Normalization of Left Ventricular Dysfunction in Systemic Hypertension

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Summary

Background: In hypertensive heart disease, it is uncertain whether the impairment of left ventricular (LV) systolic function might be reverted by antihypertensive treatment.

Hypothesis: This study was undertaken to address the likelihood of recovery of LV dysfunction and to identify factors potentially related.

Methods: Twenty-six patients with primary ($n = 16$) and renovascular ($n = 10$) hypertension participated in the study and were classified into Groups A ($n = 12$) and B ($n = 14$) according to normalization or persistent left ventricular dysfunction (fractional shortening < 0.30) after 36 weeks of follow-up. All patients received standard medical therapy and appropriate procedures for renovascular disease correction. Logistic regression analysis was used to identify variables associated with recovery.

Results: Patients in Group A compared with those in Group B were younger (41 ± 14 vs. 52 ± 10 years; $p < 0.05$), had a greater frequency of renovascular hypertension (8 vs. 2; $p < 0.05$), showed shorter LV end-diastolic (54 ± 5 vs. 61 ± 8 mm; $p < 0.05$) and end-systolic dimensions (41 ± 6 vs. 49 ± 9 mm; $p < 0.05$), and lower mass index (215 ± 64 vs. 261 ± 47 g·m⁻²; $p < 0.05$) before treatment, whereas fractional shortening (0.24 ± 0.4 vs. 0.20 ± 0.5 ; $p > 0.05$) and diastolic blood pressure (116 ± 12 vs. 122 ± 19 mmHg; $p > 0.05$) were similar. On follow-up, Group A patients showed lower diastolic blood pressure (89 ± 15 vs. 105 ± 20 mmHg; $p < 0.05$) and mass index (142 ± 34 vs. 222 ± 40 g·m⁻²; $p < 0.05$). Logistic regression analysis identified systolic dimension and renovascular hypertension as factors associated with fractional shortening normalization.

Conclusion: The recovery of LV dysfunction is expected to occur most likely in patients with renovascular hypertension and the shortest systolic dimensions.

Key words: left ventricular dysfunction, hypertension, renovascular disease

Introduction

Left ventricular (LV) hypertrophy is a compensatory myocardial response to chronic pressure overload that hemodynamically characterizes systemic hypertension. Thickening of the ventricular walls with the resultant decrease in internal chamber dimensions contribute to the preservation of systolic function by counteracting the impending elevation of systolic wall stress.^{1,2} Nevertheless, systolic dysfunction is identified in as many as 13% of patients with systemic hypertension,³ indicating a true but not yet completely elucidated limitation of this adaptive process. In contrast to the larger accumulated experience in patients with valvular heart disease, in whom end-systolic dimension was demonstrated to predict the recovery of LV dysfunction after surgery,^{4,5} in hypertension it remains to be determined whether recovery of systolic function⁶ actually occurs and which are the related factors. Based on clinical and experimental evidence,^{7,8} it is conceivable that any treatment that can possibly interfere with the process of myocardial remodeling is likely to play a beneficial role in cardiac function.

This prospective study was undertaken to investigate the occurrence of recovery of LV systolic dysfunction in hypertensive heart disease and to identify the potential determinants related to a favorable response after long-term antihypertensive treatment.

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Received: June 21, 1999

Accepted with revision: September 3, 1999

Methods

Study Population

All procedures were carried out in accordance with institutional guidelines, and the protocol was approved by our institutional review committee. The primary inclusion criterion

was the presence of echocardiographic LV fractional shortening of less than 30% in patients with systemic hypertension. To avoid the inclusion of patients with cardiac dysfunction other than presumably hypertensive in origin, both diastolic posterior wall thickness and interventricular septal thickness needed necessarily to be > 10 mm. In addition, patients with diabetes mellitus, end-stage renal failure, hemodynamically significant valvular heart disease, bundle-branch block and conduction disturbances on surface electrocardiography, and positive serologic test for Chagas disease were excluded from the study.

Twenty-six patients, 10 of whom had arteriographically documented significant renal artery stenosis ($\geq 70\%$), fulfilled the above criteria, gave informed consent, and took part in the study. There were 15 men and 11 women, with a mean age of 47 years, ranging from 21 to 73 years.

The mean values of two casual blood pressure measurements taken at 2-week intervals were recorded during enrollment at the beginning of the study and compared with those values determined the same way at the 9th month of follow-up.

Twelve patients with clinical symptoms suggestive of coronary artery disease were submitted to coronary arteriographic studies. Only two patients showed single-vessel disease located in the right coronary artery and in the left anterior descending coronary artery, respectively.

According to previously established arteriographic criteria,⁹ the etiology of renovascular disease was defined as atherosclerosis in four patients, as fibromuscular dysplasia in another four patients, and as arteritis in the remaining two patients. Eight patients had unilateral renovascular disease. A total occlusion of one of the main renal arteries was evident in two patients.

Percutaneous transluminal renal angioplasty was performed in seven unilateral nonoccluded vessels, according to Tegtmeier's techniques.¹⁰ Technical success, defined by the presence of a < 30% residual stenosis 15 min after dilatation, was achieved in all patients, with no major vascular or renal complications.

Surgical revascularization of the renal artery was performed in three arteries by means of a saphenous graft, a splenic anastomosis, and an autologous kidney autotransplantation. Both kidneys with completely obstructed arteries were nephrectomized.

Therapeutic drug regimens were adjusted at 1-month intervals. As a general rule, hydrochlorothiazide (25–50 mg/day) was the first drug employed, followed by methyl dopa (500–1500 mg/day) and by hydralazine (50–200 mg/day). Either captopril (50–150 mg/day) or nifedipine (30–60 mg/day) were added to the therapeutic regimen, as necessary, in order to try to maintain diastolic blood pressure levels < 90 mmHg. This was the case in four patients, all with essential hypertension.

Echocardiography

Two-dimensionally guided M-mode echocardiography was performed using an ALOKA SSD 870 equipment (Aloka Co. Ltd., Japan) with 2.5 and 3.5 MHz transducers. Tracings

were recorded on strip chart papers at 50 mm/s. All echocardiograms were performed by the same investigator who was blinded to the clinical status of the patients. The following parameters were recorded according to the recommendations of the American Society of Echocardiography:¹¹ LV end-diastolic internal dimension (LVID), LV end-systolic internal dimension (LVIS), LV posterior wall thickness (PWT) and interventricular septal thickness (IVST). Left ventricular mass was calculated based on the following formula and normalized by body surface area (BSA) to obtain LV mass index:¹²

$$\text{Mass index (g}\cdot\text{m}^{-2}\text{)} = 1.04 \times (\text{LVPWT} + \text{LVIVST} + \text{LVID})^3 - (\text{LVID})^3 / \text{BSA}$$

Left ventricular fractional shortening (LVFS) was used as a measure of systolic performance and calculated as follows:¹³

$$\text{LVFS (\%)} = [(\text{LVID}) - \text{LVIS}] / \text{LVID} \times 100$$

After 36 weeks of renovascular disease correction and consistent medically conducted antihypertensive treatment, patients were classified into Groups A and B according to either normalization (FS $\geq 30\%$) or persistent impairment (FS < 30%) of LV systolic dysfunction, respectively.

Statistical Analysis

Both the unpaired Student's *t*-test and the Pearson chi-square test¹⁴ were performed for group comparisons at the beginning of the study, whereas the analysis of variance for repeated measures was employed to compare the effects of antihypertensive treatment between groups.¹⁵ The stepwise logistic regression analysis was performed to identify among the variables showing statistically significant differences, the prognostic factors for recovery of LV dysfunction.¹⁶ The significance level was established at 0.05. Data are expressed as mean value $\pm$ 1 standard deviation.

Results

The values of blood pressure and the respective number of antihypertensive drugs currently taken by each patient during enrollment at the beginning of the study and 9 months after are summarized in Table I. Renovascular hypertension was cured in three patients, improved in five patients, and remained unaltered in the remaining two patients.

There were 12 patients in whom LV fractional shortening normalized during follow-up (Group A), while the remaining 14 patients showed permanent LV systolic dysfunction (Group B). Compared with patients in Group B, patients in Group A were younger (41 ± 14 vs. 52 ± 10 years, respectively; $p < 0.05$) and had a greater frequency of renovascular hypertension. Accordingly, 8 of the 12 patients in Group A, compared with only 2 of the 14 patients in Group B had renovascular hypertension. Although not showing a complete restoration of LV dysfunction at the end of the study, the two

TABLE I Etiology of hypertension, blood pressure, and number of antihypertensive drugs of the entire population studied, before and at 9 months of follow-up

Etiology	Before			Follow-up		
	SBP	DBP	Drugs	SBP	DBP	Drugs
EH	200	120	0	130	80	2
EH	190	120	0	160	96	2
EH	200	140	0	160	80	3
EH	207	140	0	200	140	3
EH	200	120	0	170	90	2
EH	166	100	0	150	80	1
EH	210	135	0	190	116	3
EH	187	110	0	160	90	3
EH	250	140	0	170	100	3
EH	240	160	1	200	130	4
EH	200	120	2	200	120	2
EH	212	144	2	160	90	3
EH	136	100	2	130	100	2
EH	223	143	3	230	140	4
EH	196	120	3	170	100	4
EH	140	90	4	180	90	4
RV	180	110	0	120	80	0
RV	200	110	0	180	70	0
RV	170	104	3	110	60	0
RV	160	102	2	120	88	2
RV	200	100	2	150	80	2
RV	200	120	2	170	90	2
RV	210	120	3	210	120	2
RV	170	120	3	170	106	3
RV	200	110	3	150	90	3
RV	170	110	4	130	90	3

Abbreviations: EH = essential hypertension, RVH = renovascular hypertension, SBP = systolic blood pressure, DBP = diastolic blood pressure.

patients with coronary artery disease, one of them with renovascular hypertension and the other with primary hypertension, showed partial improvement of fractional shortening from 20 to 28% and from 19 to 24%, respectively.

At the beginning of the study, there was no significant difference in either systolic or in diastolic blood pressure when Groups A and B were compared (Fig. 1). Both groups showed significant reductions in both systolic and diastolic blood pressure after 9 months of follow-up. However, patients in Group A achieved the lowest values of blood pressure in spite of the fact that the number of antihypertensive drugs used was quite similar (2.08 ± 1.04 in Group A and 2.64 ± 1.17 in Group B).

Left ventricular mass index was significantly different when compared between Groups A and B at the beginning of the study (215 ± 67 vs. 261 ± 48 g·m⁻², respectively, $p < 0.05$). The same was true for LV posterior wall thickness (11.7 ± 1.4 vs. 12.6 ± 1.3 mm, respectively; $p < 0.05$). Left ventricular hypertrophy was similarly reduced in both groups during follow-up. Consequently, the values of both LV mass index (142 ± 36 vs. 222 ± 41 g·m⁻², respectively, $p < 0.05$) and LV poste-

FIG. 1 Systolic and diastolic blood pressure (SBP and DBP) at the beginning (1) of the study and at 9 months of follow-up (2) in Groups A and B. -○-- = Group A, —■— = Group B.

rior wall thickness (9.6 ± 1.4 vs. 11.4 ± 1.6 , respectively; $p < 0.05$) remained lower in Group A than in Group B at 9 months of follow-up.

In addition, LV end-diastolic and end-systolic internal dimensions were significantly shorter in Group A at the beginning of the study. The normalization of LV fractional shortening observed in Group A during follow-up (Fig. 2) was associated with significant reductions in LV internal dimensions. As anticipated, LV dimensions did not change in Group B.

Based on these results, the following variables were selected for entering the stepwise logistic regression model: etiology of hypertension, age and pretreatment LV end-diastolic and end-systolic internal dimensions, mass index and posterior wall thickness, as well as the magnitude of decrease in blood pressure accomplished during follow-up. The magnitude of decrease in LV internal dimensions was not included in the model.

Results showed that pretreatment LV end-systolic dimension and renovascular hypertension were the variables associated with the normalization of LV fractional shortening. The

FIG. 2 Left ventricular systolic and diastolic internal dimensions (LVID and LVIS), and fractional shortening (FS) at the beginning (1) and at 9 months of follow-up (2) in Groups A and B. -○-- = Group A, —■— = Group B.

probability (p) of recovery of systolic function estimated in the logistic regression model is expressed by the following formula:

$$\log(p/1-p) = 6.85 + 3.8(E) - 0.28(LVSD)$$

where E (etiology) = 2 for renovascular hypertension and E = 1 for essential hypertension.

In addition, to investigate the likely interference of blood pressure changes in LV function of patients with renovascular disease, blood pressure and LV dimensions were compared against those in patients with primary hypertension. Results are depicted in Figures 3 and 4, respectively. Systolic blood pressure did not differ between these groups of patients either before or after treatment. There was a significant difference in diastolic blood pressure at the beginning of the study, which was unchanged after treatment.

Left ventricular parameters were comparable between both groups at the beginning of the study. In contrast to patients with primary hypertension, treatment was associated with significant reductions of LV dimensions in patients with renovascular hypertension, resulting in greater LV fractional shortening at the end of the study.

Discussion

In hemodynamic states characterized by chronic pressure overload, such as it occurs in systemic hypertension, the advent of a poorly contracting left ventricle is thought to represent the late stage of transition from an adaptive hypertrophic process toward the progressive and ultimate myocardial failure.^{17,18} Nonetheless, it has yet to be determined whether the unloading effects of chronic antihypertensive treatment may favorably affect LV dysfunction when LV dilatation has already supervened.

The present prospective study showed that the advent of LV dysfunction in hypertensive heart disease may not be necessarily permanent but is conceivable to be reverted, depending on the magnitude of increase in LV systolic internal dimension, and appearing to occur more likely in those patients with renovascular disease. As a matter of fact, in almost 50% of the patients studied LV fractional shortening normalized during follow-up, accompanied by reductions of LV wall thickness and internal dimensions.

Although in the past there were initial concerns that regression of LV hypertrophy would perhaps be detrimental to systolic performance,¹⁹ subsequent clinical studies demonstrated that there is either no change or quite a small improvement in systolic function.²⁰⁻²⁶

Similarly to our present findings, Dall'Aglio *et al.*⁶ had previously demonstrated the normalization of LV dysfunction in six patients with hypertensive heart disease characterized by dilated and poorly contracting left ventricles. This favorable outcome appears to be related, at least in part, to the cardiac unloading effects of blood pressure reduction. In fact, patients in Group A, with normalization of LV fractional shortening, showed better control of blood pressure than patients in Group B, with persistent systolic dysfunction. Accordingly, it is well established in normal subjects that isometric exercise may cause the impediment of LV performance by increasing arterial blood pressure and elevating LV systolic wall stress.²⁷ Conversely, the reduction in afterload by means of vasodilator drugs may improve systolic function²⁸ which is in agreement with the inverse relationship found between LV systolic wall stress and ejection fraction in different forms of myocardial disease.^{1,2} The accumulated evidence indicates that whenever LV hypertrophy becomes inappropriate to maintain systolic wall stress, pumping dysfunction usually takes place.^{1,29,30} Thus, it is conceivable that in particular circumstances ventricular dysfunction may be the consequence of maladjusted hypertrophy to the degree of afterload increase. In such circumstances there might not be a true and definite impairment of myocardial contractility, but a state in which cardiac perfor-

FIG. 3 Systolic and diastolic blood pressure (SBP and DBP) at the beginning (1) of the study and at 9 months of follow-up (2) in patients with renovascular and primary hypertension. -◇-- = Primary, -◆- = renovascular.

FIG. 4 Left ventricular systolic and diastolic internal dimensions (LVID and LVIS), and fractional shortening (FS) at the beginning (1) and at 9 months of follow-up (2) in patients with renovascular and primary hypertension. -◇-- = Primary, -◆- = renovascular.

mance would be temporarily impaired by the high levels of blood pressure.

The restoration of depressed ejection fraction responses to isotonic exercise after medical treatment has already been reported in systemic hypertension.³¹ Whether or not these findings might be extensive to patients who already exhibit LV dysfunction at rest was still a matter of debate. The present results indicate that, indeed, this may be the case at least for those patients with the lowest LV end-systolic dimensions.

Corresponding to what has been previously observed in different forms of valvular heart disease after surgery,^{4,5} the logistic stepwise regression analysis identified pretreatment end-systolic dimension as an independent factor related to the normalization of pumping performance. Thus, it is reasonable to admit that whenever LV systolic dimension has not yet reached a nonreturn limiting value, the decrease in blood pressure is expected to be associated with the recovery of cardiac dysfunction. In agreement with this view, it is interesting to notice that the 4 patients with essential hypertension in Group A had the smallest values of LV end-systolic internal dimension, ranging from 29 to 41 mm, roughly in contrast to the 12 patients with essential hypertension in Group B whose LV end-systolic dimension ranged from 42 to 69 mm. In Group A, patients with renovascular hypertension had intermediary values of LV end-systolic internal dimension, ranging from 37 to 50 mm.

Similar to the systolic chamber dimension, the renovascular etiology of hypertension has been also demonstrated to be related to the recovery systolic function. Apart from the benefits achieved from blood pressure control, the treatment of renovascular disease might have directly interfered with myocardial structure, thus affecting ventricular remodeling. Evidence brought about by experimental studies suggests that some components of the renin-angiotensin system may play an important role in ventricular remodeling.^{32,33} Reactive fibrosis was found to occur in the adventitia of intramyocardial coronary arteries and within the interstitium of the hypertrophied myocardium.³⁴ It has been speculated that the disproportional accumulation of fibrillar collagen relative to the increase in myocardial mass might interfere with diastolic chamber properties and at last compromise systolic function.³⁵ These detrimental effects have already been reported to be prevented by treatment with angiotensin-converting inhibitors in experimental hypertension.³⁶ In human hypertension, diastolic dysfunction and impairment of coronary flow reserve have been shown to be improved, preferably by angiotensin-converting inhibitors.⁷

Accordingly, in the present study we were able to demonstrate that pumping dysfunction could be reversed in 8 of the 10 patients with renovascular hypertension. In these patients, pathologic hypertrophy might have been repaired by the intervention in renovascular disease. Regression of LV hypertrophy has been previously demonstrated in patients with secondary hypertension, including renovascular hypertension.³⁷ Although systolic function has been reported to be more adversely affected in renovascular hypertension compared with primary hypertension of similar severity, the reversibility of

systolic dysfunction in human renovascular hypertension has not been reported before.

It remains unclear, however, whether the benefits achieved in LV function were the result of better blood pressure control apart from the interference with the renin-angiotensin system. In this regard, blood pressure and LV dimensions were additionally compared between patients with renovascular and primary hypertension. As can be seen in Figure 3, these two groups showed reductions of similar magnitude in both systolic and diastolic blood pressures. While systolic blood pressure was comparable between groups before and after treatment, the magnitude of differences found in diastolic blood pressure remained constant throughout the study. Conversely, although LV enlargement and dysfunction were similar at the beginning of the study, the changes in chamber dimensions and the improvement in LV dysfunction were of greater magnitude in patients with renovascular hypertension (Fig. 4). Thus, although end-systolic stress was not measured in the present study and, hence, a more appropriate assessment of afterload is lacking, it appears that other factors beyond the reduction of blood pressure may have interfered with LV remodeling. The finding that the improvement of systolic dysfunction is more likely to occur in renovascular hypertension deserves, however, the study of a larger number of patients to be conclusively established.

The present results raise the possibility of achieving similar beneficial effects obtained with renovascular disease treatment in patients with essential hypertension treated with angiotensin-converting inhibitors. In this regard, it was demonstrated that there was a significant improvement in systolic performance evaluated by midwall fractional shortening with the use of an angiotensin-converting inhibitor as opposed to a calcium antagonist for antihypertensive treatment.³⁸ The benefits on morbidity and mortality reported by the Survival and Ventricular Enlargement (SAVE) study³⁹ have been attributed at least in part to the attenuation of ventricular enlargement induced by enzyme-converting inhibition therapy.

Conclusions

In hypertensive heart disease, left ventricular systolic impairment is not necessarily permanent, but recovery is likely to occur after antihypertensive treatment, especially in patients with renovascular disease and in those with the shortest left ventricular systolic dimensions. Whether the present reported favorable effects would occur immediately after blood pressure control or were a consequence of chronic antihypertensive treatment was not specifically addressed by this study and thus requires further investigations.

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