Rapid Left Ventricular Filling in Untreated Hypertensive Subjects with or without Left Ventricular Hypertrophy*

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In this study, independent contribution of age, HR, BMI, casual and ambulatory blood pressure, LVM and LVEF in evaluating diastolic filling have been investigated in 34 never-treated hypertensive patients and in 15 healthy normotensive subjects. All the subjects were free from coronary artery disease, valvular disease, heart failure, renal disease and psychiatric problems. All the hypertensive subjects (never treated) were subgrouped according to presence or absence of LVH. The PFR decreased significantly and tPFR increased significantly in hypertensive patients in comparison with normotensive subjects and they did not change in the presence vs absence of LVH. The PFR was inversely correlated with BMI, age, 24-h mean SBP and with 24-h DBP. In multiple regression analysis, PFR decreased with BMI, age, 24-h mean SBP and DBP but not with LVMI. These results suggest that BMI, age and 24-h mean blood pressure were the major determinants of PFR abnormalities in hypertensive patients.

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EDV = end-diastolic volume; LVH = left ventricular hypertrophy; LVM = left ventricular mass; LVMI = left ventricular mass index; MBP = mean blood pressure; PFR = peak filling rate; tPFR = time to PFR

In the last years, relevant interest has been directed to the diastolic properties of the left ventricle in hypertension.[1] Some abnormalities in LV diastolic function have been reported in hypertensive patients concerning those related to early filling and those related to compliance. These findings were derived from data obtained in man with noninvasive methods such as radionuclide and echocardiographic techniques.[1-5] Although abnormalities in diastolic parameters are generally attributed to myocardial hypertrophy or to an increase in fibrous tissue or a change in its distribution, other factors such as age, HR, systolic parameters, overweight status, blood pressure and adrenergic activity could also influence LV filling.[3,6]

Moreover, in several studies antihypertensive treatments have been discontinued for a few weeks before the diastolic function evaluation, but the possibility of altered function of the left ventricle cannot be excluded. For these reasons evaluating diastolic parameters in never-previously-treated hypertensive patients could reveal more correct data. It is already known that diastolic abnormalities commonly found in several cardiovascular diseases can be related to degree or duration of disease or reversibility of LVH and to adequacy of control of blood pressure.[4,7]

According to some authors,[1,2,5] LV rapid filling impairment may be present in patients with coronary artery disease or hypertension even in the absence of alterations in systolic function and in the lack of LVH. In this case, impaired LV filling could represent an early marker of the pathologic effects of some diseases on the heart.[8,9]

In the present study we evaluated LV rapid filling in a group of unselected and untreated mild to moderate hypertensive patients and in a group of healthy normotensive subjects. Our final goal was to determine whether LVH can influence diastolic early filling in hypertensive patients and to evaluate the independent role exerted by age, blood pressure, HR, BMI and echocardiographic LVMI. For these reasons hypertensive patients were subgrouped according to the presence or absence of LVH.

Patients and Methods

Patient Population

Thirty-four mild to moderate hypertensive patients (20 males and 14 females) from 35 to 52 years of age and 15 healthy normotensive control subjects (seven males and eight females) from 37 to 54 years of age were included in the study. No significant differences in age, weight, height, BMI, sex distribution and HR were observed between normotensive and hypertensive subjects (Table 1).

All the subjects studied were consecutive never-treated essential hypertensive subjects or healthy subjects attending our hypertension research unit at University of Palermo, Italy, since November 1989 and meeting all the following criteria:

1. No antihypertensive drug treatment.
2. Good quality of echocardiographic and radionuclide imaging.
3. Agreement within 5 mm Hg between ambulatory blood pressure recording unit and standard mercury sphygmomanometer in at least three consecutive measurements taken simultaneously on the same arm before beginning the ambulatory recording.
4. Absence of clinical, electrocardiographic or echocardiographic evidence of coronary artery disease, valvular disease, heart failure, renal disease or psychiatric problems.

Based on history and physical examination data, secondary causes

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of hypertension were excluded. When necessary, specific instrumental investigations also were performed. We also had excluded from the study all subjects with symptoms and signs that may be associated with decreased blood volume such as dizziness, syncope and orthostatic hypotension.

Essential hypertension was defined according to WHO criteria and with DBP values >90 mm Hg measured with the subject in the supine position on at least three visits at one-week intervals. Diastolic blood pressure refers to Korotkoff V phase. The MBP was calculated from the sum of DBP plus one third of the arterial pulse pressure. Arterial pressure also was measured with an appropriate large cuff in overweight subjects.[9] The known duration of hypertension was more than two years in all the hypertensives. Heart rate was evaluated by electrocardiographic tracing. Healthy normotensive subjects were volunteer subjects chosen from among a group of subjects undergoing a clinical checkup and found to be healthy.

All the subjects gave informed consent after they were given detailed information about the study procedure, and the study was approved by the Sicily regional ethics committee.

Methods

Ambulatory Blood Pressure Measurements

Ambulatory blood pressure was recorded by the portable fully automatic Takeda TM2420 system connected through the serial interface (RS232) to an IBM personal system 2 computer which in our laboratory showed a correlation of r = 0.96 with both SBP and DBP measured in the same arm using a mercury sphygmomanometer. The reading, editing and summary analysis of data provided by the unit was done by a dedicated software. The unit was set to take readings automatically every 15 min throughout the 24-h period. This approach has been well tolerated by many patients who were recruited. Only two hypertensive patients were excluded since the frequent recording of blood pressure during the night interfered with their sleep.

A 24-h mean SBP and DPB reading was taken.

Criteria for deleting individual blood pressure readings included a pulse pressure that was less than 12 mm Hg or an inconsistent increase and decrease in SBP or DBP greater than 30 mm Hg from previous or subsequent readings. Recordings were included in this study only if at least 80 percent of the maximal number of 96 readings during the 24-h period passed the deletion criteria. Journals of activity, symptoms and emotions were carefully kept by the subjects for aid in the editing process.

Echocardiographic Study

Two-dimensional and M-mode echocardiography examination was performed by an Esaote Biomedica computer-aided ultrasound system equipped with 2.5- and 3.5-MHz phased-array transducers, and a standard VHS video format was used to record it. Left ventricular mass and LVMI was calculated according to the Devereux method from necropsy validation studies.[10]

Left ventricular hypertrophy was assumed in the presence of a LVMI>2 standard deviations of the sex-specific mean of a group of 110 normotensive subjects without a family history of hypertension providing the normal values for our laboratory (88 ± 16 g/sq m for men and 75 ± 14 g/sq m for women). Accordingly, patients were considered to have LVH when the LVMI values were >120 g/sq m for men and >103 g/sq m for women.

The first assessment of LVM was performed by a preliminary M-mode echocardiogram under two-dimensional control, also excluding either abnormal regional septal and parietal thickenings or wall motion abnormalities. When enrolled, patients underwent a new echocardiogram which was coded and used for the study. The most selective criterion was the complete absence of any previous antihypertensive therapy in the history.

According to these criteria, nine hypertensive subjects (six males and three females) with LVH and 25 without LVH were individuated. No significant differences in age, height, HR, casual and 24-h MBP and in BMI among two hypertensive groups was observed (Table 1).

Table 1—*Summary Data for Normotensive and Hypertensive Subjects (Mean Value ± SEM)*

	Normotensives	Hypertensives without LVH	Hypertensives with LVH
No.	15	25	9
Age (years)	44.70 ± 2.180	45.90 ± 1.800	44.30 ± 1.700
Height (m)	1.65 ± 0.004	1.64 ± 0.003	1.65 ± 0.002
BMI (kg/m²)	25.10 ± 0.400	26.50 ± 0.490	27.10 ± 0.500
HR (b/min)	74.50 ± 1.300	77.50 ± 1.200	76.20 ± 1.400
SBPc (mm Hg)	120.20 ± 1.500	161.50 ± 3.500*	165.00 ± 3.200*
DBPc (mm Hg)	75.20 ± 1.900	99.10 ± 1.600*	100.00 ± 1.500*
MBPc (mm Hg)	90.40 ± 1.600	120.00 ± 1.900*	121.67 ± 2.000*
SBP 24h (mm Hg)	118.20 ± 2.000	140.10 ± 2.100*	143.00 ± 2.000*
DBP 24h (mm Hg)	77.50 ± 1.500	92.60 ± 1.900*	95.00 ± 2.000*
PFR (EDV/s)	3.58 ± 0.250	2.77 ± 0.390†	2.74 ± 0.400†
tPFR (ms)	143.70 ± 6.200	182.00 ± 7.500†	184.00 ± 8.000†
EF (%)	64.00 ± 1.500	61.00 ± 1.400	60.00 ± 1.300
LVMI (g/m²)	94.70 ± 3.800	110.00 ± 6.000	129.00 ± 7.500‡

*p<0.001 vs normotensives; †p<0.05 vs normotensives; ‡p<0.05 vs hypertensives without LVH.

Radionuclide Study

Systolic and diastolic function was evaluated by radionuclide angiography with the subjects at rest using the blood pool gated method according to Bonow et al[5] and a computerized large field scintillation camera (Starcam 400, General Electric) with a high resolution 1.5-inch parallel hole collimator.

Radionuclide angiography was performed at 9 AM with the subjects in the supine position using red blood cells labeled with 20 to 25 mCi of technetium 99m in the left anterior oblique position to isolate the left ventricle. A minimum of 300,000 counts per frame was reached before stopping data collection. High temporal resolution (10 to 20 ms per frame) cardiac image sequences were constructed by computer-based ECG gating, with the use of list mode data acquisition with exclusion of extrasystolic and postextrasystolic cycles and combined forward and reverse gating from the R wave.

Left ventricular time activity curves representing relative changes in LV volume during the average cardiac cycle were generated from the cardiac image sequence after background correction with an automatically fixed LV region of interest to the borders of the LV as identified from the end-diastolic image, the stroke volume image and the amplitude image. This latter functional image was created by approximating each single picture element time-activity curve with the first harmonic of its temporal Fourier expansion. The time-activity curve was constructed from the raw image sequence without spatial or temporal smoothing processes.

Indices of LV function were derived by computer analysis of the background corrected time-activity curves. Left ventricular ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. Peak filling rate was determined by fitting third-order polynomial function to the systolic ejection squares technique. The time of occurrence of the PFR was obtained by setting the second derivative of the polynomial function to zero. Time to PFR was relative to end-systole (minimal volume on the time-activity curve). The PFR was computed in LV counts per second, normalized for the numbers of counts at the end-diastole and expressed as fractional end-diastolic counts (or EDV/s).

Statistical Analysis

Comparison between normotensive and hypertensive subjects and between hypertrophied or not hypertrophied hypertensive patients was performed using one-way analysis of variance. When the difference was statistically significant, the Student-Newman-Keuls test also was detected.

Linear and multiple regression analysis was used to calculate coefficients of correlation among PFR and BMI, age, casual and 24-h mean SBP, DBP and MBP, left ventricular ejection fraction and LVMI. Independent variables in multiple regression analysis were BMI, age, 24-h mean SBP and DBP and LVMI.

A p value <0.05 was considered statistically significant. All results in text and in tables are presented as mean value ± standard error of the mean.

Results

Comparisons and Differences

To evaluate the effects of hypertension on LV diastolic function, we compared findings in normotensive and in hypertensive subjects both with and without LVH. As shown in Table 1, age, height, HR and BMI did not significantly differ in all the groups studied. In addition, casual and 24-h MBP values were not significantly different in both hypertensive groups, while LVMI was obviously greater ($p<0.05$) in LVH-hypertensive subjects in comparison both with normotensive subjects and with no-LVH-hypertensive patients.

A significant decrease ($p<0.05$) in PFR and a significant ($p<0.05$) prolonged tPFR were observed in both hypertensive groups in comparison with normotensive controls. No significant change in EF among all the groups was found. In addition, PFR and tPFR values did not differ significantly in LVH-hypertensive or no-LVH-hypertensive patients.

Correlations

In hypertensive patients with or without LVH, PFR was inversely correlated with BMI ($r=-0.602$; $p<0.001$), age ($r=-0.674$; $p<0.001$), 24-h mean SBP ($r=-0.621$; $p<0.001$) and with 24-h mean DBP ($r=-0.500$; $p<0.001$) (Fig 1 and 2). No correlation between PFR and HR ($r=0.16$), casual SBP ($r=-0.25$), casual DBP ($r=-0.14$), casual MBP ($r=-0.20$), LVEF ($r=0.20$) and LVMI ($r=-0.30$) was found.

Multiple regression analysis was performed to ascertain the independent role of variables correlated to PFR (Table 2). After adjustment for all variables examined, PFR values significantly ($p<0.01$) decreased with age ($r=-0.48$), BMI ($r=-0.45$), 24-h SBP ($r=-0.46$) and 24-h DBP ($r=-0.44$) but not with LVMI ($r=-0.23$). The multiple correlation coefficient was 0.53 ($p<0.01$).

Discussion and Conclusion

This study indicates the presence of diastolic abnormalities in unselected and untreated hypertensive patients consisting of a reduction of PFR and in a prolonged tPFR. These changes represent results

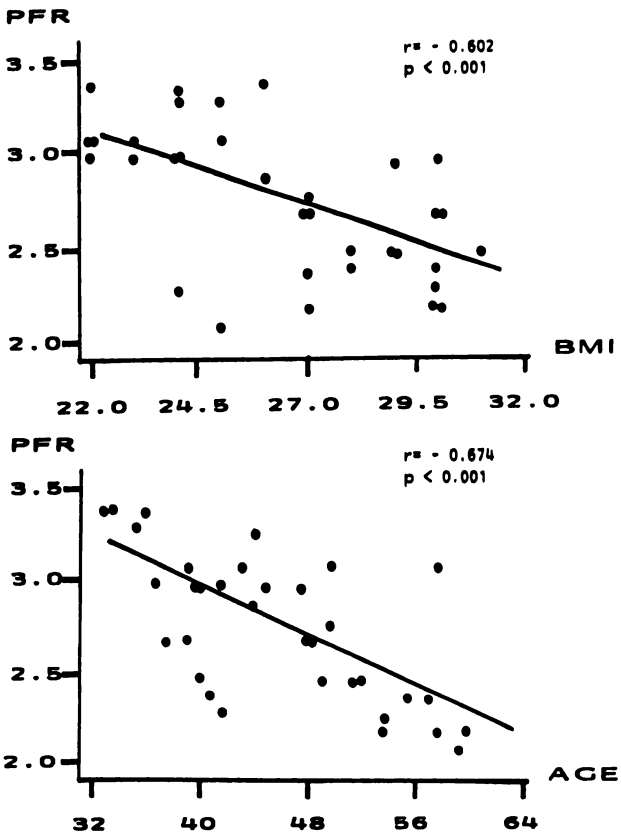

FIGURE 1. Correlation among PFR and BMI *(top)* and between PFR and age *(bottom)*.

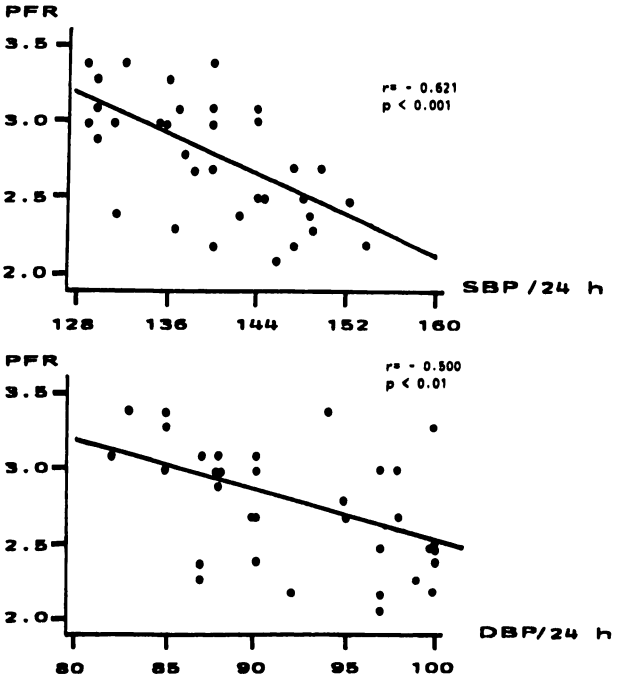

FIGURE 2. Correlation among PFR and 24-h mean SBP *(top)* and between PFR and 24-h mean DBP *(bottom)*.

independent of the presence or absence of LVH but age, BMI and ambulatory blood pressure appear to be the major independent predictors of PFR in such hypertensive patients. An attempt was made to clinically exclude loading alterations unrelated to hypertension.

There are several possible explanations for the abnormal PFR in arterial hypertension. In fact, in the presence of chronic blood pressure overload, the myocardial content of collagen may increase not only when hypertrophy has developed, but even before.[11] In addition, it has been reported that structural and functional abnormalities in coronary vessels could influence LV filling in hypertensive subjects with or without LVH.[12,13]

In our study, ambulatory blood pressure, but not casual blood pressure, showed an independent relationship with PFR, as noted by other studies where diastolic function was evaluated by echo-Doppler examination.[2,3] In hypertensive patients, ambulatory blood pressure also is more closely related to LV wall thickness and mass than casual blood pressure.[14] Another finding is related to the inverse correlation observed among PFR and age that confirms previous studies.[3,15] In fact, it is known that aging is associated with an increased amount of collagen localized in the subendocardial and subepicardial layers;[16] myocardial collagen becomes increasingly insoluble and stiff showing an increased number or stability of the crosslinks of the polymer subunits.[17] These changes may account for the impaired ventricular diastolic performance with increasing age.

In our study, the lack of correlation between PFR and LVMI disagrees with other authors who reported an inverse univariate correlation between PFR and LVM.[2,3] However, in some studies, this univariate relationship disappeared when multivariate analysis was performed, suggesting that the progressive decline of LV diastolic performance with increasing LVM could be related to increased afterload more than to increased LVM itself.

In addition, Granger et al[18] did not report abnormalities in rapid filling in athletes with LVH equal in degree to hypertensive LVH. It is to date difficult to establish the effect of LV afterload on early LV filling. Some authors reported that increased afterload prolonged LV relaxation.[19] Another complicating factor is the duration of increase in afterload. In fact, Gaasoh et al[20] clearly demonstrated a marked difference in alteration of diastolic indices between acute and steady state changes in afterload.

In view of this, our results are in agreement with those reported by Verdecchia et al[2] and by White et al[3] in untreated and treated hypertensive patients. We observed another important finding regarding the negative correlation between PFR and BMI, which

Table 2—*Multiple Regression Analysis*

	Partial Coefficients of Correlations					Multiple Coefficient
	Age	BMI	SBP 24 h	DBP 24 h	LVMI	Correlations
PFR	−0.480*	−0.458*	−0.460*	−0.442*	−0.235	−0.529*

*$p<0.01$

Explanatory variables are BMI, SBP 24h, DBP 24h and LVMI. $y = a + b \times BMI + c \times SBP24h + d \times DBP24h + e \times LVMI$ where a, b, c, d, and e are partial regression coefficients. The first value for partial correlation coefficient, for example, is the correlation coefficient between PFR and age after adjustment for BMI, SBP24h, DBP24h and LVMI.

was confirmed by multivariate analysis: a fact that has not been previously reported.

This finding confirms our previous data indicating that severity and duration of obesity could influence LV function both at rest and after exercise in normotensive subjects free from diabetes, hyperlipoproteinemia and other known risk factors for cardiovascular disease.[21,22]

However, age, BMI, 24-h SBP and DBP partially explain the changes in PFR. In fact, r^2, the square of the correlation coefficient, is 0.44, 0.36, 0.39 and 0.25, respectively, for PFR and age, BMI, 24-h SBP and DBP which means that 44, 36, 39 and 25 percent, respectively of the variation of PFR can be explained by these measurements.

This study was not designed to analyze all the determinants of ventricular filling abnormalities. Nevertheless our results indicate a number of clinical implications, most important of which is that age, BMI and ambulatory blood pressure must be taken into consideration when interpreting the results of rapid filling from the time-activity curve analysis. In view of this, although LVH in mild to moderate hypertensive patients can be associated with impaired diastolic performance, age, average daily blood pressure and BMI can be more important determinants of PFR than cardiac size.

In fact, in hypertensive patients the development of LVH is probably a slow and gradual phenomenon; thus, the LVM may increase in several patients and yet remain below the threshold value for conventional diagnosis of hypertrophy. This could represent another explanation for why the prevalence of diastolic filling abnormalities usually exceeds that of frank hypertrophy.[2]

In this study, atrioventricular pressure difference has not been evaluated. It is known that changes in LV pressure can produce remarkable alteration of PFR. However, none of the subjects showed a third heart sound or other signs of heart failure, and left atrial diameter was comparable in the normotensive

and hypertensive groups and unaffected by LVH. It is unlikely that in the present study an increased left atrial pressure may have enhanced PFR in the subgroup with LVH, leading to underestimation of left ventricular filling abnormalities. In fact, the nine hypertensive patients with LVH had mild LVH (LVMI was 17 percent higher in the LVH group in comparison with hypertensive patients without LVH).

In conclusion, longitudinal studies are needed to individuate the hypertensive patients with PFR abnormalities that tend to evolve toward LVH and to identify the possible predictors of such evolution. This approach could be useful to evaluate the possible preventive effects on cardiac function of pharmacologic or nonpharmacologic management or both in hypertensive subjects.

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