Relationship of Plasma Norepinephrine to Ventricular-Load Coupling in Patients with Heart Failure

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The relationship of plasma norepinephrine levels to the adaptational changes in ventricular-load coupling were studied at rest and during exercise in subjects with variably depressed ventricular function. Peak body oxygen consumption (\(\text{VO}_2\)) and gas exchange anaerobic threshold (ATge) were measured to assess exercise capacity. Ventricular contractile properties were expressed by the slope (Ees) of the end-systolic pressure-volume relation and mechanical arterial properties were expressed by the slope (Ea) of the end-systolic pressure-stroke volume relation. Resting plasma norepinephrine was significantly elevated in patients with severe heart failure (New York Heart Association class III, IV) and correlated well with the magnitude of reduction in peak \(\text{VO}_2\) and ATge. In these patients, Ea/Ees ratio was also increased and correlated with the levels of resting plasma norepinephrine. Although pump efficiency of the left ventricle progressively fell with the development of heart failure, stroke volume was maintained within normal range by virtue of a compensatory increase in end-diastolic volume. Sympathetic activity was much higher in anaerobic exercise than in aerobic exercise. However, Ees (ventricular contractility) remained at the same value throughout the exercise period. Thus, an increase in stroke volume during anaerobic exercise was caused more by an increase in end-diastolic volume than by an enhanced contractility. Our results suggest that the level of resting plasma norepinephrine can be a good predictor of the modulation of ventricular-load coupling in patients with heart failure and that when contractile reserve is decreased, the Frank-Starling mechanism plays an important role in the control of stroke volume.

The cardiovascular system provides adequate blood flow to peripheral tissues and supports this normal function. In order to achieve adequate cardiac output in the failing heart, the cardiovascular control system uses a combination of ventricular contractility, heart rate, preload and afterload. The sympathetic nervous system plays the most important role in mediating the responses to reduced peripheral perfusion or to exercise. The augmentation of sympathetic activity initially serves to ensure cardiovascular homeostasis but in later phases it may impede left ventricular performance through excessive peripheral vasoconstriction. Thus, as heart failure develops, ventricular-load coupling is modulated largely by the degree of sympathetic nervous activity. Although the sympathetic nervous system has been confirmed to be overly active in congestive heart failure, there is limited quantitative information about the relationships between sympathetic activity and ventricular-load coupling. This is due to the lack of suitable framework for quantitatively describing the properties of the ventricle and vascular system. An analytically

Key words:
End-systolic pressure-volume relation
End-systolic pressure-stroke volume relation
Frank-starling mechanism
Aerobic and anaerobic exercise

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Derivation of equation relating cardiac output or stroke volume (SV) to the properties of these two systems would provide a useful insight into the relevance of adaptational changes in ventricular-load coupling in heart failure. Recently, Sunagawa et al.\textsuperscript{3,4} developed a framework of analysis to predict SV resulting from the complex mechanical interaction between the ventricle and arterial system. They characterized the left ventricle by end-systolic pressure-volume relationship and the arterial system by end-systolic pressure-SV relationship and predicted SV from the interaction of the two relationship lines on the pressure-volume plane. In the present study, we employed the same framework and analyzed the ventricular-load coupling in patients with heart failure.

The purpose of this study is to determine whether the level of plasma norepinephrine (reflecting sympathetic activity) can predict the severity of heart failure (Study 1) and to clarify the relationship between sympathetic activity and ventricular-load coupling at rest and during exercise in patients with heart failure (Study 2, 3).

**METHODS**

**Study 1**

The study population consisted of 14 patients with valvular heart disease, 14 with cardiomyopathies, 13 with old myocardial infarction, 1 with atrial septal defect and 5 with atypical chest pain. Forty-two patients had supporting chest radiographic and echocardiographic evidence of impaired cardiac dysfunction. Twelve patients were in New York Heart Association (NYHA) class I, 14 in class II, 12 in class III, and 9 in class IV. In all patients, blood samples were taken from an indwelling catheter introduced into an antecubital vein in supine position. Resting plasma norepinephrine levels were determined by a high performance liquid chromatographic method (KYOWA K-505).

In 26 patients, exercise capacity was determined by anaerobic threshold (ATge) and
peak body oxygen consumption (VO₂) using a one-minute incremental sitting ergometer. Breath by breath measurements of oxygen utilization, carbon dioxide output, ventilation volume and end-tidal oxygen and carbon dioxide concentrations were performed using a Minato RM-200 metabolic measurement cart equipped with oxygen and carbon dioxide analyzers. Anaerobic threshold was discerned where minute ventilation and carbon dioxide production begin to increase non-linearly in spite of a linear increase in oxygen uptake⁵,⁶ The break point of increasing end-tidal oxygen concentration without a concomitant decrease in end-tidal carbon dioxide concentration was also determined to corroborate anaerobic threshold.

Study 2

Ten patients with symptoms and signs of chronic heart failure and 10 normal subjects were entered in this study. Seven patients with heart failure were in NYHA class II and 3 in class III. Two-dimensional echocardiography or contrast left ventriculography revealed diffuse and uniform impairment of the left ventricular contraction pattern in all patients. Patients with regional wall motion abnormalities and valvular heart disease were excluded. All subjects were in sinus rhythm and were studied in the supine postabsorptive state. Direct arterial pressure and two-dimensional targeted echocardiograms of left ventricular cavity were recorded simultaneously as the pressure was changed by phenylephrine or nitroprusside. Left ventricular volume was determined using the formula of Teichholz⁷ Left ventricular end-systolic pressure was approximated from the arterial dicrotic pressure. Ventricular-load coupling was analyzed in the framework recently developed by Sunagawa et al⁸,⁹ and Burkhoff and Sagawa⁸ Namely, the ventricular contractile properties were quantified by Ees and Vo parameters, the slope and volume
Fig. 3. The relation between resting plasma norepinephrine levels and exercise capacity as measured by peak oxygen consumption ($VO_2$) and anaerobic threshold.

Fig. 4. The relation between resting plasma norepinephrine levels and stroke volume and end-systolic pressure.

Fig. 5. The relation between resting plasma norepinephrine levels and ventricular and arterial properties.

axis intercept of the end-systolic pressure-volume relationship 9:

\[ \text{ESP} = \text{Ees} (\text{ESV} - \text{Vo}) \]  \hspace{1cm} (1)

where ESP and ESV are the ventricular end-systolic pressure and volume, respectively. The arterial input impedance properties were expressed in terms of the effective arterial elastance, Ea, which is the slope of arterial end-systolic pressure-SV relationship 2. It was shown that when ventricle and arterial systems were coupled, the resulting SV and ESP could be predicted by a single equation:

\[ \text{SV} = \frac{(\text{EDV} - \text{Vo})}{(1 + \text{Ea}/\text{Ees})} \] \hspace{1cm} (2)

\[ \text{ESP} = \text{SV} \cdot \text{Ea} \] \hspace{1cm} (3)

where EDV is the end-diastolic volume. These relations are depicted in Fig. 1.

**Study 3**

Five patients with previous myocardial infarction and no angina pectoris and 2 with dilated cardiomyopathy were enrolled in this study. The functional cardiac status as described by NYHA was class II in 5 and class III in 2. Left ventricular ejection fraction was 36 ± 12% in these patients at rest. In all patients, we estimated ATge and chose the work rates about 30% below ATge as aerobic exercise and that about 30% beyond ATge as anaerobic exercise. Under local anesthesia, a 7-French balloon-tipped thermolysis Swan-Ganz catheter was introduced into the right pulmonary artery, and a 19 gauge cannula was introduced percutaneously into the left brachial artery. Subjects were then transferred to the exercise facility. Simultaneous hemodynamic, radionuclide and gas exchange measurements were recorded at rest, during pressure elevation with phenylephrine and then at each workload of aerobic and anaerobic ergometer exercise in a supine position. During each stage of exercise, measurements were strictly timed so that arterial and mixed venous blood were sampled simultaneously with expired gas analysis during the third minute of each exercise stage. Gated equilibrium radionuclide angiograms, after in vivo labeling of red blood cells with 30 mCi technetium-99m, were acquired.

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*Japanese Circulation Journal Vol. 33, February 1989*
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Fig. 8. Responses of left ventricular volumes and stroke volume to aerobic and anaerobic exercise.

Fig. 9. Responses of ventricular and arterial properties to aerobic and anaerobic exercise.

during the 2nd and 3rd minute of each exercise stage. Left ventricular end-diastolic and end-systolic volumes were derived from radionuclide ejection fraction and Fick SV. Ventricular-load coupling was analyzed as in the framework mentioned before.

The slope (Ees) and the volume axis intercept (Vo) of the end-systolic pressure-volume relationship were determined from dicrotic arterial pressures and end-systolic volumes at rest and during pressure manipulation. We also obtained Ees during exercise by connecting end-systolic pressure-volume point during exercise with the same Vo as in the resting state, assuming that Vo was not altered by exercise. Plasma norepinephrine levels were also measured at rest and during each exercise stage in 6 patients. Informed consent and ethical approval were obtained from all subjects.

Data analysis

All results were given as mean ± standard deviation. Linear regression by a least squares method was used to fit each subject's plasma norepinephrine level and hemodynamic variables. The statistical significance of differences in plasma norepinephrine levels were tested by analysis of variance, and multiple comparisons were made by the Bonferroni method. P value less than 5% was considered to represent a statistical significance.

RESULTS

1. Plasma norepinephrine and severity of heart failure

The plasma norepinephrine concentrations exhibited a progressive increase along with the increased severity of cardiac failure (Fig. 2). The levels of plasma norepinephrine in class III and class IV were significantly elevated above the values of those in class I. There were significantly inverse correlations between plasma norepinephrine and peak VO$_2$ ($r = -0.56$, $p < 0.01$) and between plasma norepinephrine and ATgE ($r = -0.59$, $p < 0.01$) (Fig. 3).

2. Plasma norepinephrine and ventricular-load coupling at rest

The relationships of resting plasma norepinephrine to SV and ESP are illustrated in Fig. 4. In patients with moderate heart failure, despite a significant elevation in plasma norepinephrine, SV and ESP were maintained within normal range. In contrast, ventricular-load coupling variables (Ea/Ees and EDV or EDV-Vo) as determinants of SV and ESP changed quickly with the development of heart failure. With increasing levels of plasma norepinephrine, the ratio of Ea to Ees also linearly increased ($r = 0.76$, $p < 0.01$), though an increase in Ea did not reach statistical significance (Fig. 5). The maintainance of SV appears to be mediated essentially by the use of the Frank-Starling mechanism in severe heart failure (Fig. 6).

3. Plasma norepinephrine and ventriculo-arterial coupling during exercise

Plasma norepinephrine increased more markedly in anaerobic exercise than in aerobic exercise. This indicates that sympathetic outflow is more responsible for control of the cardiovascular system during anaerobic exercise (Fig. 7).

SV, EDV and ESV did not change consistently during aerobic exercise, while SV increased during anaerobic exercise in 5 of 7 patients. This increase in SV resulted from an increase in EDV rather than a decrease in ESV except in one patient (Fig. 8). Data related to ventricular and arterial properties are presented in Fig. 9. Neither Ees or Ea changed significantly during aerobic exercise. Furthermore, in spite of the marked increase in sympathetic drive during anaerobic exercise, Ees and Ea remained the same as in the resting state. Therefore, the ratio of Ea to Ees was unaltered throughout the exercise period.

DISCUSSION

In patients with heart failure, activity of the sympathetic adrenergic system is known to be increased. Norepinephrine, primarily a neurotransmitter, is released from terminal sympathetic neurons during excitation of sympathetic nerve. It is generally agreed that plasma norepinephrine levels provide a useful index of average sympathetic nervous system activity. Lower perfusion pressure and impaired oxygen saturation in the vascular bed have the potential to influence both intrinsic and extrinsic regulatory mechanisms of adrenergic activity. The former is mediated locally whereas the latter is mediated
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by the cardiopulmonary and arterial baroreceptors. In heart failure, an attenuation of afferent inhibitory signals from these baroreceptors to the vasomotor center is partly responsible for excessive sympathetic nervous activity\(^\text{13}\) In the present study, the patients with clinical symptoms of heart failure had higher resting plasma norepinephrine levels than did asymptomatic patients. Furthermore, the resting levels of plasma norepinephrine showed inverse correlations with exercise capacity as expressed by peak VO\(_2\) and ATge. Francis et al\(^{14}\) also showed that the basal plasma norepinephrine paralleled peak VO\(_2\). Recently, Wilson et al\(^{15}\) reported that impaired nutritive flow to skeletal muscle is most likely the principal factor responsible for the reduce maximal exercise capacity of patients with heart failure. Therefore, the rise in plasma norepinephrine in patients with heart failure might indicate inadequate peripheral perfusion as a consequence of impaired augmentation of cardiac output during exercise. Thus, our data support the view that basal supine plasma norepinephrine can be a marker for the severity of congestive heart failure and a good predictor of exercise capacity\(^{14}\).

The severity of heart failure is frequently reflected in hemodynamic abnormalities such as magnitude of reduction in cardiac output and arterial pressure and of elevation in systemic and pulmonary venous pressures. Levine et al\(^{16}\) found a significant correlation between plasma norepinephrine levels and various hemodynamic parameters. On the other hand, Viquerat et al\(^{17}\) demonstrated that the circulating norepinephrine levels did not correlate with the hemodynamic abnormalities. We also observed that the increase in plasma norepinephrine levels was not necessarily related to the hemodynamic parameters such as SV and ESP. In contrast, ventricular-load coupling variables (Ea/Ees, EDV or EDV-Vo) as determinants of SV correlated well with the levels of resting plasma norepinephrine. Ventricular-load coupling in heart failure was characterized by the increase in Ea/Ees ratio which was mediated primarily by decreased contractility and by a slight increase in afterload (Fig. 10). The equation\(^{2}\) represents that this increase in Ea/Ees ratio directly reduces SV. However, a compensatory reaction such as Frank-Starling mechanisms permitted the heart to yield an almost normal SV. Importantly, such modulation of ventricular-load interaction precedes the development of arterial flow impairment and more sensitively reflects the severity of heart failure.

Suga and co-workers\(^{18,19}\) have proposed left ventricular pressure-volume area (PVA) as a measure of the total mechanical energy generated by ventricular contraction because of a linear relation between myocardial oxygen consumption and the PVA. The PVA is defined as the area on the ventricular pressure-volume diagram circumscribed by the end-systolic and end-diastolic pressure-volume trajectory. Therefore, the ratio of stroke work (SW) to the PVA represents the pump efficiency of the left ventricle. If we assume that the time averaged ventricular ejection pressure is close to ESP and that ventricular end-diastolic pressure is negligible compared with pressure during ejection, SW can be approximated by the product of SV and ESP and the ratio of SW to PVA (pump efficiency) is formulated\(^{8}\) as

\[
\text{SW/PVA} = \frac{1}{[1 + (\text{Ea/Ees})/2]}
\]

Thus, pump efficiency is a monotonically decreasing function of the rise in Ea/Ees. Therefore, the increase in Ea/Ees shown in this study indicates a deterioration of pump efficiency in heart failure.

In mild to moderate degrees of exercise, cardiovascular adjustment can be sufficient to supply oxygen to working muscle. This condition is termed aerobic exercise. If a discrepancy exists between metabolic need and flow during more stressful exercise (anaerobic exercise), the feedback signals of the muscle afferent system are supposedly increased\(^{20}\) and a marked increase in sympathetic outflow results. Under these circumstances, the hemodynamic profile in the control of SV would be altered. Higginbotham et al\(^{21}\) have reported in normal subjects that during low levels of upright exercise, SV increased primarily due to an increase in EDV, while SV at high levels of exercise was maintained through a progressive decrease in ESV. Other studies\(^{22,23}\) also demonstrated that in vigorous supine exercise, the augmentation of SV was largely caused by the reduction of ESV in normal subject. This suggests that the increase in SV during strenuous exercise is accounted for predominantly by enhanced contractility related to an increased sympathetic activity rather than by means of the Frank-Starling mechanism. An increase in the peak systolic pressure-end-systolic volume relation during strenuous exercise also indicates an augmented contractile state in normal subjects\(^{24}\). The present study demon-
strated that in patients with severe cardiac dysfunction, Ees failed to increase in spite of an exaggerated increase in plasma norepinephrine during anaerobic exercise. Decreased effectiveness of β-adrenergic modulation of myocardial contractility\textsuperscript{25} loss of myocardium or exercise-induced ischemia could be proposed as the mechanisms for this reduction in contractile reserve. The observed variability in SV during anaerobic exercise was accounted for by the extent to which preload reserve was used\textsuperscript{26,27} Thus, with advancing heart failure, there is a shift from a catecholamine-mediated reduction in ESV to a greater reliance on the Frank-Starling mechanism in the control of exercise SV.

In conclusion, we examined ventricular-load coupling to quantitatively predict SV under different sympathetic drives in patients with heart failure. In these patients, Ea/Ees ratio correlated well with the levels of plasma norepinephrine. Although plasma norepinephrine levels rose substantially during anaerobic exercise, Ees (ventricular contractility) did not appreciably increase in patients with severe cardiac dysfunction. Under these conditions, SV was maintained predominantly by the increase in EDV. Thus, the levels of resting plasma norepinephrine can be good predictors of the modulation of ventricular-load coupling in patients with heart failure. The Frank-Starling mechanism plays an important role in the regulation of SV when contractile reserve is decreased.

Acknowledgment

The authors thank Miss Masumi Kosugi for preparation of the manuscript.

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