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Rapid Ventricular Filling in Left Ventricular Hypertrophy: II. Pathologic Hypertrophy

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To define the extent of left ventricular ejection and filling abnormalities in patients with mild hypertension, a nonimaging nuclear probe was used to generate high resolution time-activity curves in 25 patients with an average systolic blood pressure of 154 ± 20 mm Hg and diastolic pressure of 98 ± 8 mm Hg. The hypertensive patients did not meet electrocardiographic criteria for left ventricular hypertrophy, and none had evidence of ischemic or other cardiac disease. Compared with 25 age-matched normal subjects who had average systolic and diastolic pressures of 123 ± 10 and 79 ± 8 mm Hg, respectively, the hypertensive patients had a significantly lower ejection rate (2.00 ± 0.20 versus 2.34 ± 0.36 end-diastolic counts/s for the control group, $p < 0.05$) and ejection fraction (58 ± 4.9 versus 62 ± 4.4) ($p < 0.05$). The hypertensive patients had a markedly lower average rapid left ventricular filling rate (1.87 ± 0.32 versus 2.69 ± 0.41 counts/s for the control group, $p < 0.001$).

Although there was a modest inverse relation between echocardiographic left ventricular mass index and filling rate in the hypertensive patients ($r = -0.59$, $p < 0.01$), 4 of 12 hypertensive patients with normal left ventricular mass index had a depressed filling rate. All of the hypertensive patients with increased left ventricular mass index had an abnormal left ventricular filling rate (<1.89 end-diastolic counts/s). There was an inverse correlation of filling rate with age in both hypertensive patients and control subjects ($r = -0.59$, $p < 0.01$ and $r = -0.65$, $p < 0.001$, respectively). These findings suggest that this radionuclide technique can detect very early effects of hypertension on the left ventricle.

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Left ventricular hypertrophy in systemic arterial hypertension may result in impaired cardiac function, increased mortality from congestive heart failure and coronary artery disease (1). Thus, early detection of the effects of hypertension on the heart remains an important goal. The electrocardiogram is a relatively insensitive means to detect left ventricular hypertrophy when evaluated by echocardiography and autopsy data (2). Although the echocardiogram is highly sensitive and specific, the structural abnormalities detected by this method may not represent the initial abnormality caused by the chronic pressure overload. Recently, Fouad et al. (3) and Inouye et al. (4) used radionuclide-derived left ventricular volume curves to detect early functional effects of hypertension on the ventricle. Because abnormal patterns of left ventricular filling may represent a very early abnormality in the pressure overloaded heart, we examined rapid left ventricular filling in patients with mild to moderate essential hypertension who had no electrocardiographic evidence of left ventricular hypertrophy.

Methods

Study patients. Twenty-five patients with mild to moderate essential hypertension (diastolic blood pressure between 90 and 115 mm Hg in the untreated state) who did not meet electrocardiographic criteria for left ventricular hypertrophy (5) were recruited from the outpatient clinics of the John Dempsey Hospital (Table 1). Patients with a history of angina, myocardial infarction, significant Q waves on electrocardiogram, or valvular heart disease were excluded. Twenty-five control subjects, selected from a group of normal subjects, had similar age, rest heart rate and sex distribution (Table 1) and had no history of cardiac disease or hypertension. All had normal physical examination, 12 lead electrocardiogram and exercise radionuclide ventriculography. All subjects gave informed consent.

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Table 1. Patient Characteristics

	Hypertensive Patients	Control Subjects
Age (yr)	48 ± 12	45 ± 13 (NS)*
Sex	24 men, 1 woman	24 men, 1 woman
SBP (mm Hg)	154 ± 20	123 ± 10 ($p < 0.001$)
DBP (mm Hg)	98 ± 8	79 ± 8 ($p < 0.001$)
HR	66 ± 12	65 ± 11 (NS)

*All values are expressed as the mean ± 1 standard deviation. DBP = diastolic blood pressure; HR = heart rate; NS = not significant; SBP = systolic blood pressure.

Blood pressure and heart rate determinations. Antihypertensive medications were withdrawn from patients 1 to 3 weeks before testing. At the time of the gated blood pool study, supine heart rate and cuff systolic and diastolic blood pressures were measured.

Radionuclide studies. A single technician performed all of the left ventricular filling investigations using a Nuclear Stethoscope (Bios, Inc.). Each patient's red blood cells were labeled with technetium-99m in vivo after a standard injection of stannous polyphosphate. The region of interest, that is, the left ventricle and its background, was selected according to the algorithm described by Wagner et al. (6) and Berger et al. (7). Temporal smoothing of data was done by the system's internal microprocessor, but data were not fitted to any mathematical function. Studies were acquired over a 60 second interval.

To determine ejection fraction (EF), the operator-placed cursors were located on the time-activity curve at positions corresponding to end-diastolic counts (EDC) and end-systolic counts (ESC). The system's internal microprocessor was then used to determine the corresponding counts and perform standard calculation of ejection fraction after subtraction of background activity:

$$EF = \frac{EDC - ESC}{EDC}.$$

The average rapid left ventricular filling rate (LVFRav) and average rapid left ventricular ejection rate (LVERav) were calculated from three points on the left ventricular time-activity curve (Fig. 1): point A, corresponding to EDC (T1); point B, corresponding to ESC (T2) and point C, corresponding to counts at the end of rapid filling (RFC, T3). Points A, B and C were established by visual inspection of the time-activity curves. Average left ventricular filling rate was calculated after subtraction of background activity by dividing the rapid filling volume [RFV = (RFC − ESC)] by the rapid filling time [RFT = (T3 − T2)] and normalizing for EDC:

$$LVFRav = \frac{RFC - ESC}{(T3 - T2)}/EDC.$$

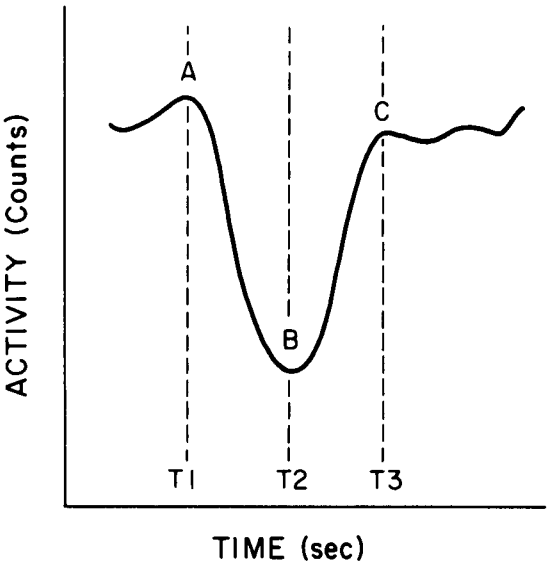


Figure 1. Schematic left ventricular time-activity curve. **A** = end-diastolic counts (EDC) measured at time T1, **B** = end-systolic counts (ESC) measured at time T2 and **C** = rapid filling counts (RFC) measured at time T3. **Dashed vertical lines** define the ejection period (T2 − T1) and rapid filling period (T3 − T2).

Average left ventricular ejection rate (LVERav) was calculated after subtraction of background activity by dividing the stroke volume (EDC − ESC) by the ejection time (T2 − T1), and normalizing for EDC:

$$LVERav = \frac{EDC - ESC}{(T2 - T1)}/EDC.$$

For each variable reported in Table 2, data from three separate selections of region of interest and background were averaged. The variability of three repeated measurements of average rapid filling rate was 0.05 or less. At a mean heart rate of 65 beats/min, with an acquisition time of 60 seconds, the data for each patient represent approximately 195 cardiac cycles. Representative time-activity curves for a control (C) and a hypertensive patient (H) are shown in Figure 2.

Exercise ventriculography. To exclude occult coronary artery disease, exercise ventriculography was performed in all subjects (8). Exercise was terminated due to exhaustion and not angina or dyspnea in either the normal or hypertensive group.

Echocardiography. M-mode echocardiograms were obtained in all hypertensive patients using an Irex System II ultrasonograph. Twenty patients had images of satisfactory quality for measurements of left ventricular dimensions. Left ventricular mass was calculated using the method of Devereux and Reichek (9). Relative wall thickness was calculated as the ratio 2 PWT/LVEDD, where PWT = posterior wall thickness in diastole and LVEDD = left ventricular internal dimension at end-diastole.

Table 2. Radionuclide Studies

	Hypertensive Patients	Control Subjects
LVEF (%)	58 ± 4.9	62 ± 4.4 ($p < 0.05$)
LVERav (EDC/s)	2.00 ± 0.20	2.34 ± 0.36 ($p < 0.05$)
LVFRav (EDC/s)	1.87 ± 0.32	2.69 ± 0.41 ($p < 0.001$)
RFT (seconds)	0.23 ± 0.03	0.20 ± 0.02 ($p < 0.001$)
Filling volume		
As percent of stroke counts	73 ± 5.6	80 ± 8.7 ($p < 0.01$)
As percent of EDC	45 ± 6.4	52 ± 7.0 ($p < 0.01$)

All values are expressed as mean ± 1 standard deviation. EDC = end-diastolic counts; LVEF = left ventricular ejection fraction; LVERav = average left ventricular ejection rate; LVFRav = average rapid left ventricular filling rate; RFT = rapid filling time.

Statistics. Analysis was performed using the two-tailed Student's *t* test for group data and Pearson linear regression.

Results

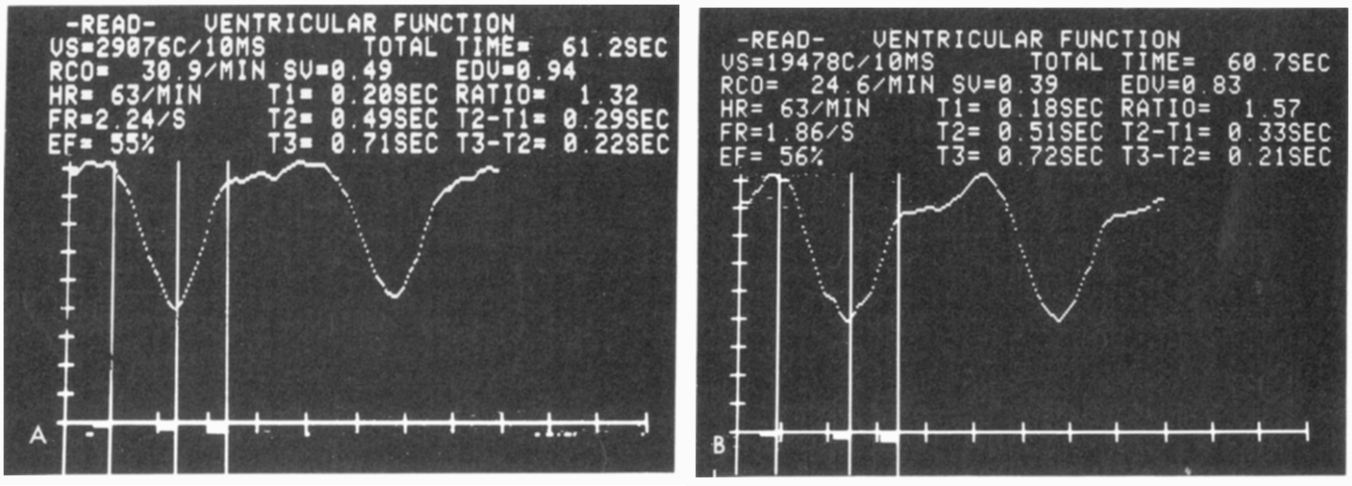
Blood pressure and heart rate (Table 1). Rest systolic and diastolic blood pressures were higher in the hypertensive patients than in the control group, but rest heart rate was not different in the two groups.

Left ventricular ejection variables (Table 2). Rest ejection fraction was slightly higher in the control group than in the hypertensive group. Three of the twenty-five hypertensive patients had a "flat" ejection fraction response to exercise, defined as failure of ejection fraction to increase by at least five absolute percent. None of the control or hypertensive patients exhibited either a decrease in ejection fraction or a regional wall motion abnormality indicative of coronary disease.

The left ventricular ejection rate (Table 2) was 17% greater in the control than in the hypertensive group; this difference was statistically significant. A slight correlation of ejection rate and filling rate was noted for hypertensive patients but not for control subjects ($r = 0.40$, $p = 0.045$ versus $r = 0.06$, NS).

Left ventricular filling variables (Table 2). The average rate of rapid left ventricular filling was significantly lower in the hypertensive patients than in the control group (Fig. 3). This difference reflected both a significantly reduced rapid filling volume (expressed as a percent of either end-diastolic or stroke counts) and a prolonged phase of rapid filling. Average left ventricular filling rate was positively correlated with ejection fraction in both hypertensive ($r = 0.49$, $p < 0.02$) and control subjects ($r = 0.52$, $p < 0.01$). Of note, there was a significantly inverse correlation between filling rate and age for both hypertensive ($r = -0.59$, $p < 0.01$) and control subjects ($r = -0.65$, $p < 0.001$).

Figure 2. Representative time-activity curves from a control subject (**A**) and a hypertensive patient (**B**) showing similar heart rates and ejection fractions, but a greater filling rate in the control than the hypertensive subject. Significant derivations provided by the instrument computer include: EF = ejection fraction, FR = filling rate, HR = heart rate. The three **vertical lines** represent T1, T2 and T3.



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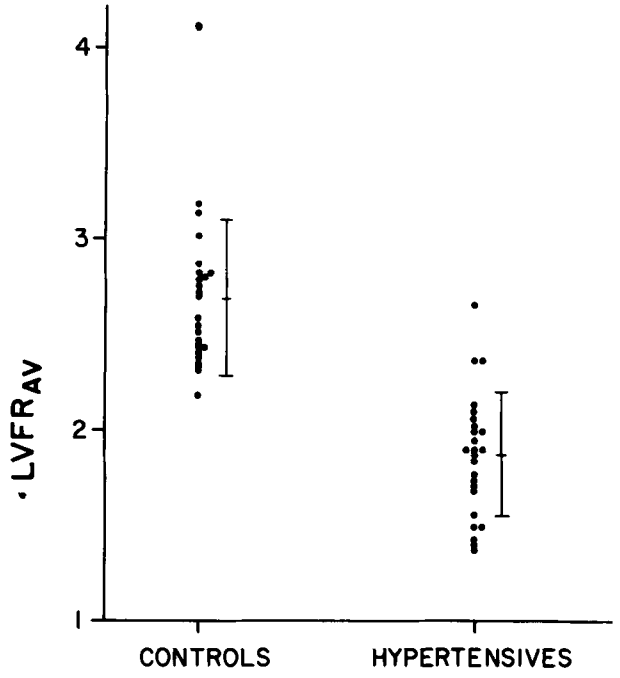

Figure 3. Individual values and means of average left ventricular rapid filling rates (LVFRAV) in control and hypertensive patients, expressed as end-diastolic counts/s. **Vertical bars** represent ± 2 standard deviations.

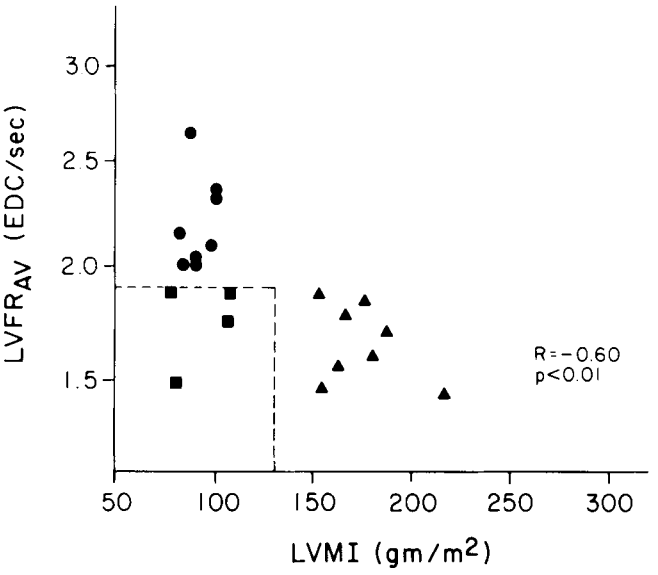

Figure 4. Relation between average left ventricular rapid filling rates (LVFRAV) and left ventricular mass index (LVMI) in hypertensive patients. The **dashed horizontal line** represents −2 standard deviations of the mean for control LVFRAV; the **dashed vertical line** represents +2 standard deviations of normal reported values for LVMI in men (13). Symbols identify patients with normal LVMI and LVFRAV (●), normal LVMI but decreased LVFRAV (■) and increased LVMI but decreased LVFRAV (▲).

Left ventricular mass and relative wall thickness. Of the 20 hypertensive patients in whom echocardiographic calculation of left ventricular mass was technically possible, 12 had a normal mass index according to previously reported normal values (10). All of the eight patients with an increased left ventricular mass index had an abnormal filling rate (less than 2 standard deviations below the mean for controls). However, 4 of the 12 patients with a normal left ventricular mass index had a reduced average left ventricular filling rate (Fig. 4). There was a moderate inverse linear correlation of mass and filling rate ($r = -0.59$, $p < 0.01$). When only patients with relative wall thickness greater than 0.6 were considered, a moderate negative correlation between relative wall thickness and average left ventricular filling rate was noted ($r = -0.61$, $p < 0.01$), although for the entire group with increased mass no significant correlation was noted.

Discussion

Findings. This study demonstrates that both rapid left ventricular filling time and volume are reduced in patients with mild systemic arterial hypertension. Moreover, these diastolic abnormalities occurred in the absence of left ventricular hypertrophy by electrocardiogram, and in some cases without increased left ventricular mass by echocardiogram.

Methods to study ventricular filling. Several previous investigations (11–13) have demonstrated abnormalities of ventricular relaxation and filling in the heart already hypertrophied in response to chronic pressure overload. Hanrath et al. (14), using echocardiography, found that the chronically pressure overloaded ventricle exhibits a diminished velocity of posterior wall isovolumic relaxation and an abnormal pattern of dimensional increase in diastole. Fouad et al. (3) showed that ventricular filling may be abnormal in hypertensive patients using radionuclide-derived ventricular volume curves, but did not relate this abnormality to ventricular mass. In a more recent study, Inouye et al. (4) used gamma camera-derived left ventricular volume curves to assess three indexes of left ventricular filling (first third filling fraction, peak filling rate and time to peak filling rate) in hypertensive patients. Abnormalities of these variables in hypertensive patients compared with controls were noted, and reduced filling variables correlated with increased left ventricular mass, as was observed in the present study. The use of average rather than peak filling rate in this study may allow better separation of hypertensive patients from control subjects because of the differences in the way that these rates are calculated. The peak rate considers only the first derivative of the rapid filling segment of the derived time-activity curve, whereas the average rapid filling rate considers the ratio of the rapid filling volume to the rapid filling time. Since both the extent of rapid filling and the time for rapid filling were reduced in the hypertensive patients examined in the present study, inclusion of the

rapid filling volume in the analysis of filling rate may enhance the sensitivity of this calculation in defining abnormalities in hypertensive patients.

A probe rather than a gamma camera was used in this project because the probe generates high resolution time-activity curves with more modest isotope doses and shorter imaging times, an advantage for a test to be applied serially. Berger et al. (7) reported a good correlation between probe and camera-derived ejection fractions. A nonimaging system may be less reliable than a camera in patients with marked heterogeneity of ventricular wall motion, but none of the patients in the present study had such abnormalities. Parallel studies conducted in our laboratory have shown that average filling rates from the probe are comparable to those from a camera when the approximate ejection fraction is known by the operator. First derivative plots of the camera-derived curves resulted in no significant difference in the location of the onset of diastasis compared with the visual choice made from probe-derived curves. In both the normal and the hypertensive patients who comprised this series, the inflection marking the end of rapid filling was obvious. A simple two point average rate can be readily applied to any gamma camera-derived volume curve as well, and does not require specialized mathematical software. The unfitted curve from which it is calculated makes no assumptions about how the ventricle fills.

Role of heart rate and age. The effects of heart rate and age were controlled in the present study as these variables were found to affect left ventricular filling rate in this and previous studies (15–17). Thus, the reduced filling rate in the hypertensive patients (Fig. 3) cannot be attributed to slower heart rates or more advanced age. Although it is possible that a few of the hypertensive patients, notably those with flat ejection fraction responses to effort, had occult coronary disease, none of the patients had a history of angina or myocardial infarction, electrocardiographic Q waves or resting or exercise-induced wall motion abnormalities.

Relation of ventricular filling and ejection variables. The finding that the ejection rate in the hypertensive patient was slightly slower than in the control subjects (Table 2) could be due to increased afterload, because the hypertensive patients were untreated at the time of the study and so had higher blood pressures during their radionuclide studies. It is also possible that the reduced ejection rate could be due in part to an intrinsic myocardial abnormality in hypertensive patients (18). The correlation of filling rate and ejection fraction suggests that end-systolic volume may itself be a factor which determines rapid filling rate. The relatively modest correlation of ejection rate with filling rate in hypertensive patients and lack of correlation in normal subjects raises the possibility that afterload affects filling in human beings only when elevated.

Abnormal ventricular filling in hypertensive patients. Reduced rapid filling rate in the hypertensive patients without obvious ventricular hypertrophy may be a manifestation of subtle hypertrophy occurring within a normal range. On the other hand, relaxation may be abnormal in some hypertensive patients as a consequence of some as yet undefined abnormality of calcium handling in early diastole which precedes the appearance of frank hypertrophy.

There are several possible explanations for abnormal left ventricular filling once cardiac hypertrophy is established. Because coronary flow reserve and capillary luminal volume may be abnormal in the hypertrophied ventricle (19), an imbalance between energy production and energy utilization could explain the slowing of rapid filling in the hypertrophied hypertensive heart, even without obstructive coronary disease. It is possible that impaired relaxation in the hypertensive heart with or without hypertrophy arises from an allosteric effect caused by a slight reduction in left ventricular adenosine triphosphate (ATP) level, since it is well established that ATP content and high energy phosphate levels are reduced by a pressure overload (20). The reduction in high energy phosphate levels caused by an increase in pressure work is small, however, and is unlikely to influence the ability of ATP to interact with the high affinity substrate binding sites of such energy consuming systems as the sarcoplasmic reticulum. However, high concentrations of ATP exert a regulatory effect that accelerate calcium transport by the sarcoplasmic reticulum (21), so that even a slight decrease in ATP concentration in the hypertensive heart could inhibit calcium uptake by this intracellular membrane system. Such an effect might contribute to the filling abnormalities observed in the present study. Another explanation for this abnormality is suggested by the "plasticizing" effect of ATP on the contractile proteins (22). This effect, which is seen at ATP concentrations higher than those needed to saturate the myosin ATPase enzyme, might contribute to a loss of compliance in the pressure overloaded left ventricle of the hypertensive patients.

Increased myocardial collagen content might also diminish the distensibility of the hypertensive ventricle. Increased collagen occurs in the chronically pressure overloaded heart, even without hypertrophy (23). It is well established that substantial increases of myocardial collagen content, which occur once frank hypertrophy has developed (24), adversely affect the diastolic properties of the heart (25).

Geometry itself can influence the diastolic performance of the left ventricle independent of increased mass (26). Our finding that increased relative wall thickness but not increased mass alone predicts abnormal filling agrees with the observation of Grossman et al. (26).

Increased coronary artery turgor due to the elevated aortic pressure in the hypertensive patients may represent another factor that could reduce left ventricular compliance (27). Coronary arteries also manifest structural changes in hypertension (28) which could decrease the elasticity of the chamber.

Clinical implications. The principal finding of this study is that left ventricular filling may be reduced and delayed in patients with mild hypertension. Left ventricular mass and rapid filling rate were found to be inversely related in hypertensive patients, so that more marked hypertrophy is accompanied by greater diastolic dysfunction (Fig. 4). The finding of abnormal filling in four patients with normal mass suggests that a diastolic filling abnormality may represent the initial clinically detectable manifestation of the effects of hypertension on the left ventricle. Since it is still possible that patients with a filling abnormality, but apparently normal left ventricular mass, have already undergone an increase in mass within the normal range, serial studies of patients with mild hypertension are needed to define more precisely the initial abnormality in the pressure-overloaded ventricle.

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