Title: **Acute response to a 2-minute isometric exercise test predicts the long-term blood pressure-lowering efficacy of isometric resistance training in young healthy adults.**

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Abstract:

Objective: The purpose of this work was to explore whether different forms of a simple isometric exercise test could be used to predict the blood pressure (BP)-lowering efficacy of different types of isometric resistance training (IRT) in healthy young adults. In light of the global emphasis on strategies for the primary prevention of hypertension , identifying those with normal BP who will respond to IRT is important. Also, heightened BP reactivity increases hypertension risk, and as IRT reduces BP reactivity in patients with hypertension, it warrants further investigation in a healthy population.

Methods: Forty-six young men and women (24 ± 5 years; 116 ± 10/ 68 ± 8 mmHg) were recruited from two study sites (Windsor, Canada; n=26; 13 women), and Northampton, United Kingdom (n=20; 10 women). Resting BP and BP reactivity to an isometric exercise test were assessed prior to and following 10 weeks of thrice weekly IRT. Canadian participants trained on a handgrip dynamometer (isometric handgrip, IHG), while participants in the UK trained on an isometric leg dynamometer (ILE).

Results: Men and women enrolled in both interventions demonstrated significant reductions in systolic BP ($P<0.001$) and pulse pressure (PP; $P<0.05$). Additionally, test-induced systolic BP changes to the isometric handgrip (IHG) and isometric leg extension (ILE) tests were associated with IHG and ILE IRT-induced reductions in systolic BP after 10 weeks of training respectively (r= ? and r=?; for IHG and ILE respectively; $P<0.05$).

Conclusions: The acute BP response to an isometric exercise test appears to be a viable, simple tool to identify individuals who may respond to traditional IRT prescription. Future work should explore its use by healthcare professionals to help identify those individuals who may gain the

most benefit from IRT, and to test alternative isometric resistance training programmes in non-responders.

Introduction

Isometric resistance training (IRT) is recognized as a promising blood pressure (BP)-lowering therapy by the American Heart Association (Brook et al., 2015).The most recent meta-analysis of randomized controlled trials cites post-training reductions in resting BP of ~5/4 mmHg (Carlson et al., 2014). IRT is most commonly performed on a programmable handgrip dynamometer (isometric handgrip, IHG) or leg isokinetic dynamometer (isometric leg extension, ILE), but has also been successfully performed using spring loaded handgrip devices (Millar et al., 2008) and via a double leg wall squat routine (Wiles et al., 2016). Protocols usually consists of 4 separate 2 minute periods of exercise (with ~1 minute of rest between each exercise period), sustained at a moderate intensity (~20-30% of maximal voluntary contraction; MVC) and performed 3 times per week for up to 10 weeks (Millar et al., 2014).

Although the BP-lowering effects of IRT have been demonstrated across a variety of healthy and clinical adult populations, the weight of the existing evidence suggests that men, patients with diagnosed hypertension, and individuals over 45 years of age experience the largest magnitude of IRT-induced BP reductions (Inder, 2016). With respect to hypertension, work from our research group shows that reductions in resting BP with IRT in this patient cohort are predicted by the acute systolic BP response to a short isometric exercise test (2 minutes of sustained isometric exercise at 30% MVC; Badrov et al., 2013) prior to training. In other words, individuals with the largest systolic BP increase in response to the test, prior to training, experienced the greatest chronic post-training BP reductions. Similarly, Liu et al. (2012) have reported that the magnitude of the acute BP reductions following an acute bout of aerobic exercise can predict the post-hypotensive response to chronic aerobic training in middle aged (45-60 years) pre-hypertensive individuals. An important extension to the work of Badrov et al.

(2013) is the evidence suggesting that the magnitude of the haemodynamic response to an isometric exercise test can predict the future risk of hypertension (Chaney & Eyman, 1988; Badrov et al., 2013). Taken together, a simple isometric exercise test that is easy to use, and can be easily administered in a clinical setting may allow health care providers the opportunity to (i) identify their patients at risk of future hypertension and (ii) recommend an IRT intervention as a viable BP-lowering treatment strategy.

In light of the global emphasis on strategies for the primary prevention of hypertension by the World Health Organization (WHO, 2013), investigating whether this test offers a means of identifying healthy individuals who will respond to IRT, is important. Also, since it is known that heightened acute BP responses to exercise increase the risk of future hypertension and since IHG training reduces this BP response in hypertensive patients, the potential of this type of test warrants further investigation in healthy cohorts. In those with normal BP, the effectiveness of the acute BP response to an isometric exercise test, in predicting who will respond to IHG training is unknown, as is its applicability to ILE training.

The **overall aim** of this work was to identify whether the BP-lowering effects of IRT can be predicted in young healthy normotensive men and women. The purpose of our study was to test the following **specific** hypotheses: 1) Following 10 weeks of either IHG or ILE training, performed 3 days per week, resting BP would be reduced by a similar magnitude in both young men and women, and 2) these reductions would be predicted by the acute systolic BP response to a protocol specific (IHG or ILE) isometric exercise test.

Methods

Study Design and Experimental Protocol

This two-site investigation was cleared by the University of Windsor and the University of Northampton Research Ethics Boards, and all participants provided written, informed consent. Following informed consent, the completion of standard intake questionnaires and the determination of initial eligibility, participants were familiarized to all parts of the investigation. Baseline tests were then conducted, under standard laboratory conditions, on 2 separate days, separated by at least 24-hours. Following baseline testing, participants underwent 10 weeks of IHG (Windsor site) or ILE (Northampton site) IRT. Post-testing occurred the week following training, at least 48-hours following the last training session and within 2 hours of baseline testing time. All testing occurred in a quiet, temperature-controlled room (20-23ºC), following consumption of a light meal, 24-hour abstinence from alcohol and vigorous physical activity, and a 12-hour abstinence from caffeine (Badrov et al., 2013). Participants voided their bladder prior to each testing session to avoid a potential rise in BP due to bladder distention (Fagius et al., 1989).

At both testing sessions, resting seated BP and heart rate (HR) measures were acquired in triplicate using the dominant arm following a 10-minute seated rest period (Dinamap Carescape v100, Critikon, Tampa, FL, USA). To assess acute cardiovascular responses (systolic BP, diastolic BP, and HR response), participants enrolled at the Windsor site performed an IHG exercise test (IHGT; 2-minutes of sustained isometric exercise at 30% of MVC), while participants at the Northampton site undertook an ILE test (ILET, 2-minutes of sustained isometric exercise at 20% of MVC). BP and HR responses were measured every minute via brachial artery oscillometry (Dinamap Carescape v100, Critikon, Tampa, FL, USA) at the beginning and throughout each test. Subsequently, participants underwent a minimum stabilization period of at least 10 minutes to ensure a return of BP and HR to baseline values.

Training protocols.

Participants performed supervised IRT sessions 3 times per week for 10 weeks. Each exercise session consisted of 4 separate 2-minute periods of IHG or ILE exercise at 30% or 20% MVC, respectively. IHG exercise was performed using alternating hands on a computerized handgrip dynamometer (ZonaPLUS; Zona Health, Boise, Idaho, USA), each interspersed by 1 minute rest. ILE exercise was performed bilaterally on an isokinetic dynamometer (Biodex Medical Systems Inc. New York, USA) interspersed by 2-minute rest periods.

Prior to the start of each training session, participants had their resting seated BP and HR measured following a 10-minute seated rest. MVC scores, protocol compliance (% of time MVC was maintained for the duration of the protocol) for each bout of exercise, as well as any changes in diet, exercise, or nutrition over the 10-week intervention period were recorded at each training session.

Statistical Analysis

In order to examine differences in baseline data between men and women, one way ANOVAs were performed on all resting variables. Normality of the data was assessed and a two way repeated measure ANOVA was used to examine the efficacy of both the IHG and ILE intervention in lowering resting cardiovascular measures (systolic BP, diastolic BP, mean arterial pressure (MAP), pulse pressure (PP), and HR) in men and women.

Acute systolic BP responses to the IHGT and ILET were assessed by calculating the difference between peak stress task value and mean baseline resting value for systolic BP

(Jennings et al., 1992; Somani et al., 2017). Diastolic BP and HR response was calculated in the same manner. Pearson correlation coefficients were employed to determine the relation between the acute systolic BP response to the isometric exercise task and the observed reductions in resting systolic BP following IRT. BP adaptations were calculated as residualized change in systolic BP and were used for regression analyses, as baseline BP and post training BP have known correlated effects (Millar et al., 2007; Llabre et al., 1991; Badrov et al., 2013; Somani et al., 2017). These values were obtained by regressing change in resting systolic BP following both IRT interventions over pre-training resting systolic BP.

To determine all potential predictors of responsiveness to the 10-week training intervention, baseline diastolic BP, baseline HR, the acute systolic BP, diastolic BP, and HR responses to the isometric task, sex, HR, BMI, age, training method, and compliance measures were entered into a multi-variate regression . In order to assess any changes in acute cardiovascular responses to the isometric exercise task, as well as to determine potential sex differences following IRT, a 2 way repeated measure ANOVA was employed. IBM SPSS Statistics 21 software (SPSS Inc., Chicago, Illinois, USA) was used for all data analyses and statistical significance was set at $P \leq 0.05$.

Results

Study Participants

A total of 46 men and women, without overt hypertension (116 ± 10 mmHg/ 68 ± 8 mmHg) were recruited from Windsor, Canada (n=26; 13 women) and Northampton, United Kingdom (n=20; 10 women). Of the 46 participants recruited, 15 were pre-hypertensive (126 ± 5 mmHg/75 ± 3 mmHg; 6 women), and 31 were normotensive (111 ± 8 mmHg/65 ± 7 mmHg; 17 women). Exclusion criteria for the study included a prior diagnosis of hypertension or cardiovascular disease (CVD), prescribed anti-hypertensive medication and pharmacotherapies known to effect neurovascular function, and/or physical limitations hindering proper performance of exercise. Please see Table 1 for participant characteristics.

All 46 participants enrolled in the two-site study completed the 10-week training protocol consisting of either 30 IHG or ILE training sessions. Compliance values for the 26 participants enrolled in the IHG training was 97%, and averaged 98% for men and 96% for women. The 20 men and women participating in ILE training had a calculated compliance of 99% and 98%, respectively, with a combined average of 99%. Upon review of exercise, diet, and medication log books, no significant changes in any of these variables were recorded in either sex. Importantly, no adverse events were reported by participants in response to either the testing or IHG and ILE training sessions. Lab personnel asked participants about any pain and/or discomfort at the beginning and throughout both testing and training sessions, and no adverse events were reported.

Men and women at both sites did not differ in age, body mass index, or resting diastolic BP (all $P>0.05$). Conversely, height and weight at baseline were significantly different between the two groups for both interventions ($P<0.05$). Men enrolled in IHG training had higher pre-training resting systolic BP, MAP, and PP values than women (*P*<0.05), while these differences were not observed in men participating in ILE training. Instead, women had significantly higher pre-training resting HR values than men at the Northampton site where ILE training took place (*P*<0.05). Outcome variables for the study were not influenced by these initial differences as the multilevel ANOVA that was employed accounted for this, and no interactions between men and women were found (*P*>0.05). Refer to Table 1 for participant baseline characteristics.

Effects of IRT on resting BP and HR

Men and women enrolled in both interventions demonstrated equal, significant reductions in systolic BP (*P*<0.001) and PP (*P*<0.05), and no sex interactions were observed for these variables across the interventions (*P*>0.05). Additionally, significant reductions in MAP were observed in both men and women who participated in 10-weeks of ILE training. Similarly, no sex interaction was observed across the interventions (*P*>0.05). These findings can be found in Table 2.

Cardiovascular responses to isometric exercise as a predictor of IRT effectiveness

Men demonstrated a significantly higher systolic BP response to the isometric exercise tests than women (*P*<0.05). Test-induced systolic BP responses to the IHGT and ILET were correlated with IHG and ILE training-induced reductions in systolic BP, respectively (*P*<0.05; Table 3). The significant association found in both men and women for each intervention is illustrated in Figure 1 and Figure 2, respectively. In contrast, no associations were observed between diastolic BP and HR responses to the IHGT and ILET with residualized change in systolic BP following IRT in men and women (*P*>0.05; Table 3).The regression analysis also revealed that all other variables tested as potential correlates were not statistically significant (baseline diastolic BP, baseline HR, sex, BMI, age, training method, and compliance; P>0.05)

Effect of IRT on HR and BP responses to isometric exercise

Following 10 weeks of IHG and ILE training, all measures of cardiovascular responses to the IHGT and ILET remained unchanged (all $P>0.05$). These data are presented in Table 4.

Discussion

The utility of a simple isometric exercise test that could identify those at risk of future hypertension and can predict responsiveness to IRT carries with it many implications, particularly in relation to the potential benefits of IRT prescription. Our findings suggest that both common forms of IRT are equally effective in lowering resting systolic BP in men and women. Perhaps even more interesting is our finding that the acute response to either isometric exercise test can predict those participants who will experience the greatest reductions in systolic BP with equal efficacy, in both normotensive men and women, following either IRT intervention.

The fact that the haemodynamic responses to isometric exercise might be able to predict both future hypertension and the effectiveness of IRT, could also be indicative of a common mechanism that is responsible for both development of hypertension and for training-induced reductions in resting BP. Indeed, it appears that one counteracts the other. Because most types of exercise stimuli elicit an acute increase in cardiac output (Williams et al., 2007), a rise in systolic BP is a natural consequence of it. Conversely, diastolic BP remains unchanged or slightly increased as a consequence of metabolic vasodilatation of the peripheral vessels (Miyai et al., 2002). However, some researchers have observed a significantly greater rise in diastolic BP during isometric training versus maximal endurance training, even in normotensive subjects, suggesting an increased resting peripheral vascular resistance and impaired capacity for exercise-induced vasodilation (Wiles et al., 2010; Singh et al., 1999; Chaney, 1981). This hemodynamic pattern can be explained by a hyper-reactivity of the sympathetic nerves and an increased vascular response to adrenergic stimulation, or by a thickening of the arteriolar wall that alters its ability to respond to vasoconstrictor stimuli (Miyai et al., 2002). Among individuals with such vascular characteristics, higher cardiac output not only raises systolic BP but also causes marked diastolic BP elevations such as those occurring in established hypertension.

Recently, an exaggerated BP response to a submaximal step test was shown to be associated with an attenuated increase in forearm blood flow and significantly higher plasma angiotensin II levels (Tzemos et al., 2015). These authors suggested that the concerted effect of endothelial dysfunction, decreased proximal aortic compliance and increased exercise-related neuro-hormonal activation was probably responsible for the exaggerated response to exercise. Because isometric exercise is known to elicit a potent BP response (arguably more so than dynamic exercise) and because IRT has also been shown to alter markers of endothelial function in both young healthy and medicated hypertensive populations (McGowan et al., 2006; Badrov et al., 2016), it is plausible that this mode of exercise could be the most suitable for this type of predictive test.

Our findings also reaffirm the association between an exaggerated hemodynamic response to an acute isometric exercise task and reductions in resting BP following repeated exposure, as previously shown by Badrov and colleagues (2013) in hypertensive participants. As we hypothesized, individuals who exhibited the highest systolic BP responses to an isometric exercise test elicited the greatest reductions in BP following IRT. The reasons behind this relation warrant further investigation to determine the precise mechanisms responsible for the observed alterations in BP control.

In conclusion, our work suggests that determining the acute BP response to an isometric exercise test would be a viable, simple and efficient tool for healthcare professionals to identify young individuals who may be at risk of future hypertension development and for whom prescription of IRT might be a beneficial prevention strategy. Our findings also have implications for identifying individuals who are least likely to respond to IRT, such that the IRT program could be modified to optimise the BP-lowering effects in these participants. Future studies should aim to explore how IRT protocols can be modified, thereby optimizing the effects, even in ‘non-responders’, to ensure that they too experience reductions in resting BP.

Limitations

We acknowledge the lack of a control group at both sites. Despite the absence of a true control group, both studies were adequately powered to test sex differences (or lack thereof) in the effects of IRT in young individuals. Our study also represents the first direct comparison between young men and women with respect to determining the association between the acute response to an isometric exercise task and the BP lowering effects of IRT.

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