Arterial Baroreflex Abnormalities in Heart Failure
Reversal After Orthotopic Cardiac Transplantation

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Arterial baroreflex control of the heart and peripheral circulation is markedly impaired in humans and animals with congestive heart failure. After reversal of heart failure in animal models, arterial baroreflex control of heart rate remains impaired for up to 8 months. Cardiac transplantation restores normal ventricular function and completely reverses heart failure, but does it normalize arterial baroreflex control of heart rate in humans? We studied baroreflex sensitivity in 11 patients with severe heart failure, six normal control patients, and 23 patients at 2 weeks to 4 years after orthotopic cardiac transplantation. Baroreflex sensitivity was assessed with intravenous bolus injections of phenylephrine and is expressed as change in RR or PP interval (msec) per millimeters of mercury rise in systolic arterial pressure. Atrial rate of both donor (denervated) and recipient (innervated) atria were measured in the transplant group. Baroreflex sensitivity in patients with severe heart failure was 2.0±0.3 msec/mm Hg, but in patients after cardiac transplantation, it was 13.0±0.9 msec/mm Hg (p<0.001). The responses in the transplant group were similar to those observed in normal controls (10±1.2 msec/mm Hg, p=NS). Our data indicate that patients with severe congestive heart failure have marked abnormalities of baroreflex control, which are reversed as early as 2 weeks after cardiac transplantation. In view of this rapid reversal, we consider it unlikely that abnormal baroreflex sensitivity seen in heart failure is due to structural alterations in the baroreceptors. We speculate that neurohumoral rather than structural abnormalities account for depressed baroreflex sensitivity in heart failure. (Circulation 1989;79:51-58)

Cardiovascular reflexes play an important role in the regulation of the circulation in both physiologic and pathophysiologic states. In the presence of congestive heart failure, the function of these reflexes is profoundly impaired.1-4 Moreover, the heart failure state in animals and humans is characterized by increased neurohumoral drive manifested by elevated levels of circulating catecholamines, plasma renin, and angiotensin as well as arginine vasopressin.5-8 Increased levels of plasma norepinephrine have been shown to be an important predictor of mortality in congestive heart failure.9,10 Microneurographic techniques, which permit direct measurement of sympathetic nerve activity in humans, have demonstrated increased sympathetic nerve activity in patients with heart failure.11 Arterial and cardiopulmonary baroreflexes, which play a critical role in modulating changes in neurohumoral drive to the heart and circulation, are markedly depressed in the heart failure state.12-14 Increased sympathetic drive, enhanced neurohumoral excitatory state, and impaired arterial baroreflex control of the heart and circulation are all findings intrinsic to the pathophysiology of the vasoconstricted, volume-overloaded heart failure state.

The mechanism(s) for abnormalities in arterial baroreflex control in heart failure has not been determined. There may be structural abnormalities in the baroreceptors, central neural abnormalities, or impaired neuroeffector mechanisms. Baroreflex control of heart rate has been investigated in dogs with high output heart failure (arteriovenous fistula model). After reversal of the heart failure by ligation of the fistula, arterial baroreflex control of heart
rate remains markedly depressed for as long as 8 months after reversal of the heart failure state. The failure of arterial baroreflexes to return to normal after reversal of high output heart failure has been attributed to structural changes in the arterial baroreceptors.16-18

There may be important differences in the pathophysiology of baroreflex abnormalities observed in human low output heart failure compared with the high output heart failure studied in animal models. Heart transplantation restores cardiac function to normal and eliminates the neurohumoral excitatory state associated with congestive heart failure.19,20 In addition, the technique of orthotopic cardiac transplantation leaves in situ portions of both atria along with their respective venoatrial junctions. The recipient atrial remnant, which retains the sinoatrial node, is thought to remain normally innervated. It would be expected that this sinoatrial node, unlike its counterpart in the denervated donor atrium, would slow its rate in response to increases in arterial pressure and stimulation of arterial baroreceptors. Thus, transplantation provides a unique model to examine the effects of complete reversal of low output heart failure and normalization of cardiac function. Our study determined the effects of elimination of low output congestive heart failure and normalization of cardiac function on arterial baroreflex control of heart rate in humans.

Subjects and Methods

We studied three groups of male patients, all less than 70 years of age. The protocol was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia and the McGuire Veterans Administration Medical Center. All patients gave written informed consent before participation in the study. All cardiac (β-blockers, nitrates, digoxin, and calcium channel blockers) and antihypertensive medications were discontinued at least four half-lives before study. Diuretics were discontinued 24 hours before study. Medications used for the prevention of rejection (e.g., cyclosporine, prednisone, or immuran) were continued without interruption. The protocol was performed with subjects in the fasting state after premedication with oral or intravenous diazepam.

Protocol

Each patient was studied in the clinical electrophysiology laboratory after resting quietly in the supine position for 10–15 minutes. In all groups, except for the normal controls, a 10-ml blood sample was obtained for determination of plasma catecholamines. The blood was drawn into heparinized tubes and cooled on ice. The plasma was separated in a refrigerated centrifuge and stored at −75° C until assayed. We used high-performance liquid chromatography with electrochemical detection to measure plasma norepinephrine. Sensitivity of this assay is less than 0.03 nmol/l.

Phenylephrine was injected intravenously over 5–10 seconds, beginning with a dose of 50 μg followed by a 20-ml saline flush. Arterial pressure was monitored continuously with an 18-gauge needle placed in the brachial artery or 7F sheath in the femoral artery (transplant patients). Respiratory movements were recorded with a pneumograph along with surface electrocardiographic leads (II or V1) and atrial intracavitary electrograms. All signals were recorded simultaneously on a multichannel recorder (VR-16, Electronics for Medicine) at a paper speed of 100 mm/sec. Measurements of sinus cycle length and systolic arterial pressure was made during expiration. Sufficient time was permitted to allow blood pressure to return to baseline, followed by a 10-minute rest period before administration of the next bolus of phenylephrine. Additional doses of intravenous phenylephrine were given until a 20–30 mm Hg increase of blood pressure was induced on a minimum of two consecutive trials.

Group 1 consisted of 11 male patients referred for evaluation for cardiac transplantation because of medically refractory heart failure (New York Heart Association Class IV). Patients were excluded from study if angiotensin converting enzyme inhibitors or intravenous pressors (dopamine or dobutamine) could not be discontinued without marked exacerbation of heart failure.

Group 2 consisted of six control male subjects without evidence of cardiac dysfunction. Three were referred for cardiac catheterization and found to have normal coronary arteries and normal ventricular function. Three patients were referred for clinical electrophysiologic study because of a history of syncope. All three patients demonstrated normal ventricular and valvular function (by two-dimensional echocardiography and Doppler flow velocity profile), as well as normal sinus and atrioventricular nodal function.

Group 3 consisted of 23 men studied 2 weeks to 4 years after orthotopic cardiac transplantation. Three patients were studied before and after transplantation. Each patient was studied at a time when there was minimal or no allograft rejection based on cardiac biopsy performed within 2 days of study. Ten patients were receiving cyclosporine, immuran, and prednisone; 10 were receiving cyclosporine and immuran, and three were receiving immuran and prednisone. Eighteen patients were normotensive at the time of study, and five patients had evidence of mild intermittent hypertension with systolic pressures between 140 and 165 mm Hg and diastolic pressures between 90 and 110 mm Hg.

All transplant patients had a 6F or 7F quadrupolar catheter positioned in the right atrium to record both donor and recipient atrial electrograms (Figure 1). In cases in which both donor and recipient atrial intracavitary electrograms could not be recorded from a single catheter, the recipient atrial electrogram was recorded with the catheter electrode, and the donor atrial electrogram was recorded from the
surface electrocardiographic leads that provided the optimal donor P wave. Four additional patients were brought to the laboratory but excluded from the study because of atrial flutter (n=1), atrial fibrillation (n=2), and frequent premature atrial contractions (n=1) recorded from the recipient atrial remnant. The surface electrocardiogram was used in the normal and heart failure groups to measure RR intervals. All of these patients were in normal sinus rhythm, with infrequent premature atrial or ventricular contractions.

**Statistical Analysis**

All results are reported as mean±SEM. Changes in systolic arterial pressure induced by phenylephrine during exhalation were plotted against the subsequent RR interval (or interval between consecutive atrial electrograms, A'A' interval) or linear regression analysis was performed. Baroreflex slope was defined as the slope, M of the function A'A' or RR=M+Δ systolic blood pressure + a. In all patients, we were able to obtain regression lines with correlation coefficients more than 0.90 and p less than 0.05. In each patient, the slopes for all phenylephrine injections that produced a systolic blood pressure rise more than 20 mm Hg were averaged to provide a mean baroreflex slope. The differences in clinical descriptors among groups were assessed by an unpaired t test, with Bonferroni’s correction for multiple comparisons. Analysis of variance was used to compare baroreflex slopes in different age groups. Probability levels less than 0.05 were considered significant.

**Results**

The baseline clinical characteristics of the heart failure, transplant, and control patients are illustrated in Table 1. Eight patients in the failure group had coronary artery disease, and three had idiopathic dilated cardiomyopathy. Patients in this group had a lower mean arterial pressure than those who had undergone cardiac transplantation (p<0.001). Before transplantation, 12 patients in the transplant group had coronary artery disease, and 11 patients had idiopathic dilated cardiomyopathy The mean duration of severe heart failure before cardiac transplantation was 18±5 months. Plasma catecholamine levels and mean phenylephrine dose received were higher in failure patients than in transplant patients (p<0.001). Patients with heart failure received 3.2±0.3 doses phenylephrine, whereas patients studied after cardiac transplantation received 4±0.5

**Figure 1.** Analog tracing from a patient with cardiac transplantation demonstrating measurement of AA interval in donor and A'A' interval in recipient atria after intravenous phenylephrine bolus. Top panel: Recorded during the injection of phenylephrine. Bottom panel: Recorded as arterial pressure reached its peak. Surface traces from top to bottom include electrocardiogram, intracardiac lead (A, donor intracardiac atrial electrogram; A', recipient intracardiac atrial electrogram; V, ventricular intracardiac electrogram), arterial pressure, and respiratory pneumograph tracing.
TABLE 1. Characteristics of Patient Groups Studied

<table>
<thead>
<tr>
<th></th>
<th>Congestive heart failure (n=11)</th>
<th>After transplantation (n=23)</th>
<th>Normal controls (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50±3</td>
<td>45±2</td>
<td>54±6</td>
</tr>
<tr>
<td>Duration of congestive heart failure (mo)</td>
<td>18±5</td>
<td>16±3</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>16±2</td>
<td>56±2†</td>
<td></td>
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<tr>
<td>Norepinephrine (nmol/l)</td>
<td>1.9±0.1</td>
<td>0.6±0.05*</td>
<td>57±3†</td>
</tr>
<tr>
<td>Epinephrine (pmol/l)</td>
<td>306±27</td>
<td>180±11</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87±3</td>
<td>90±4‡</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>82±3</td>
<td>105±2†</td>
<td>93±5</td>
</tr>
<tr>
<td>Mean dose of phenylephrine (µg)</td>
<td>770±66</td>
<td>230±15†</td>
<td>250±50†</td>
</tr>
<tr>
<td>Baroreflex slope (msec/mm Hg)</td>
<td>2.0±0.3</td>
<td>13.0±0.9†</td>
<td>10±1.2†</td>
</tr>
</tbody>
</table>

*p<0.01 compared with patients with congestive heart failure; †p<0.001 compared with patients with congestive heart failure.

‡Mean heart rate for donor sinus node is 90±4 beats/min and for recipient sinus node is 83±4 beats/min.

doses phenylephrine. The mean dose of phenylephrine used in the heart failure group (770±66 µg) was significantly more than was used in the transplant group (230±15 µg, p<0.001). A markedly diminished arterial baroreflex slope was noted in the heart failure patients (2.0±0.3 msec/mm Hg) compared with the responses of the recipient atrium (innervated) in the transplant patients (13.0±0.9 msec/mm Hg, p<0.001) (Figure 2). As expected, there was no change in the (denervated) donor AA interval in the transplant group during phenylephrine-induced increases in arterial pressure.

Three patients were studied before and after transplantation. The striking improvement in these patients' baroreflex slopes after cardiac transplantation is illustrated in Figure 3. All three patients had mild hypertension of 1–3 months’ duration at the time of their second study, and the patient with the lowest baroreflex slope was the oldest subject in our transplant population (patient 15; Table 2).

The mean age of the six subjects without heart disease in group 2 was 54±6 years. The mean ejection fraction was 57±3%. These subjects received a mean of 3±0.3 doses. The average dose of phenylephrine received was 250±50 µg, which was similar to the dose used in the transplant group but significantly less than was used in the heart failure group. The mean baroreflex slope in this group was 10±1.2 msec/mm Hg, which was not significantly different from either the transplant group or from other normal subjects of similar age and blood pressure studied previously.24

There was a trend toward decreased baroreflex sensitivity with increasing age among the transplant patients when age was examined as a discontinuous variable (p=0.11) (Figure 4). However, age correlated poorly (r=0.30) with baroreflex sensitivity. Individual patient’s age, mean arterial pressure, time of study after transplantation, and baroreflex slope are shown in Table 2. Half of our patients were studied within 6 weeks of transplantation. Subjects with the lowest baroreflex slopes generally had the highest mean arterial blood pressures.

Discussion

Our study demonstrates that marked abnormalities of baroreflex sensitivity seen in patients with severe low output congestive heart failure are com-

**FIGURE 2. Bar graph of baroreflex slopes in control, heart failure, and transplant patients.** There was a statistically significant difference (p<0.001) between the mean slope for the heart failure patients compared with control subjects and transplant patients. There was no significant difference between the baroreflex slope in control patients and transplant patients.

**FIGURE 3. Plot of arterial baroreflex slope in three patients who underwent study before and after cardiac transplantation.** Each patient had a striking increase in arterial baroreflex slope after cardiac transplantation.
pletely reversed after cardiac transplantation. Baroreflex sensitivity may return to normal as early as 2–4 weeks and may remain normal for up to 4 years after transplantation. This early reversal of baroreflex abnormalities suggests that depressed baroreflex sensitivity may be the result of the neurohumoral excitatory state characteristic of heart failure rather than of structural damage to the arterial baroreceptors. The few patients in whom baroreflex sensitivity failed to reach 10 msec/mm Hg were generally hypertensive or elderly or both, and it is likely that in these patients the persistence of lower baroreflex sensitivity is related to hypertension and age.

In normal subjects, arterial baroreceptors exert a tonic inhibitory influence on the sympathoadrenal drive to the heart and peripheral circulation as well as a tonic excitatory influence on vagal outflow to the heart. With the development of heart failure, arterial baroreflexes are blunted. There is marked blunting of arterial baroreflex sensitivity in dogs with congestive heart failure. Baroreflex sensitivity also has been shown to be markedly depressed in humans with heart failure resulting from a variety of etiologies. Moreover, baroreflex dysfunction may be noted early when cardiac function is impaired but before the onset of clinical symptoms of heart failure. It has been suggested that increased sympathetic outflow and reduced vagal efferent activity seen in heart failure result from blunted baroreflexes and a reduction in their tonic influence. This would be expected to lead to augmented peripheral vasoconstriction, tachycardia, and increased circulating levels of catecholamines, renin, and vasopressin.

![Bar graph of effect of age on arterial baroreflex slope in cardiac transplant patients after orthotopic cardiac transplantation.](http://circ.ahajournals.org/)

**Figure 4.** Bar graph of effect of age on arterial baroreflex slope in cardiac transplant patients after orthotopic cardiac transplantation. There was a trend toward decreased slope with increasing age, but it did not reach statistical significance ($p < 0.11$).
In animals with high output congestive heart failure due to an arteriovenous fistula, baroreflex dysfunction has been demonstrated by blunted heart rate response to phenylephrine induced increases in arterial pressure. Complete reversal of heart failure in this model, by surgical ligation of the fistula, was not associated with total reversal of baroreflex abnormalities.\textsuperscript{12,15} Moreover, most of the improvement in baroreflex sensitivity was noted during the first few weeks after ligation with little additional improvement noted up to 8 months after ligation. Thus, our data demonstrating normalization of baroreflex sensitivity in the first few weeks after transplantation suggest that the mechanisms of baroreflex abnormalities in low and high output heart failure may be quite different. In high output heart failure, the widened arterial pulse pressure may cause structural damage to baroreceptors located in the wall of the aorta and carotid arteries.\textsuperscript{16} This may explain the failure to note complete recovery of baroreflex sensitivity after surgical correction of high output heart failure. The rapid and complete correction of baroreflex sensitivity seen after cardiac transplantation in our patients suggests that structural damage to baroreceptors is not a component of impaired arterial baroreflexes in low output heart failure. We speculate that the early partial recovery of baroreflex sensitivity noted in dogs with high output failure is due to mechanisms similar to those operative in the recovery of baroreflex function in our transplant patients and that failure to detect full recovery is related to structural changes in the region of the aortic arch and carotid sinus.

In animals and humans, medical treatment of heart failure with digitalis, nifedipine, and captopril all have been shown to increase baroreflex sensitivity, although normalization does not occur with these treatments.\textsuperscript{26,30} The failure of pharmacologic agents to completely normalize baroreflex sensitivity in humans with heart failure is probably related to their failure to completely reverse the heart failure state and to normalize cardiac function.\textsuperscript{25}

Previous studies that have evaluated arterial baroreflex control of the sinus node in heart failure have examined patients with mild degrees of failure.\textsuperscript{1,27} All of our patients had severe but stable heart failure and were awaiting cardiac transplantation. At our institution, approximately 40\% of patients undergoing cardiac transplantation are unstable and require intensive care unit management with intravenous inotropic agents or intra-aortic balloon pump and Swan-Ganz catheterization before surgery. The patients with heart failure who we studied were not in this severely ill group. Our heart failure patients were the least severely ill of our patient population awaiting transplantation. Evaluation of baroreflex slope in these heart failure patients required very large doses of phenylephrine to obtain a 20–35 mm Hg rise in systolic blood pressure. In these patients, baroreflex sensitivity was markedly diminished even when compared with that reported previously for patients with milder degrees of heart failure.\textsuperscript{1,27}

Age may modify arterial baroreflex function, and other studies have shown that baroreflex sensitivity is diminished with increased age.\textsuperscript{23,31} In our study, there was a trend for younger transplant patients to have a baroreflex slope higher than was seen in older transplant patients.

It could be argued that the reduced baroreflex sensitivity in patients with heart failure is the result of structural changes in the arteries and that reversal of these structural abnormalities accounts for baroreflex normalization after cardiac transplantation. Data from Sinoway and colleagues\textsuperscript{32} suggest that this is unlikely. They studied basal and hyperemic forearm blood flow before and at 18 and 114 days after cardiac transplantation.\textsuperscript{32} Their study demonstrated that reactive hyperemic blood flow increased significantly only at 114 days. This slow recovery of reactive hyperemic response was most likely due to the slow reversal of structural changes that do not account for the rapid normalization of baroreflex sensitivity after transplantation.

Three patients had baroreflex slope determined before and after cardiac transplantation. Each patient’s baroreflex slope improved strikingly after transplantation. As noted above, these patients all had mild hypertension of only short duration, and all were older than the mean age of our transplant group (48, 51, and 62 years old). Approximately two thirds of our heart transplant patients develop hypertension requiring treatment with one or more drugs within 6 months after transplantation. Because hypertension also is known to decrease baroreflex sensitivity, we excluded all patients who developed hypertension with diastolic pressures more than 110 mm Hg or systolic pressures more than 165 mm Hg when not on medication.\textsuperscript{33} As noted above, patients with the lowest baroreflex slopes generally had the highest arterial pressures at the time of study.

Our study could be criticized because we studied different groups of patients before and after transplantation. We believe that this concern is of minimal significance. Our heart failure patients had markedly impaired baroreflex sensitivity as reported previously by others.\textsuperscript{1,17,24–27} This is most likely a universal finding in heart failure. The patients studied after transplantation had normal responses. Had they been impaired, then it probably would have been more important to study responses in more patients both before and after transplantation.

Concern also could be expressed about the influence of immunosuppressive therapy on these findings. We have previously shown that patients who have undergone renal transplantation have normal cardiopulmonary baroreflexes, whereas cardiac transplant patients on similar immunosuppressive regimens have markedly impaired cardiopulmonary baroreflexes.\textsuperscript{34} It is unlikely, therefore, that the immunosuppressive drug regimens we used are
responsible for the normalization of arterial baroreflex control of heart rate.

Phenylephrine is known to be an α-adrenergic agonist that may produce venoconstriction and arteriolar vasoconstriction. This agent may have differing effects on cardiac preload and afterload in each of our three patient groups. This raises the issue of differing arterial and cardiopulmonary baroreflex interactions in each group. Although phenylephrine may elevate cardiac filling pressures more in heart failure patients, we have reported that cardiopulmonary baroreflexes are markedly impaired in heart failure, and thus, it is unlikely that decreased baroreflex sensitivity in heart failure is due to excessive stimulation of cardiopulmonary baroreflexes. Second, the available evidence in humans does not suggest an important interaction between arterial and cardiopulmonary baroreflexes for control of heart rate. Baroreflex dysfunction may contribute importantly to activation of the sympathetic nervous system and the development of the neurohumoral excitatory state of heart failure. Our data establish that arterial baroreflex sensitivity returns to normal as early as 2 weeks after cardiac transplantation after reversal of the heart failure and elimination of the neurohumoral excitatory state. Recovery of baroreflex function may contribute to the reversal of the neurohumoral excitatory state of heart failure after heart transplantation. Our data do not permit us to determine the locus for abnormal arterial baroreflex control of the sinus node in heart failure. It is possible that abnormalities of arterial baroreceptor endings or other abnormalities in the central nervous or in neuroeffector mechanisms may be responsible for impaired baroreflexes in heart failure. It seems unlikely that structural alteration in the baroreceptors or in the arterial wall in which they are located can account for these abnormalities since reflex abnormalities are rapidly reversed after transplantation while recovery of vascular responses in markedly delayed.

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References

KEY WORDS • arterial baroreceptors • congestive heart failure • cardiac transplantation • norepinephrine
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