Regression of Left Ventricular Hypertrophy in Hypertensive Heart Transplant Recipients Treated With Enalapril, Furosemide, and Verapamil

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Background. This prospective study was designed to examine whether left ventricular (LV) hypertrophy of the denervated transplanted heart may be reversed by medical therapy and, if so, to investigate the time course of this process and its effect on exercise capacity, myocardial function, and cardiac hemodynamics.

Methods and Results. Ten hypertensive heart transplant recipients with LV hypertrophy were evaluated before therapy with enalapril plus furosemide alone or combined with verapamil, at initial blood pressure (BP) control and after 3, 6, 9, and 12 months, using 24-hour noninvasive ambulatory BP monitoring, M-mode and two-dimensional echocardiography, and supine bicycle ergometry. Average 24-hour systolic and diastolic BP declined from 158±10 and 104±7 mm Hg to 129±9 and 84±10 mm Hg at initial BP control (p<0.005 and p<0.025, respectively) and total peripheral resistance from 1,687±177 to 1,376±122 dyne·sec·cm⁻⁵ (p<0.025), remaining normal thereafter. Exercise capacity remained unchanged during the study. LV mass, mass-to-volume ratio, and end-diastolic septal plus posterior wall thickness decreased progressively from 211±30 g, 2.49±0.62 g/ml, and 25.7±2.6 mm to 184±26 g, 2.22±0.46 g/ml, and 22.5±1.9 mm after 3 months (all p<0.025) and to 174±25 g, 2.07±0.38 g/ml, and 21.5±1.5 mm after 6 months (all p<0.005), remaining unaltered at 9 and 12 months. A correlation was found between the decrease in average 24-hour mean BP and LV mass after 3 months of antihypertensive therapy (r=0.71, p<0.05). Systolic meridional wall stress, LV end-diastolic and stroke volume, ejection fraction, and cardiac output remained unchanged throughout the observation period.

Conclusions. The results indicate that regression of LV hypertrophy is induced by effective antihypertensive therapy in the denervated transplanted heart. The extent of decrease in average 24-hour BP appears to be the main determinant for the extent of reduction in LV mass. LV afterload as characterized by systolic meridional wall stress, LV size and pump function, and physical exercise capacity of the transplant patients are not influenced by the therapeutic regimen chosen in this study. (Circulation 1991;84:583–593)

Introduction of cyclosporine as an immunosuppressant has emerged as the crucial step forward in the evolution of heart transplantation, leading to significant improvement of long-term survival. However, numerous serious side effects are associated with this agent, including nephrotoxicity, interference with prostaglandin metabolism, changes in vascular tone and sympathetic nerve traffic, and elevation of systemic blood pressure. Although only 20% of heart transplant recipients receiving azathioprine and prednisone alone develop hypertension, a significant early increase in arterial blood pressure occurred in as many as 92% of patients in whom cyclosporine was added to this...
combination.\textsuperscript{8,9,11} Cyclosporine seems thus to play the key role for the genesis of posttransplant hypertension. In addition, persistent denervation of the allograft\textsuperscript{12-14} is bound to exert an influence on central nervous blood pressure control, as arterial pressure is modulated also through baroreceptor and chemoreceptor reflexes. We and others have shown that the circadian blood pressure profile of cardiac transplant patients lacks the usual nocturnal decline that characterizes the profiles of normotensives and of most individuals with essential hypertension.\textsuperscript{15,16} Accelerated cardiac hypertrophy might be the consequence;\textsuperscript{17} we have observed that in heart transplant recipients with unsatisfactory blood pressure control, ventricular wall thickness increases within only a few months of the onset of hypertension. This phenomenon occurs without concomitant histological evidence of acute cardiac rejection. It is, therefore, unrelated to the reversible augmentation of left ventricular mass due to myocardial edema, which may be associated with the rejection process itself.\textsuperscript{18}

This prospective study was designed to examine whether regression of left ventricular hypertrophy can be induced in the denervated transplanted heart and, if so, to investigate the time course of regression and the effects on exercise capacity, myocardial function, and cardiac hemodynamics as assessed by serial echocardiography.

Enalapril was chosen as an antihypertensive because in patients with essential hypertension this long-acting angiotensin converting enzyme inhibitor has been shown to reduce left ventricular hypertrophy.\textsuperscript{19-22} Recent evidence suggests also that these agents have an inhibitory effect on bradykinin degradation;\textsuperscript{23} angiotensin converting enzyme inhibitors may thus directly counteract the inhibition of prostaglandin-mediated vasodilatation caused by cyclosporine.\textsuperscript{4} Enalapril was regularly combined with furosemide; besides the synergistic antihypertensive effect,\textsuperscript{23} this served to control increases in serum potassium during treatment with two potassium-sparing substances (cyclosporine and angiotensin converting enzyme inhibitor). If a triple-drug antihypertensive regimen was required, verapamil was added. The combined use of angiotensin converting enzyme inhibitors and calcium channel blockers has been effective even in resistant essential hypertension;\textsuperscript{24} furthermore, it appeared sensible from a pathophysiological point of view to aim at further reduction of the markedly elevated systemic vascular resistance, which characterizes the hypertension after orthotopic heart transplantation.\textsuperscript{8}

Methods

Selection and Characterization of Patients

From August 1981 to July 1987, 83 adult patients underwent orthotopic heart transplantation at Munich University for end-stage congestive heart failure. For the purpose of this study, patients were selected from this population and recruited if they met the following entry criteria: 1) no history of high blood pressure before transplantation, 2) development of sustained arterial hypertension requiring medical therapy within 3 months of surgery, 3) unsatisfactory blood pressure control before participation in the study, 4) no evidence of transplant atherosclerosis defined as absence of regional wall motion abnormalities and/or significant stenoses of extramural coronary arteries at the last routine annual cardiac catheterization, 5) no evidence of pulmonary hypertension, 6) technically satisfactory two-dimensional echocardiogram with clear visualization of the left ventricular endocardial and epicardial borders in left parasternal short-axis and apical four-chamber views to permit reliable quantitative analysis of still frames; 7) presence of symmetric ventricular hypertrophy according to echocardiographic criteria (M-mode diastolic septal plus posterior wall thickness equal to or greater than 23 mm), and 8) no evidence of acute cardiac rejection as assessed by an endomyocardial biopsy performed within 7 days of the initial echocardiogram on which the diagnosis of ventricular hypertrophy was based.

The 10 study patients (nine men and one woman) ranged in age from 24 to 56 years (mean age, 39.8±11.2 years); the time interval from surgery to inclusion in the study was 10-41 months (mean interval, 14.9±8.0 months). Congestive heart failure had been caused by dilated cardiomyopathy in seven patients and by coronary artery disease in three patients. At the time of study all individuals were in clinically stable condition and in New York Heart Association (NYHA) functional class I; immunosuppressive therapy consisted of prednisone and cyclosporine A in all and additional azathioprine in three patients. Previous antihypertensive medication, which included various diuretics and nifedipine in all, \(\beta\)-blockers in five patients, and captopril in two patients, was discontinued at least 3 weeks before entering the study. The study protocol was approved by the local Ethics Committee for Human Research. Informed, written consent was obtained from every patient.

Study Protocol

All patients were hospitalized for pretreatment evaluation, which included M-mode and two-dimensional echocardiography, a 12-lead electrocardiogram (ECG), a routine laboratory screen (complete blood count, serum electrolytes, renal function parameters, and whole blood cyclosporine trough level), and determination of resting plasma renin activity (radioimmunoassay;\textsuperscript{25} normal range, 0.2-2.8 ng angiotensin I/ml/hr) and catecholamines (high-performance liquid chromatography, electrochemical detection;\textsuperscript{26} normal range, 50-250 pg/ml and 2-20 pg/ml for noradrenaline and adrenaline, respectively). Additionally, exercise capacity was tested by supine bicycle ergometry; workload was increased by 25 W every 3 minutes until symptom-limited maximum exercise (Ergo-metrics 900 Marquette Electronics Inc., Milwaukee, Wisc.). Ambulatory blood
pressure and heart rate monitoring with automated hourly recordings of systolic and diastolic blood pressures was performed throughout 24 hours with a commercially available portable device (ABP-Monitor 90202, SpaceLabs Inc.). Subsequently, antihypertensive therapy was initiated with 2.5 mg enalapril. Enalapril was increased stepwise to a maximum dosage of 20 mg/day and combined with furosemide in a dosage of 20–80 mg/day. The therapeutic goal was optimal blood pressure control throughout a 24-hour monitoring period (resting systolic values, ≤140 mm Hg; diastolic values, ≤90 mm Hg). If this was not achieved with enalapril and furosemide alone, verapamil was added in a dosage of 120–360 mg/day. Once the optimal dose of each drug was established, patients remained on that therapy. M-mode and two-dimensional echocardiography and ambulatory 24-hour blood pressure monitoring were repeated during follow-up at 3, 6, 9, and 12 months. A laboratory screen, determination of resting plasma renin activity and catecholamines, an ECG, and supine bicycle ergometry were repeated at initial blood pressure control and after 6 and 12 months of antihypertensive therapy.

Echocardiography

Imaging technique. Quantitative M-mode and two-dimensional echocardiograms were performed on a Toshiba SSH-65 electronic sectorscanner (Toshiba Medical Systems Europe, Delft, The Netherlands) by two of the investigators according to mutually agreed-on criteria. Patients were placed in the left lateral decubitus position. Left ventricular chamber sizes were maximized and respiration was suspended before recording. A simultaneous lead II ECG was documented to aid the choice of end-diastolic and end-systolic frames. The transducer position was noted for each individual and kept constant throughout the investigation. Before each follow-up examination, the patient’s previous study was reviewed to ensure reproducible imaging of the left ventricular short axis at midpapillary level and of the apical four-chamber view. M-mode echocardiograms of the left ventricle were recorded at a paper speed of 50 mm/sec.

Data analysis. A commercially available phantom-calibrated image processing computer with video input/output unit for real-time digitization and display of two-dimensional echocardiograms was used for quantitation (MIPRON, Kontron Electronics, Eching, FRG). This system also facilitates frame-by-frame display of stored images. Three cardiac cycles of both left ventricular short-axis and apical four-chamber views were digitized from each study. In the short-axis views, the black-and-white interface of end-diastolic endocardial and epicardial borders was traced on frames at the peak of the R wave (ECG) or just after closure of the mitral valve. End-systolic endocardial and epicardial borders were traced on the frames immediately preceding mitral valve opening. Papillary muscles were considered part of the left ventricular chamber and were included in the cavity area. The left ventricular major axis was measured in corresponding frames of the apical four-chamber view from the midpoint of the atrioventricular groove to the apical endocardium and epicardium. Measurements from the three cardiac cycles were averaged. To minimize involuntary bias, evaluation was performed in a random fashion, that is, data sets of the same individual were analyzed out of chronological order and interposed with studies of other patients. Quantification of M-mode echocardiograms was performed in accordance with the recommendations of the American Society of Echocardiography.28 Again, measurements from three cardiac cycles were averaged.

Parameters. Left ventricular myocardial volume was determined using a cylinder hemiellipsoid model as described by Wyatt et al29,30 and validated by Stack et al.31 The combination of formulas for the volumes of a cylinder and an ellipse results in the following equation:

\[ V = \pi/4 \times L^2 + 2/3 \pi \times A^2 = 5/6 \pi \times A^2 \]

where \( V \) is volume, \( A \) is cross-sectional area at midpapillary level, and \( L \) is length of the major axis. The calculated volume of the endocardial shell was subtracted from the epicardial shell to determine myocardial volume. Myocardial volume was then multiplied by the specific gravity of myocardium to obtain left ventricular mass. Left ventricular end-diastolic and end-systolic volumes corresponding to the respective calculated volumes of the endocardial shell were used to derive stroke volume and ejection fraction. Heart rate was measured from the simultaneously recorded ECG, and cardiac output was computed as the product of stroke volume and heart rate. As an index of left ventricular hypertrophy, the mass-to-volume ratio was obtained by dividing left ventricular myocardial mass by end-diastolic chamber volume.32

Systemic vascular resistance was calculated using the following equation:

\[ SVR = (MAP/CO) \times 80 \]

where SVR is systemic vascular resistance, MAP is mean arterial blood pressure, and CO is cardiac output.

Left ventricular end-diastolic diameter and septal plus posterior wall thickness were obtained from M-mode recordings of the left ventricle. As a parameter of myocardial work load, systolic meridional wall stress was determined as proposed by Grossman et al33:

\[ MWS = (SBP \times D/2)/2(T+1/2(D/2)) \]

where MWS is meridional wall stress, SBP is systolic arterial blood pressure, \( D \) is left ventricular end-diastolic diameter, and \( T \) is left ventricular end-diastolic wall thickness calculated as end-diastolic septal plus posterior wall thickness divided by 2.
Electrocardiography

From the standard 12-lead ECGs obtained before and 1 year after initiation of antihypertensive therapy, voltage was determined as the sum of the S wave in lead V₁ and R wave in lead V₅ or V₆ (whichever was larger) and as the sum of the R wave in lead I and S wave in lead III.

Statistical Analysis

Results are expressed as mean±SD. For statistical evaluation, two-way analysis of variance was performed with a Friedman test followed by a Wilcoxon-Wilcox test, allowing for multiple comparisons of the consecutively obtained data sets. The biological and technical variability of M-mode and two-dimensional echocardiographic parameters in heart transplant recipients has been previously determined in our laboratory. In this study, the 95% confidence limits of a given measurement were calculated as 2 SDs of the mean of paired differences in consecutive rejection-free examinations.

Results

Clinical Data and Laboratory Parameters

All patients completed the study; clinical condition and NYHA classification remained unaltered. Satisfactory blood pressure control was achieved with enalapril plus furosemide alone in five patients (mean dosages, 20 mg/day enalapril and 48±18 mg/day furosemide). In the remaining five patients, additional verapamil was required (mean dosages, 20 mg/day enalapril, 40 mg/day furosemide, and 168±66 mg/day verapamil). Both regimens were tolerated equally well. During the 1-year observation period, none of the patients experienced acute rejection requiring intensified immunosuppression and none developed coronary artery disease as assessed by the subsequent annual coronary angiography. Mean pretreatment maximum exercise capacity was 100±26 W and remained unchanged (103±25 W at initial blood pressure control, 105±39 W at 6 months, and 105±37 W at 12 months). The usual reason for termination of exercise was muscular weakness rather than cardiopulmonary exhaustion.

Laboratory parameters. Pretreatment serum creatinine and blood urea nitrogen were elevated in all patients (see Table 1). During follow-up, a small but significant increase in serum creatinine occurred at 6 months. However, no significant changes in renal function were observed at the end of the study. Serum sodium remained unaltered, whereas potassium increased slightly for the group. In two patients, enalapril had to be reduced because of hyperkalemia. Plasma renin activity, which served as marker of patient compliance and drug absorption, was normal in eight patients and increased in two patients before therapy, resulting in a slightly elevated mean value. During treatment, plasma renin activity rose significantly, reflecting effective interruption of the feedback loop by interference with angiotensin II generation. Plasma catecholamine levels did not change significantly, although mean plasma noradrenaline showed a tendency to increase during therapy. Because of the known interaction between verapamil and cyclosporine, cyclosporine dosage had to be reduced in all patients receiving verapamil. 

Blood pressure and heart rate. At initial blood pressure control, mean systolic pressure as calculated from hourly measurements throughout 24 hours had declined by 18.4% (from 158±10 to 129±9 mm Hg,
TABLE 2. Systolic and Diastolic 24-Hour Average Blood Pressures and 24-Hour Average Heart Rate Before and During Therapy With Enalapril Plus Furosemide Alone or Combined With Verapamil in 10 Hypertensive Heart Transplant Recipients

<table>
<thead>
<tr>
<th></th>
<th>Before therapy</th>
<th>Initial blood pressure control</th>
<th>3 Months of therapy</th>
<th>6 Months of therapy</th>
<th>9 Months of therapy</th>
<th>12 Months of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average systolic</td>
<td>158±10</td>
<td>129±9</td>
<td>124±8</td>
<td>118±10</td>
<td>122±14</td>
<td>118±12</td>
</tr>
<tr>
<td>blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average diastolic</td>
<td>104±7</td>
<td>84±10</td>
<td>82±9</td>
<td>77±8</td>
<td>79±9</td>
<td>79±7</td>
</tr>
<tr>
<td>blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average heart rate</td>
<td>92±8</td>
<td>90±7</td>
<td>92±12</td>
<td>96±9</td>
<td>91±8</td>
<td>96±8</td>
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<tr>
<td>(beats/min)</td>
<td></td>
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</tbody>
</table>

Values are mean±SD.
*p<0.025 vs. pretreatment values.
f*p<0.005 vs. pretreatment values.
P<0.005) and mean diastolic pressure by 16.7% (from 104±7 to 84±10 mm Hg, p<0.025) (see Table 2). Blood pressure remained well controlled throughout the observation period (Figure 1). As a consequence of cardiac denervation,12-14 mean pretreatment heart rate was increased in all patients; no significant changes occurred during therapy.

Echocardiography

Left ventricular mass and wall thickness. During the 12-month observation period, left ventricular mass and wall thickness declined in every patient irrespective of the combination of drugs used to normalize blood pressure (Figure 2, top and middle panels; see also Table 3). Mean left ventricular mass decreased by 17.5% (from 211±30 to 174±22 g, p<0.005). Our serial measurements demonstrated, however, that most of this reduction (12.8%) occurred during the first 3 months with another smaller decrease at 3-6 months. No further significant changes were observed between 6 and 12 months. There was a significant although not very close correlation between the extent of reduction in 24-hour average mean arterial blood pressure and the extent of reduction in left ventricular mass after 3 months of antihypertensive therapy (r=0.71, p<0.05; Figure 3). M-mode septal plus posterior wall thickness also decreased in every patient. Mean values declined by 18.6% during follow-up (from 25.7±2.6 to 21.1±1.2 mm; p<0.005). The time course of regression paralleled that of mass; 12.5% of the total reduction was attained during the first 3 months followed by a smaller decrease at 3-6 months and no changes thereafter.

Left ventricular volumes, ejection fraction, and total peripheral resistance. Initial left ventricular end-diastolic volumes were within normal limits in all patients. No significant changes occurred during antihypertensive treatment, although mean end-diastolic volume dropped slightly at 3 months and tended to increase thereafter. Left ventricular hemodynamic performance as assessed by stroke volume, ejection fraction, and cardiac output was also normal in all patients and remained so throughout the observation period although mean ejection fraction tended to decrease for the group. Total peripheral resistance was elevated at pretreatment evaluation in all patients. As mean blood pressure decreased,
whereas cardiac output was unaltered, this parameter dropped by 26.6\% (from 1,672±189 to a minimum of 1,238±176 dyne · sec · cm⁻²; \(p<0.005\)) during antihypertensive therapy and remained normal throughout the observation period.

**Left ventricular mass-to-volume ratio and systolic meridional wall stress.** Because left ventricular mass decreased and end-diastolic volume remained unaltered, the mass-to-volume ratio decreased also, with a similar time course (Figure 2, bottom panel). Due to a proportional decrease of systolic pressure and the ratio of wall thickness to radius, left ventricular afterload as assessed by systolic meridional wall stress remained unaltered throughout the entire study.

**Electrocardiography**

ECG voltage determined as the sum of the S wave in lead V₁ and the R wave in lead V₅ or V₆ declined in every patient. For the group, this index decreased from 2.4±0.8 mV (pretreatment period) to 1.8±0.6 mV after 12 months of antihypertensive therapy \( (p<0.01) \). At the same time, the sum of the R wave in lead I and the S wave in lead III declined from 1.1±0.6 mV to 0.8±0.5 mV \( (p=NS, \text{ voltage decreased in six patients and remained unchanged or increased in two patients each}) \). By voltage criteria, left ventricular hypertrophy was present in two patients before antihypertensive therapy and in none of the patients at the 12-month follow-up examination.

**Discussion**

**Clinical Data and Laboratory Parameters**

Antihypertensive therapy with enalapril plus furosemide alone or combined with verapamil caused a highly significant reduction in systolic and diastolic blood pressures and normalized total peripheral resistance. These therapeutic effects were maintained throughout the entire observation period with high patient tolerance. The somewhat reduced maximum
TABLE 3. Echocardiographic Parameters Before and During Therapy With Enalapril Plus Furosemide Alone or Combined With Verapamil in 10 Hypertensive Heart Transplant Recipients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before therapy</th>
<th>3 Months of therapy</th>
<th>6 Months of therapy</th>
<th>9 Months of therapy</th>
<th>12 Months of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass (g)</td>
<td>211±30</td>
<td>184*±26</td>
<td>174†±25</td>
<td>172†±23</td>
<td>174†±22</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume (ml)</td>
<td>87.5±17.3</td>
<td>85.1±16.3</td>
<td>86.8±17.7</td>
<td>88.4±19.1</td>
<td>89.2±17.3</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>56.1±12.9</td>
<td>53.0±13.7</td>
<td>54.5±14.3</td>
<td>54.0±13.7</td>
<td>54.0±15.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63.7±2.6</td>
<td>61.6±6.1</td>
<td>62.1±4.6</td>
<td>60.7±3.5</td>
<td>59.4±6.9</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.85±0.60</td>
<td>5.62±0.49</td>
<td>5.94±0.69</td>
<td>5.53±0.32</td>
<td>5.70±0.78</td>
</tr>
<tr>
<td>Left ventricular mass-to-volume ratio (g/ml)</td>
<td>2.49±0.62</td>
<td>2.22±0.46</td>
<td>2.07†±0.38</td>
<td>2.00†±0.35</td>
<td>1.99†±0.28</td>
</tr>
<tr>
<td>Septal plus posterior end-diastolic wall thickness (mm)</td>
<td>25.7±2.6</td>
<td>22.5*±1.9</td>
<td>21.5†±1.5</td>
<td>21.4†±1.1</td>
<td>21.1†±1.2</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>46.8±4.7</td>
<td>47.9±3.7</td>
<td>47.7±5.3</td>
<td>47.7±4.5</td>
<td>48.0±4.7</td>
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<tr>
<td>Systolic meridional wall stress (10^3 dyne/cm²)</td>
<td>116±27</td>
<td>109±23</td>
<td>109±25</td>
<td>113±25</td>
<td>111±23</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne · sec · cm⁻²)</td>
<td>1,687±177</td>
<td>1,367*±122</td>
<td>1,238†±176</td>
<td>1,354*±147</td>
<td>1,311†±197</td>
</tr>
</tbody>
</table>

Values are mean±SD.
* p<0.025 vs. pretreatment values.
†p<0.005 vs. pretreatment values.

Exercise capacity before and during therapy should be attributed to effects of chronic glucocorticoid therapy on peripheral musculature rather than to cardiac causes, as muscular weakness rather than cardiopulmonary exhaustion was always the exercise-limiting factor.

In all study participants, elevated pretreatment serum creatinine and blood urea nitrogen indicated renal injury, which was most probably related to chronic cyclosporine administration.² Because no major changes in renal function occurred during follow-up, long-term use of the antihypertensive regimen used in the present study appears to also be safe in cyclosporine-treated patients with preexisting renal damage.

Despite effective blood pressure control, heart rate and plasma catecholamines did not increase significantly, although there was a trend to higher noradrenaline levels. This confirms the results of a study by Nakashima et al²⁰ in which enalapril lowered blood pressure and vascular resistance without inducing a reflex hyperadrenergic state. However, exercise

FIGURE 3. Scatterplot showing relation between decrease in mean 24-hour average blood pressure (Δ MAP) and extent of reduction in left ventricular mass (Δ LV mass) within first 3 months of antihypertensive therapy in 10 hypertensive heart transplant recipients. A significant linear relation is demonstrated by regression line.
plasma catecholamines measured in a similar group of transplant patients before and during antihypertensive treatment suggest that latent reflex sympathetic activation occurs when enalapril is combined with a diuretic. In the five patients receiving oral verapamil, no change in 24-hour average heart rate was observed, although a direct negative chronotropic effect on the denervated donor sinus node has been proven for intravenous verapamil in transplanted dogs. However, because the potential for development of bradycardia is likely to depend on dosage as well as on mode of administration, higher oral doses of verapamil must be used with caution in transplant patients.

Left Ventricular Mass and Size

Normal heart muscle grows to match the work load imposed on the ventricle, maintaining a constant relation between systolic pressure and the ratio of wall thickness to ventricular radius. More recent evidence indicates that other nonhemodynamic factors also play a role in the structural adaptation of the myocardium to chronic pressure overload. Results from the present study suggest that the same adaptive processes are active in the denervated transplanted heart. Posttransplant hypertension is a likely cause for development of concentric left ventricular hypertrophy. Pretreatment evaluation demonstrated augmented wall thickness and muscle mass, normal systolic meridional wall stress and end-diastolic volume, and an increased mass-to-volume ratio. These ventricular characteristics correspond closely to those described by Grossman et al for various other types of left ventricular pressure overload in patients with innervated hearts.

Echocardiography has become an established method for evaluating cardiac involvement in arterial hypertension and for serial assessment of the effects of antihypertensive therapy on the left ventricle. A significant reduction in ventricular mass has been reported with angiotensin converting enzyme inhibitors, beta-adrenoceptor- and alpha-blocking agents, adrenergic inhibitors, or calcium channel blockers; on the other hand, no such changes were observed with diuretics or direct-acting vasodilators. These differences were attributed to nonhemodynamic factors as adrenergic drive and humoral influences.

Previous studies in which no correlation between blood pressure reduction and decrease in ventricular mass was found also support the concept that myocardial growth is not determined by blood pressure alone. However, in these studies, the pressures obtained to relate to mass and wall thickness did not reflect integrated measurements throughout a 24-hour period, which better represents the total work load imposed on the ventricle. The significant correlation between changes in mean 24-hour average blood pressure and ventricular mass indicates that, at least in the setting of this study, the decrease in blood pressure was the most important determinant for reversal of left ventricular hypertrophy within the first 3 months of antihypertensive therapy.

Regression in wall thickness and mass paralleled the decrease in blood pressure, with a major reduction within the first 3 months, another smaller decrease at 3–6 months, and no significant changes thereafter. As ventricular size remained unchanged, the mass-to-volume ratio, which before therapy indicated concentric hypertrophy in all patients, decreased toward normal values with a similar time course. Systolic meridional wall stress was also unaltered throughout the study. However, because the sudden decrease in blood pressure must initially have resulted in reduced systolic wall stress, adaptation to the altered loading conditions must already have occurred within the first 3 months, during which no measurements were taken. Our results appear to confirm for the denervated transplanted heart the hypothesis by Grossman et al that increased systolic tension development by myocardial fibers results in fiber thickening just sufficient to return systolic wall stress to normal; they suggest, in addition, that systolic wall stress may also be an important determinant for the extent of reduction in myocardial mass, which appears to occur as an adaptive response to a lasting decrease in systemic blood pressure. Whether the decrease in wall thickness and mass represents a true reversal of cellular growth and how far it can diminish the risks associated with left ventricular hypertrophy is unclear. In view of the high incidence of accelerated allograft vasculopathy in long-term survivors of heart transplantation, however, the reduction in myocardial oxygen demand associated with both normalization of blood pressure and regression of hypertrophy appears particularly desirable. It is unknown whether untreated hypertension augments the primary risk of heart transplant recipients to develop coronary disease and whether cardiac hypertrophy worsens atherosclerotic endothelial lesions within the transplant vasculature.

Left Ventricular Pump Function

At pretreatment evaluation, left ventricular function as assessed by cavity size, stroke volume, ejection fraction, and cardiac output was normal. During regression of hypertrophy, neither these parameters nor ventricular afterload as characterized by systolic meridional wall stress changed significantly. Thus, reduction in ventricular mass was not associated with a deterioration of systolic performance. This is in accordance with animal experiments, in which regression of hypertrophy during treatment with captopril produced little change in ventricular function. Similar clinical data were obtained by Grandi et al and Nakashima et al during therapy with enalapril. Long-term observations in patients treated with either atenolol or verapamil confirm also for these agents that systolic function does not change during reversal of hypertrophy. All of these studies were conducted at normal or controlled pressure loads; however, when in an animal experiment after-
load was increased after regression of hypertrophy, pump function deteriorated, indicating impaired functional reserve of the myocardium. In contrast with that, no clinically apparent decline in pump function was found in the setting of this study during the exercise-induced increase in blood pressure.

Electrocardiography

Our electrocardiographic findings confirm previous observations that the ECG is less sensitive in detecting ventricular hypertrophy than echocardiography. Before therapy, hypertrophy was suspected in two cases only, when voltage criteria were applied. However, regression of hypertrophy was paralleled by a significant decrease in maximal sum-

ated precordial voltage after 12 months. Acute rejection can also cause a decrease in ECG voltage but would have been associated with an increase rather than a decrease in myocardial mass. In addition, there was no clinical evidence of rejection when the ECGs were recorded. Thus, the observed voltage changes are likely to truly reflect the lessen-
ing of hypertrophy in the allograft.

Limitations

In this study, only a small number of the total patient population undergoing heart transplantation at our institution was included; to minimize the impact of clinical baseline differences and method-

ologic problems on the results of the investigation, strict selection criteria had to be applied. Despite a possible selection bias, however, age, sex distribution, and underlying cardiac disorders in the study group were representative of the overall adult transplant population. Another possible weakness of the study concerns the lack of untreated controls, but it did not appear ethical to follow a similar group of transplant patients without antihypertensive medication. All study participants showed a uniform response to normalization of blood pressure with a decrease in left ventricular wall thickness and mass. In addition, the serial changes of these parameters during the 1-year follow-up period greatly exceeded biological and technical variability. This suggests strongly that our echocardiographic findings, although obtained in only a small number of individuals, represent genuine effects of the therapeutic intervention on the hyper-
trophied left ventricle of the allograft. Finally, for a thorough evaluation of cardiac performance, addi-
tional analysis of diastolic function would have also been desirable. However, after orthotopic transplanta-
tion, ventricular filling dynamics are influenced by the independent electrical and mechanical activity of recipient and donor atrial components. Because recipient atrial electrical activity (P wave) could not be clearly identified in all patients throughout the study, selection of beats not influenced by recipient atrial contraction, which would have been required to obtain meaningful and reproducible measurements, was not feasible.

Conclusion

Left ventricular hypertrophy in hypertensive heart transplant recipients can be reversed by medical therapy without concomitant changes in cavity dimensions, pump function, or physical exercise capacity. The results of this study provide evidence that regression of hypertrophy occurs independent of cardiac innervation; the extent and time course correspond to observations in individuals with inner-
vated hearts during treatment with angiotensin con-

verting enzyme inhibitors. In our selected group of patients, who were characterized by high pretreat-

ment total peripheral resistance, concentric myocar-
dial hypertrophy, normal ventricular size and geometry, and normal systolic meridional wall stress, the decrease in total work load imposed on the ventricle appeared to be the most important factor for the extent of regression of hypertrophy. Our data suggest that myocardial growth as well as the reduction of myocardial mass may have occurred as a response to changes in systolic tension development by the myocar-
dium. Systolic meridional wall stress may have played an important role in this adaptive process.

Acknowledgment

We thank Bodo E. Strauer, MD, University of Duesseldorf, Germany, for critical reading and con-

structive discussion of the manuscript.

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KEY WORDS • cardiac denervation • antihypertensive therapy • left ventricular function • systolic wall stress • heart transplantation
Regression of left ventricular hypertrophy in hypertensive heart transplant recipients treated with enalapril, furosemide, and verapamil.

C E Angermann, C H Spes, S Willems, P Dominiak, B M Kemkes and K Theisen

_Circulation_. 1991;84:583-593
doi: 10.1161/01.CIR.84.2.583

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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