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# Prognostic Significance of Post-Exercise Blood Pressure Response in Patients With Dilated Cardiomyopathy

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**Abstract**

***Background and Objectives***. The occurrence of an abnormal cardiovascular response during exercise in patients with chronic heart failure is well known. Post-exercise blood pressure response is also useful in assessing the severity of heart failure and impaired exercise capacity. This study evaluated the prognostic significance of post-exercise blood pressure response in patients with dilated cardiomyopathy.

***Methods***. Thirty patients with dilated cardiomyopathy (left ventricular ejection fraction: 32±9%) were studied and the relationship between post-exercise blood pressure response and cardiac events (sudden death, heart failure death and readmission for heart failure) were evaluated. The post-exercise blood pressure response was defined as PBP3 (systolic blood pressure at 3 min after exercise divided by peak systolic blood pressure during exercise).

***Results***. Seven cardiac events (one sudden death, two deaths for heart failure and four readmissions from heart failure) were observed during the follow-up period (3.3±1.8 years). The PBP3 in patients with these cardiac events was higher than that in patients without cardiac events (0.95±0.09 vs 0.84±0.10, $p<0.05$). The area under the curve for the receiver-operating characteristic curve with PBP3 used to predict the cardiovascular events was 0.79 (95% confidence interval: 0.62–0.97, $p=0.02$).

***Conclusions***. Post-exercise blood pressure response is a simple and useful predictor of adverse cardiac events in patients with dilated cardiomyopathy.

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**Key Words**
■Heart failure ■Cardiomyopathy, dilated ■Exercise tests ■Prognosis ■Blood pressure

## INTRODUCTION

The prognosis for patients with heart failure remains poor, despite improved treatments. Therefore, classification of patients with heart failure according to risk is important for timely consideration of further intervention including heart transplantation. Several parameters, including left ventricular function, exercise capacity, and neurohormonal factors, have been established as prognostic indicators for patients with chronic heart failure[1–4].

In patients with chronic heart failure, exercise capacity is limited by inadequate oxygen transport to the working skeletal muscle due to reduced cardiac output during exercise. Furthermore, cardiovascular response after exercise is important in patients with chronic heart failure[5–10]. In particular, delayed recovery of blood pressure after exercise reflects impaired exercise capacity and disease

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severity in patients with chronic heart failure secondary to left ventricular systolic dysfunction[5]. The measurement of this post-exercise blood pressure response is simple and useful in daily clinical practice. However, the prognostic significance of post-exercise abnormal blood pressure response in patients with dilated cardiomyopathy is unresolved.

The present study investigated the significance of the post-exercise blood pressure response for risk evaluation in patients with dilated cardiomyopathy.

## SUBJECTS AND METHODS

Thirty patients (58 ± 11 years old) with dilated cardiomyopathy (left ventricular ejection fraction: 32 ± 9%) were studied. Twenty-seven patients had New York Heart Association (NYHA) class II functional capacity and three patients had class III functional capacity at diagnosis. Medical history, physical examination, routine blood test, chest radiography, standard electrocardiography, exercise stress test, and cardiac catheterization, including coronary angiography and biplane left ventriculography, were investigated for all patients. Patients with acute myocarditis, significant coronary artery stenosis or valvular disease were excluded. Patients with NYHA class IV functional capacity and/or atrial fibrillation were also excluded in this study.

### Cardiopulmonary exercise test

All patients underwent symptom-limited cardiopulmonary exercise testing, which was performed on an upright bicycle ergometer. Exercise workload was increased by the ramp incremental protocol of 15 W/min after a 1 min warm-up at 0 W. All patients stopped exercise due to either dyspnea or leg fatigue, perceived as 18 on the Borg scale. The electrocardiographic findings and blood pressure measured by sphygmomanometer were recorded at rest, at every minute during exercise, and for 5 min after exercise.

The expired gas was measured on a breath-by-breath basis during the exercise testing with a respiromonitor AE280 (Minato Medical Electronics) connected to a personal computer equipped with analyzing software. The system was calibrated carefully before each study.

### Post-exercise blood pressure response

Post-exercise blood pressure response (PBP3) was defined as the systolic blood pressure at 3 min after exercise divided by the peak systolic blood pressure during exercise.

### End-points

Follow-up was carried out from the time of cardiopulmonary exercise test, using available medical records and telephone interviews with the patients and/or referring physicians. The specified end-points were sudden death, death related to heart failure, and rehospitalization for heart failure.

### Statistical analyses

Unpaired $t$ and Fisher's exact tests were used for comparison of patients with or without cardiac events. Odds ratio and 95% confidence interval (CI) were calculated by use of the Cox proportional-hazard regression model. The predictive significance of PBP3 was studied using the receiver-operating characteristic (ROC) curve. Results are expressed as the area under the curve and 95% CI for this area. A $p$ value $< 0.05$ was considered statistically significant.

## RESULTS

### Basic characteristics

During the follow-up period (3.3 ± 1.8 years), seven cardiac events were observed: one sudden death, two heart failure deaths, and four rehospitalization for heart failure. The basic characteristics of the patients with or without events are shown in **Table 1**. Baseline left ventricular ejection fraction and medications were not significantly different between the two groups, although left ventricular end-diastolic pressure and mean pulmonary artery pressure were significantly higher in the patients with cardiac events than in those without events.

### Blood pressure response during and after cardiopulmonary exercise test

The results of the cardiopulmonary exercise tests are shown in **Table 2**. There were no significant differences in indices such as peak oxygen consumption and the slope of the per minute ventilation in relation to the per minute production of carbon dioxide between the two groups, although patients with cardiac events showed a relatively poor exercise capacity compared to those without events.

Blood pressure during the cardiopulmonary exercise tests is also shown in **Table 2**. Although blood pressure during and after exercise did not differ significantly between the two groups, PBP3 in patients

**Table 1 Basic characteristics of the patients**

| Variable | Cardiovascular events | | *p* value |
|---|---|---|---|
| | Yes ($n$=7) | No ($n$=23) | |
| Age (yr) | 54±17 | 59±7 | NS |
| Female | 2(29) | 6(26) | NS |
| NYHA class (II/III) | 5/2 | 20/3 | NS |
| Hemodynamic findings | | | |
| LVEF (%) | 30±11 | 32±8 | NS |
| LVEDV index (ml/m$^2$) | 188±55 | 154±54 | NS |
| LVESV index (ml/m$^2$) | 133±48 | 107±48 | NS |
| LVEDP (mmHg) | 21±10 | 11±6 | 0.007 |
| PCW (mmHg) | 15±11 | 9±5 | NS |
| Mean PA (mmHg) | 26±15 | 17±6 | 0.03 |
| RVEDP (mmHg) | 11±6 | 7±3 | NS |
| Mean RA (mmHg) | 7±6 | 6±4 | NS |
| Cardiac index (l/min/m$^2$) | 2.1±0. | 2.3±0.5 | NS |
| Medication | | | |
| Diuretics | 7(100) | 22(96) | NS |
| ACE inhibitor | 7(100) | 22(96) | NS |
| Digitalis | 5( 71) | 16(70) | NS |
| Beta-blocker | 3( 43) | 13(57) | NS |

Continuous values are mean±SD. ( ): %.
NYNA=New York Heart Association; LV=left ventricular; EF=ejection fraction; EDV=end-diastolic volume; ESV=end-systolic volume; EDP=end-diastolic pressure; PCW=pulmonary wedge pressure; PA=pulmonary artery pressure; RV=right ventricular; RA=right atrium pressure; ACE=angiotensin converting enzyme.

**Table 2 Cardiopulmonary exercise test**

| | Cardiovascular events | | *p* value |
|---|---|---|---|
| | Yes ($n$=7) | No ($n$=23) | |
| Peak power (W) | 88±21 | 98±26 | NS |
| Blood pressure response (mmHg) | | | |
| Rest | 119±23 | 124±12 | NS |
| Peak exercise | 150±32 | 171±23 | NS |
| Three min after exercise | 142±31 | 142±15 | NS |
| PBP3 | 0.95±0.09 | 0.84±0.10 | 0.01 |
| Heart rate (beats/min) | | | |
| Rest | 74±13 | 83±10 | 0.04 |
| Peak exercise | 131±34 | 140±17 | NS |
| Three min after exercise | 91±26 | 99±14 | NS |
| Peak oxygen consumption (ml/min/kg) | 16±4 | 18±4 | NS |
| Anaerobic threshold (ml/min/kg) | 11±2 | 11±2 | NS |
| Slope of per minute ventilation/carbon dioxide output | 36±9 | 31±6 | NS |

Values are mean±SD.
PBP3=systolic blood pressure at 3 min after exercise divided by the peak systolic blood pressure during exercise.

**Table 3 Multivariate analysis of prognostic predictors**

| Variable at diagnosis | Odds ratio(95% CI) | *p* value |
|---|---|---|
| Age | 0.97(0.84−1.13) | 0.71 |
| Peak oxygen consumption | 0.89(0.62−1.31) | 0.57 |
| PBP3 | 1.63(0.03−2.59) | 0.04 |
| LVEF | 0.82(0.59−1.14) | 0.05 |
| LVEDP | 2.24(0.99−5.08) | 0.05 |
| Mean PA | 0.56(0.31−1.02) | 0.06 |

CI=confidence interval. Other abbreviations as in Table 1.

with cardiac events was higher than that in patients without cardiac events.

### Analysis of clinical predictors of cardiac events

Multivariate analysis, including age, peak oxygen consumption, PBP3, left ventricular ejection fraction, left ventricular end-diastolic pressure, and mean pulmonary artery pressure, was performed (**Table 3**). Among these parameters, PBP3 was the only significant predictor. The ability of PBP3 to predict the cardiovascular events was assessed with the ROC curve(**Fig. 1**). The area under the curve for the ROC curve with PBP3 used to predict the cardiovascular events was 0.79(95% CI: 0.62−0.97, $p=0.02$). PBP3 of 0.85 had a sensitivity of 71% and specificity of 44% for the prediction of cardiovascular events in patients with dilated cardiomyopathy.

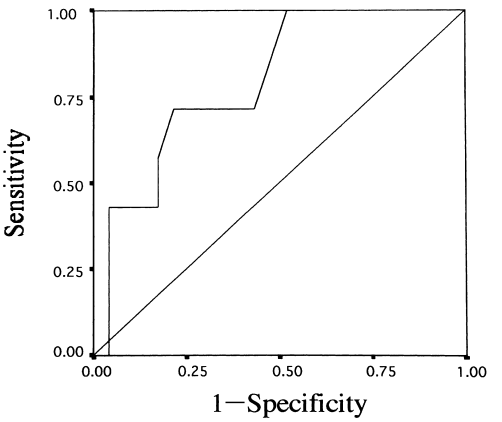


**Fig. 1 Area under the curve for the receiver-operating characteristic curve with PBP3 used to predict the cardiovascular events**
Abbreviation as in Table 2.

## DISCUSSION

The present study demonstrates that PBP3 is a simple and useful prognostic indicator for patients with chronic heart failure secondary to dilated cardiomyopathy.

### Abnormal blood pressure response in patients with chronic heart failure

Hemodynamic abnormalities during exercise may occur in patients with heart disease[10−14]. A normal increase in systolic blood pressure during exercise was found in patients with only mildly impaired exercise capacity and an attenuated increase in systolic blood pressure in those with severely impaired exercise capacity[13]. Low maximal exercise systolic blood pressure was a predictor of mortality in patients with previous myocardial infarction[15]. Patients with maximal exercise systolic blood pressure of $\leq 140$ mmHg had a significantly higher mortality rate over 3 years compared with patients with higher level of maximal exercise systolic blood pressure. The integration of systolic blood pressure and peak oxygen consumption improved the prognostic value of each indicator in patients with chronic heart failure[16]. Therefore, peak blood pressure is a significant prognostic predictor, but impairments in hemodynamics are relatively mild during exercise in patients with mild to moderate heart failure, such as the patients in our study. Peak oxygen consumption also was not significantly different in our patients because almost all patients had mildly impaired exercise capacity. Therefore, further markers are needed to establish the prognosis.

Blood pressure response after exercise has been investigated, mainly in patients with ischemic heart disease[17−20]. Post-exercise blood pressure response was more sensitive than electrocardiographic changes in identifying patients with coronary artery disease. Also, cardiovascular response after exercise is important in patients with chronic heart failure[5−10]. In particular, we have shown that the measurement of blood pressure response after exercise is simple and useful in assessing exercise capacity and disease severity in patients with chronic heart failure secondary to left ventricular systolic dysfunction[5]. However, there is little information regarding prognostic significance of this abnormal post-exercise blood pressure response in patients with chronic heart failure.

**Mechanism and significance of abnormal PBP3 in patients with chronic heart failure**

In this study, we used the 3-minute systolic blood pressure ratio(PBP3)to evaluate postexercise systolic blood pressure response[5,19]. PBP3 was found to be useful for predicting the outcome of patients with chronic heart failure secondary to dilated cardiomyopathy. Several mechanisms may be considered to explain this result. First, delayed decrease of cardiac output after exercise, due to the impairment of left ventricular function during exercise, may contribute to delayed decline in blood pressure after exercise[6–9]. We reported that abnormal PBP3 in patients with chronic heart failure was correlated with delayed kinetics of oxygen consumption, which reflects the kinetics of cardiac output[5]. Recent invasive studies also support this hypothesis[7–9]. The relationship between oxygen uptake kinetics and cardiac output during the recovery period from maximal exercise was studied in 30 patients with chronic heart failure[8]. In their study, prolonged kinetics of oxygen consumption after exercise represented delayed decrease of cardiac output after exercise. This prolonged recovery of oxygen consumption was also a significant predictor of mortality. The prognostic information derived from indexes after exercise was assessed in 153 patients with dilated cardiomyopathy and 55 control subjects[7]. Recovery of oxygen consumption was significantly delayed and this delay was related to the degree of exercise intolerance. Moreover, in a subgroup of patients with moderate exercise intolerance, the delayed recovery of oxygen consumption was a significant predictor of mortality.

Second, abnormal peripheral vascular resistance after exercise may also be involved. Abnormal peripheral vasoconstriction is one of the well-known features of chronic heart failure[21–23]. The mechanism of abnormal post-exercise blood pressure response in patients with coronary artery disease was investigated using a supine ergometer with invasive hemodynamic measurement[18]. Abnormal post-exercise blood pressure response was caused not only by exercise-induced impairment of left ventricular systolic function but also by high peripheral vascular tone during recovery. Our previous study also demonstrated increased sympathetic activity in patients with abnormal post-exercise blood pressure response[5]. High peripheral vascular resistance may be partly responsible for high PBP3 in patients with chronic heart failure.

In this study, peak blood pressure and systolic blood pressure at 3 min after exercise were not statistically different between patients with events and those without events, although peak blood pressure in patients with events tended to be lower than that in those without events. PBP3 reflects hemodynamic abnormalities not only during exercise but also during recovery. Therefore, integration of the indicator measured during exercise and that after exercise may be superior to the separate indicators in prediction of the outcome in patients with chronic mild to moderate heart failure. Measurement of this parameter is simple and useful in daily clinical practice.

**Study limitations**

The retrospective design and small study population limit the interpretation of the present findings. Cardiac medications were not withheld at the time of the exercise tests, so beta-blockers may have modified the hemodynamic response during exercise. However, there were no significant differences in the ratios between beta-blockers and placebo[17]. The measurement of blood pressure by sphygmomanometer during exercise may not be accurate, although such blood pressure measurements did not differ significantly from those measured using invasive methods[19]. Finally, neurohormonal factors such as norepinerphrine or natriuretic peptides were not measured in this study. Further study concerning the prognostic value of PBP3 is required.

## 要　約

### 拡張型心筋症の予後予測における運動負荷回復期血圧反応の有用性

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**目　的**: 慢性心不全患者において，運動負荷回復期における血圧反応異常が重症度と相関することが報告されている．本研究の目的は，拡張型心筋症患者おける運動負荷回復期血圧反応が，予後予測に有用か検討することである．

**方　法**: 拡張型心筋症患者30例(左室駆出率32±9%)に対して，症候限界性心肺運動負荷試験を施行した．運動時の最大血圧に対する運動終了後3分目の血圧の比(PBP3)を求め，心事故(突然死，心不全死，心不全増悪による再入院)との関連を他の運動負荷試験の結果や血行動態指標と比較検討した．

**結　果**: 3.3±1.8年の経過観察中に7例の心事故が発生した．心事故発生群におけるPBP3は，非発生群に比べて有意に高値であった(0.95±0.09 vs 0.84±0.10，$p<0.05$)．PBP3が心事故を予測するためのreceiver-operating characteristic曲線下面積は0.79(95%信頼区間: 0.62−0.97，$p=0.02$)であった．

**結　論**: 拡張型心筋症において運動負荷回復期血圧反応は心事故発生と関連し，拡張型心筋症患者の予後予測に有用であることが示唆された．


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