Exercise-Induced Hypertension, Cardiovascular Events, and Mortality in Patients Undergoing Exercise Stress Testing: A Systematic Review and Meta-Analysis

Martin G. Schultz1, Petr Otahal1, Verity J. Cleland1, Leigh Blizzard1, Thomas H. Marwick2 and James E. Sharman1

BACKGROUND
The prognostic relevance of a hypertensive response to exercise (HRE) is ill-defined in individuals undergoing exercise stress testing. The study described here was intended to provide a systematic review and meta-analysis of published literature to determine the value of exercise-related blood pressure (BP) (independent of office BP) for predicting cardiovascular (CV) events and mortality.

METHODS
Online databases were searched for published longitudinal studies reporting exercise-related BP and CV events and mortality rates.

RESULTS
We identified for review 12 longitudinal studies with a total of 46,314 individuals without significant coronary artery disease, with total CV event and mortality rates recorded over a mean follow-up of 15.2 ± 4.0 years. After adjustment for age, office BP, and CV risk factors, an HRE at moderate exercise intensity carried a 36% greater rate of CV events and mortality (95% CI, 1.02–1.83, P = 0.039) than that of subjects without an HRE. Additionally, each 10 mm Hg increase in systolic BP during exercise at moderate intensity was accompanied by a 4% increase in CV events and mortality, independent of office BP, age, or CV risk factors (95% CI, 1.01–1.07, P = 0.02). Systolic BP at maximal workload was not significantly associated with the outcome of an increased rate of CV, whether analyzed as a categorical (HR=1.49, 95% CI, 0.90–2.46, P = 0.12) or a continuous (HR=1.01, 95% CI, 0.98–1.04, P = 0.53) variable.

CONCLUSIONS
An HRE at moderate exercise intensity during exercise stress testing is an independent risk factor for CV events and mortality. This highlights the need to determine underlying pathophysiological mechanisms of exercise-induced hypertension.

Keywords: exercise, hypertension, prognosis, mortality, cardiovascular risk; blood pressure.

Correspondence: James E. Sharman, (James.Sharman@menzies.utas.edu.au)

Initially submitted September 28, 2012; date of first revision October 14, 2012; accepted for publication October 18, 2012.
done. The present study was done to undertake a systematic review and meta-analysis of published literature to determine the predictive value of exercise BP for subsequent CV events and mortality.

METHODS

Literature search strategy

The research methods used in the study adhered to the protocol presented in the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement for reporting systematic reviews and meta-analyses. Two reviewers (M.G.S. and V.J.C.) independently conducted a literature search of seven online databases (Pubmed, Embase, Web of Science, Cochrane, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SportDiscus, and Scopus) for published studies reporting data on exercise BP and CV event and mortality outcomes for all years through March 2012. Search strings included the terms: “exercise” or “sport”; “blood pressure” or “arterial pressure”; “mortality” or “death”; “myocardial infarction” or “coronary” or “heart failure” or “cardiovascular” or “vascular” or “stroke”; “prognosis”; “follow-up” or “prospective” or “retrospective” or “longitudinal” or “observational” or “cox” or “survival.” Search filters or “limits” for English language, human studies and adults (> 18 years) were included when the options were available. Reference lists of relevant individual publications and review articles were also searched for additional studies.

Criteria for study inclusion

Studies were included in the systematic review if they met the criteria of: (i) being a full-length publication in a peer-reviewed, English language journal; (ii) being a human study involving adults > 18 years of age; (iii) reporting office BP; (iv) reporting exercise BP (measured either during or immediately following exercise at a submaximal (moderate) workload and/or maximal workload as reported in each individual study; (v) reporting CV outcomes (as below); (vi) having a population that included subjects with a clinical indication for exercise stress testing or who were otherwise healthy.

Studies in which participants had a known history of CV or cerebrovascular disease were excluded. This was considered important because of the possibility that impaired left ventricular systolic function could lead to an abnormally low exercise BP, which would have confounded our analyses given that this also increases CV risk. With this in mind, studies were excluded from analysis if any of the study population were reported to have a history of myocardial infarction, coronary artery disease, coronary artery bypass procedure, percutaneous coronary intervention, heart failure, valvular heart disease, other vascular diseases, or any form of cerebrovascular disease (stroke). Studies in which exercise BP was measured during recovery periods (not during exercise) were also excluded. No restrictions were applied to the duration of follow up, presence of hypertension, use of antihypertensive medication, or presence of type 2 diabetes. Studies of all designs were eligible for inclusion, and attention was focussed on exercise systolic BP because this is less prone to exercise-induced artefact and more susceptible to an HRE than is exercise diastolic BP.

Outcomes

The primary outcome of interest was a composite of CV events or mortality or both, which may have included any of the following outcomes: fatal or nonfatal myocardial infarction, fatal or nonfatal cerebrovascular event (stroke), or the development of coronary artery disease. In the remainder of this report, these CV events are referred to as CV outcomes.

Data extraction

Data were extracted independently by two reviewers (M.G.S and P.O.). All discrepancies were reviewed and resolved by consensus. For the systematic review, the following data concerning the individual study populations were extracted from each paper: years of follow-up, age, sex, exercise-test modality, number of CV outcomes, exercise BP values, reference and HRE cutoff values, study design, and covariates included in any adjusted models. Additionally, for the meta-analysis, data that were extracted from nine studies also included estimates of the hazard ratio (HR) and associated 95% confidence intervals (CIs).

Statistical analysis

For pooled analysis, all risk estimates were treated as HR, whether reported in individual studies as HR, relative risk (RR), or odds ratio (OR). Hazard ratios from multivariable models that included adjustment for age, sex (where appropriate), office BP, and other CV risk factors were included in meta-analyses. Pooled HRs were reported for two methodologies of analysis and two workloads: (i) either grouped exposure levels (categorical) or per-unit increase in exposure (continuous); and (ii) at either a moderate or a maximal exercise workload. Four meta-analyses were done separately, one for each combination of workload and methodology. Studies could be included in more than one meta-analysis if appropriate HRs were reported or could be derived (see Table 1).

Analysis of categorical data compared the HRs for HRE vs. non-HRE (taken as the reference group). An HRE was defined as the highest category of exercise systolic BP reported in each individual study, and the reference category was defined as the reference category from each individual study (with the values outlined in Table 1). Hazard ratios for continuous analyses were typically reported according to the change in standard deviation per unit increase (e.g. 20 mm Hg) in exercise systolic BP. To allow direct comparisons of studies, all continuous HRs were re-expressed on the natural logarithm scale and rescaled to represent 10 mm Hg increases in exercise systolic BP. Standard errors (SEs) were also calculated on the logarithmic scale from reported 95% CIs, and were similarly rescaled. A continuous trend across categories of exercise BP was estimated for three studies that reported only categorical data using the methods of Shi and Copas. This required information about the distribution of individuals within categories,
Exercise, Blood Pressure, and Cardiovascular Outcomes

the category cutpoints, and the overall mean exercise BP mean and standard deviation (SD). For two of these three studies,\textsuperscript{16,17} the statistics required for trend estimation were extracted directly from within the studies. Kohl \textit{et al.}\textsuperscript{15} did not report the overall mean or SD for exercise BP, which we estimated from similar studies, using techniques also outlined by Shi and Copas.\textsuperscript{18} We also performed a sensitivity analysis excluding these three studies, and showed that no notable change in estimates or \(P\)-values resulted from their exclusion.

Two studies containing data on the same cohort\textsuperscript{19,20} were included in separate analyses, one in the categorical analysis,\textsuperscript{19} and one in a continuous form.\textsuperscript{20} The study by Shalnova \textit{et al.}\textsuperscript{21} reported HRs for two separate cohorts, and these data were therefore analyzed as if they were from separate studies. Further subgroup meta-analyses on continuous HRs were conducted on studies in which bicycle ergometers were used for exercise stress testing. We used random-effects estimates in all meta-analyses in this study because of heterogeneity of the categorical analyses, and variation in outcomes, cutpoints, and designs of the studies. Publication bias was assessed visually with funnel plots and with Egger's test for bias. Statistical calculations were done with Stata for Windows version 12.1 (StataCorp, College Station, TX).

\section*{RESULTS}

\textbf{Overview of literature search results}

A schematic diagram of the literature search procedure used in the present study is shown in Figure 1. The initial search of the seven online databases used in the study revealed a total of 7,508 original articles. Of these, 7,438 were excluded after review of the title or abstract or both, leaving 72 potentially relevant articles requiring full text reviews. Of these articles, 60 were excluded, leaving 12 studies for systematic review (Table 1) and 9 for meta-analysis. Of the three studies not pooled for meta-analysis,\textsuperscript{10,22,23} two reported HRs that were not adjusted for office BP and one did not include 95% CIs for the HR.\textsuperscript{10} The 12 studies that were included had a total of 56,055 study participants, of which 46,314 were analyzed in meta-analyses (not including the duplicate cohort). The average duration of follow-up in these studies was 15.2 ± 4.0 years.

\textbf{Exercise BP and CV outcomes: moderate intensity exercise}

An HRE at moderate exercise workloads increased the pooled rate of CV outcomes by 1.36 (95% CI, 1.02–1.83, \(P = 0.039\)) above those in the reference group after adjustment for office BP, age, and other CV disease risk factors (Figure 2, upper panel). In continuous analysis, there was a 4% increase (HR = 1.04, 95% CI, 1.01–1.07, \(P = 0.02\)) in the pooled rate of CV outcomes per 10 mm Hg increase in exercise systolic BP after adjustment for office BP, age, and other CV risk factors (Figure 3, upper panel).

\textbf{Exercise BP and CV outcomes: maximal intensity exercise}

The systolic BP at maximal workloads was not significantly associated with an increased rate of CV outcomes,
### Table 1. Continued.

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>Reference group</th>
<th>Hypertensive response to exercise (HRE)</th>
<th>Variables in multivariate models</th>
<th>Included in meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Categorical</td>
<td>Mod: SBP ≤ 146 mmHg Max: SBP ≤ 160 mmHg</td>
<td>Mod: SBP &gt;180 mmHg Max: SBP &gt; 200 mmHg</td>
<td>Age, sex, office BP, T2DM, LDL, HDL, triglycerides, smoking, BMI, family history.</td>
</tr>
<tr>
<td>2</td>
<td>Categorical</td>
<td>Mod: ≤ 80th percentile (≤ 180 mm Hg)</td>
<td>Mod: &gt; 80th percentile (&gt; 180 mm Hg)</td>
<td>Age, sex, office BP, BMI, T2DM, current smoking, total HDL, VHD, ECG LVH, exercise test variables.</td>
</tr>
<tr>
<td>3</td>
<td>Categorical</td>
<td>Max: SBP &lt; 171 mm Hg Max: SBP &gt; 200 mm Hg</td>
<td>Age, BMI, office BP, treadmill time, cholesterol, glucose, CV family history, ECG changes, smoking.</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Categorical</td>
<td>Max: 115–185 mm Hg Max: &gt;230 mm Hg</td>
<td>Age, office BP, year, antihypertensives, alcohol, smoking, LDL, HDL, T2DM, BMI, exercise ischaemia LVH, VO2max, HR, energy expenditure of physical activity.</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, examination years, alcohol consumption, smoking, LDL, T2DM, BMI.</td>
</tr>
<tr>
<td>6</td>
<td>Categorical</td>
<td>Mod: SBP &lt; 200 mmHg Mod: SBP ≥ 200 mmHg</td>
<td>Age, office BP, exercise capacity, smoking, HR, BMI, cholesterol, triglycerides, glucose.</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, office BP, exercise capacity, smoking, HR, cholesterol, glucose tolerance.</td>
</tr>
<tr>
<td>8</td>
<td>Categorical</td>
<td>Mod: SBP &lt;190 mm Hg Mod: SBP &gt; 230</td>
<td>Age, office SBP, BMI, exercise SBP, baseline HR, LVH, smoking, total cholesterol and sports activities.</td>
<td>No (no CI reported)</td>
</tr>
<tr>
<td>9</td>
<td>Categorical</td>
<td>Mod SBP ≤ 215 mm Hg Mod SBP &gt; 215 mm Hg</td>
<td>Age, sex, BMI, smoking, family history, physical work capacity, self-reported elevated cholesterol and abnormal glucose.</td>
<td>No (not adjusted for office BP)</td>
</tr>
<tr>
<td>10</td>
<td>Categorical</td>
<td>Mod SBP ≤ 215 mm Hg Mod SBP &gt; 215 mm Hg</td>
<td>Age, sex, office BP, BMI, smoking, family history, physical work capacity, self-reported elevated cholesterol and abnormal glucose.</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, office BP, BMI, smoking and total cholesterol.</td>
</tr>
<tr>
<td>12</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, age squared, office BP.</td>
</tr>
</tbody>
</table>

Abbreviations: Max, maximal; Mod, moderate; CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; SD, standard deviation; AMI, acute myocardial infarction; ECG, electrocardiogram, LVH, left ventricular hypertrophy; HR, heart rate; w, watts.

*Estimated continuous trend (see methods)
whether analyzed as a categorical (HR = 1.49, 95% CI, 0.90–2.46, \( P = 0.12 \)) or a continuous (HR = 1.01, 95% CI, 0.98–1.04, \( P = 0.53 \)) variable after adjustment for office BP, age, and other CV risk factors (Figures 2 and 3, lower panels, respectively).

**Subgroup analyses: cycle ergometer exercise modality**

Studies utilizing cycle ergometers under moderate exercise workloads\(^{17,20,24}\) showed a significant 6% increase in the rate of CV outcomes (HR = 1.06, 95% CI, 1.01–1.12, \( P = 0.02 \)) for each increase of 10 mm Hg in systolic BP. Under maximal workloads\(^{21,25,26}\) there was a nonsignificant 3% increase in the rate of CV outcomes (HR = 1.03, 95% CI, 0.97–1.09, \( P = 0.35 \)).

**Publication bias**

It was difficult to assess publication bias with the relatively small number of individual studies included in each analysis. However, funnel plots (Figure 4) and Egger’s test indicated a relative absence of any publication bias in the continuous models, with some potential for bias in the categorical models, particularly at maximal exercise workloads.

**DISCUSSION**

In this study, comprising data from 46,314 individuals followed for a mean of 15 years, we have demonstrated that an HRE at a moderate exercise workload predicts CV outcomes independently of office BP, age, or multiple CV risk factors. To our knowledge, this is the first comprehensive evaluation of the literature and first presentation of robust pooled risk estimates for the prognostic value of an HRE. These findings highlight the importance of determining the pathophysiological mechanisms underlying an HRE.

Current guidelines for the management of hypertension provide no information about the diagnosis, management, or potential clinical utility of identifying an HRE.\(^{14,27}\) One of the main issues in interpreting the findings of studies of
an HRE is the disparate nature of the research used in them. Within the published literature are a wide variety of study designs, outcome measures, exercise modalities, exercise intensity (at which BP is measured), and participant characteristics (including patient populations with or without established coronary artery disease). Thus, the clinical relevance of an HRE is not easily determined. The strength of the present study is that we used only adjusted risk estimates for our pooled analysis, which allowed us to determine the independent prognostic value of an HRE at both moderate and maximal-intensity workloads.

**Exercise intensity and the prognostic value of an HRE**

In the present study, an HRE at moderate, but not maximal, exercise workloads was predictive of CV outcomes. The pooled HR for predicting CV outcomes with maximal exercise was 1.49 (see Figure 2), which could indicate a trend toward biological relevance. On the other hand, the lack of significance could have been related to low statistical power as a result of the relatively small number of studies available for pooled analysis at maximal exercise workloads. Alternatively, measurement of BP during exercise is challenging and may lead to the recording of unreliable values, especially during high-intensity exercise, in which noise and movement artefact pose problems. This may be particularly applicable to treadmill exercise, given our observation of a greater prognostic value of systolic BP measured during cycle ergometry at moderate intensity. There may also be difficulties in determining whether a true maximal exercise workload was reached in an exercise test, and the sudden stopping of an exercise test (by the patient or physician) in its early phase, after an increase in the grade of exercise intensity, limits the time available for recording a maximal BP. These deficiencies may create errors that limit the clinical utility and prognostic value of BP measurements made at high workloads.

However, under the more stable conditions of exercise at moderate intensity, or during cycle ergometry, the limitations described above may be less influential, allowing for greater precision in BP measurement. Furthermore, given that individuals may spend a large proportion of each day in an ambulatory state, exercise BP at a moderate workload is perhaps more akin to the values of BP encountered in ordinary daily activity and therefore more representative of the chronic BP than is the maximal or office BP or both. With this regard, an HRE during exercise of light to moderate intensity could be indicative of uncontrolled BP. Indeed, we have previously shown that systolic BP measured during light to moderate exercise predicts the presence of masked hypertension with high specificity in individuals with an HRE.28 There is also a greater prevalence of masked hypertension (up to 58 %) among individuals with an HRE.29

Masked hypertension is associated with an increased risk of mortality and the future development of sustained hypertension,30 and this may explain the increased CV risk associated with an HRE at moderate exercise workloads. None of the studies included in our meta-analysis recorded out-of-office BP, and further work is required to ascertain the exact cause of the increased CV risk associated with an HRE.

### Figure 2.
Pooled hazard ratios and 95% confidence intervals for a hypertensive response to exercise at moderate (upper panel) and maximal (lower panel) exercise workloads, adjusted for age, office blood pressure and multiple cardiovascular risk factors. Moderate P-value = 0.039, I² = 51.8%. Maximal P-value=0.12, I² = 65.0%.
Exercise, Blood Pressure, and Cardiovascular Outcomes

What is the underlying physiology of a hypertensive response to exercise?

The mechanisms underlying an excessive increase in systolic BP with exercise are unknown. Although an HRE is likely to be multifactorial, a possible causative factor is the stiffening of large arteries that occurs with the aging process or which is accelerated in disease states. Under resting conditions, increased large artery (aortic) stiffness is an independent predictor of mortality, and is strongly related to elevated arterial BP. A reduction in aortic compliance during exercise will reduce the buffering capacity of BP and may result in an abnormal increase in systolic BP. Alternatively, structural abnormalities in the peripheral vasculature or an inability of the peripheral vasculature to appropriately vasodilate and allow peripheral runoff of increased blood flow could also increase BP during exercise. Indeed, some studies have shown impaired endothelial function to be associated with an HRE. Additionally, increased levels of serum cholesterol and insulin resistance have been shown to positively correlate with changes in BP with exercise, but not at rest. These metabolic impairments may hinder vascular reactivity during exercise and increase vascular resistance, also leading to an HRE. Physical fitness may also be an important factor, because it is related to insulin resistance and exercise BP responses. However, more work is needed to elucidate the exact physiological mechanisms of an HRE.

Our study has several limitations. Rather than acquiring individual patient data from each of the studies, we relied on published aggregate data to calculate our pooled risk estimates. Subsequently, it was not possible to correct for all potential biases, such as the use of antihypertensive medications or fitness levels. Additionally, only a small number of studies met the inclusion criteria for our meta-analysis, which made it difficult to assess publication bias in a robust manner, and the meta-analysis included a predominance of male-only cohort studies, which may limit the generalizability of the study findings to females. Besides this, many of the studies included participants with a clinical indication for exercise stress testing, preventing generalization of the results of the meta-analysis beyond this population. Lastly, the significant heterogeneity in design of the studies included in the meta-analysis prevented the designation of a standard cutoff value as denoting either an HRE or the establishment of normal reference values for exercise-related BP through comparison of the HRs in the categorical analyses in our study. This problem can be overcome with individual data-point analysis in future work. In any case,
The present study is significant because it is the first systematic review and meta-analysis of the prognostic value of an HRE for predicting CV outcomes. We have shown that an excessive increase in systolic BP recorded during moderate exercise workloads predicts CV outcomes independent of age, office BP, or other CV risk factors. Therefore, an abnormal increase in systolic BP with exercise may act as

Figure 4. Funnel plots representing the publication bias for individual studies from each analysis group (categorical, upper panels; continuous, lower panels) and for the different exercise workloads (moderate, left panels; maximal, right panels) included in the meta-analyses done in the study. Results depict a relative absence of publication bias in the continuous models, with some potential for bias in the categorical model at maximal exercise workload.

the principal findings of the present review and meta-analysis are valid because the cutoff values used to denote HRE were representative of the highest category of exercise systolic BP (typically the highest quintile or quartile), and the reference value was the lowest category of exercise systolic BP in each study, which was reflective of a normotensive response to exercise.
a forewarning to clinicians of increased CV risk, irrespective of office BP. However, further studies are required to determine the physiological mechanisms and reasons for increased mortality in people with an HRE.

ACKNOWLEDGMENTS

Dr. Sharman was supported by a National Health and Medical Research Council of Australia Career Development Award.

REFERENCES


