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Original article

Variable prognostic value of blood pressure response to exercise

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ABSTRACT

Aim: The aim of this study was to evaluate the impact of patient background including exercise capacity on the relationship between the blood pressure (BP) response to exercise and prognosis in patients visiting a cardiovascular hospital.

Methods: A total of 2134 patients who were referred to our hospital underwent symptom-limited maximal cardiopulmonary exercise testing, and were followed through medical records and mail. The BP response to exercise was defined as the difference between peak and rest systolic BP. The end point was set as cardiovascular events including cardiovascular death, acute coronary syndrome, hospitalization for heart failure, and cerebral infarction.

Results: During a median follow-up period of 3 years, 179 (8%) patients reached the end point (2.5%/year). Multivariate analysis showed that BP response was independently and negatively associated with the occurrence of the end point. This prognostic significance of BP response was consistent regardless of left ventricular ejection fraction, renal function, presence of heart failure symptoms, the presence of organic heart disease, and hypertension. However, peak VO_2 showed a significant interaction with the effects of BP response on the end point, suggesting that the prognostic value of BP response was limited in patients with preserved exercise capacity.

Conclusions: The role of BP response to exercise as the predictor depends on exercise capacity of each patient.

Introduction

Physiological responses to exercise provide vital information about the capacity of the heart, lung, and exercising muscle, and can aid in understanding a patient comprehensively and therefore be good prognostic predictors [1]. The blood pressure (BP) response to exercise is one such factor, and BP increases according to increments in exercise intensity [2], reflecting the performance of cardiac pump; having an ability of producing blood flow and pressure [3]. The prognostic role of the BP response to exercise has been previously investigated; however, there seems to be inconsistencies in the interpretation of data among the study cohorts. Although most studies involving relatively younger and healthy persons showed that the increase in BP during exercise was positively and independently associated with the incidence of hypertension [4] and the occurrence of cardiovascular events [5–7], studies involving patients with heart failure (HF) or with suspected/diagnosed cardiovascular disease showed an inverse association [8–14]. The apparent inconsistencies raise the hypothesis that the prognostic value of BP response might vary according to patient background. Moreover, whether the impact of BP response is same irrespective of exercise tolerance remains unknown. To test this hypothesis, we investigated the prognostic impact of the BP response to exercise in a wide variety of patients who visited cardiovascular hospital and determined the interaction effects with various clinical background including exercise tolerance.

Methods

The cohort of the present study was retrieved from the Shinken Database, which was established in 2004 and documents all patients who newly visited our hospital. All registered patients gave written informed consent after being provided a description of the study requirements. The local ethics committee of our

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institute approved this study. As of 2013, the database included a total of 22,230 patients. The details of the database have been reported previously; all data about patient health status, incidence of cardiovascular events, and mortality are stored in the database connected to electronic medical records [15]. All events were ascertained by exchanging letters with each patient/patient's family or medical records. Of the total, 2134 patients who underwent symptom-limited maximal cardiopulmonary exercise testing (CPET) from 2004 to 2013 were analyzed.

The cardiovascular status of each patient in the present study was evaluated with electrocardiography, chest radiography, blood test, echocardiography, and exercise testing at the initial visit. Information on structural heart diseases was also obtained through magnetic resonance imaging or computed tomography, when available. Valvular disease was defined as valvular dysfunction of more than moderate grade, irrespective of its primary or secondary cause. The baseline patient characteristics, including age, sex, height, body weight, cardiovascular diseases, and medications, were obtained together with cardiovascular risk factors, which were defined in the present study as follows: hypertension, use of antihypertensive drugs, systolic BP $\geq$140 mmHg or diastolic BP $\geq$90 mmHg, diabetes mellitus, use of hypoglycemic drugs or insulin or glycosylated hemoglobin $\geq$6.5%, dyslipidemia, use of statins, low-density lipoprotein $\geq$140 mg/dL, high-density lipoprotein $\leq$40 mg/dL, or fasting triglyceride $\geq$150 mg/dL. The estimated glomerular filtration rate (eGFR) was calculated by using the Japanese Society of Nephrology formulas for Japanese persons [16]: $194 \cdot \text{serum creatinine}^{-1.094} \cdot \text{age}^{-0.287}$ for men and $194 \cdot \text{serum creatinine}^{-1.094} \cdot \text{age}^{-0.287} \cdot 0.739$ for women.

All patients underwent maximal incremental CPET on an upright cycle ergometer within 3 months after the initial visit, with a protocol of 10–20 watts/min continuous ramp after a 4-min period of rest and a 4-min period of unloaded exercise (Mitsubishi Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan), with electrocardiogram and BP monitoring. Expired gas analysis was performed by the breath by breath method (AE-310S; Minato Medical Science, Osaka, Japan). Peak VO_2 was defined as the highest O_2 uptake value, as averaged over 30 s during the last minute of the symptom-limited exercise. As a marker of ventilatory efficiency, the VE-VCO_2 slope was calculated as the slope of the linear regression analysis from the start of exercise to just before the respiratory compensation point. BP response was calculated by subtracting the resting systolic BP from the peak systolic BP.

The end point was set as cardiovascular events including cardiovascular death, hospitalization for HF, acute coronary syndrome, and cerebral infarction. The time interval from the date of CPET to cardiovascular events was defined as the duration of follow-up. All end points were censored in March 2015.

SPSS version 19 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant. All continuous, normally distributed measurements are summarized as mean $\pm$ standard deviation and non-normally distributed data are summarized as median (first, fourth quartile). Categorical data are reported as percentages. Univariate and multivariate Cox regression models were developed for the evaluation of the impact of the BP response to exercise on the end point, with adjustments for confounding factors related to the outcome. Additionally, we created binary or ternary categories concerning left ventricular ejection fraction (LVEF), $\geq$50% vs. <50%; HF symptom (present vs. absent), organic heart disease (present vs. absent), and hypertension (present vs. absent); eGFR, >55 mL/min vs. $\leq$55 mL/min (median value); peak VO_2 divided into tertiles, <17, 17–23, $\geq$23 mL kg^{-1} min^{-1}; VE-VCO_2 slope divided by the generally used cut-off value, <35 vs. $\geq$35; and use/nonuse of β-blocker, renin–angiotensin–aldosterone (RAS) inhibitor and calcium antagonist. To test the statistical significance of the predictive power of BP response in these subclinical categories, Cox regression analysis was employed in each category, with adjustments for age and sex. The interaction was also tested in Cox regression models creating the multiplicative interaction term, in which a value of $p < 0.05$ was considered statistically significant. After deciding the cut-off value of BP response for the end point by using the receiver operating curve, a Kaplan–Meier curve was drawn for depicting the discriminative power of the binary BP response tested by using the log-rank test.

Results

The clinical characteristics of the study patients are shown in Table 1. Most patients were men; approximately half of the patients had organic heart diseases; and the prevalence of HF was 37%. Hypertension and diabetes mellitus was observed in 44% and 16% of the patients, respectively. The mean LVEF and eGFR was 61% and 56 mL/min, respectively. The exercise characteristics are shown in Table 2. The average peak respiratory exchange ratio was 1.13, indicating enough volume of exercise. The BP response to exercise showed a normal distribution. The mean value was 64 mmHg, and the 20th and 80th percentiles were 40 and 90 mmHg, respectively.

Table 1
Clinical characteristics.

Variables	Value
Age (years)	57 ± 13
Male (%)	70
AF (%)	14
HT (%)	44
DLP (%)	31
DM (%)	16
Body mass index (kg/m^2)	23.3 ± 3.5
Ischemic heart disease (%)	19
Cardiomyopathy (%)	8
Valvular disease (%)	13
History of valvular surgery (%)	12
Heart failure (%)	37
eGFR (mL/min)	56 ± 17
BNP (pg/mL)	87 (31–250)
LVEF (%)	61 ± 15
β-Blocker (%)	23
RAS inhibitor (%)	29
Calcium antagonist (%)	12

AF, atrial fibrillation; HT, hypertension; DLP, dyslipidemia; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; RAS inhibitor, renin–angiotensin–system inhibitor.

Table 2
Exercise characteristics of the study patients.

Variables	Value
Peak VO_2 (mL kg^{-1} min^{-1})	20.9 ± 6.9
VE-VCO_2 slope	29.8 (26.3–33.9)
Peak RER	1.13 ± 0.08
Resting heart rate (bpm)	78 ± 14
Peak heart rate (bpm)	142 ± 31
Resting systolic BP (mmHg)	124 ± 22
Peak systolic BP (mmHg)	188 ± 37
BP response (mmHg)	
Mean ± SD	64 ± 28
20th percentile	40
80th percentile	90

Peak VO_2, peak oxygen consumption; VE-VCO_2 slope, slope of minute ventilation to carbon dioxide production; RER, respiratory exchange ratio; bpm, beats per minute; BP, blood pressure; SD, standard deviation.

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