Impairment of cardiopulmonary baroreflex after cardiac transplantation in humans

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ABSTRACT There is ample evidence for efferent cardiac denervation in patients after cardiac transplantation. However, little is known regarding the effects of the cardiac deafferentation that also results. We examined responses to graded lower-body negative pressure and thus cardiopulmonary baroreceptor unloading in 23 patients 3 to 12 months after cardiac transplantation and compared their responses with those of nine normal subjects. Responses of mean arterial pressure, forearm vascular resistance, and plasma norepinephrine were assessed during lower-body negative pressure and the cold pressor test. Reflex increases in forearm vascular resistance (1.5 ± 1, 5.0 ± 1.4, and 6.4 ± 2.1 vs 14.5 ± 4.5, 20.3 ± 6.5, and 34 ± 11 units) and plasma norepinephrine (42 ± 12, 58 ± 15, and 62 ± 13 vs 49 ± 14, 94 ± 25, and 173 ± 36 pg/ml) were strikingly smaller in cardiac transplant patients than in normal subjects. The impaired responses of the cardiac transplant patients were not the result of the nonspecific depression of cardiovascular reflexes, since increases in mean arterial pressure (12 ± 3 vs 10 ± 2 mm Hg), forearm vascular resistance (19.5 ± 3.4 vs 18 ± 5.8 units), and plasma norepinephrine (56 ± 8 vs 42 ± 11 pg/ml) during cold pressor test were not significantly different in the two groups. Furthermore, the impaired responses were not caused by the immunosuppressive agents used to treat the cardiac transplant patients, since patients with renal transplants on similar regimens had augmented forearm vasoconstrictor responses. The technique of orthotopic transplantation we used resulted mainly in ventricular deafferentation. Thus our data suggest that cardiopulmonary baroreflex control of forearm vascular resistance is impaired after cardiac transplantation and that this is due mainly to ventricular deafferentation.


THE HEART has efferent sympathetic and parasympathetic innervation as well as afferent or sensory innervation. When the heart is transplanted, both the efferent nerves passing to the heart and the afferent nerves that originate in the heart are interrupted. Although there have been several investigations of the effects of efferent cardiac denervation in humans and animals after cardiac transplantation, much less is known regarding the consequences of the cardiac deafferentation associated with cardiac transplantation.

There are sensory receptors in all of the cardiac chambers, although animals studies suggest that they are concentrated on the left side of the heart. These sensory receptors send signals to the brain via the vagal and spinal nerves, and this sensory input has important effects on the level of sympathetic outflow to the heart and peripheral circulation. Atrial receptors are clustered around the junctions of the great veins with the atria. These areas are not disturbed during cardiac transplantation, and thus atrial receptor function may remain intact, although this has not been tested directly. Transplantation interrupts all of the nerves to the ventricles. Evidence from several sources suggests that sensory endings in the ventricles play a major role in the bradycardia and hypotension associated with inferior wall myocardial infarction, in the syncope of aortic stenosis, and in vasovagal syncope. They also are important in reflex responses to hemorrhage in animals and to stimulated orthostatic stress that occurs during venous pooling induced by application of suction to the lower half of the body. We hy-
pithesized that the cardiac deafferentation that results from cardiac transplantation is sufficient to impair reflex responses normally mediated by sensory endings in the cardiopulmonary region. To test this hypothesis, we determined the changes in forearm vascular resistance and plasma norepinephrine resulting from lower-body negative pressure (LBNP), a technique that reduces the stimulus mainly to cardiac rather than arterial baroreceptors. Unloading receptors in the cardiopulmonary area by lower body suction normally results in forearm vasoconstriction and increased circulating norepinephrine.23-25

Our data show striking impairment of responses to lower-body suction after cardiac transplantation, most likely due to ventricular deafferentation.

Methods

Patient selection. Twenty-three consecutive patients who underwent orthotopic cardiac transplantation at the VA Medical Center, Richmond, formed the transplant group. All patients were men aged 19 to 51 years (mean ± SE, 39 ± 4.5) who were studied 2 to 12 months after cardiac transplantation. Orthotopic cardiac transplantation was performed according to the technique described previously by Lower et al.13 Seventeen patients were receiving immunosuppressive therapy with cyclosporine and prednisone; three patients were receiving cyclosporine, prednisone, and azathioprine; and three patients were treated with prednisone and azathioprine. Ten of 23 patients were receiving diuretics for fluid retention and seven others were treated with captoril for mild-to-moderate hypertension. No other cardiac medications were used in these patients at the time of the study.

All medications except for the immunosuppressive agents were withheld for 48 hr before study. No patient was diabetic and none were studied during an acute episode of rejection, infection, or other major illnesses. All patients were in regular sinus rhythm (transplanted heart) and all had a normal posttransplant echocardiogram.

Nine normal subjects (ages 31 to 48 years, mean age 36 ± 3) served as the first control group and four patients (ages 33 to 49 years, mean age 39 ± 3) who were receiving a similar immunosuppression regimen (cyclosporine and prednisone) after renal transplantation formed the second group of control subjects for comparison of hemodynamic and hormonal responses to LBNP. Informed consent was obtained from all subjects, and the research protocol was approved by the Human Subjects Review Committee of Virginia Commonwealth University and McGuire VA Medical Center. All patients were studied in the supine postabsorptive state.

Procedures. On the morning of testing, the patients were brought to the human physiology laboratory. A peripheral venous cannula was inserted into the left antecubital vein for blood sampling at least 30 min before starting the protocol. In five patients, internal jugular venous cannulation was accomplished and right atrial pressure was measured continuously via a No. 5F Swan-Ganz catheter connected to a Statham P23ID pressure transducer and recorded simultaneously with heart rate (electrocardiogram) and forearm blood flow on a direct-writing Gould Physiologic recorder (2800 S). Arterial pressure was measured by an automatic cuff method (Critikon Model 1160, Tampa, FL).

Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-Silastic strain gauge and plethysmograph (EC-3 or EC-4; DE Hokanson, Inc. Seattle). The technique of venous occlusion plethysmography used has been described previously in detail.26 The strain gauge was placed approximately 5 cm below the antecubital plethysmography and increased circulating norepinephrine.

Our data show striking impairment of responses to lower-body suction after cardiac transplantation, most likely due to ventricular deafferentation.

Echocardiography. Two-dimensional echocardiographic studies were performed with a commercially available mechanical sector scanner (ATL, MK-300, Seattle) with a real-time, high-resolution 2.5 MHz transducer, a 90 degree sector angle, displays at tissue depth of 16 and 21 cm, and a videotape recording rate of 30 frames/sec. These studies were obtained to determine whether the levels of suction used reduced cardiac chamber dimensions and thus the stimulus to cardiac mechanoreceptors. Echocardiograms were recorded with subjects in the supine position. Standard apical four-chamber and two-chamber views were used for calculations of left ventricular volumes. The end-diastolic frame was chosen at the peak of the R wave of the simultaneously recorded electrocardiogram. The frame in which smallest left ventricular volume was recorded was identified as end-systole. Volumes (normalized for body surface area) were calculated by the modified Simpson’s rule method24,25 with a microcomputer–based image analysis system (Microsonic, Inc., Indianapolis).

M mode left atrial echocardiographic tracings were derived from the parasternal short-axis view of the two-dimensional echocardiogram at the level of the aortic-tricuspid valve plane. Left atrial end-systolic dimension (normalized for body surface area) was measured according to the standard method26 at baseline, during each level of LBNP, and during the recovery phase after each intervention. Baseline values were reestablished during each recovery phase.

LBNP was used to unload receptors in the cardiopulmonary region, which normally results in reflex sympathetic activation. This was done by positioning each subject in a chamber that encases the body below the iliac crest. The chamber was sealed and connected to an adjustable vacuum source. Graded LBNP was applied at –10, –20, –40 mm Hg. LBNP was maintained at each level for 5 min, after which a 10 min recovery period was interposed before application of the next level of LBNP. Measurements of forearm blood flow were recorded every 15 sec. Values of forearm blood flow were taken as the average of flows (five flow curves) during the last 60 sec of each control or intervention period. The order of application of the three levels of suction was randomized.

Responses to cold pressor stimulus were determined after immersion of the patient’s left hand in ice water for 90 sec while blood pressure and forearm blood flow were determined as described above. The cold pressor test was used to assess responsiveness to another stimulus for reflex sympathetic activation and thus to determine whether abnormal responses to LBNP were specific rather than a manifestation of generalized alteration in responsiveness to reflex sympathetic activation.

Study protocol. The protocol was begun a minimum of 30 min after preparation of the patient for study was completed. Baseline hemodynamic and blood sampling for hormonal measurements were then initiated. We studied the hemodynamic
and plasma norepinephrine responses to graded levels of LBNP at −10, −20, and −40 mm Hg as well as the responses to cold pressor testing.

Blood samples (6 ml) were obtained before and during the last minute of each level of LBNP and cold pressor testing. Samples for catecholamines were collected in prechilled heparinized tubes and the plasma was stored at −75°C until assayed. Catecholamines were assayed by high-performance liquid chromatography with electrochemical detection. Detection in this system is coulometric and the sensitivity is less than 5 pg/ml.

Statistical analysis. The relationship between the level of LBNP and the responses of arterial pressure, plasma norepinephrine, and forearm vascular resistance was determined for the three groups by a multivariate analysis of variance that also permitted us to determine whether the responses were different between groups. The differences in basal values among the groups were assessed by a paired t test with the level of significance adjusted for the number of comparisons according to Bonferroni. Probability levels less than .05 were considered significant. Results are presented in the text, tables, and figures as mean ± SE.

Results

The basal values of heart rate, mean arterial pressure, forearm blood flow and forearm vascular resistance in the three groups are shown in table 1. The baseline heart rate, mean arterial pressure, and forearm vascular resistance are significantly higher (p < .01) in cardiac transplant patients than in the normal group.

The mean arterial pressure and forearm vascular resistance were higher in renal transplant patients compared with normal subjects, although heart rate was similar in both groups.

Heart rate and mean arterial pressure responses to LBNP. Figure 1 illustrates the heart rate and mean arterial pressure responses to graded LBNP. The data for cardiac transplant patients show that the heart rate and mean arterial pressure are consistently higher than those in normal subjects both at baseline and during LBNP. However, neither heart rate nor mean arterial pressure changed significantly at any level of LBNP compared with control. Although the data are not shown here, heart rate and mean arterial pressure did not change significantly during graded LBNP in renal transplant patients and thus suggest unloading of mainly cardiopulmonary baroreceptors. Because there was little change in heart rate or mean arterial pressure in normal subjects, cardiac transplant patients, or renal transplant patients, we have assumed that application of LBNP in our patients unloaded mainly cardiopulmonary baroreceptors with little or no unloading of sinoaortic baroreceptors.

Forearm vasoconstrictor responses to cardiopulmonary baroreceptor unloading with LBNP and to cold pressor testing. Representative continuous plethysmographic tracings from a normal subject and from a patient 8 weeks after cardiac transplantation are illustrated in figure 2. The baseline flow curves are shown on the left side of each figure and the flow curves in response to LBNP at −20 mm Hg are shown on the right. The slope of the tracing is proportional to forearm blood flow. The normal response to LBNP is characterized by a striking decrease of the slope, indicating marked reduction in forearm blood flow due to forearm vasoconstriction. In contrast, there is no response to the same level of suction in the cardiac transplant patient. The mean change in calculated forearm vascular resistance in response to LBNP for normal subjects and transplant

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 9)</th>
<th>Cardiac transplant (n = 23)</th>
<th>Renal transplant (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>65 ± 3</td>
<td>90 ± 3&lt;sup&gt;A&lt;/sup&gt;</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>89 ± 4</td>
<td>104 ± 2&lt;sup&gt;A&lt;/sup&gt;</td>
<td>108 ± 4&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/100 ml forearm volume)</td>
<td>4.2 ± 0.7</td>
<td>3.0 ± 0.3</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Forearm vascular resistance</td>
<td>23 ± 4</td>
<td>42 ± 4&lt;sup&gt;A&lt;/sup&gt;</td>
<td>28 ± 1</td>
</tr>
</tbody>
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<sup>A</sup>p < .01 vs normal control.
PATHOPHYSIOLOGY AND NATURAL HISTORY—CARDIAC TRANSPLANTATION

Normal Control

**FIGURE 2.** Plethysmographic tracings from a normal subject (top tracing) and a patient 8 weeks after cardiac transplantation (bottom tracing). The left portion of each tracing illustrates the baseline forearm blood flow and the right portion demonstrates the effects of LBNP (−20 mm Hg). Calculated values of forearm blood flow (FBF) and forearm vascular resistance (FVR) and corresponding mean arterial pressure (MAP) and heart rate (HR) are shown on the left for baseline values and on the right for the responses to LBNP. The reflex response in normal (top tracing, right) demonstrates an appropriate increase in calculated FVR, whereas the response in the transplant patient (bottom tracing, right) is markedly impaired.

patients is illustrated in figure 3. In the normal group, there was the expected significant increase in forearm vascular resistance with unloading of cardiopulmonary baroreceptors by LBNP, whereas changes in forearm vascular resistance were significantly impaired at all levels of suction in patients 2 to 12 months after cardiac transplantation. Since the cardiac transplant patients had a significantly higher basal forearm vascular resistance, we analyzed the changes in forearm vascular resistance normalized for the baseline value (percent change). As illustrated in figure 4, the percent changes in forearm vascular resistance in the transplant patients

**FIGURE 3.** Mean (± SEM) forearm vascular resistance responses to graded LBNP (−10, −20, −40 mm Hg) and cold pressor test in nine normal subjects and in 23 cardiac transplant patients. Cold pressor responses were assessed in 15 of 23 cardiac transplant patients. Significant differences between normal subjects and cardiac transplant patients are indicated.

**FIGURE 4.** Normalized forearm vascular resistance responses (percent change) (mean ± SEM) to LBNP and cold pressor test in nine normal subjects and in 23 cardiac transplant patients. Cold pressor response was assessed in 15 of 23 cardiac transplant patients. Significant differences between normal subjects and cardiac transplant patients are indicated.
are significantly smaller than in the normal subjects. In contrast, there was no difference in the absolute or relative forearm vasoconstrictor responses to cold pressor testing in these two groups (figures 3 and 4).

To assess whether immunosuppressive therapy independent of cardiac denervation may have had an influence on cardiopulmonary baroreflex, we determined the forearm vascular resistance responses to LBNP in a small group of renal transplant patients who were receiving similar immunosuppressive therapy consisting of cyclosporine 3 to 5 mg/kg/day plus prednisone 0.2 to 0.3 mg/kg/day. Figure 5 illustrates the comparative data on percent change in forearm vascular resistance resulting from graded LBNP and color pressor testing in both renal (n = 4) and cardiac transplant (n = 23) patients. The relative responses of forearm vascular resistance to LBNP were markedly impaired (p < .001) in cardiac transplant patients with similar antirejection treatment. The forearm vascular resistance responses to cold pressor testing were not different for the two groups, although the responses of the renal transplant patients tended to be augmented.

Plasma norepinephrine responses to reflex sympathetic activation by LBNP in cardiac transplant patients vs normal subjects. Baseline plasma norepinephrine levels were lower (131 ± 12 vs 270 ± 29 pg/ml; p < .05) in cardiac transplant patients. As illustrated in figure 6, plasma norepinephrine increased with LBNP in both groups, but the responses in cardiac transplant patients were markedly attenuated. The plasma norepinephrine responses to cold pressor testing were not different between the two groups.

Effect of LBNP on cardiac filling pressure and cardiac dimensions in cardiac transplant patients. In five of the cardiac transplant patients we obtained continuous right atrial pressure and two-dimensional echocardiographic estimates of left ventricular end-diastolic volumes and M mode derived left atrial end-systolic size at baseline and during LBNP. These results are summarized in table 2. During graded LBNP, cardiac filling pressure decreased significantly as expected and there was also a concomitant decrease in left ventricular end-diastolic volume index and left atrial dimension compared with baseline.

Discussion

Our data provide clear evidence that the forearm vasoconstrictor and plasma norepinephrine responses to application of LBNP are impaired in humans after orthotopic cardiac transplantation. This is most likely the result of the ventricular deafferentation that results from cardiac transplantation. The impaired responses are not caused by a nonspecific effect of transplanta-
tion or of immunosuppressive treatment. Our discussion will focus on these points.

Under normal circumstances, sensory receptors in the cardiopulmonary region exert a tonic restraining influence on sympathetic outflow to the heart and peripheral circulation.2-3,32 This has been established in animals by demonstrating increased sympathetic traffic, peripheral vasoconstriction, and increased neural mediately mediated renin release in response to vagotomy or vagal cold block or to hemorrhage.33,34 The afferent limb of this restraining influence originates in mechanosensitive sensory endings in the cardiopulmonary region subserved by vagal afferent fibers. When cardiac filling pressures and volumes are decreased, the activity of these sensory endings decreases and this decreased sensory input and tonic inhibition results in excitation of sympathetic outflow. There is evidence that receptors in the atria, ventricles, and lungs each contribute to the tonic inhibitory influence on sympathetic outflow that originates from the cardiopulmonary region.32 However, the relative contributions of the sensory inputs from these three receptive regions to the total inhibitory influence that originates in the cardiopulmonary region remain unknown. We interpret our results to indicate that most of the tonic inhibitory input originates from the ventricles based on the following reasoning. The technique used for cardiac transplantation leaves undisturbed portions of the left and right atria and interatrial septum of the recipient's own heart. It also leaves intact the superior and inferior venae cavae and pulmonary veins at their junctions with the right and left atria. Most of the atrial mechanoreceptors are clustered in these areas14 and presumably are left intact after transplantation. Sensory endings in the lungs also remain undisturbed, thus making cardiac transplantation a model mainly of ventricular deafferentation. On this basis, we suggest that ventricular deafferentation accounts for the striking reductions in forearm vasoconstrictor responses to LBNP and thus in the tonic inhibitory influence that originates from the cardiopulmonary region. We emphasize that little is known regarding the residual atrial receptors in the untransplanted atria after cardiac transplantation. Impairment in the function of these receptors related to the operation or to preexisting heart disease cannot be excluded by our studies and is an area we plan to investigate.

Other studies suggest that ventricular receptors exert a tonic inhibitory influence on sympathetic outflow in humans. It has been reported recently that administration of propranolol attenuated the forearm vasoconstrictor responses to LBNP but did not change the vasoconstrictor responses to the cold pressor test or to carotid baroreceptor unloading.22 Since propranolol decreases the activity of ventricular but not atrial mechanoreceptors, the authors interpreted their findings to indicate that ventricular mechanoreceptors play an important role in reflex adjustments to orthostatic stress in humans.

It also has been reported that the plasma renin responses to hemorrhage are impaired in dogs after cardiac autotransplantation.12 This abnormality was found to be present after efferent sympathetic and parasympathetic reinnervation of the heart. Five of the six dogs studied had no bradycardia and hypotension (Bezold-Jarisch reflex) in response to left ventricular injection of cryptenamine, a Veratrum alkaloid mixture. On the basis of those findings the authors suggested that the abnormalities in the reflex control of renin release were caused by the cardiac deafferentation that persisted after autotransplantation. They further suggested that the abnormality was due mainly to ventricular deafferentation, since the areas around the junctions of the great veins with the atria were left undisturbed during cardiac transplantation.

In this study we had to control for several variables in the cardiac transplant patients: the immunosuppressive regimen, the mild hypertension, and the increased vascular resistance. As in the cardiac transplant patients, the renal transplant patients had a very similar immunosuppressive regimen, mild hypertension, and modestly increased forearm vascular resistance. They had exaggerated forearm vasoconstrictor responses to LBNP. Compared with those of the renal transplant group, the responses of the heart transplant group were nearly abolished. If the renal transplant patients are the most appropriate controls, then our comparisons with the normal subjects we studied may have underestimated the extent of the impairment in reflex control present in the cardiac transplant group.

We determined the changes in central venous pressure and in cardiac dimensions (echocardiography) that resulted from LBNP because it could be argued that the failure of the transplant patients to respond to LBNP was due to an inadequate stimulus. Our data show that LBNP induced significant decreases in left atrial dimension and in computed left ventricular volumes along with marked decreases in central venous pressure. Receptors that were still functioning after cardiac transplantation should have had a striking decrease in discharge frequency during LBNP as a result of these changes. The finding of strikingly impaired responses is thus explained best by interruption of cardiac, especially ventricular, afferents.
There was close concordance between the responses of forearm vascular resistance and of plasma norepinephrine in all groups. Circulating catecholamines can be viewed as an indicator of net changes in global sympathetic activity. Although they parallel the forearm responses, it cannot be assumed that impaired control of other vascular beds is present after transplantation. Abboud et al. have shown that in humans the splanchic circulation is controlled mainly by arterial rather than cardiopulmonary baroreflexes. We speculate that reflex control of this regional circulation may not be altered importantly after cardiac transplantation.

Concern has been expressed that the forearm vasoconstrictor responses to LBNP observed in normal subjects is not due just to unloading of receptors in the cardiopulmonary region but may also be due to stimulation of afferents present in the abdominal viscera included in the suction box. It is possible that engagement of these viscera during application of suction gives rise to increased activity of visceral afferents and to reflex vasoconstriction. Our data indicate that if this mechanism contributes to the responses of the forearm to LBNP, then the contribution must be extremely small. Such visceral afferents and the reflexes they mediate should have been operative in our cardiac transplant patients. The cardiac deafferentation associated with transplantation is the likely mechanism for the impairment in reflex control we observed.

It has been suggested previously that the responses to LBNP are mediated by arterial baroreflexes, even when the levels of suction produce little or no detectable change in arterial pressure. Our findings indicate that at moderate levels of suction the reflex vasoconstriction in the forearm is caused by unloading of cardiopulmonary baroreflexes, since the forearm responses were impaired after cardiac transplantation and the resulting cardiac deafferentation but the carotid and aortic baroreceptors and the reflexes they mediated were left intact. It could be argued that the responses were still mediated by arterial baroreflexes but that these reflexes were abnormal because of the hypertension present in the majority of our patients. This seems unlikely since the abnormalities in the responses of forearm vascular resistance to LBNP were marked in cardiac transplant patients with normal arterial pressure.

It also could be argued that there is a general alteration in baroreflex control that results from heart failure, which persists after cardiac transplantation and which may contribute to the abnormal forearm vasoconstrictor responses to LBNP. Although our data do not eliminate this possibility, there are several reasons to consider this unlikely. First, arterial in contrast to cardiopulmonary baroreflexes exert a very weak effect on forearm vascular resistance. Thus any abnormality in forearm vasoconstrictor responses to LBNP must be due mainly to abnormal cardiopulmonary baroreflexes. Second, responses to cold pressor testing were not impaired. Finally, preliminary data from our laboratory indicate that forearm vasoconstrictor responses to isometric exercise are similar in normal subjects and patients with cardiac transplants. Although the responses to cold pressor testing and to isometric exercise indicate that this is not a nonspecific abnormality in reflex control, we acknowledge that they do not completely rule out altered baroreflex mechanisms unrelated to transplantation and the resulting cardiac deafferentation.

What are the implications of our findings as they relate to reflex control of the circulation in humans? First, we interpret our findings to indicate a major role for ventricular receptors in reflex circulatory control in humans. Second, there are many disease processes that may alter the number or function of these endings. They may be reduced in number by myocardial infarction, or their function may be altered in the hypertrophied ventricle or in the dilated failing heart. These conditions frequently are associated with abnormalities in circulatory control, especially in the presence of congestive heart failure. We consider it likely that cardiac receptors, especially those in the ventricles, play an important role in the pathophysiology of altered circulatory control in patients with heart disease.

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