Loss of nocturnal decline in blood pressure after cardiac transplantation

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ABSTRACT Twenty-four hour noninvasive ambulatory blood pressure and heart rate monitoring was performed on patients who underwent orthotopic cardiac transplantation, as part of the investigation of the de novo hypertension that develops in such patients. Patients with essential hypertension served as control subjects. The results demonstrated a highly significant loss of the usual decline in blood pressure and heart rate during sleep in the transplant patients. A similar loss of nocturnal decline in blood pressure was noted in a group of 10 patients with autonomic neuropathy secondary to diabetes mellitus. The de novo hypertension associated with cardiac transplantation is probably multicausal. Impairment of renal function by cyclosporin-A with associated salt and water retention and persistent elevation of the systemic vascular resistance in the presence of a restored normal cardiac output by the “new” heart are major factors. In addition, loss of the normal nocturnal decline in blood pressure and heart rate, which probably is related to the denervated state of the transplanted heart, may play an important role in blood pressure control.


THE INCREASING SURVIVAL of patients after orthotopic human cardiac transplantation,1,2 has provided an opportunity to study cardiovascular physiologic alterations resulting from this procedure. As part of the investigation of the de novo hypertension that we have reported when cyclosporin-A (CyA) is used as an immunosuppressive agent,3 24 hr noninvasive ambulatory blood pressure and heart rate monitoring was performed on patients who had undergone cardiac transplantation. This article presents data on the day/night blood pressure and heart rate patterns in these patients and compares them with control subjects with essential hypertension. In addition, 10 patients with mild-to-moderate hypertension associated with diabetes mellitus and autonomic neuropathy were studied.

Methods

Twenty-four hour ambulatory noninvasive blood pressure and heart rate measurements were made automatically every 30 min with a self-inflating cuff and electrocardiographic electrodes (P-III Pressurometer, Del Mar Avionics, Irvine, CA). Several groups of patients were studied.

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Initial groups. The first group of patients consisted of 23 recipients of orthotopic heart transplants (one woman, 22 men; mean age 40 years) performed at the University of Pittsburgh between 1980 and 1983 (table 1). Only one patient gave a prior history of hypertension. The etiology of cardiac dysfunction included atherosclerotic coronary disease (10 patients), viral or idiopathic cardiomyopathy (10 patients), rheumatic valvular disease (two patients), and postpartum cardiomyopathy (one patient). All blood pressure and heart rate monitoring was performed in the hospital setting, either during the postoperative period just before discharge, when subjects were no longer confined to bed, or on occasions of readmission for follow-up study (range 2 to 45 weeks after surgery, mean 14, for 22 patients on CyA; one patient on azathioprine was studied at 110 weeks).

The second group consisted of 15 patients with essential hypertension (nine men, six women; age 17 to 66 years, mean 51) who had been monitored as part of the assessment of their hypertension during the same period. This group was selected from our larger series4,5 because they were monitored in the hospital and thus had activity levels similar to those of the first group; they were further selected to match the transplant group for degree of hypertension by excluding any subject with a mean daytime systolic blood pressure greater than 180 mm Hg. With these exceptions, they were otherwise consecutive admissions to the hospital. The diagnosis of essential hypertension had been made according to standard clinical practice; these patients were receiving diuretics (three patients), β-blockers (one patient), combination therapy with diuretics and β-blockers (three patients), diuretics and vasodilators (two patients), or no therapy (six patients).

Based on patient diary information, each record was divided into day (awake) and night (asleep).4,5 Each record had up to 50 data points. All clearly artifactual blood pressure data points (diastolic <50 mm Hg; systolic/diastolic ratio <115%) were deleted by visual inspection of the data printouts. Six transplant
patient records and one control record had incomplete heart rate data because of failures in electrocardiographic leads; these records were kept in the analysis. Mean day and night systolic and diastolic blood pressure and heart rate were then calculated for each subject and were expressed as the percent decrease of each during sleep, by means of a computer program we had previously established. Comparison between the two groups was by two-tailed t test, and p < .05 was considered significant. Values given are group means ± SE.

**Replication groups and diabetic subjects.** The two groups described above were compared directly in our initial examination of the data. Subsequently, to replicate the observations, monitoring was performed on 46 additional patients undergoing transplantation during 1983 and 1984 at our institution, at periods ranging from 3 to 84 weeks after the procedure (mean 8.7, median 4.5). The majority of these patients were studied as inpatients, as in the initial group; six were outpatients. All were receiving CyA; 30 were judged as having mild-to-moderate hypertension at the time of the study and were receiving antihypertensive therapy similar to that described in table I for the initial transplant group. In the remaining 16, daytime hypertension requiring therapy had not been noted at the time of monitoring.

During this same period, monitoring was performed on an additional 30 patients with mild essential hypertension from our Hypertension Clinic as part of their initial evaluation. This group consisted equally of inpatients and outpatients (average age 41 years) and 22 were on no therapy. In addition, 10 patients with type I diabetes mellitus, mild-to-moderate hypertension, and evidence of autonomic neuropathy as manifested by some degree of orthostatic hypotension were monitored in the hospital during this period. The records of these three groups were analyzed in the same manner as those of the two initial groups.

It should be emphasized that this was a retrospective study performed as part of the postoperative follow-up of these complex cardiac transplant patients, in whom many procedures are necessary to guide their clinical care. We attempted to match the essential hypertensive patients and diabetics in terms of age, level of activity, and time of observation, but we did not believe we could accomplish a precisely matched prospective study in a clinical situation, beset with many variables as is the case in cardiac transplantation. In this sense, we cannot firmly establish causality, but our study should be viewed as a set of carefully observed blood pressure phenomena. The replication study was done to confirm the findings in the initial groups and hence is presented separately.

**Results**

**Initial two groups (table I)**

**Heart rate.** The transplant group had a higher day time heart rate than is usual for an in-hospital activity

level: 93 ± 2.5 beats/min; this value was significantly greater than that in the control group, 77 ± 3.2 beats/min (p < .001). Two transplant patients who were receiving β-adrenergic blocking drugs had daytime heart rates of 77 and 89 beats/min, which did not change significantly with sleep (72 and 90 beats/min, respectively). The four control patients on β-blocker therapy, alone or in combination, demonstrated an average daytime heart rate of 66 beats/min and a nighttime rate of 59 beats/min.

Blood pressure. Hypertension (i.e., diastolic blood pressure >90 mm Hg as observed by cuff pressures taken repeatedly on the ward and/or requiring therapy) developed postoperatively in 20 of 22 transplant recipients receiving CyA. The one patient receiving azathioprine had only a slight elevation of diastolic pressure at the time of ambulatory recording of blood pressure and was not receiving any antihypertensive therapy. Preoperative blood pressures were not meaningful for comparison, since most subjects were then in severe NYHA class IV heart failure with low blood pressures and many were receiving afterload-reducing medications or parenteral inotropic agents. When monitored postoperatively, all but two were receiving antihypertensive medication (table 1), and the average daytime blood pressure of the group, as determined on the blood pressure recorder, was 134/90 mm Hg. Of the two nontransplanted subjects with untreated average daytime pressures less than 140 mm Hg systolic and 90 mm Hg diastolic, one (No. 15) had borderline cardiac function and eventually rejected the transplant. The other untreated subject (No. 6) did not display daytime hypertension but did develop a blood pressure greater than 140/90 mm Hg at night (table 1). The control patients had a slightly higher daytime blood pressure (148/92 mm Hg) in the hospital.

Renal function. Serum creatinine levels were within the normal range in all control patients. With one exception, transplant recipients were receiving CyA (range 350 to 1200 mg/day) plus prednisone (range 15 to 30 mg/day) as immunosuppressive therapy. Eleven of these 22 showed evidence of mild-to-moderate impairment of renal function (defined as a serum creatinine level of 1.4 mg/dl and greater); the mean serum creatinine level was 1.4 ± 0.11 mg/dl (range 0.7 to 3.1). The single patient (No. 23) receiving azathioprine (75 mg/day) plus prednisone (20 mg/day) when studied 110 weeks after cardiac transplantation had a serum creatinine level within normal limits and an average daytime blood pressure of 110/92 mm Hg in the absence of antihypertensive medication. Similar to the patients receiving CyA, however, he showed only a 4% fall in diastolic blood pressure and had a 0.4% rise in systolic blood pressure with sleep. Likewise, his average heart rate was 96 beats/min over the entire 24 hr period, and it did not decrease with sleep.

Percent change in blood pressure and heart rate with sleep (figure 1). All 15 control patients experienced a decrease in blood pressure with sleep (average decreases: systolic, −12 ± 1.5%; diastolic, −12 ± 1.7%) and all but one experienced a decrease in heart rate (average decrease −16 ± 2.1%). The transplant recipients demonstrated a very different pattern: 12 of 23 actually had an increase in blood pressure at night, resulting in a nocturnal decrease for the group of only −0.3 ± 1.9% in systolic blood pressure and −1.0 ± 2.2% in diastolic blood pressure (p < .001 for both). The decrease in heart rate was also blunted (−8 ± 1.6%; p < .01).

Among the transplant recipients, the pressure change with sleep showed no correlation with age, time after surgery, presence or type of antihypertensive treatment, change in heart rate with sleep, serum creatinine level, or day or night mean blood pressures. Furthermore, there was no significant difference between the percent change in mean blood pressure in 11 patients with creatinine levels of 1.4 and greater and in 12 with creatinine levels of less than 1.4 mg/dl (−2.9 ± 3.3% vs −0.3 ± 1.4%, respectively; p > .05). In the control group, age, day or night blood pressure, and the type of treatment were also unrelated to the nocturnal changes in blood pressure or heart rate, as we have also shown in a larger series previously reported. 4, 5 Figure 2 shows an actual recording in a transplant patient, illustrating the failure of blood pressure to fall at night.
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**Figure 2.** Data from a transplant patient with daytime hypertension and no decrease in blood pressure during sleep. Cross-hatched areas represent periods during which blood pressure was greater than 140/90 mm Hg. BSPc and DBPc are the integrals of this area in mm Hg × hr.

**Replcation groups.** The average daytime and nocturnal blood pressure and heart rate data and the percent nocturnal change for the 46 transplant recipients and 30 patients with mild hypertension are displayed in tables 2 and 3. The systolic and diastolic blood pressures rose (6.7 ± 4.1%) in the transplant recipients at night in contrast to a fall (−14.5% ± 16.2%) in the patients with essential hypertension (p < .001). The heart rate fell only −7.9% in the former in contrast to −14.5% in the latter (p < .001). Of note also is the daytime heart rate of 93.4 beats/min in the transplant recipients in contrast to the rate of 76.5 beats/min in the patients with essential hypertension. These differences are highly significant, replicating in perhaps an even more striking fashion the findings in the initial two groups studied from 1980 to 1983. Figure 3 shows data from a transplant patient from this group who showed his first major evidence of hypertension at night; subsequently, he became significantly hypertensive throughout the 24 hr period.

In the initial 23 transplant recipients, we had noted a lack of correlation between the day or night blood pressures and the pressure change with sleep. This observation was extended in the replication group by the fact that the systolic and diastolic changes in the 16 normotensive transplant patients were not significantly different from those in the 30 hypertensive transplant recipients (a rise of 7.3 ± 1.5% vs 5.2 ± 1.9% vs 6.4 ± 2.1% vs 7.9 ± 1.8%, respectively; p > .05 in both systolic and diastolic). Similarly, the decrease in heart rate was −9.4 ± 1.2% vs −7.1 ± 1.8% (p > .05).

To extend the observation in the initial group that there was a lack of correlation between the nocturnal change and the duration of time after surgery, the data in all the transplant recipients were then analyzed in terms of the time after transplant and time of monitoring. This analysis included the initial 23 patients, the 46 in the replication group, five with a second monitoring, and two with a third monitoring, yielding a total of 76 (table 4). In patients studied even more than 1 year after transplant, no significant change in the decreased nocturnal fall was noted. In fact, four of the nine patients showed a significant increase.

**Table 2**

<table>
<thead>
<tr>
<th>Blood pressures and heart rates in replicate and diabetic groups</th>
<th>Day (mm Hg ± SE)</th>
<th>Night (mm Hg ± SE)</th>
<th>Change (% ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant recipients (n = 46)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.9 ± 2.5</td>
<td>136.9 ± 2.5</td>
<td>6.7 ± 1.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.4 ± 1.5</td>
<td>87.0 ± 1.7</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>93.4 ± 1.8</td>
<td>85.8 ± 1.9</td>
<td>−7.9 ± 1.3</td>
</tr>
<tr>
<td><strong>Mild essential hypertensives (n = 30)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127.6 ± 2.5</td>
<td>108.8 ± 2.7</td>
<td>−14.5 ± 1.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84.4 ± 1.5</td>
<td>70.7 ± 1.7</td>
<td>−16.2 ± 1.6</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>76.5 ± 2.1</td>
<td>65.3 ± 1.8</td>
<td>−14.5 ± 1.4</td>
</tr>
<tr>
<td><strong>Diabetic patients (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>148.7 ± 9.5</td>
<td>150.7 ± 8.7</td>
<td>1.8 ± 2.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87.6 ± 2.5</td>
<td>91.0 ± 4.3</td>
<td>3.1 ± 2.9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>94.7 ± 3.3</td>
<td>86.2 ± 4.6</td>
<td>−9.6 ± 3.0</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Comparison of percent changes in replicate groups and diabetics</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
<td>t</td>
</tr>
<tr>
<td>EH vs CT</td>
<td>9.6</td>
<td>&lt;.001</td>
<td>9.5</td>
</tr>
<tr>
<td>EH vs DM</td>
<td>5.6</td>
<td>&lt;.001</td>
<td>5.9</td>
</tr>
<tr>
<td>CT vs DM</td>
<td>1.8</td>
<td>NS</td>
<td>0.3</td>
</tr>
</tbody>
</table>

EH = mild essential hypertensives (n = 30); CT = cardiac transplant recipients (n = 46); DM = diabetics with hypertension (n = 10).

**Figure 3.** Data from a transplanted patient with normal blood pressure during the day and hypertension during sleep. Other details as in figure 2.
TABLE 4
Percent nocturnal change according to weeks after transplant

<table>
<thead>
<tr>
<th>Week studied</th>
<th>n</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 4</td>
<td>33</td>
<td>8.9</td>
<td>7.3</td>
<td>-8.8</td>
</tr>
<tr>
<td>4 to 12</td>
<td>22</td>
<td>3.6</td>
<td>0.7</td>
<td>-6.2</td>
</tr>
<tr>
<td>12 to 24</td>
<td>6</td>
<td>-5.5</td>
<td>-3.7</td>
<td>-11.6</td>
</tr>
<tr>
<td>24 to 52</td>
<td>6</td>
<td>2.0</td>
<td>-0.4</td>
<td>-9.2</td>
</tr>
<tr>
<td>Greater than 52</td>
<td>9</td>
<td>-3.7</td>
<td>-4.5</td>
<td>-7.3</td>
</tr>
</tbody>
</table>

tients studied after 52 weeks had undergone transplant more than 2 years previously and still had a nocturnal rise of 2.9/4.9%.

In the five patients who were monitored on two occasions, the second measurement was an average of 90 weeks after transplant. The loss of nocturnal fall was still present. Three of these subjects had been switched to azathioprine at the time of the second study.

As mentioned earlier, in the replication groups six of the transplant patients and a number of the patients with essential hypertension were studied as outpatients; they showed no differences from inpatients in their nocturnal changes.

Diabetic group. The data for the day and night blood pressures and heart rates in the 10 diabetic patients also are shown in tables 2 and 3. The percent change in this group was 1.8/3.1% for blood pressure, which was significantly different than the patients with essential hypertension and equivalent to that seen in the transplant recipients. The heart rate decline of -9.6% was slightly less than that in the hypertensive patients and more than that in the transplant recipients, but these differences did not reach a level of significance.

Discussion

Our data demonstrate that orthotopic cardiac transplantation in human beings is associated with loss of the normal fall in blood pressure during sleep, a finding that, to our knowledge, has not been reported previously. The absence of a fall in blood pressure with sleep is a remarkable pattern, previously noted almost exclusively in patients with neurogenic orthostatic hypotension.6,7 Even bed-bound patients show some nocturnal change in blood pressure,8 and studies of patients with essential hypertension have consistently found 10% to 20% decreases in blood pressure and heart rate with sleep, even when activity is restricted.9 This pattern is unaltered by antihypertensive therapies.4,5,10,11 Patients with hypertension related to renal disease also preserve this diurnal blood pressure rhythm.4,5,12

The loss of the normal nocturnal decline in blood pressure and heart rate after cardiac transplantation is the phenomenon with which we are particularly concerned. This anomalous behavior is probably related to the denervated state of the transplanted heart. Studies of baroreceptor activity in patients undergoing orthotopic cardiac transplantation have shown that the remnant of native atrium remains normally innervated and responds with appropriate rate changes to stimulation of the carotid baroreceptors, but that this is not transmitted across the suture line to the sinus node of the transplanted heart, which persistently is totally denervated and devoid of baroreceptor control for periods at least up to 36 months.13,14 In the present study, the loss of the nocturnal decline was still noted as long as 2 years after transplant, with only slight evidence that it might return. As noted earlier, in patients with neurogenic orthostatic hypotension caused by generalized degeneration of the autonomic nervous system, loss of the normal nocturnal blood pressure decline is also present.7 We have now similarly noted it in patients with type I diabetes and autonomic neuropathy in this study. Our data in transplant patients suggest that this loss of nocturnal decline is probably more a consequence of the concomitant absence of cardiac innervation than a result of the impairment of innervation of the peripheral vascular system, which remains intact after cardiac transplantation. Thus cardiac denervation with absence of a vagal heart rate response to baroreceptor stimulation seems to be the common factor in individuals who exhibit an attenuation of the nocturnal fall in blood pressure. However, from the present results we have no information as to the relative contribution of efferent or afferent innervation to its development.

A "mismatch" between intrinsic autonomous cardiac function and the peripheral vascular tree can also be considered in evaluating the day/night blood pressure variation. After cardiac transplantation, an increased cardiac output in recumbency may result from a shift in blood volume from the periphery to a more central location;15 this increase in cardiac output may exceed the capacity of the arteriolar resistance vessels to dilate, thus leading to the nocturnal elevation in blood pressure. This may be abetted by the elevated resting heart rate, which fails to fall normally during sleep in the denervated transplanted heart because of the lack of vagal control. After cardiac transplantation, control of heart rate is influenced mainly by intrinsic stretch receptors and circulating catecholamines.16 Sympathetic control also is not reestablished even as long as 1 year later,17 but a decrease in circulating catecholamines...
during sleep could explain why the heart rate still decreased slightly at night in our patients.18

Other possible explanations of this nocturnal phenomenon can be invoked such as the role of renin activity and catecholamines. Systemic studies of the diurnal variations of these factors in blood pressure control in transplant patients have not been done. Patients with other types of transplantation (renal and hepatic) need evaluation while on azathioprine as well as on CyA. The diurnal variability in patients who have undergone coronary bypass surgery should be of interest to determine, particularly because an undefined number of such patients may experience a degree of cardiac denervation.19 It seems clear, however, that the loss of nocturnal fall we have observed in the transplant patients is consistent, as indicated by our replication in 46 patients, and persistent, as demonstrated by the minor and insignificant change in the phenomenon as late as 2 years after the surgery.

As we have reported earlier,1 the postoperative hypertension we noted in most transplant patients is a de novo event in which several mechanisms may be involved. First, CyA causes well-recognized renal toxicity and sometimes severe hypertension;20 postoperatively, most of our patients developed progressive impairment of renal function as demonstrated by slowly rising serum creatinine concentrations. Renal impairment may lead to sodium retention and increased fluid volume, a situation that may be exacerbated by prednisone therapy, and this in turn will elevate cardiac output and may lead to chronic hypertension21 in transplant recipients.

Second, in the low-output end-stage heart failure that precedes cardiac transplantation, high circulating catecholamines and other vasoressor mechanisms lead to intense peripheral vasoconstriction,22 which can result in structural changes in the arteriolar resistance vessels. If so, restoration of cardiac output to normal levels by the “new” heart may result in hypertension because of the inability of the narrowed vasculature to adequately vasodilate, and our data in transplant patients does indeed indicate persistent increase in systemic vascular resistance with no significant improvement with prolonged follow-up.3, 23 Supporting the concept of increased resistance, the development of hypertension has been seen early in the postoperative period before the appearance of any clinical evidence of renal toxicity. However, elevation of blood pressure has been noted in situations unassociated with previous heart failure, i.e., within 24 hr of starting CyA in patients undergoing bone marrow transplantation24 and within 1 to 2 weeks after liver transplantation,20 suggesting that factors other than structural changes in the arteriolar resistance vessels contribute to the development of hypertension.

It is possible that CyA may act directly on arterioles to raise peripheral vascular resistance. In patients undergoing cardiac transplantation in whom azathioprine is used as the immunosuppressive agent, the development of postoperative hypertension is reported with much less frequency;25 however, these patients also show no evidence of renal impairment.26 In any case, neither the presence of persistent hypertension or renal impairment in the transplant patients seemed to influence their loss of the nocturnal decline.

Other possible factors involved in the hypertension in these patients include disturbances in renin activity, catecholamines, and perhaps even in the atrial natriuretic factor (ANF) in the remnant native atria or those of the “new” hearts. We have reported a lack of change in renin activity and urinary catecholamines previously,3 but comments regarding ANF would be purely speculative.

A number of concerns about our data should be mentioned. First, the accuracy of Avionics recorder, as compared with intra-arterial readings, has been criticized.27, 28 However, the recorder does produce reasonable relative data and technical errors should have affected our control and transplant patients equally. Moreover, it is difficult to do invasive studies routinely in large numbers of patients; particularly in transplant recipients, who have many problems that inhibit controlled investigations and who are immunosuppressed, it would be inappropriate to insert an intra-arterial line for 24 hr for this purpose. We have made frequent reliability checks with the usual cuff technique, while the cooperative study in 199 normal subjects by Wallace et al.29 further confirms the utility of the Avionics device. It is of interest with regard to our data that these investigators noted that the average declines in systolic and diastolic blood pressure and heart rate in their subjects were 12%, 15%, and 20%, respectively, results that are equivalent to our observations in patients with essential hypertension. Second, what we have referred to as “sleep periods” were determined from patient diaries supported by observations of nursing personnel, but accurate estimations require electroencephalographic recordings and sleep stage analysis. Thus some of the time we have designated as “sleep” may indeed represent only recumbency at night. Nevertheless, the blood pressure and heart rate changes in this period are different between transplant patients and control subjects.

Third, sleep may have been more erratic in the
sicker, presumably more anxious, transplant patients than in the hypertensive control subjects — again a problem that would require electroencephalographic monitoring for elucidation. However, one may assume that such sleep problems are diminished with time, and as already mentioned, the loss of nocturnal decline persisted as long as 2 years after transplantation. Fourth, although our retrospective data have not shown any correlations of the nocturnal findings, either in patients with essential hypertension or in transplant recipients, to types and amounts of antihypertensive agents, prospective studies with different medications in cross-over designs would be important to settle this issue. There is obviously a need for further investigation with more sophisticated techniques, insofar as they can be tolerated in the setting of the clinical problems of patients after cardiac transplantation, before our hypothesis that cardiac denervation is the major cause of the diurnal blood pressure variation can be confirmed.

In summary, we have noted the new onset of hypertension after human orthotopic cardiac transplantation and in this article report the loss of the normal nocturnal fall in blood pressure and heart rate. In these patients, the mechanisms for the hypertension may include sodium and water retention as a result of renal dysfunction from the CyA given as an immunosuppressive agent. In addition, structural changes in the arteriolar resistance vessels may persist, which limit their ability to dilate after restoration of the cardiac output to normal by the transplanted heart. However, a loss of the usual fall in blood pressure and heart rate during sleep, which may be caused by absence of autonomic control in the denervated transplanted heart, is a factor that appears to influence postoperative blood pressure control in these patients.

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