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Review

The impact of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects: A systematic review and meta-analysis

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ABSTRACT

Background: Debate concerning aerobic exercise decreasing arterial stiffness in pre- and hypertensive individuals still exists. We sought to systematically review and quantify the effect of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects.
Methods: MEDLINE, Cochrane, Scopus and Web of Science were searched up until August 2013 for trials assessing the effect of aerobic exercise interventions lasting 4 or more weeks on arterial stiffness in (pre)hypertensive subjects. Standardized mean difference (SMD) in arterial stiffness parameters (PWV, B-stiffness, Compliance, AIx) was calculated using a random-effects model. Subgroup and meta-regression analyses were used to study potential moderating factors.
Results: Fourteen trials comprising a total of 472 (pre)hypertensive subjects met the inclusion criteria. Arterial stiffness was not significantly reduced by aerobic training in (pre)hypertensive subjects (14 trials, SMD = −0.19; $P = .06$). Likewise, post-intervention arterial stiffness was similar between the aerobic exercise-trained and control (pre)hypertensive subjects (8 trials, SMD = −0.10; $P = .43$). Neither heterogeneity nor publication bias was detected in either of these analyses. In the subgroup analyses, arterial stiffness was significantly reduced in aerobic exercise-trained (pre)hypertensive subgroups below the median value in post minus pre-intervention systolic blood pressure (SBP) (SMD = −0.38, $P = .04$) and in subgroups above the median value in the duration of the intervention (SMD = −0.28, $P = .03$). Similar results were obtained in the meta-regression analysis.
Conclusions: Arterial stiffness is not reduced in (pre)hypertensive subjects in response to aerobic training unless associated with a substantial reduction in SBP and/or prolonged duration.

1. Introduction

Arterial hypertension is a major public health issue associated with all-cause and vascular mortality [1] and it is among the most important modifiable risk factors for cardiovascular disease [2]. Arterial stiffness precedes, contributes and is correlated to hypertension [3–7]. In this regard, age-related degeneration of elastin fibers and increased collagen deposition are known mechanisms that lead to arterial stiffness and hypertension [8]. Moreover, endothelial dysfunction and elevated proinflammatory cytokines, both reported in pre- and hypertensive subjects after adjustment for confounding factors [9], may promote arterial stiffening through decreased nitric oxide bioavailability, increased endothelin-1 production and stimulation of vascular smooth muscle proliferation [9,10].

Regular physical activity, such as walking, jogging or cycling (i.e. aerobic exercise), is known to reduce stiffness of central and peripheral arteries in healthy normotensive adults [11–15]. Arterial remodeling, improved endothelial function and decreased sympathetic tonus and proinflammatory cytokines have been suggested as mechanisms underlying the direct beneficial effect of aerobic exercise on arterial compliance [11,16,17]. Likewise, current recommendations by American and European hypertension guidelines include daily aerobic exercise for 30 to 45 min on a regular basis [18,19]. However, previous trials that have measured the effect of aerobic exercise interventions on arterial stiffness in (pre) hypertensive subjects included small sample sizes and subsequently yielded variable results [20–33], leading to some uncertainty concerning the effect of aerobic exercise on arterial stiffness. Therefore, the main objective of this study was to systematically review, using the meta-analysis procedure, the effect of

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aerobic exercise training on arterial stiffness in (pre)hypertensive subjects.

2. Methods

This study is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [34].

2.1. Data sources and searches

The search strategy was developed to identify all relevant studies assessing the effect of aerobic exercise interventions on arterial stiffness in obese subjects. Our systematic search included MEDLINE, Cochrane, Scopus and Web of Science, since their inceptions until August 2013. We used combinations of the subject headings 'hypertension', 'arterial stiffness', 'arterial compliance', 'arterial distensibility', and 'aerobic exercise training'; the search strategy for MEDLINE is shown in Supplemental Fig. 1. We also performed manual searching in reference citations of identified reviews and original research articles selected for full-text retrieval.

2.2. Study selection

To be included in our analysis, an original research article had to meet the following criteria: 1) the research had to be a trial involving (pre)hypertensive subjects; 2) arterial stiffness values had to be reported at baseline and after an aerobic exercise intervention; 3) the duration of the aerobic exercise intervention had to be ≥4 weeks. An aerobic exercise intervention was defined as a deliberate and supervised program of aerobic physical activity, described within the corresponding manuscript. Studies following the above criteria but including, concurrent with aerobic exercise, other interventions deemed likely to influence arterial stiffness were excluded. In the event of multiple publications pertaining to the same research, the first published or more comprehensive study was used. Inclusion of studies in our analysis was not limited by publication status or language. Study selection was performed independently and in duplicate by two investigators (D.M.) and (A.M.). Discrepancies on inclusion/exclusion were solved by consensus or through consultation with a third reviewer (E.R.).

2.3. Data extraction and quality assessment

The following variables were abstracted into a preformatted spreadsheet: authors, year of publication, characteristics of study participants (*n*, age, % females, weight, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), comorbidities, medication status), vascular variables (vascular region assessed, assessment method, arterial stiffness outcome) and aerobic exercise training characteristics (type, frequency, session length, duration of the intervention, intensity). Furthermore, if data were unclear or were not available in the published articles, we contacted the corresponding and/or first author by e-mail to request this information. The methodological quality of each included trial was evaluated using a validated 10-point scale to rate intervention trials [35–37]. Data extraction and quality assessment were performed independently and in duplicate by two investigators (D.M.) and (A.M.). Discrepancies were solved by consensus or through consultation with a third reviewer (E.R.).

2.4. Data synthesis and analysis

The meta-analysis and statistical analyses were performed using Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-analysis software (version 2; Biostat, Englewood, NJ, USA). In each trial, the size of the effect of the intervention was calculated by the difference between post and pre-intervention arterial stiffness in aerobic exercise-trained (pre)hypertensive subjects. For controlled trials, the size of the effect of the intervention was also calculated by (i) the difference in arterial stiffness after the intervention between aerobic exercise-trained and control (pre)hypertensive subjects, and (ii) the difference in the change in arterial stiffness after the intervention between aerobic exercise-trained and control (pre)hypertensive subjects. Each mean difference was weighted according to the inverse variance method [38]. Since arterial stiffness was assessed by different methods (Table 2), the mean differences were standardized by dividing them by the within-group standard deviation. The standardized mean difference (SMD) values in each trial were pooled with a random effects model [39]. According to Cohen guidelines [40], SMD values of 0.2, 0.5, and 0.8 represent small, medium and large effect sizes, respectively.

Heterogeneity between studies was assessed using I^2 statistics. Potential moderating factors were evaluated by subgroup analysis comparing trials grouped by dichotomous or continuous variables potentially influencing arterial stiffness. Median values of continuous variables were used as cut-off values for grouping trials. Changes in potential moderating factors were expressed and analyzed as post minus pre-intervention values. Meta-regression analysis was performed to further explore which variables best predicted the SMD between post and pre-intervention arterial stiffness. In all meta-regression models, trials were weighted by the inverse variance of the dependent variable [38]. Potential moderating factors were entered as independent variables in regression models with the SMD between post and pre-intervention arterial stiffness as the dependent variable. Publication bias was evaluated by estimating Begg and Mazumdar's funnel plot asymmetry and Egger's weighted regression test [41]. A *P* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Study selection and characteristics

The flow diagram of the study selection process is depicted in Fig. 1. The search of MEDLINE, Cochrane, Scopus and Web of Science and our manual review of articles cited in the identified and related publications retrieved 284 articles, with 185 remaining after removal of duplicates. Of these, 143 were excluded because they were review articles or guidelines ($n = 47$), were irrelevant to our present meta-analysis ($n = 41$), did not assess arterial stiffness ($n = 30$), were cross-sectional studies ($n = 22$) or were animal studies ($n = 3$). We obtained and reviewed the full text of the remaining 42 articles and excluded 28 for the following reasons: 13 articles did not involve a hypertensive population, 10 included an additional intervention, 2 implemented a non-aerobic exercise intervention [42,43], 2 did not implement any intervention [44,45] and one article reported duplicate data [46]. Finally, 14 articles were included in the meta-analysis.

Table 1 shows the main clinical characteristics of the resulting 14 trials, comprising a total of 472 pre-, stage 1 and higher hypertensive subjects, of whom 293 subjects were assigned to aerobic exercise-trained groups and 179 subjects to control groups. The total sample size ranged from 8 to 79. The mean clinical characteristics of aerobic exercise-trained subjects ranged from 44 to 70 years for age, 69 to 93 kg for weight, 27.7 to 32.6 kg/m^2 for BMI, 131 to 156 for SBP and 73 to 94 mm Hg for DBP. Ten trials included 50% or more female subjects [20,21,23–25,29–33], while one trial included male subjects alone [26]. Regarding the characteristics of the aerobic exercise interventions (Table 2), 10 trials consisted of conventional land-based exercise such as walking or treadmill workout [20–24,27,28,30–32], 3 of these trials also including cycling [20,27,28], and 4 studies consisted of cycling [25], soccer training [26], swimming [29] and arm ergometry [33], respectively. They all had a mean of 3.4 sessions per week, 42.8 min per session, 13.5 weeks of duration, resulting in 2213 min on average in total. Arterial stiffness was assessed in 9 trials in both central and peripheral arteries [20–22,24,25,27–30], in 4 trials in peripheral arteries of non-predominantly trained limbs [23,26,31,32] and in one trial in peripheral arteries of predominantly trained limbs [33].

3.2. Quality assessment and potential bias

The quality of the trials, according to a previously validated scale [35–37] was moderate. The mean (SD) score was 5.6 ± 1.6 out of a possible 10 points (Supplemental Table 1). As for the evaluation of potential bias, the Begg and Mazumdar's plot for the SMD between post and pre-intervention arterial stiffness in aerobic exercise-trained (pre)hypertensive subjects was notably symmetrical, suggesting the absence of significant publication bias ($P = .67$). Egger's significance test also showed no significant publication bias ($P = .23$). Similar results were obtained for the evaluation of potential bias of the SMD in post-intervention arterial stiffness between aerobic exercise-trained and control (pre)hypertensive subjects.

3.3. Arterial stiffness

Arterial stiffness was determined in all of the included trials by previously validated methods in central and peripheral arteries (Table 2) [47]. After data pooling, SMD between post and pre-intervention arterial stiffness in aerobic exercise-trained (pre)hypertensive subjects did not reach statistical significance (14 trials, −0.19; 95% CI = −0.39, 0.01, $P = .06$) (Fig. 2). Likewise, post-intervention arterial stiffness was similar between the aerobic exercise-trained and control (pre)hypertensive subjects (8 trials, SMD = −0.10; 95% CI = −0.34, 0.14, $P = .43$) (Fig. 3). Similarly, the change in arterial stiffness after the intervention did not differ between aerobic exercise-trained and control (pre)hypertensive subjects