Impaired Force-Frequency Relations in Patients With Hypertensive Left Ventricular Hypertrophy
A Possible Physiological Marker of the Transition From Physiological to Pathological Hypertrophy

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Background—The extent to which force-frequency and relaxation-frequency relations (FFR and RFR, respectively) and exercise-induced adrenergic stimulation affect myocardial inotropic and lusitropic reserves has not been established in patients with left ventricular (LV) hypertrophy (LVH).

Methods and Results—We calculated the maximum first derivative of LV pressure (LV dP/dt_{max}) and the LV pressure half-time (T_{1/2}) during pacing, exercise, and isoproterenol infusion in 17 patients with hypertensive LVH and 9 control subjects to investigate the influence of increases in heart rate (HR) and adrenergic stimulation on inotropic and lusitropic reserves. Group A consisted of 10 LVH patients who showed a progressive increase in the HR-LV dP/dt_{max} relation. Group B consisted of 7 LVH patients in whom the HR-dP/dt_{max} relation at physiological pacing rates was biphasic. The LV mass index was larger and the LV ejection fraction was smaller in group B than in group A (244\pm 72 g/m^2 versus 172\pm 22 g/m^2 and 55\pm 18% versus 72\pm 6%, respectively; both P<0.05). The increase in LV dP/dt_{max} was greater during exercise than pacing alone for similar increases in HR in all groups (P<0.05) (group A, 111\pm 22% versus 25\pm 14%; group B, 105\pm 35% versus 14\pm 10%; control, 111\pm 24% versus 25\pm 12%). T_{1/2} was shorter (P<0.05) during exercise than with pacing alone in all groups (group A, 41\pm 6% versus 11\pm 3%; group B, 38\pm 9% versus 14\pm 4%; control, 44\pm 6% versus 12\pm 5%). Isoproterenol infusion caused similar increases in LV dP/dt_{max} and similar decreases in T_{1/2} in all groups.

Conclusions—The FFR was biphasic in patients with severe LVH irrespective of LV function but was preserved in patients with less severe LVH and control subjects. Importantly, the RFR and adrenergic control of both inotropic and lusitropic reserves were well preserved in all LVH patients. A biphasic FFR at physiological pacing rates may be one of the earliest markers of the transition from physiological adaptation to the pathological process in LVH patients. (Circulation. 1999;99:1822-1830.)

Key Words: myocardial contraction ■ hypertrophy ■ hypertension

Left ventricular hypertrophy (LVH) caused by pressure overload is a compensatory response designed to normalize wall stress and to allow normal left ventricular (LV) function. However, it is also part of a pathological process that may ultimately lead to mechanical cardiac failure. Recent studies in animal models suggest that there is a gradual transition from compensated hypertrophy to decompensated heart failure. A similar transition is not uncommon in patients with pressure overload, in whom gradual chronic pressure overload of the LV results in myocardial hypertrophy with subsequent cardiac dysfunction. Recognition of the earliest manifestations of the transition from physiological to pathological hypertrophy is an important clinical issue. Heart rate (HR) is an important determinant of myocardial performance, and several studies have confirmed the existence of chronotropic effects on myocardial contractility (the positive force-frequency relation, FFR) in normal human subjects. In addition, exercise and dobutamine infusion have been found to markedly enhance the positive FFR in normal dogs and in healthy humans. However, the HR-dependent changes in myocardial contractility and relaxation and the effects of adrenergic stimulation, such as dynamic...
exercise, have not been fully investigated in patients with hypertensive LVH in the presence or absence of depressed LV function. Liu et al\textsuperscript{10} have shown that the positive contraction response to rapid pacing at physiological rates is markedly diminished in patients with symptomatic LVH. Recently, studies from our laboratory demonstrated that exercise-induced enhancement of the relaxation-frequency relation (RFR) was attenuated in all patients with hypertrophic cardiomyopathy (HCM), irrespective of the degree of LVH.\textsuperscript{7,11} The RFR and adrenergic control of lusitropic reserves are well preserved in patients with compensated hypertensive LVH as well as in normal control subjects.\textsuperscript{11} Furthermore, the exercise-induced enhancement of FFR was preserved in patients with moderate HCM but was blunted in patients with more severe HCM, even in the absence of LV dysfunction.\textsuperscript{7} Thus, both FFR and RFR and adrenergic control of both inotropic and lusitropic reserves may be related to the cause, as well as the severity, of LVH.

The goal of the present investigation was to characterize chronic and \( \beta \)-adrenergic regulation of myocardial contractile and relaxation and to investigate a possible physiological marker of the transition from physiological to pathological LVH in patients with essential hypertension. We examined inotropic and lusitropic responsiveness to rapid atrial pacing, dynamic exercise, and isoproterenol infusion in patients with hypertensive LVH in the presence or absence of mildly depressed LV function.

**Methods**

**Study Group**

We studied 17 patients (mean age, 52 years) with essential hypertension. Hypertension was defined as a systolic blood pressure \( >160 \text{ mm Hg} \) and/or a diastolic pressure \( >95 \text{ mm Hg} \) in the sitting position in the untreated state. All patients had LVH documented by echocardiography, with a mean LV mass index of 201\( \pm \)59 g/m\( ^2 \) (mean\( \pm \)SD). They also had ECG evidence of LVH.\textsuperscript{12} None of the patients had valvular heart disease or \( >50\% \) narrowing of the coronary arteries as determined by coronary arteriography. The control group consisted of 9 patients (mean age, 55 years) who underwent diagnostic cardiac catheterization to evaluate atypical chest pain. All control subjects had normal ECGs, echocardiograms, coronary arteriograms, and contrast ventriculograms. All subjects were in normal sinus rhythm. The study protocol was approved by the appropriate institutional review committee. Written informed consent was obtained from all subjects.

**Measurement of LV Mass**

M-mode and 2-dimensional echocardiograms at rest were obtained with a Hewlett-Packard Sonos 2500 system. Echocardiographic measurements were made from recordings of at least 10 consecutive cardiac cycles by 2 observers who were unaware of the patients' clinical status. The interventricular septal thickness, posterior wall thickness, and LV internal dimension were measured at the peak of the R wave on the ECG and were determined according to the Penn convention. The echocardiographic LV mass was calculated according to the formula developed by Devereux and Reichek.\textsuperscript{13}

**Cardiac Catheterization Procedures**

Right heart catheterization was performed with a 7F triple-lumen thermistor Swan-Ganz catheter (Baxter Health Care Co). A 6F fluid-filled pigtail catheter with a high-fidelity micromanometer (model SPC-464D, Millar Instruments) was advanced into the LV through the right brachial artery for measurement of LV pressure. The micromanometer pressure was matched to the pressure of the fluid-filled lumen. A 20-gauge catheter was placed in the left brachial artery for measurement of arterial pressure. A 6F bipolar pacing catheter was introduced through the right subclavian vein and positioned in the right atrium. After completion of the pacing study, the isoproterenol study, and the exercise study, selective coronary angiography and left ventriculography were performed. Micromanometer pressure signals and bipolar standard ECG leads were recorded simultaneously and continuously with a multichannel recorder (MR-40, TEAC Co) during the study.

**Pacing Study**

After catheters were in place and baseline hemodynamic data had been collected, right atrial pacing was initiated at 80 bpm and increased in increments of 10 bpm. We defined the critical HR as the HR at which \( \frac{dP}{dt_{max}} \) reached the maximum value during progressive increases in HR. Thus, the value beyond which \( \frac{dP}{dt_{max}} \) declined by 5% was the critical HR\textsuperscript{14} for isovolumic contraction. This point occurred in 7 LVH patients at physiological pacing rates. The peak pacing rate was defined as the HR at which either second-degree atrioventricular block or pulsus alternans occurred.

**Isoproterenol Study**

After the pacing study had been completed, 9 of 17 patients in the LVH group and 5 of 9 control subjects were selected randomly to receive continuous isoproterenol infusions (isoprenaline hydrochloride, Nikken Kagaku). The dose of isoproterenol was gradually increased to obtain an HR of \( \approx 130 \text{ bpm} \). The maximal isoproterenol dose was similar in the two groups (control, 0.018\( \pm \)0.002 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \); LVH, 0.014\( \pm \)0.001 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)).

**Exercise Study**

Exercise testing was performed with patients in the supine position on a bicycle ergometer, as described previously,\textsuperscript{15} at least 30 minutes after completion of the pacing study or 1 hour after completion of the isoproterenol infusion study. The workload was initiated at 25 W for 3 minutes and then increased by 25 W at 3-minute intervals until the HR reached a level similar to the peak pacing rate or the appearance of leg fatigue.

**Data Analysis**

LV pressure signals were digitized at 3-ms intervals and analyzed with software developed in our laboratory with a 32-bit microcomputer system (PC-9821-ST20, NECT Co). We selected steady-state LV pressure data at baseline, at each pacing rate, and at 7 to 10 points during exercise and isoproterenol infusion for analysis. We used the ratio of LV \( \frac{dP}{dt} \) to developed LV pressure at a developed LV pressure of 40 mm Hg [LV (\( \frac{dP}{dt} \)/DP40)] as an index of contractility.\textsuperscript{16} To evaluate LV isovolumic relaxation, \( \tau (T_D) \) was calculated in 2 ways. The pressure half-time (\( T_{1/2} \)) was computed directly, according to the method of Minsky.\textsuperscript{17} We also measured \( \tau \) on the basis of a modification of the method described by Raff and Glantz.\textsuperscript{18} The correlation coefficients (\( r \)) were generally between 0.992 and 0.995, LV end-systolic and end-diastolic volumes were determined by biplane ventriculography and calculated by the area-length method.\textsuperscript{19} Wall stress was calculated by the equation wall stress (g/cm\( ^2 \))=\( PD^2/4WT(D+WT) \), where \( P \) is LV peak systolic pressure, \( D \) is LV diameter measured by echocardiography, and \( WT \) is LV wall thickness.\textsuperscript{20}

**Plasma Concentrations of Catecholamines**

Blood samples (5 mL) were collected from the brachial artery at rest and at peak HR during pacing, isoproterenol infusion, and/or exercise. The plasma levels of catecholamines were analyzed by high-performance liquid chromatography.\textsuperscript{7}

**Statistical Analysis**

Results are expressed as mean\( \pm \)SD. One-way factorial ANOVA was used to compare baseline characteristics and hemodynamic variables at peak HR during pacing, exercise, and isoproterenol infusion among groups. Within-group comparisons were performed for the hemodynamic changes during pacing, exercise, and isoproterenol infusion by 2-way repeated-measures ANOVA. When a significant
Subgroup Classification

We divided the LVH patients into 2 groups on the basis of the analysis of FFRs during pacing. Group A consisted of 10 patients in whom LV dP/dt max increased progressively with increases in HR up to the peak pacing rate (the positive FFR). Group B consisted of 7 patients in whom FFRs at physiological pacing rates were biphasic, with an initial positive slope (ascending limb) and a subsequent negative slope (descending limb).

Baseline Data

The LV mass index was increased in both groups A and B, but the increase was greater in group B. The LV ejection fraction (LVEF) was significantly greater in group A and in the control group than in group B. All 4 patients whose LVEF was ≥50% belonged to group B. LV peak systolic pressure at baseline was significantly higher in groups A and B than in the control group. LV end-diastolic pressure (LVEDP) at baseline was significantly higher in group A than in group A and in the control group. There was no difference in LV dP/dt max or LV (dP/dt)/DP at baseline among groups, but T1/2 and T2 were significantly prolonged in groups B and compared with the control group. LV peak systolic wall stress was 47.1±11.3 g/m² in the control group, 49.5±11.7 g/m² in 13 LVH patients with normal LVEF, and 118.5±41.6 g/m² in 4 LVH patients with impaired LVEF (≤50%).

Responses to Pacing-Induced Tachycardia

There was no difference in peak pacing rate among groups. Increases in the pacing rate induced progressive increases in LV dP/dt max in group A and in the control group (Figure 2). HR was significantly correlated with LV dP/dt max in group A and in the control group (r=0.93±0.13) and in the control group (r=0.95±0.11). The slope of the regression curve for the HR–LV dP/dt max relation was similar in the two groups. Patients in group A and control subjects showed a similar increase in LV dP/dt max at the peak pacing rate. The HR–LV dP/dt max relation was biphasic in group B (Figure 3). The critical HR ranged from 100 to 130 bpm (mean, 114±10 bpm). At the critical HR, LV dP/dt max increased significantly, by 24%, and then decreased by 10% at the peak pacing rate. HR was significantly correlated with T1/2 (r=-0.94±0.13) during pacing in all groups (Figure 2). The slope of the regression curve for the HR–T1/2 relation was similar in all groups. The pacing-induced increase in HR to ≈130 bpm reduced T1/2 in all groups. LVEDP at the peak pacing rate decreased in all groups.

Responses to Dynamic Exercise

Exercise increased LV dP/dt max and reduced T1/2 in all groups. In group B, exercise abolished the biphasic FFR. HR was significantly correlated with LV dP/dt max (r=0.94±0.18) and T1/2 (r=-0.91±0.24) during exercise in all subjects (Figure 2). The slopes of the regression curve for the HR–LV dP/dt max relation were steeper during exercise than during atrial pacing in group A and the control group (P<0.05, ANCOVA), and for the HR–T1/2 relation they were steeper during exercise than during atrial pacing in all groups (P<0.05, ANCOVA). Exercise-induced changes in LVEDP were greater in groups A and B than in the control group (P<0.05).
Changes in Plasma Levels of Catecholamines

Exercise increased the plasma level of norepinephrine in all groups, but there were no significant differences among groups in the plasma level of norepinephrine at rest (control, 230±73 pg/mL; group A, 235±91 pg/mL; group B, 235±128 pg/mL), at peak pacing (control, 221±91 pg/mL; group A, 237±125 pg/mL; group B, 253±146 pg/mL), or at peak exercise (control, 625±149 pg/mL; group A, 805±380 pg/mL; group B, 881±423 pg/mL). The plasma level of epinephrine was also similar in all groups.
previous studies of LVH have indicated that the process of hypertrophy is physiological in that it acts to normalize wall stress and maintain LV function. Actually, in the present study, LV peak systolic wall stress at rest in LVH patients with normal LVEF was not different from that in control subjects. However, others have suggested that the process is pathological in that the hypertrophied heart exhibits depressed function. But most of these prior observations were based on assessments made only at rest. It is conceivable that even when the hypertrophied heart is well compensated at rest, it does not function appropriately in response to stress, such as occurs during exercise or rapid pacing. However, this hypothesis has not been extensively investigated. One of the primary goals of the present investigation was to address this question in patients with hypertensive LVH in the presence or absence of LV dysfunction.

The present study presents a novel finding regarding the FFR at physiological pacing rates in patients with hypertensive LVH. The FFR was biphasic, with an initial positive slope (ascending limb) and a subsequent negative slope (descending limb), in patients with severe LVH in the presence or absence of mildly depressed LV function. However, the FFR was preserved during rapid pacing in patients with less severe LVH in the absence of depressed LV function, as well as in control subjects. Furthermore, the RFR was preserved at physiological pacing rates in all patients with LVH, irrespective of the presence of the biphasic FFR, as well as in control subjects. Importantly, adrenergic control of both inotropic and lusitropic reserves was well preserved in all subjects. A biphasic FFR at physiological pacing rates may be one of the earliest markers of the transition from physiological to pathological LVH in patients with hypertension.

Force-Frequency Relationship

HR is an important determinant of cardiac performance. The present data indicate that HR has a significant positive effect on myocardial contractility (positive FFR) in normal human subjects. Incremental pacing produced a significant 25% increase in LV dP/dt\textsubscript{max} at a pacing rate of \(\approx 130\) bpm in normal human subjects. Because LV dP/dt\textsubscript{max} is preload-dependent and because an increased HR resulted in variable reduction in LV preload, it is likely that the magnitude of the force-frequency effect was underestimated in the present study. Khoury et al\textsuperscript{14} first reported that the FFR in the sedated adult baboon was biphasic. In this regard, Freeman et al\textsuperscript{25} demonstrated that neither LV dP/dt\textsubscript{max} nor the slope of the end-systolic pressure-volume relation showed a biphasic response to incremental atrial pacing up to 200 bpm in conscious dogs. It should be noted that a descending limb of the FFR has never been described in intact normal humans at physiological pacing rates.

In the present study, LVH patients were divided into 2 groups on the basis of the differences in the FFR. In patients with more severe LVH or with LVH in the presence of mild LV dysfunction, the FFR was biphasic at physiological pacing rates. The critical HR was between 100 and 130 bpm. To the best of our knowledge, no previous studies have observed a descending limb of the FFR at physiological pacing rates in patients with hypertensive LVH. The precise mechanisms involved in such an impaired FFR are not clear. However, it is possible that the descending limb of the FFR is related to altered sarcoplasmic reticulum Ca\textsuperscript{2+} handling\textsuperscript{26} or to delayed mechanical restitution because of inadequate time for recovery of the Ca\textsuperscript{2+} release channel.\textsuperscript{27} Drake-Holland et al\textsuperscript{28} demonstrated that mechanical restitution was enhanced by \(\beta\)-adrenergic stimulation in normal isolated papillary muscles. Furthermore, Ryu et al\textsuperscript{29} reported that dobutamine infusion corrected the descending limb in rabbits. In the present study, dynamic exercise and isoproterenol infusion corrected the descending limb at physiological HRs in patients with severe LVH. It is unlikely that the descending limb is due to myocardial ischemia, because exercise-induced and isoproterenol-induced increases in myocardial oxygen consumption should have the opposite effect on the critical HR (ie, an earlier onset of the descending limb).

Relaxation-Frequency Relationship

In the present study, the RFR was preserved during atrial pacing in all patients with LVH, irrespective of the presence...
or absence of mild LV dysfunction and even in the presence of impaired FFR, as well as in control subjects. However, systolic and diastolic deterioration have been found to occur simultaneously in many LVH pacing studies. Gwathmey et al suggested that calcium overload in isolated hypertrophied muscle strips simultaneously led to systolic and diastolic dysfunction at rapid pacing rates. However, Liu et al clearly demonstrated that despite the presence of contractile abnormalities, diastolic function did not deteriorate further in response to rapid pacing and thus did not appear to be closely

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**Figure 2.** Relations between HR and LV dP/dt max (left) and time constant of isovolumic relaxation T 1/2 (right) normalized as percentage of value at baseline HR during pacing (●) and during exercise (○) in control group (top), in group A (middle), and in group B (bottom). Data are mean±SEM of values. Numerals in figure are numbers of subjects analyzed.
linked to systolic changes in patients with symptomatic LVH. Although significant diastolic abnormalities existed at baseline, pacing caused no further significant decline in diastolic function. In fact, T1/2, which was prolonged at rest, shortened progressively and to a similar degree in LVH patients and in control subjects. Indeed, simultaneous increases in systolic and diastolic Ca²⁺ levels with pacing were not found in a recent study performed in isolated hypertrophied myocytes.³¹

**Adrenergic Control**
LV dP/dt max and T1/2 were enhanced during exercise-induced and isoproterenol-induced tachycardia in both control subjects and LVH patients in the present study. Even in LVH patients with impaired FFRs, adrenergic control of both inotropic and lusitropic reserves was well preserved. During exercise, LVEDP showed a significantly greater increase in LVH groups than in the control group. LV dP/dt max is

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**Figure 3.** Relations between HR and LV dP/dt normalized as percentage of value at baseline HR during pacing in each patient of group B. HR–LV dP/dt max relation was biphasic, with an initial positive slope (ascending limb) and a subsequent negative slope (descending limb), in each patient. Critical HR was between 100 and 130 bpm.
sensitive to LV preload. Therefore, it is possible that the exercise-induced increase in LV \(dP/dt_{\text{max}}\) was preserved in patients with LVH because of an increase in LVEDP. Isoproterenol infusion also increased LV \(dP/dt_{\text{max}}\) in association with similar increases in HR during exercise in the LVH group and in the control group, whereas LVEDP decreased similarly in both groups. These observations suggest that β-adrenergic stimulation enhanced LV \(dP/dt_{\text{max}}\) independently of LV preload in both groups. In addition, LV peak systolic pressure at peak exercise increased similarly in both groups. This increase may have affected LV relaxation. However, tachycardia induced by rapid atrial pacing and isoproterenol infusion shortened \(T_{1/2}\) in association with a similar fall in LV peak systolic pressure. These results suggest that enhancement of LV relaxation during exercise is due to an improvement in myocardial relaxation properties.

The present findings are supported by several previous studies. Vatner et al reported that the in vivo response to isoproterenol and in vitro isoproterenol-stimulated adenyl cyclase activity were normal in dogs with severe but compensated LVH induced by aortic banding. In contrast to the present results, several previous reports regarding pressure-overload LVH have suggested that β-adrenergic LV contractile responsiveness is impaired in the presence of hypertension. Most previous studies were conducted in rats in different models of hypertension. Accordingly, the discordance between prior studies and the present study may be due to species differences or methodological differences. The present study is the first to demonstrate that adrenergic control of the FFR and RFR is preserved in patients with hypertensive LVH in the presence or absence of mildly depressed LV function.

Conclusions

The FFR was biphasic, with an initial positive slope and a subsequent negative slope, at physiological pacing rates in patients with severe LVH in the presence or absence of mild LV dysfunction. A biphasic FFR at physiological pacing rates may be one of the earliest markers of the transition from physiological adaptation to a pathological process in patients with hypertensive LVH. Importantly, the RFR and adrenergic control of both inotropic and lusitropic reserves were well preserved in this disease state.

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