Cardiac Adaptation to Obesity and Hypertension After Heart Transplantation

HECTOR O. VENTURA, MD,* MARY R. JOHNSON, MD, FACC, BONNIE GRUSK, RN, MSN, ROQUE PIFARRE, MD, FACC, MARIA ROSA COSTANZO-NORDIN, MD, FACC

Marywood, Illinois

Obesity and hypertension frequently develop after heart transplantation. The cardiac adaptation to obesity and hypertension was studied by determining hemodynamic and echocardiographic indexes in 10 obese hypertensive patients (body mass index $\geq 27.8$ kg/m$^2$ in men or $\geq 27.3$ kg/m$^2$ in women) matched by mean arterial pressure, age and gender with 10 nonobese hypertensive patients 1 year after cardiac transplantation. Cardiac output was $36\%$ greater ($p < 0.02$) and systemic vascular resistance $25\%$ lower ($p < 0.01$) in the obese than in the nonobese patients. Right ventricular systolic and pulmonary artery systolic, diastolic and mean pressures were also significantly higher ($p < 0.05$) in the obese patients. Left ventricular end-diastolic diameter was $25\%$ greater ($p < 0.05$), left ventricular mass $28\%$ greater ($p < 0.02$) and left ventricular end-diastolic volume $20\%$ higher ($p < 0.01$) in the obese subjects. Left ventricular ejection fraction was significantly lower in the obese than in the nonobese subjects ($34\%$ vs. $51\%$; $p < 0.05$).

These results indicate that the cardiac adaptation to obesity and hypertension after heart transplantation consists of left ventricular dilation and an increase in left ventricular mass associated with an increased cardiac output and lower peripheral vascular resistance. These adaptive changes that occur in obese hypertensive patients after heart transplantation might increase the long-term risk of graft failure, as suggested by their lower left ventricular ejection fraction 1 year after transplantation.

(J Am Coll Cardiol 1992;19:55-6)

Obesity and systemic arterial hypertension are two conditions that have been directly related. Thus, the incidence of hypertension in an obese population is greater than that in a nonobese population (1). Furthermore, epidemiologic studies (2-4) have shown that obesity and hypertension are independent risk factors for congestive heart failure and other causes of cardiovascular morbidity and mortality. In the general population the heart adapts to obesity and hypertension by the development of eccentric left ventricular hypertrophy (that is, left ventricular dilation and an increase in left ventricular mass) (11).

Heart transplantation has become an accepted therapy for end-stage heart failure, particularly since cyclosporine was introduced as an immunosuppressive agent (5). However, patients treated with cyclosporine have a significantly increased prevalence of hypertension after transplantation compared with patients treated with azathioprine and prednisone (6-9). In addition, after heart transplantation patients frequently gain weight, often to obesity (10). This weight gain is certainly caused partly by an increase in appetite due to the use of prednisone in many immunosuppressive regimens. Thus, partly in relation to their immunosuppressive therapy, many heart transplant patients develop both arterial hypertension and obesity.

The purpose of the present study was to evaluate the cardiac adaptation to obesity and hypertension after heart transplantation by reviewing systemic hemodynamics, echocardiograms and ventricular function in nonobese and obese hypertensive orthotopic heart transplant recipients 1 year after transplantation.

Methods

Patient selection. The study group consisted of 20 hypertensive patients who were evaluated 1 year after orthotopic heart transplantation. Clinical evaluation and definition of hypertension (diastolic pressure $\geq 90$ mm Hg measured by cuff method) followed established guidelines (11). Antihypertensive agents prescribed for these patients consisted of either a calcium channel blocking agent, an angiotensin-converting enzyme inhibitor or a central acting agent. Body mass index was calculated as weight in kg/height in m$^2$ and patients were classified into obese and nonobese groups by using partition values for body mass index ($\geq 27.8$ kg/m$^2$ for men and $\geq 27.3$ kg/m$^2$ for women) representing the 85th percentile of values according to the National Health and Nutrition Evaluation Survey II (12).

Ten nonobese and 10 obese hypertensive patients who
were matched by mean arterial pressure, age and gender. Most patients were receiving immunosuppressive therapy with cyclosporine, prednisone and azathioprine. Two patients in the obese group and three patients in the nonobese group were receiving cyclosporine and prednisone only. No patient had acute allograft rejection or angiographic evidence of allograft arteriopathy at the time of the study.

Hemodynamic evaluation. The hemodynamic values were measured at the time of the endomyocardial biopsy as previously reported (13). Right heart pressures were measured with use of a balloon-tipped pulmonary artery catheter. Cardiac output was measured in triplicate by the thermodilution method; the average of the three values was recorded. Mean arterial pressure was calculated from cuff blood pressure readings by adding one third of the pulse pressure to the diastolic blood pressure. Systemic vascular resistance was calculated with the following formula:

\[
\text{Mean arterial pressure} - \text{Mean right atrial pressure}
\]
\[\text{Cardiac output} \times 80.
\]

Definition and diagnosis of rejection. The diagnosis of acute rejection was made on the basis of the histologic changes observed on endomyocardial biopsy samples (13). Briefly, rejection was graded as mild, moderate or severe according to the degree of the lymphocytic infiltrate and myocyte necrosis (13).

Echocardiographic evaluation. Echocardiography was performed after the right heart catheterization and endomyocardial biopsy. Echocardiographic measurements were made according to the recommendations of the American Society of Echocardiography (14). Left ventricular end-diastolic diameter and the thickness of the interventricular septum and left ventricular posterior wall were measured at the end of diastole, as defined by the onset of the QRS complex. Left ventricular mass was calculated with use of the formula of Troy et al. (15). Left ventricular volumes were estimated by the method of Teichholz et al. (16) and peak systolic stress was measured by the noninvasive method of Wilson et al. (17).

Ventricular function. Right and left ventricular function were evaluated with use of radionuclide angiographic techniques, as previously described (18).

Renal function. Serum creatinine and creatinine clearance were measured in all study patients 1 year after orthotopic heart transplantation and were used as indicators of renal function.

Statistical analysis. Data are reported as mean values ± SD. Unpaired Student's t tests were used to compare clinical, hemodynamic, echocardiographic and ventricular function variables of nonobese and obese hypertensive orthotopic heart transplant recipients.

### Results

Patient characteristics (Tables 1 and 2). At the time of heart transplantation there was no difference in baseline weight, mean arterial pressure and ejection fraction between the two groups (Table 1). The nonobese and obese hypertensive patient groups at 1 year after heart transplantation were matched by mean arterial pressure, age and gender. The two groups also did not differ with respect to height. By design of the study, weight, body surface area and body mass index were significantly greater in the obese patients.

Renal function and the number of rejection episodes per patient were similar in nonobese and obese patients (Table 2).

Hemodynamic indexes (Tables 2 and 3). At 1 year after orthotopic heart transplantation, obese patients in comparison with nonobese patients were characterized by a significantly higher cardiac output (36.9 ± 18 vs. 18 ± 9 dynes/s per cm⁻²; p < 0.01) and lower systemic vascular resistance (25.2 ± 10 vs. 9.8 ± 3; p < 0.01) at the same level of mean arterial pressure. In addition, right ventricular systolic pressure and pulmonary artery systolic, diastolic and mean pressures were significantly higher in the obese patients (p < 0.05). At 1 year after orthotopic heart transplantation, obese patients, when compared with nonobese patients with similar mean systolic arterial pressure, had a significantly higher cardiac output (6 ± 1 vs. 4.6 ± 0.8 liters/min; p < 0.02) and lower systemic vascular resistance (1.413 ± 18 vs. 1.881 ± 19 dynes/s per cm⁻²; p < 0.01) (Table 3). Cardiac output correlated significantly with body mass index (r = 0.61; p < 0.004).

### Table 1. Baseline Characteristics of 20 Patients Undergoing Heart Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Nonobese (n = 10)</th>
<th>Obese (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>72 ± 1</td>
<td>77 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>90 ± 2</td>
<td>99 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>224 ± 16</td>
<td>219 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56 ± 2</td>
<td>64 ± 3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*These were no significant differences between groups in the baseline characteristics compared.

### Table 2. Clinical Characteristics of 20 Patients 1 Year After Heart Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Nonobese (n = 10)</th>
<th>Obese (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47 ± 6</td>
<td>47 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>8/2</td>
<td>8/2</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177 ± 3</td>
<td>173 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 1</td>
<td>105 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23 ± 2</td>
<td>37 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.9 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>35 ± 3</td>
<td>58 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Rejection episodes/patient</td>
<td>1.5 ± 1.2</td>
<td>1.5 ± 0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Cardiac output (liters/min)
Mean arterial pressure (mm Hg)
Systemic vascular resistance (dynes·cm⁻⁵)
Right ventricular systolic pressure
Pulmonary artery systolic pressure
Pulmonary artery diastolic pressure
Pulmonary artery mean pressure
Myocardial structure and function (Table 4). As measured by echocardiography and radionuclide angiocardiography at 1 year after orthotopic heart transplantation, obese patients had a significantly greater left ventricular end-diastolic diameter (25%; 6.0 ± 0.1 vs. 4.8 ± 0.3 cm; p < 0.05) and end-diastolic volume (20%; 135 ± 10 vs. 106 ± 5 ml; p < 0.01) and a greater left ventricular mass (28%; 312 ± 7 vs. 254 ± 7 g; p < 0.05) and left ventricular mass/height ratio (27%; 181 ± 3 vs. 145 ± 3 g/m²) at the same level of arterial pressure (Fig. 1). Left ventricular mass correlated significantly with body mass index (r = 0.6; p < 0.004). There were no differences in posterior wall or septal thickness. Peak systolic stress, although higher in the obese group, did not achieve statistical significance (Table 4). The left ventricular ejection fraction was significantly lower in the obese patients (33%; 34 ± 4 vs. 51 ± 3%; p < 0.05).

Discussion
The results of our study indicate that the cardiac adaptation to hypertension after transplantation in cyclosporine-treated patients differs in nonobese and obese patients. Compared with nonobese hypertensive orthotopic heart transplant recipients, obese heart transplant recipients have an increased cardiac output, left ventricular dilation and a lower ejection fraction at 1 year after transplantation.

Hypertension after heart transplantation. Arterial hypertension is a serious and frequent complication of cyclosporine therapy in heart transplant recipients (7). In orthotopic heart transplant recipients, hypertension is detected as early as the 1st postoperative week (19), is frequently established by 50 days postoperatively (7) and has been reported to occur in 38% to 92% of such recipients (20). The etiology of cyclosporine-induced hypertension is not clear but several factors may contribute to its development. Patients with hypertension after heart transplantation have an elevated systemic vascular resistance and a normal cardiac output, suggesting an alteration of vascular compliance (20). However, plasma catecholamines, plasma renin activity and plasma aldosterone and angiotensinogen levels have been found to be normal (6, 20, 21). An association between hypertension after transplantation, renal insufficiency and increased plasma volume has been reported (7) but this finding has not been confirmed in other studies (9). Because patients with cyclosporine-induced hypertension do not have a nocturnal decrease in blood pressure, it has also been suggested that abnormal central nervous system control of blood pressure may play a role in the development of hypertension after transplantation (22).

The weight gain induced by corticosteroids may also contribute to the development of increased blood pressure after orthotopic heart transplantation. The results of some previous studies (23) suggest that the blood pressure decreases and fewer antihypertensive medications are required in patients who can be withdrawn from corticosteroid therapy. Moreover, patients who gain the least weight after cardiac transplantation are more likely to remain normotensive (9). Previous studies have reported an abnormal left ventricular end-diastolic pressure, a lower ejection fraction (24) and the development of concentric left ventricular hypertrophy (25) in hypertensive patients 1 year after orthotopic heart transplantation.

Role of obesity. Obesity, as defined by an excess of body fat, has been shown to increase total body oxygen demands. To meet this demand, cardiac output, blood volume and preload increase in obese patients regardless of the level of arterial pressure (26–30). In addition, obesity may also lead to altered systolic and diastolic performance (31–33).

The increased cardiac output observed in our obese recipients 1 year after orthotopic heart transplantation is in accord with previous findings (26–30). Because we did not measure total blood volume, the mechanism of the increased cardiac output remains speculative. However, it seems likely that in these patients the increased left ventricular end-diastolic volume is produced by an increase in preload (26, 27). Heart rate and stroke volume were also somewhat higher in obese patients, thus contributing to the significant increase in cardiac output.

In the general population, arterial hypertension detected
in nonobese patients is characterized by a high systemic vascular resistance, which may make these patients more prone to end-organ damage (26). Because by study design mean arterial pressure was equal in obese and nonobese patients, a higher cardiac output is associated with a lower systemic vascular resistance. Therefore, for any given level of arterial pressure, systemic vascular resistance was lower in the obese than the nonobese transplant patients. However, no conclusions can be reached as to whether obese patients are at lower risk than nonobese patients for developing systemic vascular disease (that is, end-organ damage) because of their lower vascular resistance.

Role of increased left ventricular mass. Epidemiologic studies have shown that weight, body mass index, and arterial pressure are major determinants of left ventricular mass (34-37). Furthermore, the results of recent studies suggest that increased left ventricular mass is an independent risk factor for cardiovascular events (36-37). In nonobese individuals in the general population, the adaptation to arterial hypertension consists of ventricular hypertrophy without chamber dilation, that is, concentric left ventricular hypertrophy (1). In contrast, in obese patients the adaptation to hypertension includes the development of hypertension and ventricular dilation or eccentric left ventricular hypertrophy (11,38). Because of the increased preload and the concomitant systolic and diastolic abnormalities, patients who are both obese and hypertensive may be at higher risk for developing premature congestive heart failure, ventricular arrhythmias (39) and other cardiovascular complications (1). The cardiac adaptation to obesity and hypertension after heart transplantation was characterized by an increased left ventricular mass and left ventricular end-diastolic diameter (eccentric left ventricular hypertrophy). In fact, body mass index strongly correlated with left ventricular mass in this study group. These findings are similar to those of obese patients with essential hypertension. Although body surface area has been used as an index of obesity, it has been shown to underestimate hemodynamic variables and measurements of left ventricular structure. Therefore, the use of height or ideal body surface area may provide a better index of body habitus (14,34).

Ejection fraction. The mechanism of decreased left ventricular ejection fraction in obese patients after heart transplantation remains speculative. An increase in the number of rejection episodes can be postulated; however, there was no difference between the groups in our study. Therefore, either the increase in systolic stress not associated with an appropriate increase in wall thickness or an intrinsic decrease in ventricular contractility can account for the lower ejection fraction.

Conclusions. The present study shows that after orthotopic heart transplantation obese hypertensive patients have a higher cardiac output and lower systemic vascular resistance at any given level of mean arterial pressure than do nonobese hypertensive patients. After orthotopic heart transplantation, cardiac adaptation to both obesity and hypertension consists of eccentric left ventricular hypertrophy and impaired systolic performance. The presence of these abnormalities indicates that obesity superimposed on hypertension after transplantation may increase the risk of allograft failure. Studies on larger numbers of patients followed for longer periods of time are needed to confirm our results. However, because obese hypertensive orthotopic heart transplant recipients are at greater risk of heart allograft failure, weight loss and control of hypertension should be strongly recommended.

We gratefully acknowledge Liddi E. Lopo for her technical expertise in editing and preparing our manuscript. We also thank Franz H. Messerli, MD, for his expert critique of our manuscript.

References


