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 Carotid Artery Function Is Restored in Subjects With Elevated Cardiovascular Disease Risk After a 12-Week Physical Activity Intervention.

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1

Title: A 12-week physical activity intervention improves carotid artery function in response to sympathetic stimulation in subjects with elevated cardiovascular disease risk.

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Brief summary

Sympathetic nervous system activation elicits carotid artery vasodilation in healthy subjects, yet vasoconstriction in those with cardiovascular disease. Whether exercise training can reverse carotid artery vasoconstriction during sympathetic stimulation is currently unknown. Following a 12-week physical activity intervention, carotid artery vasoconstriction in response to sympathetic stimulation may be completely reversed in subjects at increased risk of cardiovascular disease.

ABSTRACT

Sympathetic nervous system activation elicits carotid artery vasodilation in healthy subjects, yet vasoconstriction in those with cardiovascular disease (CVD). Whether carotid artery vasoconstriction can be reversed is currently unknown. Nineteen subjects with increased risk for CVD were referred to a 12-week physical activity (PA) intervention, whilst another 12 participants with increased risk for CVD were recruited as a no treatment control group. Cardiorespiratory and vascular health measures were collected at baseline and 12 weeks. Results indicate that carotid artery vasoconstriction in response to sympathetic stimulation may be reversed in subjects at increased risk of CVD. These findings warrant further investigation.

1. INTRODUCTION

The sympathetic nervous system is an important regulator of central and peripheral blood flow. Previous work has found that sympathetic nervous system stimulation, via a cold pressor test (CPT; i.e. placing one hand in ice slush), leads to coronary [1] and carotid artery [2,3] vasodilation. In marked contrast, participants with cardiovascular risk factors and/or disease show an attenuated or even vasoconstrictive response [1]. The vasoconstrictive response in central arteries may have clinical relevance, since independent prospective studies have found that both coronary and carotid [3] vasoconstriction independently predicts disease progression and cardiovascular events.

Regular physical activity (PA) is a successful and potent stimulus that markedly reduces the risk for future cardiovascular events [4]. However, no previous study has explored the impact of PA on carotid artery responses to sympathetic stimulation. This study, therefore, investigated the hypothesis that a 12-week PA intervention can reverse carotid artery vasoconstriction to sympathetic stimulation in participants with increased cardiovascular disease (CVD) risk. To optimise ecological validity of our findings, participants completed a real-world PA intervention, where the specific training type/dose was uncontrolled by researchers.

2. METHODS

2.1. Participants

Thirty-one participants with increased CVD risk were recruited for this study. Nineteen patients (56 SD 13 years; Female (n=11); BMI 31 SD 6 kg.m^2) were referred by health professionals to a PA intervention. Twelve participants were recruited as a control group (49 SD 18 years; Female (n=8); BMI 29 SD 5 kg.m^2). Eligibility criteria included: completion of a Physical Activity Readiness Questionnaire (PARQ), increased CVD risk (e.g. high blood pressure, hyperglycaemia, obesity) and/or presence of lifestyle-related disease (e.g. CVD, diabetes, cancer, depression), and ≥18 years of age. Patient medications remained unchanged across the 12-week intervention period. Informed consent was

gained from each patient, NHS Research Ethics Committee approved this study (16/WA/0231, number 209923) and procedures adhered to the Declaration of Helsinki.

2.2 Design. This study used a nonrandomised pre-post design to explore the effects of a previously co-produced PA intervention [5]. Individuals were allocated to the 12-week intervention or control period. All measurements were collected at baseline and 12 weeks.

2.3. Intervention. The intervention included 12 weeks of subsidised access to a fitness centre (swimming baths, gymnasium, and group classes) plus PA behaviour change consultations at weeks 1, 4 and 12. Patients were encouraged to use the fitness centre and increase their habitual PA levels relative to their own personal goals. A full intervention description and theoretical underpinning can be found elsewhere [5].

2.4. Measurements (general). We examined anthropometrics (body mass, height), blood pressure (automated blood pressure device (Omron Healthcare UK Limited, Miton Keynes, UK) and estimated cardiorespiratory fitness via the Astrand-Rhyming cycle ergometer protocol [6]. Physical activity was objectively measured over a 7-day period via tri-axial ActiGraph GT3x accelerometers (ActiGraph, Pensacola, FL, USA). Vascular testing consistently started with the FMD (performed on the right arm). After a 10-minute period of rest in the supine position, carotid artery reactivity in response to sympathetic stimulus (CAR-test) was performed on the left common carotid artery.

2.5. Measurements (carotid and brachial artery vascular function). To investigate carotid artery health, we examined the carotid artery reactivity (CAR%), which examines the carotid artery diameter response to sympathetic stimulation. In brief, patients were positioned supine on a bed to facilitate movement of the left hand into a bucket of ice slush with minimal movement of the neck and instructed to turn their head laterally, by approximately 45-90° to the right. The left common carotid

artery was measured 2 cm proximal to the bulbous. A two-dimensional image of the artery was obtained via a high-resolution ultrasound machine (Terason, 3300, Teratech) and a 10-12-MHz probe. Settings were adjusted to optimise the longitudinal, B-mode image of the lumen-arterial wall interface. After a 1-minute baseline, the patient immersed their hand (up to the wrist) in ice slush (~4.0°C) for 3 minutes. Mean data were calculated across the 1 minute preceding the CPT. Following submersion, data were calculated as the mean value for 10-s intervals. Peak diameter change (CAR%, CAR_{mm}) and area-under-the-curve for diameter change (CAR_{AUC}) were calculated from the 10-s intervals. The peak diameter and CAR_{AUC} refers to a constriction or dilation. Between day coefficient of variation for CAR% has been reported as 2.8% [3].

We also examined peripheral artery vascular health by examining the brachial artery flow-mediated dilation (FMD%). Detailed description of procedures can be found elsewhere [7]. Images were obtained in a reproducible section of the distal third of the upper arm via B-mode high resolution ultrasonography (see above). Briefly, a 1-minute baseline measurement was taken, then a pneumatic rapid cuff inflator (Hokanson, Bellevue, U.S.A.), fitted around the forearm distal to the humeral epicondyle, was inflated to 220 mmHg for 5 minutes. Recording continued for a period of 3 minutes post cuff deflation [7]. Peak change in FMD from baseline (FMD%, FMD_{mm}) was calculated. Intra-observer coefficient of variation for FMD% has been reported as 6.7% [12]. Both CAR and FMD data were analysed using custom designed, validated automated edge-detection and wall-tracking software.

2.6. Statistical analysis. Data were analysed using SPSS version 23 (IBM, New York, USA) with alpha level set at $P \leq 0.05$. Intervention effects were measured 12 weeks from baseline using paired samples t tests (normally distributed) or related sample Wilcoxon Signed Rank test (non-normally distributed). Spearmen's correlations were used to assess relationships between CAR%, FMD%, and cardiorespiratory fitness.

3. RESULTS

Baseline characteristics. Patients were referred for PA due to one of the following risk factors: obesity (n=3), hypertension (n=2), (pre) diabetes (n=5), CVD or event (n=3), hypercholesterolemia (n=2), poor mental health (n=2), or inactivity / low fitness capacity (n=2). The control group was recruited based on the presence of at least one cardiometabolic risk factor and/or condition (i.e. CVD or event, diabetes, cancer, obesity, hypertension, mental illness). Baseline-to-12-week change data is reported in Table 1. Due to health problems/contraindications we did not perform the fitness test on three individuals. We found no differences in baseline characteristics between the control and intervention group (Table 1).

Intervention. Following the 12-week PA intervention we observed a significant increase in cardiorespiratory fitness and PA, a significant reduction in systolic and diastolic blood pressure, whilst no changes were observed in BMI. In addition, we observed an increase in the carotid artery dilator response (CAR%, CAR_{mm}, and CAR_{AUC}).

Prior to the intervention, six patients demonstrated carotid artery vasoconstriction during the CAR-test, whilst this response was reversed to vasodilation in all subjects following the intervention (Figure 1). Carotid artery diameter did not change from baseline to week 12. Descriptive statistics revealed differences between the patients that presented with carotid vasoconstriction (n=6) and vasodilation (n=13), with individuals demonstrating carotid vasoconstriction being younger (11 years, SD 8), having a higher BMI (2.4 kg/m^2, SD 5) and systolic blood pressure (22 mmHg, SD 17), and lower cardiorespiratory fitness (CRF; -2.5 $ml.kg.min^{-2}$, SD 2).

Brachial artery FMD% and FMD_{mm} significantly increased after the PA intervention, whilst no change was observed in brachial artery diameter. We found no significant correlation between pre-intervention CAR% and FMD% (R=0.099; P=0.596) or baseline-to-12 week change in CAR% and FMD% (R=0.240; P=0.353). CAR% was not correlated with cardiorespiratory fitness (R=0.051; P=0.864).

Control. In the control group, no changes were observed for cardiorespiratory fitness, BMI, flow-mediated dilation or carotid artery dilator response. A significant reduction in diastolic blood pressure was found.

Table I. Carotid and peripheral vascular function and cardiometabolic risk factors.

Outcome measure	Control Group (n=12)			Intervention Group (n=19)		
	Baseline Mean (SD) or Median (IQR)	Week 12 Mean (SD) or Median (IQR)	*P*	Baseline Mean (SD) or Median (IQR)	Week 12 Mean (SD) or Median (IQR)	*P*
Vascular						
CAR%[b]	2.5 (2.9)	1.8 (2.2)	0.518	1.4 (4.5)	3.1 (3.1)	<0.001
CAR_{mm}[b]	0.18 (0.13)	0.17 (0.08)	0.591	0.1 (0.05)	0.20 (0.40)	0.001
CAR_{AUC}	0.7 (1.7)	1.1 (1.4)	0.815	0.5 (1.8)	2.2 (1.7)	<0.001
Carotid artery diameter (cm)	0.7 (0.1)	0.6 (0.1)	0.474	0.7 (0.1)	0.7 (0.1)	0.716
FMD%[b]	6.7 (2.3)	5.5 (2.1)	0.12	4.4 (4.7)	7.0 (4.4)	0.003
FMD_{mm}	0.23 (0.07)	0.19 (0.08)	0.079	0.18 (0.1)	0.25 (0.08)	0.007
Brachial artery diameter (cm)	0.4 (1)	0.4 (0.1)	0.288	0.4 (0.1)	0.4 (0.1)	0.860
SBP (mmHg)	121 (13)	117 (14)	0.063	134 (20)	126 (12)	0.001
DBP (mmHg)	72 (11)	66 (8)	0.011	76 (11)	69 (7)	0.004
MAP (mmHg)	88 (10)	83 (9)	0.007	95 (12)	88 (6)	0.001
Fitness						
Estimated CRF ($ml.kg.min^{-2}$)	31.2 (9.6)	30.6 (8.7)	0.479	21.1 (4.1)	24.7 (4.6)	<0.001
MVPA (min.day)				27.2 (25.2)	39.7 (33.6)	0.007

CAR%, carotid artery reactivity (%); **CAR_{mm}**, carotid artery reactivity (mm); **CAR_{AUC}**, carotid artery reactivity (area under the curve); **FMD%**, flow mediated dilation (%); **FMD_{mm}**, flow mediated dilation (mm); **SBP**, Systolic blood pressure; **DBP**, diastolic blood pressure; **MAP**, mean arterial pressure; **CRF**, cardiorespiratory fitness; **BMI**, body mass index; **MVPA**, moderate-to-vigorous physical activity.

Baseline and week 12 measures presented as mean (SD) and compared via Paired Samples T test.

[b]Values presented as median and interquartile range due to significant skewness and/or kurtosis and compared via Wilcoxon Signed Rank test.
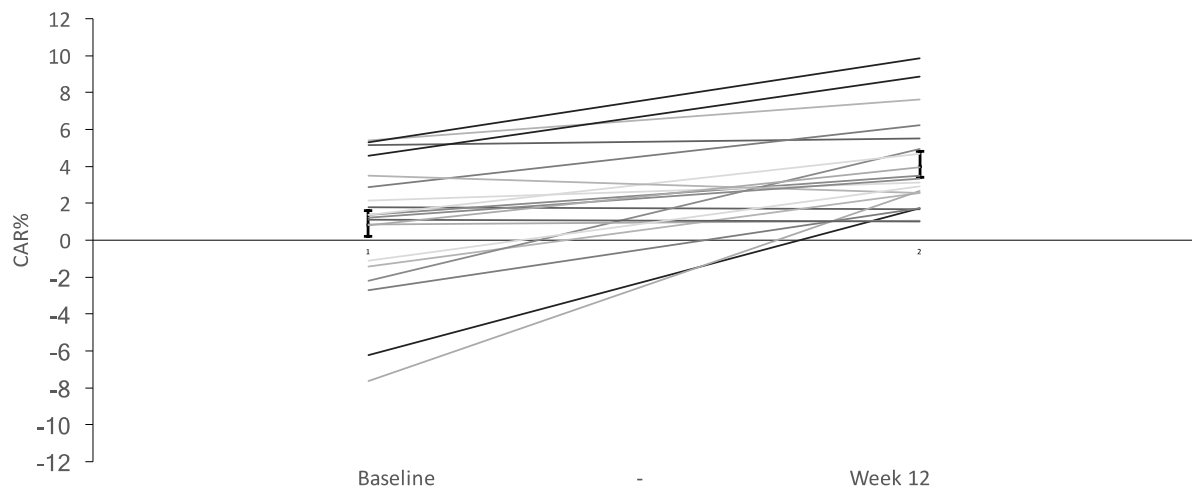
Figure I. Individual patient carotid artery reactivity (CAR% ± mean standard error) pre-post a 12-week physical activity referral scheme.

4. DISCUSSION

Several previous studies have demonstrated beneficial effects of PA and exercise (hemodynamic stimuli) on measures of vascular health, largely focusing on peripheral artery vascular health in response to increases in shear stress (see review for more information [13]). The novel finding of the present study is that following a 12-week PA intervention, vasomotor responses of the central carotid artery during sympathetic stimulation using the CPT improved. Specifically, we found carotid artery vasoconstriction in response to the CPT, a response linked to increased risk for cardiovascular events [2], to be fully reversible following a 12-week PA intervention. These altered vascular responses may, at least in part, contribute to the potent cardioprotective effects of regular PA in subjects with increased CVD risk.

Our observations may also be relevant for coronary arteries, since previous work has highlighted the similarity between carotid and coronary artery function. For example, sympathetic stimulation is known to cause dilation in both the coronary and carotid arteries in healthy individuals, whilst this deteriorates to vasoconstriction in those with coronary artery disease [2]. Moreover, the potential link between coronary and carotid artery health was recently reinforced by Van Mil and colleagues [3], who found moderate-to-strong correlation between carotid artery and coronary artery responses to sympathetic stimulation. Finally, one previous study found that 4-weeks of exercise training in patients with coronary atherosclerosis attenuated the coronary vasoconstrictive response to acetylcholine-infusion [8]. Collectively, these results highlight the ability of regular PA to reverse potentially detrimental vasoconstrictive responses of carotid arteries in humans with increased CVD risk.

One may question the potential mechanisms underlying such adaptations. In line with peripheral arteries, benefits of PA on carotid vascular health may be mediated through direct hemodynamic stimuli, leading to improvement in endothelial integrity and/or function [9,13]. Based on its ability to

regulate vascular health, an intact endothelium protects against artery vasoconstriction to catecholamine release during sympathetic stimulation [9]. Alternatively, training may elicit a shear stress-mediated upregulation of endothelium-derived nitric oxide synthase (eNOS), subsequently leading to a larger NO availability [10]. Therefore, repeated shear stress stimulation of eNOS bioactivity during PA may improve endothelial integrity and/or function, contributing to the reversal of carotid artery vasoconstriction to a vasodilator response.

We also found that brachial artery vascular function improved after training, although this improvement was not correlated with carotid artery function. It may be that adaptation of the common carotid and brachial arteries do not occur in parallel within subjects, and may be driven through distinct processes. Somewhat in agreement with such a hypothesis, both measures of vascular health seem to be mediated through distinct processes. Previous work provided ample evidence that brachial artery dilation (i.e. brachial FMD) is mediated through elevated shear stress [9], whilst the carotid artery vasomotor response to the CPT is more likely linked to activation of the sympathetic nervous system (i.e. catecholamine release) [11]. This observation suggests both tests of vascular health may provide complimentary information on the vascular system.

5. Limitations

The present study described preliminary effects of a PA intervention. Whilst measuring CAR, we did not control for end-tidal CO_2, a key regulator of cerebrovascular function. However, clear instructions on breathing patterns were provided, none of the subjects hyperventilated, and within-subject comparisons were made. It is therefore deemed unlikely that this impacted our main conclusions. Some medications may have confounded patients' endothelial function, though any medications remained constant over the 12-week period in all individuals.

6. Conclusion

We found that following a 12-week PA intervention cardiorespiratory fitness was improved. Correspondingly, carotid and brachial artery vascular health was improved in a clinical population with increased risk for CVD. More importantly, we found carotid artery vasoconstriction, a vasomotor response strongly related to an increased CVD risk and a surrogate for coronary artery dysfunction, to be reversible following a real-world PA intervention. This highlights the potential of PA interventions to reduce risk for future cardiovascular events through systemic improvements in artery vascular health.

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