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Effect of Remote Ischemic Conditioning on Heart Rate Responses to Walking in People with Multiple Sclerosis

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Abstract

Background: Remote ischemic conditioning (RIC), exposure of body parts to brief periods of circulatory occlusion and reperfusion, has been shown to improve cardiovascular responses to exercise in healthy individuals but its effects in people with MS are unknown. **Objective:** This study aimed to assess the effect of RIC on heart rate responses to walking in people with MS. **Design:** Double blind randomized controlled trial **Setting:** Multiple sclerosis clinic of tertiary care center teaching hospital in the United Kingdom. **Methods:** Three cycles of RIC were delivered by occluding the upper arm with a blood pressure cuff inflated to a pressure of 30 mmHg above the systolic blood pressure. In the sham group, the blood pressure cuff was inflated to 30 mmHg below diastolic blood pressure. Heart rate responses to the 6-minute walk test (6MWT), the tolerability of RIC using a numerical rating scale for discomfort (0-10), and adverse events were studied. **Results:** Seventy-five participants (RIC -38 and Sham-37) completed the study. RIC was well tolerated. Compared to sham, RIC significantly decreased the rise in heart rate ($P = 0.04$) and percentage of predicted maximum heart rate ($P = 0.016$) after the 6MWT. **Conclusion:** RIC was well tolerated and improved the heart rate response to walking in people with MS. Further studies on RIC in the management of MS are needed.

Keywords: Cardiovascular response, multiple sclerosis, remote ischemic preconditioning, walking heart rate

Introduction

Guidelines recommend at least 30 minutes of moderate-intensity aerobic exercise and strength training twice a week for people with multiple sclerosis (MS).[1] The benefits of exercise for people with MS include slowing of disease progression, increase in muscle strength, reduction of muscle and bone mass loss, reduction in cardiovascular comorbidities, reduction in fatigue, and improvement in mood and functional capacity.[2-4] Despite these benefits, 78% of people with MS are physically inactive.[5] A significant barrier preventing people with MS from being physically active is fatigue. Over 80% of people with MS reported fatigue, often perceived as one of the most debilitating symptoms.[6,7] The underlying mechanisms of fatigue in MS include autonomic dysfunction causing impaired blood flow to muscles, and lack of cardiorespiratory fitness.[8]

Remote ischemic conditioning (RIC) is the application of brief periods of ischemia and reperfusion to a limb.[9] In healthy individuals, RIC improves cardiovascular responsiveness and reduces skeletal muscle fatigue.[10] Experiments on animals showed that RIC reduced heart rate by increasing parasympathetic activity.[11-13] A lower resting heart rate is associated with, higher exercise tolerance, reduced risk of cardiovascular comorbidities, and mortality.[14,15] This implication is particularly significant in people with MS who have a 28% increased hazard of the acute coronary syndrome and a 1.5-fold increase in cardiovascular mortality even after controlling for risk factors.[16]

Our previously published RCT showed that MS patients who received RIC covered 5.7% more distance during 6MWT.[17] We explored whether this effect of RIC was mediated through changes in heart rate. We did a secondary analysis of the data to investigate the effect of RIC on heart rate response to a six-minute walk test (6 MWT) in people with MS. We did this post hoc analysis to explore the mechanism of action of RIC. The aim and outcome measures of this study are different from that of the original study.[17]

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Design: We did a post hoc analysis of the data obtained from our double-blind, randomized controlled trial on RIC for walking in MS.[17] The study has ethics approval (IRAS project ID: 224422) and was registered with ClinicalTrials.gov (NCT03153553). The Consort flow diagram is shown in Figure 1.

Participants: Seventy-five Participants were recruited from a regional MS clinic in Sheffield, United Kingdom. This sample size was calculated based on the results of our pilot data.[17] Interested participants were consented and screened. The inclusion criteria were: 1) MS diagnosis according to the McDonald's criteria (2017), 2) ≥18 years old, 3) sufficient cognitive ability to give informed consent, 4) ability to walk for six minutes and 5) resting systolic blood pressure (BP) <170 mmHg. Those with any of the following were excluded from the study: 1) cognitive difficulties interfering with consenting, 2) inability to walk for six minutes, 3) presence of neurological conditions that can have an impact on gait 4) Presence of systemic illness with an impact on gait and exercise tolerance and 5) resting systolic BP ≥170 mmHg. We excluded all patients with cardiovascular, respiratory or any other systemic illness which could limit walking. The most recent Extended Disability Status Score (EDSS) was obtained from the medical records.

Six-minute Walk test: Participants rested in a seated position for 10 minutes, and their resting BP and heart rate were measured with an automatic BP monitor (Dinamap, GE). Then the participants performed the 6MWT ($6MWT_1$), which involved walking on a 14 m walkway back and forth for six minutes at a self-determined steady pace. Turning points were marked by fluorescent cones placed on both ends of the walkway. The distance walked, BP, and heart rate immediately after the 6MWT were measured. On completion, the participants rested for another 10 minutes, and their BP and heart rate were measured again.

Randomisation: Participants were randomly allocated to receive either RIC or sham intervention using a random number table by the same researcher who delivered the intervention. The researcher performing the assessments and patients remained blind to group assignment.

Interventions: The cuff of a manual BP apparatus was tied around the upper arm of the participants. The RIC group had their cuff inflated to 30 mmHg above the resting systolic BP for 5 minutes, followed by five minutes of cuff deflation. We decided to limit the maximum pressure to 200 mmHg, hence we excluded people with systolic Blood pressure over 170 mmHg. In the sham group, the cuff was inflated to 30 mmHg below the diastolic BP for five minutes, followed by 5 minutes of cuff deflation. This procedure was repeated three times in both the RIC and the control group, as shown in Figure 2. As the effect of RIC is not only local but also systemic we choose to occlude the blood flow to an upper limb. The participants documented their discomfort from the intervention using a

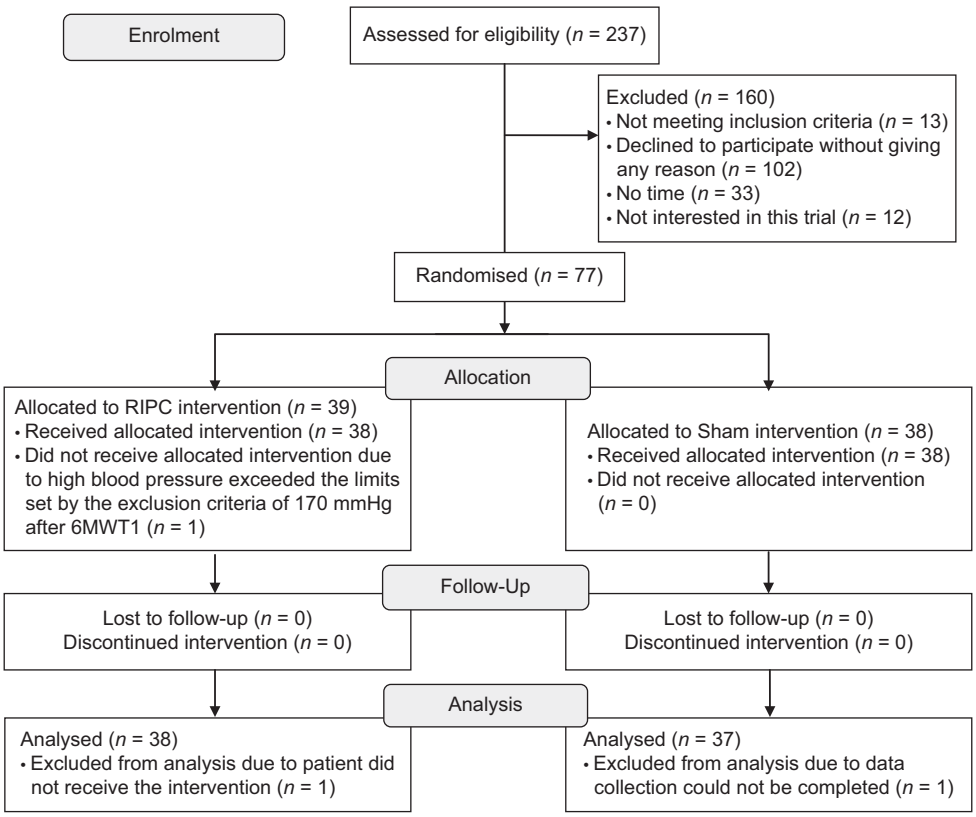

Figure 1: Consort flow diagram

Numerical Rating Scale (NRS) from 0 to 10, with 0 being no discomfort and 10 being the most imaginable discomfort. The participants were asked to report any adverse events and were examined particularly for redness of skin under the cuff, pain, discomfort, and sensory symptoms of the limb. On completion of the intervention, all participants again undertook the 6MWT (6MWT2) on the same 14 m walkway. Participants rested in sitting position for 10 minutes, and their BP and heart rate were retaken.

From the data collected, we calculated the following: The predicted maximum heart rate (HR_{max}) for each participant was calculated using the formula: $HR_{max} = 192 – (0.007 \times age^2)$.[18]

We calculated following:

1. Change heart rate (beats per minute) before intervention = Heart Rate after $6MWT_1$ – Resting Heart Rate.
2. Change in heart rate after intervention = Heart Rate after $6MWT_2$ (post-intervention) – Resting Heart Rate before intervention
3. Percentage of maximum heart rate (%HR_{max}) after $6MWT_1$ before intervention = Heart Rate after $6MWT_1 \times 100$/predicted HR_{max}
4. Percentage of maximum heart rate (%HR_{max}) after intervention = Heart Rate after $6MWT_2 \times 100$/predicted HR_{max}
5. Percentage of heart rate reserve (%HRR) used for 6MWT before intervention = (Heart rate after $6MWT_1$ – resting heart rate)/(predicted HR_{max} – resting heart rate)
6. Percentage of heart rate reserve (%HRR) used for 6MWT after intervention = (Heart rate after $6MWT_2$ (post-intervention) – resting heart rate)/(predicted HR_{max} – resting heart rate)

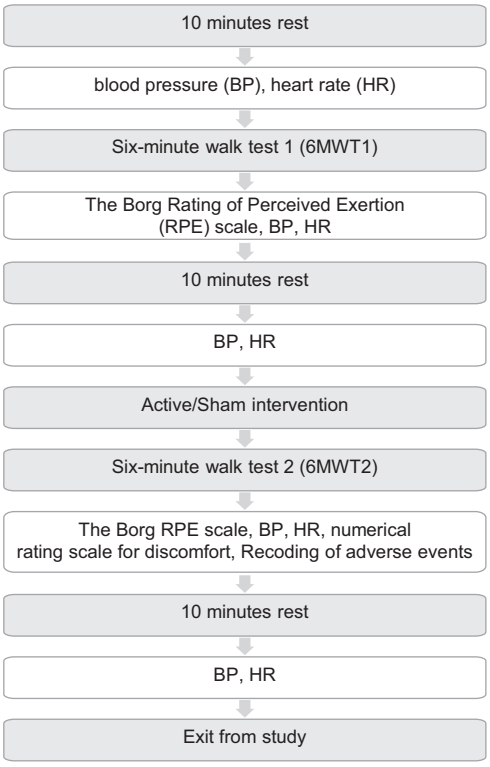

Figure 2: Study protocol

Statistical analysis

Continuous variables were reported using mean ± standard deviation (SD) for normally distributed data or median with Inter Quartile Ranges 25 and 75 (IQR25, IQR75) for non-normally distributed data (according to Kolmogorov-Smirnov and Shapiro-Wilks tests). Categorical variables were presented as number (percentage). Pearson's correlation coefficient (r) was used to look for the following relationships involving only continuous data, while Spearman's correlation coefficient (r_s) was used in relationships involving ordinal data. We compared the heart responses before and after intervention in each group using paired student t-test for normally distributed data and the Wilcoxon Signed Rank test for non-normally distributed data. All statistical analyses were performed using SPSS Statistic Version 26.0. A $p < 0.05$ was considered as statistically significant.

Results

We approached 237 patients, of whom 77 consented to participate, and 75 completed the study. Four of the recruited participants were excluded from the analysis (three in the sham group and one in the RIC group) due to incomplete data [Figure 1]. The clinical characteristics of participants are shown in Table 1.

A comparison between Sham and RIC groups is shown in Table 2. Within-group, the comparison showed that the rise in heart rate after $6MWT_2$ and % HR_{max} after $6MWT_2$ was significantly lower after RIC, but not after the sham intervention. After 10 minutes of rest following $6MWT_2$, the participants who received RIC showed a decrease in resting heart rate of four beats per minute. This was not seen in the sham group. After RIC, there was no correlation between EDSS and change in resting HR (r_s = - 0.264, P = 0.12) or change in heart rate at $6MWT_2$ (r_s = 0.016, P = 0.93). The HRR improved after RIC (P = 0.039), but not after the sham (P = 0.82) [Table 2].

Adverse events in the RIC group were tingling-17 (44.7%), skin redness- 16 (42.1%), pins and needles -10 (26.3%),

Table 1: Clinical characteristics of participants

	Sham group (n=37)	RIC group (n=37)
Age (years), mean±SD	42.9±12.8	47.1±11.4
Sex		
Women (%)	25 (73.5%)	16 (43.2%)
Men (%)	9 (26.5%)	21 (56.8%)
Type of MS		
Relapsing-remitting (%)	32 (94.1%)	26 (70.3%)
Secondary progressive (%)	1 (2.9%)	7 (18.9%)
Primary progressive (%)	1 (2.9%)	4 (10.8%)
Time since diagnosis (months)	132.9 +/- 134.4	121.0 +/- 129.8

Table 2: Comparison of heart rate response blood pressure change and distance walked before and after Sham intervention and RIC

	Group	Pre intervention	Post intervention	*P*
Change in heart rate after 6MWT in beats per minute (median and IQR)	Sham	2.50 (-2.25, 8.00)	2.00 (-1.00, 6.25)	0.781[d]
	RIC	4.00 (-0.50, 11)	2.00 (-4.50, 8.00)	0.034[d]
Change in resting heart rate before and after intervention in bpm (median and IQR)	Sham	0.00 (-3.00, 4.00)	0.00 (-2.00, 4.00)	0.9[d]
	RIC	0.00 (-3.00, 4.75)	-4.00 (0.00, 7.75)	<0.001[d]
Percentage of predicted maximum heart rate (mean±SD)	Sham	44.93±8.31	44.82±8.08	0.877[t]
	RIC	49.21±9.79	47.19±9.77	0.016[t]
Percentage of maximum heart rate reserve (median and IQR)	Sham	2.41 (-2.14, 8.13)	2.28 (-1.25, 6.06)	0.829[d]
	RIC	3.63 (-0.478, 12.2)	1.88 (-4.72, 8.11)	0.039[d]
Change in Systolic BP in mmHg, mean±SD	Sham	8.56±10.62	6.76±10.24	0.263[t]
	RIC	6.30±11.43	4.41±8.70	0.359[t]

Bpm=beats per minute, SD=standard deviation, IQR=Inter Quartile Rang [t]paired test, [d]Wilcoxon Signed Rank Test

skin marking -8 (21.7%), pain or discomfort -6 (15.8%), numbness - 2 (5.3%), tightness-1 (2.6%), feeling dizzy-1 (2.6%) and feeling hot -1 (2.6%). Participants in the sham group reported tingling-5 (13.5%), skin redness- 13 (35.1%), sensation of swelling of limb-4 (10.8%), pins and needles -2 (5.4%), skin marking -2 (5.4%), tightness-2 (5.4%), feeling cold -2 (5.4%), pain or discomfort -1 (2.7%), numbness - 1 (2.7%), feeling light headed -1 (2.7%), and feeling unbalanced-1 (2.7%)

Discussion

In healthy individuals, heart rate has a positive linear correlation with exercise intensity up to a maximum intensity due to increased sympathetic stimulation in all age groups.[19] While performing aerobic exercise at a fixed submaximal intensity, heart rate plateaus once the cardiovascular demands were met.[20] The heart rate response to exercise was affected even in the early stages of MS.[21] The autonomic dysfunction increases with the severity of MS.[22,23]

People who received the RIC group had a lower rise in heart rate after $6MWT_2$ while there was no change in the sham group. After RIC, participants also experienced a decrease in resting heart rate. This was consistent with findings reported by Gardner *et al*.[24] that RIC reduced resting HR in healthy individuals.

Gervasoni *et al*.[25] reported a higher heart rate response during exercise and slower heart rate recovery post-exercise in people with MS and attributed this to a deficiency in parasympathetic response. Similarly, Susanna *et al*.[26] also found that people with MS had a slower reduction of heart rate after exercise due to blunting of cardiac parasympathetic reactivation. The beneficial effect of RIC on cardiovascular response to walking, in our cohort, could possibly be mediated through an increase in the parasympathetic response. Our results suggest that RIC may restore the blunted parasympathetic cardiovascular response in people with MS regardless of their EDSS.

RIC leads to the activation of neural, hormonal, and inflammatory pathways leading to a downstream signaling cascade with multiple biological effectors including increased cerebral blood flow, reduction in pro-inflammatory cytokines, improved mitochondrial function, and reduced oxidative stress.[27,28] RIC activates two responses: the first occurs immediately after the application of RIC and lasts up to two hours whereas the delayed second response is activated after 12 to 24 hours and lasts up to 72 hours.[28] Given the rapidity of the effect of RIC in the present study, it is likely that the mechanism underlying the increase in vagal activation. It has previously been demonstrated that RIC augments nitrite-nitric oxide signaling.[27,28] Given that nitric oxide influences autonomic balance at both central and peripheral sites it is a plausible increase in parasympathetic activity following RIC is mediated through a nitric oxide-dependent mechanism.

Limitations

This study was a post hoc analysis of a double-blinded randomized controlled trial.[17] There is no consensus on the best and most reliable method to estimate cardiovascular response. We included both $\%HR_{max}$ and %HRR but did not measure peak oxygen uptake. The study participants were recruited from a single center and included only those who could walk for 6 minutes. We do not have data on the participants' medication history which could have influenced heart rate response. Most of our participants had relapsing-remitting or secondary progressive MS. Our RIC group had a higher median EDSS than the sham group. There were a greater proportion of women in the sham group. The response to RIC could have been influenced by age, duration of MS, number of relapses, and co-morbidities. As our sample size was small, we did not analyze these relationships. These differences could have had an impact on our results and restricted its wider application.

Future directions

It would be beneficial for future studies of MS to investigate multiple domains of the autonomic and neurovascular response of both single and repeated cycles of RIC. The use of continuous ECG or heart rate monitoring would provide further information on heart rate variability, a marker of cardiac vagal tone. Measurements of brachial artery flow-mediated dilatation before and after RIC could establish whether

there are beneficial effects on endothelial function as has been demonstrated in chronic stroke survivors. Given the pathophysiological evidence of cerebral hypoperfusion in MS, measures of cerebral blood flow could determine whether repeated cycles of RIC improve cerebral hemodynamics as has been demonstrated in ischemic small vessel disease.[27]

Conclusion

RIC decreased the rise in heart rate, and percentage of the heart rate reserve used by people with MS, for 6MWT. The effect was noted in people with varying degrees of disease severity. This intervention has the potential to increase physical activity in people with MS. Further research on the effect of RIC on cardiovascular responses and autonomic function in people with MS is warranted.

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Conflicts of interest

There are no conflicts of interest.

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