Research Letter

Relation of maximal systolic blood pressure during exercise testing to the risk of sudden cardiac death in men with and without cardiovascular disease

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Sudden cardiac death (SCD) remains a global public health problem, despite the recent development of effective antiarrhythmic agents and population-based risk prediction algorithms.[1,2] High blood pressure or hypertension is an established risk factor for SCD.[2,3] Furthermore, disproportionate increases in systolic blood pressure (SBP) in response to acute physical and/or psychological stressors are associated with an increased risk of cardiovascular events.[4]

SBP during exercise testing provides an index of blood pressure reactivity during daily physical activities.[5] An exaggerated SBP (ESBP) response to exercise testing is associated with an increased risk of cardiovascular mortality in healthy individuals,[5,6] with a more favorable prognosis in hypertensive patients and those with known or suspected coronary artery disease.[7] However, it remains unclear whether an ESBP response to maximal exercise testing is directly or inversely related to the risk of SCD in men with and without a history of cardiovascular disease (CVD). We tested the hypothesis that an ESBP response to maximal exercise testing may be associated with contrasting rates of SCD in men with and without a history of CVD.

The sample included participants from an ongoing prospective population-based cohort study in eastern Finland (the Kuopio Ischemic Heart Disease Study: KIHD), designed to investigate risk factors for CVD and related, long-term health outcomes. The present analysis evaluated 2,410 men (aged 42-61 years) who had undergone baseline medical examinations between 1984 and 1989, including participants with (n=884) and without CVD (n=1,526).

Exercise blood pressure was manually determined using a standard cuff/stethoscope during progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The peak SBP, expressed as millimeters of mercury (mmHg), was the highest value achieved during the exercise test. Although many studies have employed arbitrary thresholds to designate an ESBP at peak exercise, we used the criteria of the American Heart Association, that is, SBP ≥210 mmHg.

SCD was defined as a fatal event that occurred within 1 hour after the onset of symptoms or within 24 hours when autopsy data did not reveal a non-cardiac cause of SCD or after a fatal cardiac arrest following successful resuscitation from ventricular tachycardia and/or ventricular fibrillation. Data on SCDs were obtained from interviews with family members, hospital records, death certificates, autopsy reports and medico-legal documents.

We used Cox proportional hazard models adjusted for age, body mass index, resting SBP, cigarette smoking, alcohol intake, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, family history of heart disease, diabetes, and directly measured maximal oxygen uptake (cardiorespiratory fitness, CRF) to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of ESBP (SBP ≥210 mmHg) for SCD. Statistical significance was set at $P<0.05$ and analyses were conducted using SPSS version 21.0 (SPSS, Armonk, NY).

During a median 25-year follow-up, 226 SCDs occurred. In analysis adjusted for several potential confounders, compared with men who had a normal SBP response to exercise testing, men with an ESBP did not exhibit an increased risk of SCD in the entire cohort (HR 1.16, 95% CI 0.86-1.57). However, an increased risk of SCD was observed

with an ESBP in men without a history of CVD (HR 1.73, 95% CI 1.07-2.82), whereas the direction of effect was reversed but not significant in men with a history of CVD (HR 0.92, 95% CI 0.60-1.41) (Table 1). The Kaplan-Meier survival analysis, illustrated in Figure 1, demonstrated a differential survival rate of SCD in men with and without a history of CVD ($P<0.05$ for log rank test).

Because SCD remains a major public health problem, identifying independent and additive risk factors may help in the development and validation of prediction models to reduce the risk of SCD in the general population.[1] We found a differential effect of an ESBP on SCD outcomes in men with and without a history of CVD, and this remained after adjusting for potential confounding variables, including resting SBP and CRF.

To our knowledge, this is the first long-term study to report a heightened risk of SCD associated with an ESBP response to exercise testing in men without a history of CVD. The results were not significant in men with a history of CVD. These findings suggest that an ESBP response during exercise testing may need to be interpreted differentially in these population groups. We previously reported that an elevated SBP during recovery from exercise was related to the risk of SCD in the general population,[8] whereas an exaggerated SBP response during exercise was associated with a lower risk of SCD in patients with known or suspected coronary artery disease.[9] However, this was not statistically significant.

Although the reasons for differing outcomes of an ESBP on the risk of SCD between men with and without a history of CVD remain unclear, there are several possible explanations. An ESBP response to exercise may contribute to autonomic imbalance and endothelial dysfunction, inflammation, arterial stiffening, and the development of future

hypertension, all of which are risk factors for SCD in men without a history of CVD.[5] Conversely, populations with a high burden of CVD may not be capable of generating the inotropic reserve or myocardial contractility to permit the necessary increases in cardiac output and SBP during vigorous exercise.[10] In a cohort of 1,586 cardiac men, researchers reported a negative correlation between the maximal SBP during treadmill exercise testing and the annual rate of SCD.[11] The annual rate of SCD decreased from 97.9 per 1,000 men to 25.3 and 6.6 per 1,000 men as the range of maximal SBP increased from <140 to 140 to 199 to ≥200 mmHg, respectively. Cardiomegaly, Q waves on the resting ECG, persistent post-exercise ST-depression, 2 or 3 vessel coronary disease, reduced ejection fraction, or combinations thereof, were most common in men with the lowest SBP values at maximal exercise. Whilst an abnormal exercise blood pressure response (decrease in or failure to increase maximal SBP with exercise) may be amenable to treatment following cardiac rehabilitation in two thirds of 651 patients with heart failure,[12] future studies are needed to clarify the exact underlying mechanisms and the factors affecting resolution of the differential relation between an ESBP and the risk of SCD in men with and without a history of CVD.

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Author Contributions

All authors contributed to the conception and design of the study. JAL and SK contributed to the data acquisition. SYJ, SK and JAL contributed to the analysis, or interpretation of data for the study. SYJ, JAL, SKK, SK and BAF designed the methodoligical approach, collaborated on the statistical analyses, and drafted the manuscript. All authors provided critical scientific and editorial contributions to the manuscript draft. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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Table 1. Hazard ratio (HR) and 95% confidence interval (CI) for risk of SCD by ESBP in men with and without a history of cardiovascular disease.

Variables	226 SCD N (%)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Full cohort			
<210mmHg	128 (9.5%)	1 (ref)	1 (ref)
≥210mmHg	98 (9.2%)	1.09 (0.83-1.43)	1.16 (0.86-1.57)
Men without a history of CVD			
<210mmHg	32 (4.1%)	1 (ref)	1 (ref)
≥210mmHg	58 (7.7%)	1.96 (1.23-3.04)	1.73 (1.07-2.82)
Men with a history of CVD			
<210mmHg	96 (16.8%)	1 (ref)	1 (ref)
≥210mmHg	40 (12.8%)	0.77 (0.53-1.13)	0.92 (0.60-1.41)

CI, confidence interval; CVD, cardiovascular disease; ESBP, exaggerated systolic blood pressure; HR, hazard ratio; SCD, sudden cardiac death. Model 1: Adjusted for age, body mass index, smoking, alcohol intake, family history of heart disease, diabetes, and (history of CVD when exposed for full cohort). Model 2: model 1 plus resting systolic blood pressure and maximal oxygen uptake.

Figure 1. Differential pattern of the Kaplan-Meier survival curves for SCD by ESBP in men with and without a history of cardiovascular disease.