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Review

The blood pressure response to acute and chronic aerobic exercise: A meta-analysis of candidate gene association studies

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ABSTRACT

Objectives: To meta-analyze candidate gene association studies on the change in blood pressure beyond the immediate post-exercise phase after versus before aerobic exercise.
Design: Meta-analysis.
Methods: A systematic search was conducted. Studies retrieved included acute (short-term or postexercise hypotension) or chronic (long-term or training) aerobic exercise interventions; and blood pressure measured before and after aerobic exercise training, or before and after exercise or control under ambulatory conditions by genotype. Effect sizes were determined for genotype and adjusted for sample features.
Results: Qualifying studies ($k = 17$, $n = 3524$) on average included middle-aged, overweight men (44.2%) and women (55.8%) with prehypertension ($134.9 \pm 11.7/78.6 \pm 9.5$ mmHg). Training interventions ($k = 12$) were performed at $60.4 \pm 12.9\%$ of maximum oxygen consumption (VO_{2max}) for 41.9 ± 12.5 min session^{-1}, 3.6 ± 1.2 days week^{-1} for 15.7 ± 7.6 week; and post-exercise hypotension interventions ($k = 5$) were performed at $53.5 \pm 14.4\%$ VO_{2max} for 38.5 ± 5.4 min session^{-1}. Sample characteristics explained 54.2–59.0% of the variability in the blood pressure change after versus before acute exercise or control under ambulatory conditions, and 57.4–67.1% of the variability in the blood pressure change after versus before training ($p < 0.001$). Only angiotensinogen M235T (rs699) associated with the change in diastolic blood pressure after versus before training ($R^2 = 0.1\%$, $p = 0.05$), but this association did not remain statistically significant after adjustment for multiple comparisons.
Conclusions: Sample characteristics explained most of the variability in the change of BP beyond the immediate post-exercise phase after versus before acute and chronic aerobic exercise. Angiotensinogen M235T (rs699) was the only genetic variant that associated with the change in diastolic blood pressure after versus before training, accounting for <1% of the variance.

1. Introduction

Hypertension is a major public health issue worldwide.[1] Hypertension is the most common, costly and preventable cardiovascular disease (CVD) risk factor in the United States (US) affecting 33% of US adults.[1,2] Another 36% of Americans have prehypertension.[1] Prehypertension is a predictor of future hypertension with one in five people with prehypertension acquiring hypertension within 4 years.[1] Therefore, the prevention, treatment, and control of high blood pressure (BP) are major public health priorities.[2]

We and others have shown acute aerobic exercise reduces resting BP 5–7 mmHg among those with hypertension following a single isolated bout of exercise that is immediate and that persists for up to 24 h outside of the laboratory under ambulatory conditions during the daytime hours.[3–7] This response is termed postexercise hypotension (PEH).[8,9] Aerobic exercise training also reduces resting BP 5–7 mmHg among those with hypertension.[10] The magnitude of the resting BP reductions that occur after acute and chronic exercise rival the magnitude of those obtained with many first line antihypertensive medications and lower CVD risk by 20–30%.[2] For this reason, people with hypertension are

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encouraged to exercise in accordance with the American College of Sports Medicine's recommendations of performing moderate intensity aerobic exercise for 30–60 min on most, preferably all, days of the week.[9,11,12]

Despite this recommendation, there is considerable variation in the change in BP after compared to before aerobic exercise beyond the immediate post-exercise phase, with 20–25% of the people with hypertension not lowering their BP following exercise for reasons that are not clear.[13–17] Bouchard et al. recently consolidated the data from six large exercise studies to examine the variability in the change in systolic BP (SBP) after compared to before aerobic exercise training among sedentary populations. Unexpectedly, they found that 6% of the sample experienced an adverse increase in SBP (i.e., ≥10 mmHg increase) after compared to before exercise training, while a similar percentage experienced a large decrease in SBP (i.e., ≥10 mmHg decrease) after compared to before exercise training.[13] These findings illustrate the critical need to identify factors that explain the variability in the BP response to exercise so that exercise can be more effectively prescribed as antihypertensive lifestyle therapy.

Genetic predispositions explain up to 40–65% of the inter-individual variability in the response of health-fitness phenotypes to exercise.[8,16–18] Presently, 27 different candidate gene polymorphisms have been reported to be associated with the change in BP after compared to before acute and chronic aerobic exercise beyond the immediate post-exercise phase.[3–6,19–31] However, these polymorphisms account for only a small proportion of the variability in the BP response to exercise, and their findings are often not confirmed in subsequent studies for a variety of reasons. For these candidate gene association studies often: (a) have small sample sizes; (b) examine a small number of polymorphisms; (c) are subject to sample selection bias; (d) do not examine possible confounding sample features (e.g., age, body mass index [BMI], race, sex, resting BP); and (e) do not employ statistical corrections for multiple comparisons.[8,16–18]

Meta-analysis systematically and quantitatively integrates the results of a body of literature addressing a related hypothesis, increasing the power to detect statistical differences.[32,33] Therefore, a meta-analysis of candidate gene association studies would be able to aggregate and examine a larger number of polymorphisms in a large sample, control for confounding sample features, and adjust for multiple comparisons. Accordingly, the purpose of this study was to meta-analyze the literature examining candidate gene associations with the change in BP after compared to before acute and chronic aerobic exercise beyond the immediate post-exercise phase to circumvent limitations of the literature and increase the likelihood of detecting genotype associations with the BP change from exercise should they exist.

2. Methods

2.1. Data sources

A systematic search was conducted using the following electronic databases: MEDLINE, Biosis, Scopus, and Web of Science (to March 15, 2015). The keywords "blood pressure," "exercise," "randomized control trial," and "gene" were used in combination with medical subject heading (MeSH) descriptors by two independent researchers (MLB, KAL) to search the databases for relevant studies [Text, Supplemental Digital Content 1]. Article citation lists, non-indexed journals, and conference abstracts were also reviewed to identify additional studies. No language restrictions were applied when attempting to locate studies for inclusion.

2.2. Study selection

Studies were included if they: (a) involved an acute (i.e., short-term or [PEH]) or chronic (i.e., long-term or training) aerobic exercise intervention; (b) measured BP before and after exercise (PEH and training trials) beyond the immediate post-exercise phase and control (PEH trials only) by genotype; (c) had a randomized or non-randomized, case-control, cross-sectional, or family-based study design that was subjected to a blinded peer-review process; and (d) reported at least one polymorphism's positive or negative association with the change in BP following compared to before exercise. All PEH trials meeting selection criteria (b) and (c) involved a control comparison, ambulatory BP monitoring outside of the laboratory for the daytime hours, and two (i.e., dominant or recessive models) genotype groups. All exercise training studies meeting criteria (b) and (c) involved three (i.e., co-dominant or additive models) genotype groups in order to conduct independent genotype comparisons to minimize statistical dependence due to the lack of a control comparison. Studies were excluded if they: (a) involved animal or non-human models; (b) PEH trials that did not have a control comparison; or (c) exercise training trials with only two genotype groups. A list of the full exclusion criteria can be located in the supplemental digital content [Text, Supplemental Digital Content 2].

2.3. Data extraction

There were 645 potentially relevant studies retrieved from the systematic search [Figs. 1 and 2]. Two coders (MLB, KAL) independently screened the studies via title and abstract for inclusion/exclusion, and excluded studies were re-screened as a quality control measure. Studies that continued to meet the inclusion criteria were then subjected to data extraction via a 246-item coding form.

Extracted study and subject data included but were not limited to variables related to: age, BMI, resting SBP or diastolic (DBP) BP, sex/gender, race/ethnicity, study quality, and geographical region where the study was conducted. The complete coding form can be located in the supplemental digital content [Text, Supplemental Digital Content 3].

The coders independently performed the data extraction procedures and obtained high inter-rater reliability (mean agreement = 95%, Cohen's $\kappa = 0.75$).[34–36] A third coder (BTJ, TBHM, or LSP) mediated any unresolved discrepancies in coding if a consensus between the coders could not be reached. Inter-rater reliability was assessed with a Kappa statistic (Cohen's κ) for all categorical variables (computed as the percent agreement between raters on a 0.00 [no agreement] to 1.00 [perfect agreement] scale), and Pearson's r correlation coefficient for all continuous variables (computed as the standardized correlation between raters for a given variable on a −1 to +1 scale).[34–36] Study quality was assessed with the Downs and Black methodological quality checklist, a 26-item questionnaire with higher scores indicating better study quality.[37]

2.4. Effect size estimate

Effect size estimates were computed using Becker's $d+$ to quantify the magnitude of the change in BP following compared to before acute or chronic aerobic exercise beyond the immediate post-exercise phase, adjusting for small sample size bias.[38,39] For the aerobic exercise training studies, the standardized mean difference of Becker's $d+$ was defined as the standardized mean difference in resting BP post- versus pre-training divided by the resting BP pre-training standard deviation to control for baseline sample differences among different study designs.[40] For the PEH studies that assessed ambulatory BP outside of the laboratory for the daytime