34.8 ± 21.4 ms to 43.7 ± 26.0 ms ($p< 0.004$), and

pNN50 increased from 26.0 ± 23.8% to 34.8 ± 24.8% (p< 0.015). High-frequency (HF) power also increased significantly, from 1299.7 ± 1694.4 ms² to 1743.3 ± 2001.1 ms² (p< 0.021). In addition, SD2 increased significantly from 53.3 ± 24.4 ms to 63.9 ± 23.1 ms (p< 0.002), whereas low-frequency (LF) power increased numerically from 883.1 ± 711.2 ms² to 1278.0 ± 888.6 ms² without reaching statistical significance. Systolic blood pressure (SBP) decreased significantly from 126.4 ± 9.7 mmHg to 121.3 ± 10.5 mmHg (p< 0.03), while diastolic blood pressure (DBP) did not change significantly. In Table 2, under sham remote non-ischemic preconditioning (RNIPC), no statistically significant changes were observed in mean RR interval, SD1, pNN50, HF, SD2, LF, or DBP.

Table 2: Heart rate variability (HRV) indices and blood pressure before and after sham remote non-ischemic preconditioning (RNIPC) (n= 15)

HRV indices	Before sham RNIPC	After sham RNIPC	p-value
SBP (mm Hg)	123.5±8.3	117.8±9.5	0.002
DBP (mm Hg)	65.6±7.6	64.1±8.5	NS
Mean RR (ms)	886.5±110.5	907±145.3	NS
SD1 (ms)	33.6±20.8	38.5±27.3	NS
pNN50 %	23.3±20	27.2±21.1	NS
HF (ms2)	1043.3±1476.7	1485.1±2280	NS
SD2 (ms)	49.5±19.4	57.2±26	NS
LF (ms2)	837.5±832.7	1274.9±1365.9	NS

NN50%: Is the percentage of normal R-R intervals that differ by 50 ms. LF is the low frequency band power (0.04–0.15 Hz band). HF is the high frequency band power (0.15–0.4 Hz band). SD1 (Standard Deviation 1) on the Poincaré plot, i.e. it is the width of the plot (minor axis of the ellipse). SD2 (Standard Deviation 2) on the Poincaré plot, i.e. it is the length of the plot (major axis of the ellipse). Systolic, Diastolic blood pressure = SBP, DBP.

However, SBP decreased significantly from 123.5 ± 8.3 mmHg to 117.8 ± 9.5 mmHg (p< 0.002). Although some HRV variables showed numerical increases after sham RNIPC, none of these changes reached statistical significance. Pulse transit time (PTT) increased significantly following experimental RIPC, rising from 248.9 ± 21.3 ms before the intervention to 261.6 ± 15.0 ms afterward. This corresponded to a reduction in calculated pulse wave velocity (PWV) from 3.5 ± 0.4 m/s to 3.3 ± 0.2 m/s. In contrast, under sham RNIPC, PTT increased only modestly from 270.4 ± 19.4 ms to 277.2 ± 17.4 ms, with the corresponding PWV changing from 3.3 ± 0.3 m/s to 3.2 ± 0.3 m/s; this difference was not statistically significant (Figure 1). Heart rate-corrected left ventricular ejection time (cLVET) decreased significantly after experimental RIPC by approximately 6%, reaching 342.5 ± 19.4 ms after the intervention compared with a pre-intervention value of 364.8 ± 26.1 ms. By contrast, no meaningful change was observed after sham RNIPC, with cLVET values of 337.4 ± 24.7 ms before and 334.6 ± 17.4 ms after the sham condition (Figure 2).

DISCUSSION

The principal findings of the present showed that acute remote ischemic preconditioning (RIPC) was significantly increased, several HRV indices associated with vagal modulation, including mean RR interval, SD1, pNN50, and HF power, while also increasing SD2, prolonging pulse transit time (PTT), reducing calculated pulse wave velocity (PWV), and shortening heart rate-corrected left ventricular ejection time (cLVET).

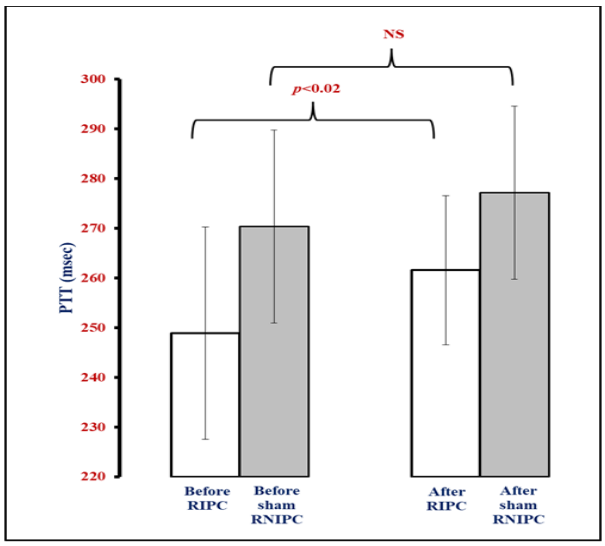

Figure 1: Pulse treatment time (PTT) before and after experimental remote ischemic precondition (RIPC) and sham RNIPC (n=15).

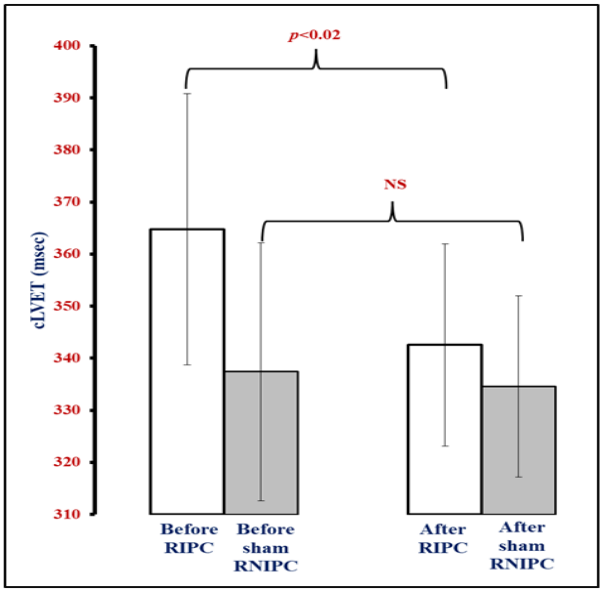

Figure 2: Heart rate-corrected left ventricular ejection time (cLVET) before and after experimental remote ischemic precondition (RIPC) and sham RNIPC (n= 15).

By contrast, sham remote non-ischemic preconditioning (RNIPC) did not significantly alter HRV indices, PTT/PWV, or cLVET, although systolic blood pressure decreased in both conditions. Taken together, these findings suggest that acute RIPC elicited coordinated

changes in autonomic and cardiovascular timing variables that were not reproduced by the sham intervention. These findings indicate that, in healthy young men, acute RIPC may affect both cardiac systolic timing and peripheral vascular function, possibly through short-term autonomic and hemodynamic influences. Nevertheless, these observations should be interpreted with caution because the study was exploratory and did not include direct measurements of the underlying physiological mechanisms. At present, direct evidence linking RIPC to changes in left ventricular ejection time (LVET) is still limited. In patients undergoing cardiac surgery, a large randomized clinical trial found no significant improvement in LVET following RIPC compared with a sham intervention [22]. In contrast, the current study demonstrated a reduction in cLVET after experimental RIPC relative to the sham condition. One possible explanation for this observation is autonomic modulation. Sympathetic activity typically enhances myocardial contractility and supports ventricular ejection; therefore, a decrease in sympathetic drive after RIPC may reduce contractile support, which could contribute to a shorter ejection period [23,6]. This explanation aligns with the understanding that LVET reflects not only intrinsic ventricular function but also the combined influence of preload, afterload, myocardial contractility, and heart rate. Another possible explanation may involve the interaction between parasympathetic activation and a simultaneous reduction in sympathetic activity. Although a lower heart rate is often associated with longer filling time, LVET does not necessarily lengthen under these conditions, particularly if stroke volume or ejection dynamics are altered simultaneously. In this context, a reduction in sympathetic support may have decreased the force and velocity of ventricular ejection, leading to a shorter cLVET despite a slower heart rate [23,24]. A third, non-mutually exclusive mechanism may be vascular in origin. Reduced sympathetic vasoconstrictor tone may decrease peripheral vascular resistance and ventricular afterload, thereby facilitate earlier ventricular emptying and shorten the duration of aortic valve opening [25]. In addition, altered venous return or preload during the post-RIPC period may also have contributed to the observed reduction in cLVET [6]. Taken together, these findings raise the possibility that acute RIPC shortens cLVET through a combined modulation of cardiac autonomic drive and vascular loading conditions. PTT is commonly used as a non-invasive index of arterial stiffness and vascular function, and in the present study it tended to increase after RIPC. Because an increase in PTT generally corresponds to slower pulse-wave propagation and lower apparent vascular stiffness, this pattern is directionally consistent with a transient reduction in vascular tone. However, the broader human literature suggests that a single session of RIPC does not consistently reduce resting peripheral pulse wave velocity (PWV), particularly in healthy individuals [14]. Therefore, the present results should not be considered as definitive proof that acute RIPC consistently reduces resting arterial stiffness under all physiological conditions. Instead, they may suggest that RIPC produces relatively small and short-term influences on vascular tone, which may become more apparent under specific experimental conditions or among individuals who show greater physiological responsiveness. Previous research has also suggested that the vascular impact of RIPC may be more clearly observed when vascular responsiveness is assessed, rather than when measurements are limited to resting arterial stiffness alone. For example, repeated RIPC exposure has been reported to improve vascular reactivity and may reduce arterial stiffness in individuals with impaired vascular function or elevated cardiovascular risk [26,27]. This distinction is important because the physiological consequences of RIPC may differ between healthy subjects and clinical populations and between single-session and repeated-intervention protocols. Accordingly, the most defensible interpretation is that single-session RIPC does not reliably lower resting peripheral PWV in healthy participants, but it may enhance vascular responsiveness and could produce more substantial vascular benefits after repeated exposure or in populations with higher baseline vascular dysfunction. A plausible mechanism linking RIPC to changes in PTT or PWV is acute modulation of sympathetic vasomotor tone. Experimental models have demonstrated that sympathetic activation can increase PWV. During lower-body negative pressure, which elevates sympathetic outflow and muscle sympathetic nerve activity, both central and peripheral PWV increase, providing within-subject evidence that sympathetic activation can acutely stiffen the arterial tree [28]. Conversely, if RIPC reduces sympathetic vasoconstrictor tone, a prolongation of PTT and a reduction in peripheral PWV would be physiologically plausible. This view is further supported by human studies showing that changes in vascular tone induced by vasoactive drug infusions can alter local PWV in muscular conduit arteries [29]. Therefore, the changes observed in the present study may reflect short-term autonomically mediated adjustments in peripheral vascular tone rather than structural alterations in the arterial wall.

Study limitations

Several limitations should be considered when interpreting these results. First, the study was limited to healthy young male participants, which limits the generalizability of the findings to women, older adults, and individuals with cardiovascular, metabolic, or autonomic nervous system disorders. Second, the research focused on the acute effects of a single session of remote ischemic conditioning; therefore, the persistence, reproducibility, and potential clinical significance of these responses remain uncertain. Third, while digital pulse wave analysis synchronized with

electrocardiography provides useful information on autonomic and vascular responses, the study did not include direct assessments of biochemistry, imaging, or endothelial function, which would elucidate the mechanisms underlying the observed changes. Finally, although the sample size was sufficient to detect many physiological responses within the study, it may not be sufficient to detect smaller or more variable effects across all outcome measures.

Conclusion

Acute RIPC induced coordinated changes in autonomic and cardiovascular timing, including enhanced vagal HRV, prolonged PTT, reduced PWV, and shortened cLVET, suggesting cLVET and PTT as useful markers for short-term autonomic-cardiovascular responses in healthy adults.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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