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Title

Immediate post isometric exercise cardiovascular responses are associated with training induced resting systolic blood pressure reductions

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ABSTRACT

**Purpose:** The purpose of this study was twofold: (1) to investigate the effect of four-weeks of bilateral-leg isometric exercise training on the immediate isometric post-exercise cardiovascular responses, and (2) to ascertain whether any changes in immediate post-exercise cardiovascular responses may be associated with training-induced adaptations in resting blood pressure.

**Methods:** Thirteen normotensive males completed both isometric exercise training (IET) and control conditions, which were separated by 6 weeks. Participants performed a total of twelve training sessions; 4 * 2-minute bilateral-leg isometric exercise bouts separated by 3-minute rest periods, 3 days.wk⁻¹.

**Results:** 4-weeks of bilateral-leg IET resulted in a reduction in resting SBP (120 ± 12 to 115 ± 12 mmHg, p = 0.01). The intercept of the 5-minute post-exercise systolic blood pressure slope was lower (p = 0.015) following the 4-week training intervention. Individual changes in immediate post-exercise response SBP were also significantly correlated with reductions in resting SBP following 4-weeks of training. There were significant differences in the slopes of the first vs. final post-exercise BRS response (p = 0.009), and the intercepts of the HRR slopes (p = 0.04) recorded during the 5-minute post-exercise periods.

**Conclusions:** Four weeks of IET altered immediate cardiovascular responses to an individual IET session. Altered immediate responses were also associated with training induced reductions in resting SBP. To our knowledge, this is the first evidence suggesting very short-term (immediate) cardiovascular responses may be important in defining chronic reductions in resting blood pressure following a period of IET.

**Keywords:** Systolic blood pressure; Exercise training; Cardiovascular risk; Mechanisms

**Abbreviations**

BP = blood pressure

BRS = baroreflex sensitivity

EMG = electromyography

HR = heart rate

HRR = heart rate recovery

IET = isometric exercise training
MVC = maximal voluntary contraction
SBP = systolic blood pressure

INTRODUCTION
The cessation of exercise is a unique challenge to blood pressure control (O’Sullivan and Bell, 2000). Central command irradiation of the cardiovascular centres ceases abruptly, which results in momentary hypotension (Rowell, 1994; Raven et al. 1997). The purpose of cardiovascular regulation in this post-exercise period appears to be maintenance of adequate blood pressure to ensure tissue perfusion. Whilst less evidence exists about immediate post-exercise responses, more is known about the subsequent phase, lasting up to several hours, during which there appears to be a residual effect of the effects of exercise and its cessation. During this protracted phase, known as post-exercise hypotension, blood pressure can fall below pre-exercising resting levels, and is associated with hyperaemia (Hagberg et al. 1987; Hoffman and Thorén, 1988; Pescatello et al. 1991; Cléroux et al. 1992).

Observations of post-exercise hypotension in the longer post-exercise phase are well documented in both hypertensive (Fisher, 2001; Legramante et al. 2002) and normotensive (MacDonald et al. 1999; MacDonald et al., 2000; Studinger et al. 2003; Lakin et al., 2013) individuals. The phenomenon of post-exercise hypotension has received considerable attention, not least because it might be beneficial to hypertensive patients, with delayed decline in systolic blood pressure (SBP) with angiographic coronary disease (McHam et al. 1999). It has been suggested that arterial baroreflex responses to mechanical stimuli may be responsible for post-exercise hypotension. Specifically, baroreceptor activity was reduced during exercise as SBP increased, but then gradually increased above initial resting levels as a hypotensive period subsists during the first 60 minutes post-exercise (Studinger et al. 2003).

However, little is known about blood pressure regulation immediately after exercise cessation (MacDonald et al. 2002; Lakin et al., 2013), and the relative importance of this regulation to resting blood pressure. There have not been any studies showing the effects of exercise training on this vasoactive response. Whilst the aforementioned extended hypotensive response (over several hours) may be beneficial to hypertensive individuals, investigating the more immediate vasoactive period in relation to cardiovascular adaptations following a period of exercise training could have important clinical implications. For example, it is not currently known how rapidly potentially important cardiovascular responses occur following a bout of isometric exercise. If acute responses and subsequent chronic adaptations in blood pressure regulation are associated in prehypertensive individuals (Liu et al., 2012), and responses differ with dissimilar modes of exercise (Lakin et al., 2013), more comprehensive evidence
may benefit general exercise prescription guidelines by challenging the notion that all modes of exercise are equally beneficial.

Whilst baroreflex control has been highlighted as an important mechanism in the short-term hypotensive response, the concept of modified baroreflex control being responsible for chronically altered cardiovascular function is a contentious one. Previous evidence both supports (Iellamo et al. 2000; Laterza et al. 2007) and disputes this hypothesis (Costes et al. 2004). If post-exercise response baroreflex control was shown to be altered following a period of exercise training, alongside other simultaneously associated cardiovascular variables, it may help support the notion that baroreflex control is indeed associated with altered blood pressure regulation. It has also been suggested that reduced peripheral vascular resistance could explain the observed reductions in resting blood pressure after exercise training (Sprangers et al. 1991; Blumenthal et al. 2000), especially after isometric exercise training [(IET) (McGowan et al. 2007)].

Total peripheral resistance may be regulated by autonomic nervous system activity, and importantly this activity is also known to be affected by acute exposure to an exercise stimulus, with parasympathetic withdrawal often accompanying increases in a sympathetic driven pressor response (Rowell and O’Leary, 1990; Kluess et al. 2000). In addition to this, it has been shown that chronic exposure to an exercise stimulus may in turn result in greater parasympathetic dominance at rest (Smith et al. 1989; Levy et al. 1998; Carter et al. 2003), which has been associated with reduced resting blood pressure and overall decreased cardiovascular risk (Levy et al. 1998; Carter et al. 2003). Heart rate recovery has been reported to represent the reactivation of parasympathetic nervous activity following exercise (Arai et al. 1989; Imai et al. 1994; Cole et al. 1999). The associated functions of baroreflex sensitivity and heart rate regulation make these two variables relevant to investigate in the immediate post-exercise response period.

The purpose of this study was twofold: (1) to investigate the effect of four-weeks of bilateral-leg isometric exercise training on the immediate post-exercise cardiovascular responses, and (2) to ascertain whether any changes in immediate post-exercise cardiovascular responses may be associated with training-induced resting blood pressure adaptations. Following previously reported data in this
publication (Devereux et al. 2010) and given isometric exercise training has been shown to be an effective means of lowering resting blood pressure (Wiley et al. 1992; Ray and Carrasco, 2000; Howden et al. 2002; Taylor et al. 2003; McGowan et al. 2004; Peters et al. 2006; Millar et al. 2007; Wiles et al. 2010), this study investigated the immediate post-exercise responses to isometric exercise and their effects on adaptations to isometric exercise training. We hypothesized it would be possible to (a) identify the immediate post-exercise response in systolic blood pressure, index of baroreflex sensitivity, and autonomic nervous system function after a single bout of moderate intensity isometric exercise. And (b), to relate potential training induced changes in these immediate post-exercise response variables to chronic reductions in resting SBP.

METHODS

PARTICIPANTS
Thirteen normotensive males (mean age 21 ± 2 years; body mass 78.1 ± 18.2 kg; height 1.77 ± 0.05 m) volunteered to participate in a crossover design. Prior to testing, and after receiving institutional ethical approval, each participant received a written explanation of the procedures including any potential risks, completed an exercise readiness questionnaire and provided informed consent, thereby adhering to the guidelines set by the 1964 Declaration of Helsinki. All participants were non-smokers and were not taking any medication. Participants were moderately physically active (8.7 hours at 7.3 METS per week) for at least 3 months prior to starting testing, and maintained consistent dietary and physical activity habits throughout the testing period. All tests were performed at least 4 hours post-prandial, and 24 hours post moderate to intense physical activity. Consistency of dietary and physical activity behaviours was confirmed verbally at the beginning of each session.

PROCEDURES

Isometric Exercise Training: Each participant completed both isometric exercise training and control conditions in a randomised order. The conditions were separated by 6 weeks. Participants performed a total of twelve training sessions; 4 * 2-minute bilateral-leg isometric exercise bouts separated by 3-minute rest periods, 3 days.wk⁻¹. The first and final training sessions were conducted at the same time of day for each participant. The bilateral-leg training required simultaneous isometric contractions in both limbs.

Intensity of training was set at an electromyography (EMG) ‘target’ that equated to 95% peak heart rate, ascertained during a discontinuous incremental exercise test which is described below (For comparative purposes exercise intensity approximated 22% MVC). Training intensity (EMG mV) was adjusted if heart rate (HR) deviated from the target (95% peak HR) by more than ±5%. Training sessions were separated by at least 24 hours (typically 48-72 hours). Real-time EMG signal was displayed to ensure the appropriate EMG activity level was maintained throughout the IET programme. Participants were instructed to breathe normally at all times during isometric exercise to avoid a Valsalva manoeuvre. The isometric bilateral-leg extension exercise was performed at a knee angle of 90 degrees (180 degrees corresponds to full knee extension) on a Biodex System 3 Pro, isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY).
Training Intensity Determination: After familiarisation, participants underwent a discontinuous incremental isometric exercise test to ascertain training session intensity. Participants began bilateral-leg isometric exercise at 10% of peak EMG for 2 minutes. Peak EMG was determined from three 2-second maximal voluntary contractions performed prior to the incremental test, each separated by a 120-second rest period. Thereafter, the intensity increased in 5% increments, interspersed by 5-minute rest periods, to volitional exhaustion (or failure to maintain EMG signal within +/- 5% of the ‘target’ value). EMG and HR were monitored and recorded, with average values for the final 60 seconds of each increment used for analysis. A linear relationship between HR and EMG during the discontinuous incremental test has been found previously (Devereux et al. 2010).

Electromyography Recording: A dual bio-amplifier was used to enable surface EMG measurement from both legs. The root mean square of the raw EMG signal was computed using the chart recording software (Chart 5 for Windows XP, ADInstruments Ltd). EMG was smoothed at 1 s using a high-pass digital filter. Surface EMG was recorded from the vastus lateralis, as this muscle has been shown to exhibit a linear relationship ($r = 0.9961$, $P<0.01$) between EMG and force when performing isometric leg extension exercise (Alkner et al. 2000). Electrode placements were consistent among all participants using the vastus lateralis location (Surface Electromyography for the Non-Invasive Assessment of Muscles, www.seniam.org). Electrodes (R ECG pads, Ambu Inc., Maryland, USA) were placed at two-thirds on the line from the anterior spina iliaca superior to the lateral side of the patella, in the direction of the muscle fibres. EMG from each vastus lateralis were combined and averaged to give a single output during simultaneous bilateral-leg exercise.

IMMEDIATE POST-EXERCISE RESPONSES
All immediate post-exercise responses were recorded during a 5-minute period immediately following cessation of the first and final (twelfth) training session bout. These responses were deemed to represent pre- and post-training measurements.

Systolic Blood Pressure: Recorded non-invasively using the beat-to-beat Finometer Pro device (Finapres, TNO Instruments, Amsterdam, The Netherlands). All measurements were taken from the same arm and finger for consistency. SBP from the Finometer Pro device has met Association for the Advancement of
Medical Instrumentation requirements following return-to-flow calibration procedures (Guelen et al. 2008), as conducted on all participants in the present study.

Heart Rate and Heart Rate Recovery: Lead II electrocardiography (ECG) was recorded during exercise using a 16-channel chart recorder (Powerlab, ADInstruments Ltd., Australia) at 1 kHz. The same arrangement was used for the 5-minute post-exercise response period. Heart rate recovery (HRR) was determined during the 5-minute post-exercise period by analysing the slopes of HR data (b.min^-1) from the point of exercise cessation to the end of the 5-minute post-exercise period.

Index of Baroreflex Sensitivity: Estimated by correlating blood pressure variance with HR variance, using the Finometer. An index of baroreflex sensitivity was calculated in the time domain (Gizdulich et al. 1996) by the regression slope of the beat-to-beat and inter-beat variables. These immediate post-exercise responses were recorded for a five-minute period immediately after the first and final (twelfth) training sessions of the intervention.

DATA ANALYSES
All data were assessed for conformity with parametric assumptions. Changes in blood pressure have been associated with initial values (Millar et al. 2007), so analysis of covariance (ANCOVA) was used to assess whether changes scores were influenced by initial baseline values. Differences in BP changes between the experimental and control condition were assessed using repeated measures one-way ANOVA within the ANCOVA test. An alpha level of < 0.05 was set as the threshold for statistical significance, and the Bonferroni post-hoc procedure was used to explore any significant differences detected. Pearson correlation was used to analyse IET-induced SBP adaptations (+/- SBP mmHg) with differences (final training session minus initial training session) in the immediate post exercise response SBP. Sixty-second interval averages were used from the post-exercise beat-to-beat data.

Continuous post-exercise SBP, BRS and HRR data were assessed by linear regression analyses, using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA). To test whether the slopes and intercepts were significantly different, Prism calculates a P value (two-tailed) by testing the null hypothesis that the slopes are all identical (the lines are parallel). If p<0.05, the intercepts are not
compared. Otherwise, Prism calculates a second P value testing the null hypothesis that the lines are identical. If \( p < 0.05 \), the lines are not identical (they are distinct but parallel). If \( p > 0.05 \) there is no compelling evidence that the lines are different (Zar, 2010). An alpha level of \( < 0.05 \) was set as the threshold for statistical significance.
RESULTS

Resting Systolic Blood Pressure: 4-weeks of bilateral-leg IET resulted in a reduction in resting SBP (120 ± 12 to 115 ± 12 mmHg, p = 0.01), with no differences in the control data (120 ± 12 to 119 ± 12 mmHg, p = 0.92). ANOVA showed that SBP changes were significantly different between experimental and control conditions (P = 0.04). The covariate of initial baseline values did not influence change scores for SBP (P = 0.35). There was no significant change in body mass over the duration of the study (78.1 ± 18.2 kg, and 78.1 ± 18.1 kg, p = 0.80). There was a reduction in resting HR (65 ± 11 b.min⁻¹, to 58 ± 6 b.min⁻¹, P = 0.02), and this was also evident in control data (62 ± 6 b.min⁻¹, to 58 ± 4 b.min⁻¹, P = 0.005).

IMMEDIATE POST EXERCISE RESPONSES

Post-Exercise Systolic Blood Pressure: There was a significant difference in SBP slope intercept between pre and post IET (p = 0.015), but not in the slope itself (p > 0.05; Figure 1). Importantly, SBP recorded during isometric exercise was not significantly different when comparing the entire first and final training sessions (189 ± 29 vs. 186 ± 27 mmHg), or the final 30 s of each session (189 ± 32 vs. 188 ± 30 mmHg). Individual change in immediate post-exercise response SBP was significantly correlated (p<0.05) with reductions in resting SBP following 4-weeks of training. The strongest relationship was observed between changes in SBP response at 300 seconds post-exercise and reductions in resting SBP (r=0.78, p=0.002; Figure 2). All correlations between 100 and 300-seconds post-exercise were significantly correlated.

Index of Baroreflex Sensitivity: There was a significant difference in the slope of the first vs. final post-exercise BRS response (p = 0.009). Due to the degree of difference recorded in the slopes, it was not possible to test whether the intercepts differed significantly (Figure 3).

Heart Rate Recovery: There was a significant difference in the intercept of the HRR slopes (p = 0.04) recorded during the 5-minute post-exercise periods, but not in the slope itself (p > 0.05); HRR slope following the final training session was significantly lower than that following the initial training session (Figure 4). Furthermore, HR’s at 5-minutes post exercise were significantly lower than the first post-exercise period (79 ± 13 vs. 72 ± 13 b.min⁻¹ respectively, p<0.05), even though there were no differences
between the mean exercising HR’s recorded during the final and first training session themselves (115 ± 20 vs. 111 ± 17 b.min⁻¹ respectively, p > 0.05).
In this study, four weeks of IET induced changes in immediate post-exercise blood pressure and index of baroreflex sensitivity responses. Furthermore, these altered immediate responses were associated with training-induced reductions in resting blood pressure. To our knowledge, this is the first suggestion that very short-term (immediate) cardiovascular responses following isometric exercise may be important in defining chronic reductions in resting SBP following a period of IET.

However, the data does not clarify cause-and-effect between altered resting and immediate response measures. Whether the rapid mechanisms of SBP regulation following the exercise-cessation induced hyperaemia influences chronic resting SBP at rest, or vice-versa, is currently unknown. Whilst the training-induced resting SBP reductions are small, it is known that the associated risk of cardiovascular disease is apparent from 115mmHg (Lewington et al. 2002), and that a reduction of just 2mmHg can have clinically significant benefits (Whelton et al. 2002).

The significant difference in immediate post-exercise SBP slope intercept (Figure 1) suggests that chronic exposure to an isometric exercise stimulus may alter post-exercise SBP control. Adaptations in immediate post-exercise responses may be important in defining resting SBP adaptations to isometric exercise training, as evidenced by the correlation between individual adaptations in immediate post-exercise responses and training-induced reductions in resting SBP (Figure 2).

It is important to note that mean SBP responses during the first and final training sessions were not different (189 ± 29 and 186 ± 27 mmHg respectively, p > 0.05), so the changes in immediate post-exercise response were not caused by higher exercising SBP pressures. Adaptations in immediate post-exercise SBP response were evident as soon as 20-seconds after exercise cessation when comparing the first and final training sessions (159 ± 26 vs. 152 ± 23 mmHg respectively, at 20-seconds after cessation of exercise, p < 0.05). Therefore, the reduction in immediate post-exercise SBP was greater after IET, suggesting that this initial 20-second period may be an important component of the mechanisms responsible for IET-induced reductions in resting SBP.
Whilst baroreceptor resetting has been shown in both hypertensive individuals compared to normotensive controls (Laterza et al. 2007), and individuals undertaking aerobic and resistance exercise training interventions (Iellamo et al. 2000; Laterza et al. 2007), little is known about the role of baroreceptor resetting in chronic resting SBP reductions following IET. The differences in the post-exercise BRS slope could be linked to changes in the intercept of the SBP slope. If index of baroreflex sensitivity increased (Figure 3), then it follows that immediate post-exercise SBP responses would likely reduce more rapidly back toward pre-exercise baseline values. Indeed, this would be supported by the current data. However, further investigation is required to discern the relative importance of BRS in IET-induced reductions in resting SBP.

Given HRR is deemed to be a valid representation of the effects of the autonomic nervous system on cardiac function (Arai et al. 1989; Imai et al. 1994; Cole et al. 1999), the differences in HRR following 4-weeks of IET suggest that parasympathetic reactivation was enhanced. It is known that a rapid reduction in arterial distending pressure may follow an exercise-induced artery constriction/compression (Studinger et al. 2003). This suggests that during the post-exercise period, any sustained sympathetic activation is overridden by potent vasodilator stimuli (Piepoli et al. 1993). Therefore, the present data suggests a heightened parasympathetic reactivation, following its withdrawal during exercise. These responses, in concert with enhanced BRS, could be related to the difference in SBP slope intercept after IET, and perhaps subsequent reductions in resting SBP. The reduction in resting HR for the control condition, whilst smaller than the training reduction (4 vs. 7 b.min\(^{-1}\) respectively) is difficult to explain. It did not affect resting SBP measures, as has been reported. Familiarisation was conducted for all measures.

The immediate post exercise response data suggest the continuum of post-exercise SBP in relation to immediate post-exercise response should be investigated over shorter periods than those previously conducted (approximately 30 minutes; MacDonald et al. 1999). It is possible that short-term immediate post exercise response may play an important role in resting SBP adaptations to isometric exercise training.
CONCLUSIONS

Four weeks of IET altered the immediate cardiovascular responses to an individual IET session. The altered immediate responses were also associated with the training induced reductions in resting SBP. It is possible to suggest that the immediate post-exercise response may play an important role in defining IET-induced reductions in resting blood pressure. However, it should be noted that whilst a cause-and-effect relationship may exist between rest and the immediate post-exercise response phase, it is still unclear which is cause and which is effect. It is possible that an alteration in these post-exercise responses could influence the net exercise stimulus, which may ultimately elicit longer-term adaptations such as reductions in resting blood pressure. Some physiological factors responsible for enhanced immediate post-exercise response, namely BRS and parasympathetic reactivation, may help to elucidate those mechanisms responsible for reductions in resting blood pressure following IET. The relationship observed in this investigation also raises the possibility that the 5-minute immediate post-exercise response could also provide a simple indicator of the efficacy of IET intensity in reducing resting blood pressure, and help to optimize IET prescription.
REFERENCES


LEGENDS

Figure 1: 5-minute post-exercise systolic blood pressure (SBP) response, following initial (♦) and final (◼) training sessions. A significant difference in intercept between pre and post IET (p = 0.015) was detected.

Figure 2: Correlation between individual changes in 5-minute post-exercise systolic blood pressure (SBP) response and reductions in resting SBP following 4 weeks of training.

Figure 3: 5-minute post-exercise baroreflex sensitivity (BRS) response, following initial (♦) and final (◼) training sessions. A significant difference in the slope of the first vs. final post-exercise BRS response (p = 0.009) was detected.

Figure 4: 5-minute post-exercise heart rate recovery (HRR) response, following initial (♦) and final (◼) training sessions. A significant difference in the intercept of the HRR slopes (p = 0.04) was detected.