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Low exercise blood pressure and risk of cardiovascular events and all-cause mortality: Systematic review and meta-analysis

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ABSTRACT

Objective: The independent prognostic significance of abnormally low systolic blood pressure (SBP) during exercise stress testing (LowExBP) across different clinical and exercise conditions is unknown. We sought by systematic review and meta-analysis to determine the association between cardiovascular/all-cause outcomes and LowExBP across different patient clinical presentations, exercise modes, exercise intensities and categories of LowExBP.

Methods: Seven online databases were searched for longitudinal studies reporting the association of LowExBP with risk of fatal and non-fatal cardiovascular events and/or all-cause mortality. LowExBP was defined as either: SBP drop below baseline; failure to increase >10 mmHg from baseline or; lowest SBP quantile among reporting studies.

Results: After review of 13,257 studies, 19 that adjusted for resting SBP were included in the meta-analysis, with a total of 45,895 participants (average follow-up, 4.4 ± 3.0 years). For the whole population, LowExBP was associated with increased risk for fatal and non-fatal cardiovascular events and all-cause mortality (hazard ratio [HR]: 2.01, 95% confidence interval [CI]: 1.59–2.53, $p < 0.001$). In continuous analyses, a 10 mmHg decrease in exercise SBP was associated with higher risk ($n = 9$ HR: 1.13, 95% CI: 1.06–1.20, $p < 0.001$). LowExBP was associated with increased risk regardless of clinical presentation (coronary artery disease, heart failure, hypertrophic cardiomyopathy or peripheral artery disease), exercise mode (treadmill or bike), exercise intensity (moderate or maximal), or LowExBP category (all $p < 0.05$). However, bias toward positive results was apparent (Eggers test $p < 0.001$ and $p = 0.009$).

Conclusion: Our data show that irrespective of clinical or exercise conditions, LowExBP independently predicts fatal and non-fatal cardiovascular events and all-cause mortality.

1. Introduction

Exercise stress testing is commonly used to identify ischemia in patients with known or suspected coronary artery disease (CAD), and blood pressure (BP) is a mandatory measurement during the test. Under normal conditions, systolic BP (SBP) increases with workload intensity, while diastolic BP remains relatively stable or decreases slightly. An excessive rise in SBP during moderate grade exercise is associated with increased cardiovascular (CV) mortality in people without CAD [1]. On the other hand, an abnormally low SBP during exercise stress testing (LowExBP) is thought to be an ominous sign because it reflects severe cardiac dysfunction [2]. LowExBP is defined as a drop in exercise SBP below the pre-test value or an initial increase followed by a decrease in SBP >10 mm Hg despite an increase in workload [3], and has ~6% prevalence among patients referred for exercise stress testing [4]. Several studies have shown LowExBP to predict CV events and mortality [4–12]. However, others have failed to identify significant differences in survival rates between patients with LowExBP and those with normal SBP responses [13–15].

The above discrepancies may be explained by the lack of consistency in patient presentation (e.g. those with or without CAD/ischemia, presence or severity of valvular disease, congenital heart disease, or other presentations of CV disease), exercise mode/intensity (e.g. treadmill vs. bike mode or moderate vs. maximal intensity) or categories/definitions of LowExBP used in analyses (e.g. exercise SBP drop below baseline vs. maximal exercise SBP <150 mm Hg). The absence of taking these study differences into

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account renders the prognostic significance of LowExBP somewhat unclear. To our knowledge, a systematic review and meta-analysis has never been completed to assess the prognostic importance of LowExBP independent of resting BP. This study aimed to conduct such an analysis whilst taking into account whether the prognostic risk varied among patients with different clinical presentations, exercise modes, exercise intensities or categories of LowExBP. We hypothesised that LowExBP would be independently associated with adverse outcomes regardless of these different conditions.

2. Methods

This systematic review and meta-analysis followed the reporting guidelines set by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [16] and MOOSE (Meta-analyses of Observational Studies in Epidemiology) [17] statements.

2.1. Literature search

Two reviewers (MGS and PAB) searched seven electronic databases (CINAHL, Cochrane, EMBASE, PubMed, Scopus, SPORTDiscus and Web of Science) including all studies through to April 2013. The search string included the following terms: ('exercise' or 'exertional' or 'stress test') and ('blood pressure' or 'hypotension' or 'BP' or 'arterial' or 'systolic' or 'haemodynamic' or 'hemodynamic' or 'pressure') and ('mortality' or 'death' or 'event' or 'prognosis' or 'survival' or 'cox' or 'incident' or 'predict') and ('coronary' or 'cardiovascular' or 'vascular' or 'chronic' or 'heart failure' or '3-vessel disease' or 'left main trunk stenosis' or 'myocardial infarction' or 'ischemia' or 'angina' or 'left-ventricular dysfunction' or 'hypertrophic' or 'cardiomyopathy' or 'stroke' or 'pulmonary embolism' or 'valvular' or 'revascularisation' or 'restenosis' or 'cardiac' or 'percutaneous'), and when possible a human limit search filter was applied. The reference lists of original and review articles were also searched.

2.2. Study eligibility

Studies were accepted for the systematic review if they met the following criteria: (1) full-length English publications, (2) longitudinal study design, (3) reported CV events and/or all-cause mortality, and (4) exercise BP reported in multivariate model with risk estimate (hazard ratio [HR], odds ratio, relative risk) and associated 95% CI. The inclusion for the meta-analysis required the risk estimate to be adjusted for resting SBP at a minimum. Additionally, studies were included if they did not specifically adjust for resting SBP, but instead reported their results as an SBP difference model (e.g. change in SBP from rest to maximal exercise, failure to rise SBP by >10 mm Hg from baseline, decrease in exercise SBP below baseline), which theoretically accounts for resting SBP. This approach allowed the prognostic value of exercise BP to be assessed independent from resting BP. In order for findings to be generalizable, we restricted selection to studies of clinical populations and excluded those studies in which only healthy participants were included. The Newcastle-Ottawa Scale was used to assess the quality of studies included. The Scale awards a maximum of nine stars over three categories; selection (4 stars), comparability (2 stars) and exposure (3 stars), with higher quality studies achieving a greater number of stars. There were no restrictions on the medications used or follow-up duration.

2.3. Outcome measures

The main outcome was fatal and non-fatal CV events. This included myocardial infarction, stroke or transient ischemic attack, hospitalisation with heart failure, pulmonary or systemic embolism, coronary artery restenosis, percutaneous coronary intervention, revascularisation, heart transplantation, hospitalisation with angina pectoris and ruptured aortic aneurysm. The secondary outcome was all-cause mortality.

2.4. Data extraction

The characteristics of the population (age, % male), follow-up duration, number and type of events, exercise conditions (mode and intensity), exercise SBP values, statistical analysis type and adjusted covariates from each eligible study were extracted for the systematic review. For the meta-analysis, the most adjusted risk estimate and associated 95% CI were extracted.

2.5. Statistical analysis

Risk estimates (all represented as an HR) and associated 95% CI were abstracted from models that were at least adjusted for resting SBP, and preferably, additionally adjusted for age, sex and other CV risk factors. The reported risk estimates were grouped into two analysis types, categorical (SBP groups/levels) or continuous SBP. Meta-analysis of categorical risk estimates compared HRs for LowExBP vs. reference exercise SBP. Categorical risk estimates were variably reported. A LowExBP was reported as either of the following: (1) a measure based on change from resting SBP, as either a drop in exercise SBP below resting values or a failure to increase SBP by >10 mm Hg from rest; (2) a measure based on the level of SBP during exercise adjusted for resting SBP, defined as the lowest category of exercise SBP (Table 1 column headed "Definition of LowExBP for categorical SBP (prevalence)" shows details of the exposure for each study). The reference SBP group in each study was identified as either of the following: (1) an increase from resting SBP >10 mm Hg in SBP; (2) the highest category of SBP response to exercise adjusted for resting SBP. Continuous risk estimates were reported as per unit or standard deviation increase in either: (1) the exercise SBP change (peak exercise SBP minus rest SBP) or; (2) the peak exercise SBP. Continuous HRs were rescaled to represent per 10 mm Hg decrease in both types of continuous risk estimates. In addition, using the method outlined by Shi and Copas [18], we were able to estimate HR for continuous risk for two studies [19,20] that reported only categorical risk. For these studies we extracted the HR, associated 95% CI, participants, outcomes/events, and the lowest and highest SBP values for each reported category of exercise SBP. Weighted regression through the exercise SBP categories was used to estimate an HR and standard error for a per unit increase in exercise SBP. Other studies did not supply sufficient information to perform this estimation. For studies reporting separate risk estimates for fatal and non-fatal CV events and all-cause mortality [7,11,21–24], analyses of the risk estimates for fatal and non-fatal CV events were chosen in preference to all-cause mortality. Two studies [4,25] did not report 95% CIs, standard errors were thus estimated from the associated p-value, in one study the p-value was reported as $p < 0.005$ [4], resulting in a conservative estimation of the standard error. All meta-analyses used random effects models with inverse variance weighting to compensate for expected heterogeneity among studies. Q and I^2 statistics were also calculated to test for heterogeneity.

To explore the prognostic risk of LowExBP between differences in study designs we conducted several pre-defined sub-group analyses, which included: (1) patient clinical presentation (suspected/known CAD vs. other clinical presentations of CV disease); (2) exercise mode (treadmill vs. cycling) and; (3) exercise intensity (moderate vs. maximal; where the intensity was defined in each individual study as described in Table 1). Further, we examined