Left Ventricular Filling in the Hypertensive Patient: Long-Term Course and Influence of Treatment

PHILIPPE GOSSE, M.D., VERONIQUE JULLIEN, M.D., PHILIPPE JARNIER, M.D., PHILIPPE LEMETAYER, M.D., JACQUES CLEMENTY, M.D.

Hôpital Saint André, Bordeaux, France

Summary

Background: Hypertension is accompanied by abnormalities in left ventricular filling; however, there is a lack of agreement on the extent of the influence of antihypertensive treatment on them.

Hypothesis: The present study was designed to evaluate the long-term course of these abnormalities in both treated and untreated hypertensive patients.

Methods: Left ventricular filling assessed by pulsed Doppler echocardiography of mitral flow was studied over a long follow-up period in both untreated and treated hypertensive patients. This retrospective study included 73 hypertensive patients who had not received any treatment. They had been followed up for at least 3 years and were divided a posteriori into two groups: Group 1 comprised the untreated patients, while Group 2 included the patients who had received antihypertensive treatment throughout the follow-up period.

Results: In the overall population, age and heart rate measured during the Doppler examination were the only parameters that correlated significantly with mitral flow. No significant changes in blood pressure or left ventricular mass were observed in Group 1 (14 patients) over the study period. There was a slight but nonsignificant decrease in E/A ratio of mitral flow. In the treated patients, there was a drop in heart rate-adjusted E/A ratio, despite a reduction in blood pressure and left ventricular mass, at mean follow-up of 5 years.

Conclusion: Antihypertensive therapy did not arrest the long-term reduction in E/A ratio in hypertensive patients despite reduction in blood pressure and left ventricular mass.

Key words: left ventricular filling, pulsed Doppler mitral flow, hypertension, antihypertensive treatment

Introduction

Hypertension is accompanied by abnormalities in left ventricular (LV) filling.^{1–3} These disturbances stem mainly from prolongation of relaxation and are seen on pulsed Doppler recordings of mitral flow as a decrease in the maximal rate of rapid early diastolic filling (E) and an increase in maximal rate of end-diastolic filling from atrial contraction (A). The significance of these abnormalities has yet to be established, as they may be found in recently diagnosed hypertensive patients without any obvious relationship to blood pressure or the extent of LV hypertrophy.^{4–8} They are held responsible for the cardiac insufficiency with normal systolic function that appears to develop in the elderly hypertensive patient.^{9–12} The true prognostic significance of these abnormalities is unknown, and there is a lack of agreement on the extent of the influence of antihypertensive treatment on them.^{13–16} The present study was thus designed to evaluate the long-term course of LV filling in both treated and untreated hypertensive patients.

Methods

Patients

The study included patients with essential hypertension, who had either not been treated or had not received any treatment over the 3 months prior to the first examination, who were in sinus rhythm, and who had been followed up in our department for at least 3 years. On first examination, all patients underwent a high-quality M-mode echocardiographic study of the left ventricle and pulsed Doppler assessment of mitral flow. The last echo Doppler examination was performed at least 3 years apart. Patients with a history of coronary artery disease, cardiac valve or muscle disorders, and bundle-branch block were excluded. The patients were allocated a posteriori into two groups: Group 1 included the patients who had received no treatment over the follow-up period (borderline hy-

Address for reprints:

Dr. Philippe Gosse
Hôpital Saint André
1 rue Jean Burguet
33075, Bordeaux, France

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pertension, refusal by patient); Group 2 included the patients who received antihypertensive treatment throughout the follow-up period, either with a single drug (Group 2a) or with different drugs alone or in combination (Group 2b). The treatments were not allocated at random and were administered in an open design.

Blood Pressure Measurement

Blood pressure (BP) was measured with a mercury manometer in the presence of a physician with the patients recumbent after a 10 min rest. All measurements were made by the same physician, and the diastolic pressure was measured in phase V. The mean of three separate determinations was noted.

Doppler Echocardiography

All tracings were performed by the same trained echocardiographer (PG) all during the study. M-mode tracings of the left ventricle were recorded using a Hewlett-Packard instrument (Hewlett Packard, Andover, Mass., USA) with a 2 MHz probe from the left parasternal view under two-dimensional guidance. At least five consecutive cycles of the left ventricle were recorded on a high-quality strip chart recorder at a speed of 100 mm/s. Mitral flow was recorded from an apical four-chamber view, with the pulsed Doppler sample placed in the middle of the mitral annulus. Five consecutive cycles were recorded at a paper speed of 100 mm/s with the patient breathing freely. All the tracings were read blindly over at least three cycles. The end-diastolic diameter (EDD), septal thickness (ST), and posterior wall thickness (PWT) in diastole were measured from the M-mode tracings according to the Penn convention. Left ventricular mass was calculated from Devereux's formula¹⁷ and indexed for height. Both E and A were measured on the Doppler tracing and the E/A ratio was calculated. Heart rate during the Doppler examinations was calculated from the R-R interval.

Statistical Analysis

The data were analyzed using PCSM software (Deltasoft, France), and the groups were compared by analysis of variance. Analysis of variance for repeated measures was employed to assess the changes over time of the various parameters. In view of the marked influence of heart rate on ventricular filling, this was introduced as a covariant (one covariant per measure) in the analysis of the filling parameters. In the event of a significant result ($p < 0.05$), the data were compared using Newmann-Keuls test. Multiple linear regression was employed to determine the factors that correlated with the E/A ratio.

Results

The study included 73 patients divided into two groups the details of which are listed in Table I. The overall follow-up pe-

riod was shorter (mean 4 years) for the patients in Group 1 (untreated) than for those in Group 2 (treated) (mean 5 years). Blood pressure and LV mass were significantly lower in Group 1. In the total population, the E/A ratio at baseline correlated significantly and independently with age ($r = -0.40$), $p < 0.0001$ and heart rate ($r = -0.38$, $p < 0.0001$), which together accounted for 31% of the variance. No significant relationship was observed between E/A and BP or LV mass. In Group 1 patients, no significant change in BP or LV mass was observed at the last follow-up examination. Heart rate was significantly lower ($p = 0.04$) and maximal rate of filling (E) was significantly reduced ($p = 0.04$) after adjustment for heart rate (Table II). The E/A tended to fall over time despite a slowing in heart rate, although the difference was not statistically significant even after introducing heart rate as covariant. The treatments received throughout the follow-up period by the patients in Group 2a and the last treatment received for those in Group 2b are listed in Table III. In the treated patients (Table IV), there was a significant reduction in heart rate, wall thickness, and LV mass, although there was a significant drop in E/A ratio ($p = 0.004$) largely due to a reduction in E wave. Among the patients receiving a single drug over the study period, 21 benefited from a second recording, under the same conditions as the first, 2 to 6 months after the start of the treatment. In this population, there was an increase in E/A ratio after treatment. The initial increase appeared to stem from the drop in

TABLE I Main details of patient population at baseline

	Group 1 (no treatment)	Group 2 (treated)	p Value
No. of patients	14	59	
M/F	10/4	46/13	NS
Follow-up (months)	52 ± 13	64 ± 13	0.008
Age (years)	47 ± 11	52 ± 10	NS
Weight (kg)	74 ± 17	76 ± 16	NS
Height (cm)	171 ± 10	169 ± 9	NS
SBP (mmHg)	154 ± 15	168 ± 16	0.006
DBP (mmHg)	96 ± 10	103 ± 8	0.007
EDD (mm)	52.2 ± 5.5	54.3 ± 5.9	NS
ESD (mm)	31.8 ± 4.5	33.3 ± 5.8	NS
ST (mm)	9.5 ± 1.5	10.9 ± 1.9	0.02
PWT (mm)	9.5 ± 1.5	10 ± 1.7	NS
LVM/H (g/m)	128 ± 34	158 ± 48	0.03
E (cm/s)	58 ± 12	52 ± 14	NS
A (cm/s)	59 ± 13	58 ± 11	NS
E/A	1.04 ± 0.34	0.92 ± 0.29	NS
HR (beats/min)	74 ± 17	72 ± 12	NS

Abbreviations: M/F = males/females, SBP = systolic blood pressure, DBP = diastolic blood pressure, EDD = end-diastolic diameter of left ventricle, ESD = end-systolic diameter of left ventricle, ST = septal thickness, PWT = posterior wall thickness, LVM/H = left ventricular mass indexed for height, E = maximum velocity of early mitral flow, A = maximum velocity of late (atrial contraction) mitral flow, HR = heart rate, NS = not significant.

TABLE II Change in parameters in untreated patients (Group 1) over follow-up period

	Inclusion	Last control	p Value
SBP (mmHg)	154 ± 15	153 ± 22	NS
DBP (mmHg)	96 ± 10	94 ± 14	NS
EDD (mm)	52.2 ± 5.5	52.2 ± 5.2	NS
ESD (mm)	31.8 ± 4.5	31.2 ± 4	NS
ST (mm)	9.5 ± 1.5	10.1 ± 2	NS
PWT (mm)	9.5 ± 1.5	9.2 ± 1.5	NS
LVM/H (g/m)	128 ± 34	131 ± 39	NS
E (cm/s)	58 ± 12	53 ± 15	0.04 ^a
(adjusted for HR)	(60)	(52)	
A (cm/s)	59 ± 13	61 ± 17	NS ^a
(adjusted for HR)	(59)	(61)	
E/A	1.04 ± 0.34	0.94 ± 0.34	NS ^a
(adjusted for HR)	(1.07)	(0.91)	
HR (beats/min)	74 ± 17	67 ± 11	0.04

^a With heart rate included as covariant.

Abbreviations as in Table I.

heart rate after treatment with beta blockers and it disappeared after adjustment for heart rate. In the long term, there was a significant reduction in E/A ratio, especially after heart rate adjustment (Table V). In this population, the decreased E/A ratio observed at the last follow-up examination can be attributed to aging, as there was no significant change in heart rate between the second and last examinations, a decrease in ventricular mass, and no change in treatment during this period.

For the total population, multiple linear regression of the alteration in E/A ratio at the last examination as a function of follow-up duration, systolic and diastolic BP, heart rate, and LV mass only demonstrated a significant relationship with heart rate ($r = -0.39$, $p < 0.0001$).

Discussion

This study evidenced a drop in E/A ratio with time in patients with essential hypertension. Antihypertensive treatment did not appear to change this tendency despite the prolonged reduction in BP and LV mass. Apart from aging, heart rate was the only parameter that appeared to influence the E/A ratio.

Aging was accompanied by an alteration in LV filling due mainly to a prolongation of relaxation, as has been evidenced in cross-sectional studies of populations of patients without cardiovascular disease.¹⁸⁻²¹ To our knowledge, the present study is the first to document this in a long-term follow-up of untreated hypertensive patients. We found that the drop in E/A with age was due essentially to a reduction in maximal rate of rapid filling (E). High blood pressure has similar consequences to that of aging²² on relaxation. The abnormalities described in the hypertensive patient appear early in the disease and are little dependent on BP or LV mass. In our population of untreated hypertensive patients, the only parameters that

TABLE III Treatments received by the patients in Group 2

	Group 2a (single drug)	Group 2b (different drugs)
Beta blockers	10	7
ACE inhibitors	8	3
Calcium antagonists	4	5
Diuretics	1	4
Others	1	1
Combination	0	15
No. of patients	24	35

Abbreviation: ACE = angiotensin-converting enzyme.

correlated significantly with this ratio were heart rate and age, but not BP or LV mass. It might be assumed that there is a relationship between these abnormalities and the onset of cardiac insufficiency in patients with normal systolic function, although there is as yet no clear evidence for a relationship between disturbances in LV filling and prognosis in the hypertensive patient. This would tend to belittle the value of a systematic search for such abnormalities.

Pulsed Doppler examination of the mitral valve is readily carried out, although the measurement of the E/A ratio depends on many factors, especially load conditions and heart rate.²³⁻²⁶ The important influence of heart rate is now well established. The acceleration in cardiac rhythm is reflected mainly by an increase in the A wave on pulsed Doppler recordings and a drop in the E/A ratio. This is a significant factor that highlights the importance of measuring heart rate at the same time as the pulsed Doppler examination. In our study, the change in heart rate measured at the same time as the Doppler recording was the only factor that correlated significantly with the long-term change in E/A ratio.

TABLE IV Change in parameters in treated patients (Group 2) over follow-up period

	Inclusion	Last control	p Value
SBP (mmHg)	168 ± 16	146 ± 13	0.0001
DBP (mmHg)	103 ± 8	90 ± 9	0.0001
EDD (mm)	54.3 ± 5.9	53.2 ± 5.3	NS
ESD (mm)	33.3 ± 5.8	33.7 ± 4.9	NS
ST (mm)	10.9 ± 2	10.3 ± 1.7	0.03
PWT (mm)	10 ± 1.7	9.5 ± 1.3	0.009
LVM/H (g/m)	158 ± 48	141 ± 36	0.001
E (cm/s)	52 ± 14	49 ± 13	0.002 ^a
(adjusted for HR)	(54)	(47)	
A (cm/s)	58 ± 11	57 ± 13	NS ^a
(adjusted for HR)	(58)	(58)	
E/A	0.92 ± 0.29	0.87 ± 0.27	0.004 ^a
(adjusted for HR)	(0.96)	(0.83)	
HR (beats/min)	72 ± 10	64 ± 10	0.0001

^a With heart rate included as covariant.

Abbreviations as in Table I.

TABLE V Change in parameters in patients treated with a single drug over follow-up period

No. of patients = 21	Inclusion	First control (3.7 ± 2 months)	Last control (63 ± 13 months)	p Value
E/A	0.97 ± 0.34	1.06 ± 0.33	0.92 ± 0.32	0.05 ^a
(adjusted for HR)	(1.03)	(1.02)	(0.90)	
HR (beats/min)	73 ± 10	63 ± 10	66 ± 11	0.01
E (cm/s)	55 ± 14	57 ± 14	49 ± 12	0.007 ^a
(adjusted for HR)	(57)	(55)	(47)	
A (cm/s)	59 ± 10	55 ± 11	55 ± 12	NS ^a
(adjusted for HR)	(58)	(56)	(55)	
SBP (mmHg)	161 ± 12	144 ± 11	146 ± 11	0.0001
DBP (mmHg)	102 ± 9	91 ± 7	90 ± 10	0.0001
LVM/H (g/m)	165 ± 54	150 ± 42	139 ± 38	0.001

^a With heart rate included as covariant.

Abbreviations as in Table I.

Study Limitations

This study is retrospective and the two groups were defined a posteriori. The untreated group included patients with the least severe hypertension and lower LV mass. The two groups were examined in strictly similar conditions and echo Doppler examinations were read blind to all clinical data. However, we cannot rule out that antihypertensive treatment was indeed able to reduce the slope of E/A ratio decrease with aging in more severely hypertensive patients. The reproducibility in the measurement of the E/A ratio is poor,^{27,28} which may well account for the lack of agreement between the results of the various studies^{13–16} and the reported effects of antihypertensive treatment. In addition, most studies have only involved a limited number of patients (between 10 and 30), and follow-up periods exceeding 1 year have not been reported. Furthermore, few studies have taken alterations in heart rate into account, especially the value determined at the time of recording of filling parameters.

Our results showed the lack of efficacy of long-term antihypertensive treatment on the E/A ratio, despite a significant lowering of BP and LV mass. The aging process thus appeared to outweigh the beneficial effects of the treatment. In the short term (2–6 months), there was an improvement in E/A ratio. This was attributed to the slowing in heart rate under beta blockers, although a direct effect of these agents could not be ruled out. Nevertheless, this effect did not appear to arrest the fall in E/A ratio with age.

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