Increased sensitivity of the denervated transplanted human heart to isoprenaline both before and after β-adrenergic blockade


ABSTRACT It is not known whether surgical denervation leads to increased β-receptor sensitivity after human cardiac transplantation. We assessed cardiac β-receptor sensitivity by studying the heart rate response to isoprenaline of the denervated donor heart as compared with the innervated recipient heart in eight patients who underwent heterotopic cardiac transplantation and in six patients with orthotopic transplantation. Changes in the donor and recipient hearts seen in these 14 patients were further compared with those seen in 10 normal volunteers. Incremental intravenous infusion of isoprenaline (5, 10, and 15 ng/kg/min) raised heart rate to a greater extent in the donor compared with the recipient hearts in the eight patients who had heterotopic grafts (slopes [beats/min/ng/kg]: donor = +2.26, recipient = +1.59; p < .01). In addition, the donor hearts of the transplant patients were more sensitive than hearts of the normal volunteers (slopes: donor = +2.26, normal = +0.94; p < .01). The changes in the two groups of donor hearts were similar (slopes: orthotopic = +2.24, heterotopic = +2.27; NS). The recipient hearts of the patients with heterotopic transplants were more sensitive than the hearts of the normal volunteers (p < .05), suggesting that the observed differences in isoprenaline sensitivity in the patients with heterotopic grafts were not caused by a decreased sensitivity of the recipient heart. After β-blockade, the heart rate responses to isoprenaline were attenuated to the same extent in denervated and innervated hearts. The donor hearts, however, continued to be more sensitive to isoprenaline than were the recipient hearts (slopes: donor = +0.72, recipient = +0.34; p < .01). In patients with cardiac transplantation, the denervated heart is more sensitive to the chronotropic effect of isoprenaline compared with the innervated hearts of both the recipients and normal volunteers. However, since β-blockers attenuated this response similarly in the denervated and innervated hearts, our observations are consistent with an increase in β-receptor density and probably no change in β-receptor affinity.


IN LONG-TERM STUDIES after human cardiac transplantation, the donor heart appears to remain both functionally and anatomically denervated. No instance of reinnervation has been documented. Experimental denervation of the heart has been shown to be associated with increased adrenergic sensitivity and an increase in β-adrenergic receptor density. However, there has been no systematic evaluation of cardiac adrenergic sensitivity after human cardiac transplantation, and studies on a limited number of patients have not been able to demonstrate increased catecholamine sensitivity. Most studies of cardiac physiologic responses in the denervated orthotopic heart have been confounded by the unavailability of a suitable innervated control that is subject to the same drug therapy, circulating hormones, and hemodynamic changes. Heterotopic cardiac transplantation, a procedure in which the donor heart is inserted in parallel to the patient’s own heart, presents a unique opportunity to compare simultaneously the responses of the innervated recipient heart and the denervated donor heart to identical stimuli in the same patient. Since the recipient heart in a patient with “end stage” heart failure may
have decreased sensitivity to \(\beta\)-adrenergic stimulation, it is essential to ascertain that the recipient heart itself does not demonstrate hyposensitivity compared with the hearts of normal volunteers.

The purpose of this study is to compare heart rate response in the denervated donor hearts of patients who underwent heterotopic or orthotopic cardiac transplantation with that in innervated human hearts (both recipient hearts and normal volunteers) to graded incremental infusions of isoprenaline as an index of \(\beta\)-receptor sensitivity. All studies were repeated after \(\beta\)-blockade to assess whether these drugs preferentially alter the response of the transplanted heart.

**Patients and methods**

**Patients.** Fourteen patients underwent cardiac transplantation 6 to 15 months before study. Eight had heterotopic and six had orthotopic cardiac transplantation. Consecutive patients who were clinically stable and gave informed consent were included in this study, and no other selection criteria were used. In addition, 10 healthy volunteers (aged 20 to 35 years) were studied to assess the normal response to isoprenaline.

Table 1 outlines the clinical characteristics of the patients as well as details of the underlying pathologic status of the recipients' hearts in patients who had heterotopic transplants, data regarding the donor hearts, drug therapy, and interval from surgery.

None of these patients was receiving \(\beta\)-blockers, digitalis, or other cardiac drugs, nor did any have diabetes or other diseases known to affect the autonomic nervous system. No patient had evidence of rejection on the most recent biopsy. All patients were on azathioprine, prednisolone, and cyclosporine; only four patients were on diuretics (table 1). All 14 donor hearts and all eight recipient hearts were in sinus rhythm. Cardiac output estimated by thermodilution was normal in all patients and intraventricular pressures were normal in the 14 donor and eight recipient hearts. Baseline venous norepinephrine levels estimated by a radioenzymatic assay were normal in all patients.

**Operative technique.** In orthotopic cardiac transplantation the recipient heart is removed, leaving the posterior walls of the right and left atria as well as most of the interatrial septum. The donor sinus node is not damaged and retains its blood supply from the coronary circulation, and all the nerves to and from the heart are interrupted.

Heterotopic cardiac transplantation involves the insertion of the donor heart into the right chest, in parallel with the recipient heart. Anastomoses are carried out between the donor and recipient superior vena cava, left atria, aorta, and pulmonary arteries. This modified technique, in which the superior vena cava instead of the right atria are anastomosed, preserves the arteries to both sinoatrial nodes and the nerves to the recipient, but not the donor, heart. In addition, aneurysmectomy with coronary artery bypass grafts to the recipient hearts were performed in six patients who had ischemic heart disease (table 1).

**Study protocol.** Informed consent was obtained from all patients. A cannula was then inserted into a forearm or antecubital vein of the right arm. Heart rates and blood pressure were recorded in all subjects after at least 30 min in the supine position.

Incremental stepwise infusion of a freshly prepared solution of isoprenaline was then started with a constant-infusion syringe pump at 5, 10, and 15 ng/kg/min for 5 min each. Heart rate and blood pressure were recorded every 2.5 min (i.e., twice at each dose level) during the infusion and for 5 min after its cessation. After a rest period of 1 hr, patients were given 0.1 mg/kg iv propranolol over 5 min. Patients were restudied an hour after

---

**TABLE 1**

**Clinical features**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age of recipient (yr)</th>
<th>Age of donor (yr)</th>
<th>Interval from operation to study (mo)</th>
<th>Underlying pathology of the old heart</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Heterotopic cardiac transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>30</td>
<td>13</td>
<td>10</td>
<td>CCM</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>34</td>
<td>12</td>
<td>8</td>
<td>IHD</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>42</td>
<td>20</td>
<td>6</td>
<td>IHD</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>50</td>
<td>30</td>
<td>12</td>
<td>IHD</td>
<td>Pr, Az, Cy</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>16</td>
<td>10</td>
<td>IHD</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>27</td>
<td>16</td>
<td>8</td>
<td>CCM</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>42</td>
<td>14</td>
<td>12</td>
<td>IHD</td>
<td>Pr, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>19</td>
<td>12</td>
<td>IHD</td>
<td>Pr, Az, Cy, Asp, Di, D</td>
</tr>
<tr>
<td>B. Orthotopic cardiac transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>30</td>
<td>49</td>
<td>6</td>
<td>CCM</td>
<td>Az, Cy, Asp, D</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>49</td>
<td>19</td>
<td>6</td>
<td>RHD</td>
<td>Az, Cy, Acy, D, H</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>24</td>
<td>15</td>
<td>CCM</td>
<td>Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>18</td>
<td>7</td>
<td>Trauma</td>
<td>Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>35</td>
<td>9</td>
<td>IHD</td>
<td>Pe, Az, Cy, Asp, Di</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>56</td>
<td>22</td>
<td>6</td>
<td>IHD</td>
<td>Pr, Cy, Az, Acy, Pe, D</td>
</tr>
</tbody>
</table>

\(Az =\) azathioprine; \(Cy =\) cyclosporin; \(Pr =\) prednisone; \(Asp =\) aspirin; \(Di =\) dipyridamole; \(D =\) diuretics; \(Acy =\) acyclovir; \(CCM =\) congestive cardiomyopathy; \(IHD =\) ischemic heart disease; \(RHD =\) rheumatic heart disease.
propranolol and the same protocol was repeated, with the exception that isoprenaline was infused at 20 and 25 ng/kg/min in addition to 5, 10, and 15 ng in 13 of the 14 patients; the first patient with a heterotopic graft studied received only an isoprenaline infusion of up to 15 ng/kg/min.

Measurement of heart rate and blood pressure. The heart rate was calculated from standard 12 lead electrocardiograms (ECGs) obtained at 25 mm/sec in all patients with orthotopic cardiac transplantation. In patients with heterotopic heart transplantation the 12 lead ECG was modified to record V6R instead of V3. The QRS complex from the donor heart produced the dominant positive deflection in V6R, while that from the recipient heart produced a dominant positive deflection in V6 (figure 1). In addition, the configuration of the QRS complexes was compared with the preoperative ECG to help distinguish the complexes from the donor and recipient hearts in the different leads. All the hearts were in sinus rhythm and the ECGs did not show any evidence of atrioventricular conduction abnormalities. The ECGs were analyzed by one of three investigators (S.Y., S.T., or N.D.) and all were checked by one of two (M.Y. or S.Y.). The data in normal volunteers were obtained by an identical method but with no knowledge of the transplant data. Similarly, the transplant analyses were carried out blinded to the data in normal volunteers.

Blood pressure was measured from the left arm with a mercury sphygmomanometer or a semiautomated electronic sphygmomanometer (Dinamap). Heart rate and blood pressure were measured at baseline, every 2.5 min during infusion of isoprenaline, and twice at similar intervals after its cessation.

Documentation of denervation in the donor hearts and intact innervation in the recipient hearts. In all 14 patients evidence of conduction from the recipient hearts of patients with heterotopic grafts or the recipient atrium in patients with orthotopic grafts to the donor heart was systematically sought during invasive studies and indirectly during 24 hr two-channel tape recordings. In addition, changes in the rates during carotid sinus massage, during change in posture, and during isometric and dynamic exercise were studied. The Valsalva maneuver was performed in four patients and an intravenous bolus dose of 3 mg of isosorbide was given in one patient.

Statistical methods. For each variable (heart rate, systolic and diastolic blood pressure) in each type of heart, the intercept μi and slope βj of the least-square regression line between infusion dose and change in variable was calculated. The model was:

\[ Y_{ij} = \mu_i + \beta_j d_i + e_{ij} \]

where i denotes the time, j denotes the type of heart (donor in orthotopic, donor in heterotopic, Yij = observed heart rate, systolic blood pressure, or diastolic blood pressure, di = i'th dose, and eij = error term for the (i,j)th observation.

The data showed no evidence of curvilinearity. The four types of hearts were compared by one-, two-, or three-way analyses of variance as appropriate. In every comparison of donor with recipient hearts among patients with heterotopic grafts, the analyses of variance models linked the two hearts within an individual. All data are presented as mean ± 1 SEM.

Results

Evidence of denervation in the donor hearts and innervation in the recipient hearts. None of the 14 donor hearts demonstrated sinus arrhythmia and satisfied the standard clinical criteria for denervation suggested by Mason and Harrison based on their extensive experience. No increase in heart rate was observed within 30 sec of standing up. These hearts also showed the characteristic delayed rate acceleration during and deceleration at the end of dynamic and isometric exercise. Carotid sinus massage and the Valsalva maneuver did not affect the rate in any donor heart.

All eight recipient hearts demonstrated sinus arrhythmia and heart rate slowed significantly (an average of about 10 beats) on carotid sinus massage. During the Valsalva maneuver, all recipient hearts showed normal responses (an early reflex tachycardia followed by a reflex bradycardia). These hearts also showed increases (by about 8 to 15 beats) in heart rate within 30 sec of standing up and during isometric and early dynamic exercise. These changes are consistent with an intact innervation in these eight recipient hearts.

All 14 patients underwent invasive studies 12 months after transplantation. In none of these patients was conduction from the right atrial remnant or from the recipient heart to the donor heart demonstrable. In all eight patients with heterotopic grafts, 24 hr two-channel ECG recordings and careful multichannel pro-

FIGURE 1. Electrocardiograms from a patient with heterotopic cardiac transplantation demonstrating separate identification of donor and recipient hearts. In V6R, the donor heart exhibits a positive wave whereas the recipient heart exhibits a negative wave. In V5, only the vector from the recipient heart is clearly seen, although the vector from the donor heart is just identifiable. In aVF, both QRS complexes can be separately identified.
longed ECG recordings demonstrated no evidence of conduction from the recipient to the donor heart or vice versa. Moreover, the QRS complexes from the two hearts appeared to be totally independent of each other. In one patient with a heterotopic transplant, an intravenous bolus of 3 mg of isosorbide dinitrate did not alter the rate of the donor heart but increased it by 15 beats in the recipient heart.

Control study: isoprenaline infusion before intravenous propranolol

Resting heart rates. In the patients with heterotopic grafts, the average resting heart rate was significantly higher in the donor heart (101 ± 4 beats/min) than in the recipient heart (87 ± 6 beats/min; p < .05). The resting heart rate in the donor hearts of the patients with orthotopic grafts was 85 ± 2 beats/min and that in normal subjects was 64 ± 2 beats/min (table 2). The resting heart rates in the donor hearts of both groups of patients were significantly different from each other (p < .01).

Changes in heart rate with isoprenaline. Incremental infusion of isoprenaline increased heart rate in the donor hearts of both transplant groups more than in the recipient hearts of the patients with heterotopic grafts or in the normal subjects (figure 2 and 3, table 2). The slopes for heart rate increase in the donor hearts of both transplant groups were almost identical (+2.27 and +2.24 beats/min/ng/kg, respectively). The heart rate increase in the recipient hearts of the patients with heterotopic grafts was significantly greater than that seen in the normal subjects, indicating that the differences in chronotropic response seen between the donor and recipient heart are not due to a decreased sensitivity of the latter (table 2).

Changes in blood pressure. The mean systolic and diastolic blood pressures at baseline in patients with heterotopic grafts were 133 ± 5 and 95 ± 5 mm Hg; in patients with orthotopic grafts the pressures were 142 ± 7 and 97 ± 5 mm Hg; in normal subjects, the pressures were 113 ± 2 and 73 ± 2 mm Hg (table 2). During infusion of isoprenaline the diastolic blood pressure decreased similarly and significantly in both patient groups and in normal subjects (figure 4) (slopes: -0.92 ± 0.19 mm Hg/ng/kg, p < .01; -1.04 ± 22, p < .01; -1.12 ± 0.09, p < .01; respectively). The systolic blood pressure decreased significantly after isoprenaline in patients with heterotopic transplant (slope: -0.70 ± 0.22, p < .01), showed little change (-0.02 ± 0.25) in the patients with orthotopic transplant, but showed an increase in normal subjects (slope: +1.31 ± 0.08, p < .01) (figure 4).

Isoprenaline infusion after intravenous propranolol

Resting heart rate. After 0.1 mg/kg iv propranolol, the resting heart rates decreased significantly (p < .01) in both donor and recipient hearts (table 2). This decrease was similar in both hearts.

Changes in heart rate with isoprenaline. After propranolol, the heart rate response to isoprenaline was markedly depressed in both the donor and recipient hearts. However, the donor hearts were more responsive to isoprenaline than were the recipient hearts in the patients with heterotopic grafts (slopes: +0.72 and +0.34, p < .003). The heart rate increases in the donor hearts of both patient groups were both +0.72 beat/ng (table 2, figures 2 and 3).

Changes in blood pressure. After propranolol, average resting systolic and diastolic blood pressure fell slightly. After the infusion of isoprenaline there was a small nonsignificant increase in the diastolic blood pressure of both patient groups and a significant and similar increase in systolic blood pressure in both groups (slopes: +0.25 ± 0.21 and +0.47 ± 0.25 in heterotopic and orthotopic transplantation; p < .01 compared with pre-β-blocker study and baseline).

Discussion

This study has demonstrated an increased chronotropic response of the denervated transplanted human heart to graded infusions of isoprenaline. To our knowledge, this has not been reported before in patients with cardiac transplantation but is consistent with experimental work demonstrating an increase in β-receptor density in transplanted rabbit, dog, and rat hearts and an increased sensitivity to isoprenaline seen in transplanted cat, dog, and rat hearts. We know of no previous study that has specifically examined β-adrenoceptor sensitivity in the transplanted human heart, but despite this most workers have concluded that the transplanted heart does not demonstrate an exaggerated response to catecholamines.

Appropriateness of control subjects. A major problem in conducting a study of chronotropic responses in transplanted hearts is the difficulty in obtaining a suitable control group for patients with cardiac transplantation, since these patients are on a variety of immunosuppressant drugs, some of which, like the corticosteroids, could potentially alter β-receptor sensitivity or density and catecholamine uptake mechanisms. We circumvented the problems by using two types of controls, neither of which is ideal but which, when taken together, overcome each other’s deficiencies: First, in patients who have undergone heterotopic transplantation, the recipient heart is subject to the
effect of the same drugs, hormones, and some of the hemodynamic changes as the denervated donor heart. Thus, the recipient heart of a patient with a heterotopic graft acts as a control for the donor heart. The recipient heart, however, is diseased; Bristow et al. have shown a decrease in β-receptor density in chronic heart failure, presumably secondary to chronically elevated circulating catecholamines. Our studies were done in patients who were hemodynamically stable for several months, with no clinical evidence of heart failure at the time of the study. Furthermore, Levine et al. have shown substantial decrease in plasma catecholamines after cardiac transplantation. Although even a modest elevation of circulating catecholamines could affect β-receptor density, this is likely to affect both the recipient and donor hearts in the same patient. Furthermore, the basal venous epinephrine and norepinephrine levels in our patients were within the limits observed in normal individuals (unpublished observations). Therefore, any difference in β-adrenergic sensitivity between the donor and recipient hearts can largely be attributed to the presence or absence of nerve supply.

TABLE 2

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Change during I</th>
<th>Systolic BP</th>
<th>Change during I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting (beats/min) Pre-BB Post-BB</td>
<td>Pre-BB Post-BB Pre-BB Post-BB</td>
<td>Pre-BB Post-BB Pre-BB Post-BB</td>
<td></td>
</tr>
<tr>
<td>Orthotopic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor (n = 8)</td>
<td>85 ± 2 78 ± 1</td>
<td>+2.24 ± 0.23 +0.72 ± 0.11</td>
<td>142 ± 7 136 ± 5</td>
</tr>
<tr>
<td>Heterotopic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor Recipient (n = 6)</td>
<td>101 ± 4 89 ± 3</td>
<td>+2.27 ± 0.34 +0.72 ± 0.13</td>
<td>133 ± 5 129 ± 7</td>
</tr>
<tr>
<td>Normal subjects (n = 10)</td>
<td>64 ± 2</td>
<td>+0.94 ± 0.10</td>
<td>113 ± 2</td>
</tr>
</tbody>
</table>

1 = isoprenaline; BB = β-blockade; BP = blood pressure.

*Refer to the text for statistical significance of relevant comparisons among the means and the slopes.

FIGURE 2. Rate increases during infusion of isoprenaline in the donor and recipient hearts of patients with heterotopic cardiac transplantation both before and after β-blockade (BB). Both before and after BB, the donor heart is more sensitive than the recipient heart. The attenuations of the slopes of the donor and recipient hearts after BB are not significantly different (p = .37).

FIGURE 3. Slopes for heart rate increases during infusion of isoprenaline in the donor hearts of the patients with heterotopic (HCT) and orthotopic (OCT) transplants before and after β-blockade. The response of the 10 normal subjects is also plotted and is significantly lower than the slope of the two groups of donor hearts before β-blockade.
PATHOPHYSIOLOGY AND NATURAL HISTORY–CARDIAC TRANSPLANTATION

TABLE 2
(Continued)

<table>
<thead>
<tr>
<th></th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting (mm Hg)</td>
</tr>
<tr>
<td>Pre-BB</td>
<td>Post-BB</td>
</tr>
<tr>
<td>97±5</td>
<td>94±2</td>
</tr>
<tr>
<td>95±5</td>
<td>91±7</td>
</tr>
<tr>
<td>73±2</td>
<td>−</td>
</tr>
</tbody>
</table>

Since the recipient hearts were diseased and the transplant patients were older, one might have expected these hearts to be less sensitive to isoprenaline than were the normal younger subjects (whose ages were 20 to 35 years, which is closer to that of the donor hearts, table 1). The heart rate responses in the recipient hearts, however, were significantly greater than the heart rate response in the normal subjects. This suggests that the apparent greater responsiveness of the donor heart compared with the recipient heart is not due to decreased sensitivity of the recipient heart. The immunosuppressant drugs given to the transplant patients may provide a possible explanation for the apparent increased sensitivity of the recipient heart compared with normal subjects. Alternatively, the systolic blood pressure fell to a greater extent in the transplant patients compared with normal volunteers during infusion of isoprenaline, and this may have resulted in a greater reflex tachycardia in the recipient heart. However, the donor hearts were found to be still more sensitive. It is likely that the differences in sensitivities to isoprenaline in our pre-β-blocker studies were underestimated because of reflex vagal withdrawal in the recipient heart. This is consistent with the observations of Vatner et al., who found that blocking the reflex tachycardia in innervated control dogs was critical in demonstrating supersensitivity to isoprenaline in denervated dog hearts. Interestingly, the ratio of slopes between the donor and recipient hearts after β-blocker (0.72±0.32 or about 2.3), when there was little fall in systolic blood pressure (rather than the pre-β-blocker study [ratio of about 1.4] when systolic pressure fell), approximates the ratio between the donor heart and normal volunteers 2.27±0.95 or about 2.4).

The second group of controls comprised 10 normal volunteers who had no history of any disease and were not on any drugs. Therefore one would not expect any change in β-receptor sensitivity in these subjects. The responses to isoprenaline in all 14 transplanted hearts was significantly greater than in these 10 normal subjects (p < .0001, table 2), confirming that the transplanted hearts were indeed supersensitive to β-agonist stimulation.

Influence of age of heart and type of transplantation. The donor hearts were obtained from subjects who were significantly younger than the transplant recipients. To exclude differences in age as the chief cause of the differences in isoprenaline sensitivity, we compared the slopes in the donor hearts with those in the normal subjects whose ages were similar. Such an analysis still demonstrated that the donor hearts were more sensitive to isoprenaline than the hearts of normal subjects (p < .001). Furthermore, within each group of hearts, age was not associated with isoprenaline sensitivity. This excludes age as the major cause for the differences in isoprenaline sensitivity among the different types of hearts. To assess whether the heterotopic position of the donor heart could itself affect the heart rate and blood pressure responses, we studied an additional six patients with orthotopic cardiac transplantation. The changes in heart rate observed in the donor hearts were almost identical to those observed in the patients with heterotopic transplant both before and after β-blockade.

![FIGURE 4. Systolic and diastolic blood pressure response during infusion of isoprenaline in patients with heterotopic and orthotopic transplants and in normal subjects. BB = β-blocker.](https://i.imgur.com/5Yz5J.png)

Vol. 75, No. 4, April 1987 701
Evidence for innervation in the controls and denervation in the transplanted hearts. After human cardiac transplantation, no instance of reinnervation has yet been recorded. Despite this, we systematically performed various physiologic stimuli to test for vagal stimulation (carotid sinus massage, decrease in heart rate within 30 sec after lying down, cessation of dynamic exercise, and the Valsalva maneuver), vagal withdrawal (increase in heart rate within 30 sec after standing up and the start of dynamic exercise and the Valsalva maneuver), and sympathetic nerve stimulation and withdrawal (isometric exercise and recovery). These tests demonstrated normal responses in the recipient hearts consistent with an intact innervation and an abnormal response in the donor hearts similar to all previous reports in human transplantation and during carotid sinus stimulation during experimental cardiac denervation. In particular, during carotid sinus massage and the Valsalva maneuver, the transplanted hearts showed no change in rates, consistent with an absence of baroreflexes. Additionally, during invasive studies or continuous 24 hr two-channel ambulatory Holter monitoring, no evidence of conduction from the recipient’s atria (orthotopic) or heart (heterotopic) to the donor heart could be demonstrated. (Note that during surgery, the recipient and donor atria are connected so that if functional reinnervation occurs, conduction between the two hearts should be evident.)

Heart rate responses during isoprenaline infusion and the effect of β-blockers. The heart rate response to isoprenaline chiefly measures the adrenergic response of the sinus node. Changes in such responsiveness have usually been thought to reflect the adrenergic sensitivity of the myocardium at large. However, this has not been directly established. Animal studies, in which similar directional changes in receptor density and chronotropic responses have been observed after denervation, support this possibility. The isoprenaline-induced tachycardia in normal subjects is thought to be caused by a combination of direct cardiac β1-stimulation and a reflex due to peripheral vasodilatation produced by β2-stimulation. Vagal withdrawal in innervated hearts may also contribute to the tachycardia after isoprenaline. The last two mechanisms would be expected to exaggerate the heart rate increase in the recipient heart or normal volunteers, leaving the donor heart unaffected. This would suggest that any true difference in β1-sensitivity is likely to be greater than that indicated by our control isoprenaline infusion studies before β-blockade.

After propranolol, the responses of both donor and recipient hearts to isoprenaline were attenuated, indicating that the entire heart rate–dose response curve was shifted to the right. Despite this, the two groups of donor hearts were more sensitive to isoprenaline than the recipient hearts, especially at the higher doses of isoprenaline. After β-blockade with propranolol, one might expect some attenuation of the β1-mediated reflex tachycardia in the innervated heart (the diastolic blood pressure was unaltered) and therefore the relative differences in rates between the two hearts after isoprenaline observed here might be more representative of their true relative adrenergic sensitivities. Furthermore, the heart rate responses to isoprenaline were attenuated to the same extent in both denervated and innervated hearts after β-blockers. This suggests that receptor affinity is probably not altered. However, in human studies, strict steady-state mass-action criteria may not be met, and definitive differentiation between changes in receptor density or affinity can be obtained only by direct studies in vitro. Nevertheless, our findings are consistent with the report of Lurie et al. and Vatner et al., who observed no change in receptor affinity but an increase in β-receptor density in experimental heterotopic cardiac transplantation or denervation. In addition, Vatner et al. observed that the increased β-receptor density correlated well with the amount of denervation supersensitivity to isoprenaline in dogs.

Although previous studies have concluded that the denervated heart does not demonstrate a greater sensitivity to isoprenaline, data from the two other studies in which isoprenaline was given to a few patients with orthotopic cardiac transplantation are consistent with our observations. For example, Cannom et al. studied three patients who received bolus doses of isoprenaline. This resulted in an average increase of only 18 beats/min in the sinus node of the recipient heart compared with an average increase of 40 beats/min in the donor hearts at the same dose. Similar results were found in one patient by Carleton et al.; recipient sinus node rate increased from 72 to 83 beats/min compared with an increase from 88 to 112 beats/min in the donor heart after 0.8 mg/min of isoprenaline.

To our knowledge, there have been no studies in transplant patients evaluating agonist response after β-blockade. Despite this, some authors claim that transplant patients may be particularly sensitive to β-blockers and that these drugs may have deleterious effects. By contrast, the current study and our previous studies during dynamic exercise suggest that β-blockers may not be deleterious when used by transplant patients.
Blood pressure changes. The blood pressure responses in these patients are difficult to interpret. In particular, in the patients with heterotopic grafts it is unclear which heart contributes to the blood pressure at any particular time. Invasive hemodynamic studies in our clinic have shown that both the recipient and donor hearts contribute to the aortic pressure, although their relative contributions at a particular time depend on which part of the cardiac cycle each heart is in with respect to the other.

During the control study, the systolic blood pressure decreased in the transplant patients after isoprenaline, whereas the systolic blood pressure increased in the normal volunteers. This observation was unexpected and has not been reported before in studies of experimental cardiac transplantation; therefore, any explanation is only conjectural. A similar drop in systolic blood pressure after isoprenaline has been observed in studies in tetraplegic patients. This suggests that afferent impulses from the heart may play an important role in modulating systolic blood pressure during isoprenaline stimulation. There may also be changes in peripheral α-receptor sensitivity. The systolic and diastolic blood pressure responses to isoprenaline appear to differ in the transplant patients before and after β-blockade. It is possible that the rise in systolic blood pressure and little change in diastolic blood pressure after β-blockade as opposed to a fall in diastolic and a similar trend for the systolic blood pressure to drop before β-blockade may represent a peripheral vascular effect due to unopposed α-activity. Alternatively, much higher doses of isoprenaline than those we used are likely to be required to lower diastolic blood pressure after β-blockade.

Implications of the study. Demonstration of the increased sensitivity to β-stimulation in the denervated transplanted heart is physiologically similar to the increased sensitivity of the β1- and β2-receptors observed in patients with autonomic neuropathies. When the heart is denervated, increased catecholamine sensitivity is probably a necessary compensatory mechanism for a variety of physiologic stimuli such as exercise, changes in posture, or stress in order to overcome the lack of sympathetic nerve stimulation. The extent to which such increased β-receptor sensitivity or density occurs is probably just sufficient to counterbalance the lack of sympathetic stimulation, since we have previously observed that at maximal exercise both the denervated and innervated hearts reach almost identical heart rates. The effect of propranolol was similar in the denervated and innervated hearts.

In conclusion, we have demonstrated that the denervated transplanted human heart exhibits an increased chronotropic response to isoprenaline, consistent with previous experimental work suggesting an increase in β1-receptor density. These findings could have important clinical implications with regard to interpreting the responses to physiologic and pharmacologic stimuli in patients with cardiac transplantation or some types of autonomic neuropathy.

We thank members of the ECG department, Dr. Peter Allen, and Mrs. Moira Markett for their help during these studies, Barbara Geraci for computer support, and Mary Ann McLaughlin and Rena Woodland for typing this manuscript. Most importantly, we are grateful to the transplant patients who readily volunteered for these studies. We are also grateful to Dr. Michael Bristow, Salt Lake City, for his helpful comments. Dr. Mathias is a Wellcome Trust Senior Lecturer in Medicine.

References

YUSUF et al.

Rowlands DJ, editors: Recent advances in cardiology. Edinburgh, 1981, Churchill Livingstone, p 323


Increased sensitivity of the denervated transplanted human heart to isoprenaline both before and after beta-adrenergic blockade.

S Yusuf, S Theodoropoulos, C J Mathias, N Dhall, J Wittes, A Mitchell and M Yacoub

_Circulation_. 1987;75:696-704
doi: 10.1161/01.CIR.75.4.696

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/75/4/696

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/