Abnormal Diurnal Variation of Blood Pressure, Cardiac Output, and Vascular Resistance in Cardiac Transplant Recipients

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Background  An attenuated or absent nocturnal decline in blood pressure has repeatedly been documented in cardiac transplant recipients. The present study was aimed at investigating the hemodynamic mechanism underlying this abnormality.

Methods and Results  In 23 cardiac transplant recipients (11 to 36 months after transplantation) and in 23 control subjects matched for age and 24-hour mean arterial pressure, invasive 24-hour ambulatory blood pressure was measured by means of the Oxford technique. Beat-to-beat relative values of stroke volume were determined by means of a pulse-contour method, and relative changes of cardiac output (stroke volume × heart rate) and total peripheral vascular resistance (blood pressure/cardiac output) over the 24-hour period were calculated. The nocturnal decline in blood pressure was 20±8% (mean±SD) in control subjects but only 5±9% (P<.001) in cardiac transplant recipients. In control subjects, the nocturnal decline in blood pressure was associated with a nocturnal fall in cardiac output of 24±13%, whereas vascular resistance compared with daytime value did not change. The small nocturnal decline in blood pressure in cardiac transplant recipients was associated with an attenuated nocturnal fall in cardiac output of 14±12% (P<.05 versus control subjects). In addition, vascular resistance compared with daytime value was increased by 9±9% (P<.05) during the night. Both in cardiac transplant recipients and in control subjects, the nocturnal changes in blood pressure were correlated with the nocturnal changes in cardiac output but not with the nocturnal changes in total peripheral vascular resistance.

Conclusions  This study confirms the attenuated nocturnal fall in blood pressure in cardiac transplant recipients. Hemodynamically, this attenuated blood pressure decline is characterized by a reduced nocturnal fall in cardiac output, and it is associated with a nocturnal increase in vascular resistance.

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Key Words  • transplantation  • blood pressure  • cardiac output  • cyclosporine  • prednisone

The normal nocturnal decline in blood pressure is absent or attenuated after heart transplantation.1-6 The mechanism underlying this hemodynamic abnormality is not known. It has been suggested that during the night, cardiac output is relatively high compared with the resistance in the arteriolar vascular tree.1,2 This “inappropriately” high cardiac output might be explained by an increase in venous return during nighttime recumbency, for which, contrary to the normally innervated heart, no compensation occurs by means of a decrease in cardiac inotropy and/or chronotropy. A contributory factor to this nocturnal mismatch between cardiac output and arteriolar vascular resistance could be the impairment of the restraint of sympathetic outflow to the vascular tree due to the interruption of the ventricular-baroreceptor reflex after heart transplantation.7,8

The use of immunosuppressive therapy may also be involved in the attenuation of the nocturnal decline in blood pressure after cardiac transplantation. Cyclosporine has been reported to induce fluid retention; hence, it may increase venous return during nighttime recumbency. An absent nocturnal decline in blood pressure has been reported in patients with Cushing’s syndrome and patients treated with high doses of glucocorticoids.10 In addition, van de Borne and coworkers6 recently provided evidence for reappearance of the normal circadian blood pressure variation in cardiac transplant recipients after reduction of the dose of glucocorticoids.

The aim of the present study was to define the hemodynamic abnormalities underlying the absent or attenuated nocturnal fall in blood pressure in cardiac transplant recipients. Therefore, the diurnal changes of ambulatory intra-arterial pressure and heart rate were measured in 23 cardiac transplant recipients and in 23 control subjects matched for age and 24-hour mean arterial pressure. Relative diurnal changes in stroke volume, cardiac output, and systemic vascular resistance were estimated by a pulse-contour method.

Methods

Subjects  Twenty-three cardiac transplant recipients (5 women) a mean of 42 years old (range, 18 to 56 years) who were all hemodynamically stable (cardiac index, 3.7±0.8 L·min⁻¹·m⁻² [mean±SD]; left ventricular ejection fraction, 65±8%) gave their consent to participate in the study, which was approved by the Ethical Committee of the University Hospital “Dijkzigt.” The time
interval between transplantation and intra-arterial blood pressure recording was 16±8 months (range, 11 to 36 months). All subjects used cyclosporine (6.6±2.4 mg·kg⁻¹·d⁻¹) and prednisone (0.14±0.03 mg·kg⁻¹·d⁻¹) as maintenance immunosuppression. Six patients were receiving antihypertensive medication, which included nifedipine in three, captopril in two, and nifedipine and furosemide in one.

Invasive ambulatory blood pressure recordings in 23 subjects matched for age and 24-hour mean arterial pressure served as controls. These blood pressure recordings were obtained from our database of subjects who were referred to us for assessment of hypertension. The mean age of these subjects (22 men and 1 woman) was 40 years (range, 18 to 60 years). They did not use any medication for at least 3 weeks before the blood pressure recording.

**Invasive 24-Hour Ambulatory Blood Pressure Recordings**

Cardiac transplant recipients and control subjects were in the hospital at the time the blood pressure recordings were performed. Although the subjects were free to move about within the hospital, they were restricted with respect to the timing of meals and bedtime. In this way, a certain degree of standardization over the registration period was obtained.

Invasive 24-hour ambulatory blood pressure was monitored according to previously described methods. By means of the Seldinger technique, a 10-cm-long, 1.0-mm-diameter Teflon catheter was introduced into the brachial artery of the non-dominant arm after local anesthesia with a 2% lidocaine solution. The catheter was connected to a miniature perfusion-transducer device, which was fitted in front of the sternum at heart level. The transducer signal was recorded on magnetic tape by means of a portable tape recorder (Medilog Recorder II, Oxford Medical Instruments).

Registrations were read into an XP7 computer system (Olivetti) with a sampling frequency of 160 Hz and a quantification level of 12 bits. A dedicated computer program calculated pulse interval and integrated mean arterial pressure of individual beats. In addition, stroke volume was assessed by a corrected pulse-contour method developed by Smith et al. and the accuracy of this method has been established by comparison of cardiac output estimated by the pulse-contour method with cardiac output simultaneously estimated by thermodilution in patients undergoing a coronary bypass graft operation. The two methods were well correlated (r=0.94; n=64), and the SD of the differences between the methods against the mean of the methods was 10.6%. Cardiac output was calculated by the equation CO=SV×HR, where CO is cardiac output, SV is stroke volume, and HR is heart rate. Total peripheral vascular resistance (TPR) was calculated as TPR=MAP/CO, where MAP is mean arterial pressure, assuming a right atrial pressure of 0 mm Hg throughout the 24 hours. Since stroke volume was not calibrated against a true value, stroke volume, cardiac output, and total peripheral vascular resistance were expressed only as percentages of their 24-hour averages, which were set at 100%. For graphical presentation of the various hemodynamic parameters, 20-minute averages were calculated. As a measure of "short-term" as opposed to long-term or day-night variability of blood pressure and heart rate, the SD of these two parameters for each subsequent 20-minute period was computed. The diurnal variation of the hemodynamic variables was quantified as the difference between the average daytime and average nighttime values. Transience periods between day and night and night and day were removed by defining the day from 8 AM to 8 PM and the night from midnight to 6 AM.

**Statistics**

Normal distribution of the parameters was verified as described by Shapiro and Wilk. Since all parameters appeared to be distributed normally, values are presented as mean±SD. The relation between the various hemodynamic parameters is expressed by Pearson's correlation coefficient. To establish a statistical difference from zero and between groups, Student's unpaired and paired t tests were used, respectively. A value of P<.05 (two-tailed) was regarded as significant.

![Graphs of Hemodynamic Parameters](image_url)
Results

The 24-hour ambulatory blood pressure recordings appeared to be of good quality. In cardiac transplant recipients, 96±4% and in control subjects, 97±4% of all beats could be analyzed.

The 24-hour profiles of the absolute values of mean arterial pressure, heart rate, and their short-term variabilities in cardiac transplant recipients and control subjects are shown in Fig 1. Compared with the control subjects, the nocturnal decline of blood pressure was considerably smaller in cardiac transplant recipients (5 versus 21 mm Hg, respectively; Table 1). The 24-hour blood pressure profile of cardiac transplant recipients showed three prominent dips in blood pressure that coincided with the timing of meals. The 24-hour blood pressure profile of control subjects showed a decrease in blood pressure in the early afternoon and a smaller decrease in blood pressure late in the evening. As expected, average 24-hour heart rate was considerably higher in cardiac transplant recipients than in control subjects, but the absolute difference in heart rate between day and night of the two groups was of the same magnitude (Table 1). As a consequence of the denervated state of the transplanted heart, the SD of heart rate over each 20-minute period as a measure of short-term variability was considerably lower in cardiac transplant recipients than in control subjects during both the day and the night. The short-term variability of blood pressure in cardiac transplant recipients was of the same magnitude as in control subjects, and as in controls, it showed a diurnal variation with a lower value during the night than during the day (Fig 1).

Twenty-four hour profiles of the relative changes of mean arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral vascular resistance of cardiac transplant recipients and control subjects are shown in Fig 2. In control subjects, the nocturnal fall in blood pressure was associated with a marked nocturnal fall in cardiac output. Nocturnal total peripheral vascular resistance compared with the daytime value did not change (Table 1). The nocturnal fall in cardiac output was caused almost completely by a fall in heart rate and only a minimal, not significant, decrease in stroke volume. In cardiac transplant recipients, the attenuated nocturnal fall in arterial pressure was associated with an attenuated nocturnal fall in cardiac output compared with control subjects. In addition, and in contrast to control subjects, nocturnal peripheral vascular resistance compared with its daytime value was increased. The attenuated nocturnal fall in cardiac output in cardiac transplant recipients compared with the control subjects was due to a slightly smaller nocturnal fall in heart rate and the tendency toward a nocturnal increase in stroke volume (Table 1).

To assess possible effects of antihypertensive medication on the diurnal changes in the hemodynamic variables, nocturnal changes of mean arterial pressure, heart rate, stroke volume, cardiac output, and systemic vascular resistance of the six cardiac transplant recipients who used antihypertensive medication at the time of the registration were compared with those changes in

| TABLE 1. Diurnal Changes of Hemodynamic Variables in Cardiac Transplant Recipients and Control Subjects |
|-------------------------------------------------|-------------------------------------------------|--------------------------------------------------|
| Mean arterial pressure, mm Hg                  | Cardiac Transplant Recipients (n=23)            | Control Subjects (n=23)                          |
| 24-Hour average                                | 105±12                                          | 105±14                                           |
| Nocturnal change                                | -5±10*                                          | -21±10‡                                         |
| Variability of mean arterial pressure, mm Hg   | 6.5±0.9                                         | 6.9±0.9                                          |
| 24-Hour average                                | -1.3±1.0‡                                       | -1.5±1.1‡                                       |
| Heart rate, bpm                                | 92±13                                           | 75±9                                            |
| 24-Hour average                                | -16±7‡                                          | -17±8‡                                          |
| Variability of heart rate, bpm                 | 3.4±1.2                                         | 7.4±1.6                                         |
| Nocturnal change                                | -0.8±0.8§                                       | -1.9±1.0‡                                       |
| Mean arterial pressure                         | -5±9*                                           | -20±8‡                                         |
| Heart rate                                     | -18±8§                                          | -22±9‡                                          |
| Stroke volume                                  | 3±10§                                          | -3±11§                                          |
| Cardiac output                                 | -14±12‡                                         | -24±13‡                                         |
| Vascular resistance                            | 9±9‡                                           | 4±13§                                          |

NS indicates not significant (P>.05); bpm, beats per minute. Values are mean±SD.

*P<.05, †P<.01, ‡P<.001 for changes within groups. §P=NS.
of the patients using antihypertensive medication, predominantly because of a tendency toward a nocturnal increase in stroke volume (Table 2).

Both in cardiac transplant recipients and in control subjects, the nocturnal change in arterial pressure was correlated with the nocturnal change in cardiac output ($r=.72, P<.001$ for cardiac transplant recipients and $r=.45, P=.03$ for control subjects) but not with the nocturnal change in total peripheral vascular resistance (Fig 3).

In cardiac transplant recipients, the dips in blood pressure during the day were paralleled by decrements in peripheral vascular resistance. The dip in blood pressure in control subjects in the early afternoon was initially also associated with a decrease in vascular resistance and subsequently with a fall in stroke volume and cardiac output, whereas the smaller dip in blood pressure in the evening ran in parallel with a decrease in stroke volume.

**Discussion**

This study, using direct ambulatory blood pressure recordings, confirms the results of previous studies showing that the nocturnal fall of blood pressure is markedly attenuated in cardiac transplant recipients.1-6 Hemodynamically, this attenuation of the nocturnal fall in blood pressure is characterized by an attenuation of the nocturnal fall in cardiac output and a moderate increase in total peripheral vascular resistance.

The nocturnal changes in hemodynamics, ie, a fall in cardiac output and an unchanged total peripheral vascular resistance, observed in our control subjects agree well with data reported in the literature in which cardiac output was measured either by indicator-dilution16-18 or bioimpedance techniques.19 This suggests that changes in stroke volume and hence cardiac output are estimated with reasonable accuracy with the pulse-contour method. Although a drawback of the pulse-contour method is that no absolute values but rather only changes in stroke volume can be measured, this was not a handicap in the present study, since we were interested in within-subject changes in hemodynamics over the 24-hour period. Obviously, an important advantage of the pulse-contour method, especially when applied to direct ambulatory blood pressure recordings, is that beat-by-beat information about systemic hemodynamic alterations can be obtained in unrestricted and undisturbed subjects outside the artificial environment of the cardiovascular laboratory.

The average nocturnal decrease in cardiac output was only 14% in cardiac transplant recipients compared with 24% in control subjects. The tendency toward a nocturnal increase in stroke volume as well as a somewhat smaller relative fall in heart rate accounted for this difference. The reason for this attenuated nocturnal fall in cardiac output remains uncertain, but probably the denervated state of the transplanted heart in this respect is most important. As a consequence of the denervated state, the transplanted heart is not exposed to the normally occurring nocturnal increase in cardiac vagal and decrease in cardiac sympathetic tone. In addition, the effects of an increase in venous return on cardiac output during the night is only indirectly and partially counteracted by cardiopulmonary- or baroreflex-mediated changes in the activity of the autonomic nervous system through changes in circulating catecholamines.

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**Fig 2.** Twenty-four-hour trend plots of the percentage changes of mean arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral vascular resistance in 23 cardiac transplant recipients and 23 control subjects. Twenty-minute averages of the various hemodynamic parameters are depicted. Closed symbols indicate cardiac transplant recipients; open symbols, control subjects.
TABLE 2. Diurnal Changes in Hemodynamic Variables in Cardiac Transplant Recipients With and Without Antihypertensive Medication

<table>
<thead>
<tr>
<th></th>
<th>With Antihypertensive Medication (n=6)</th>
<th>Without Antihypertensive Medication (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>101±7</td>
<td>107±14</td>
</tr>
<tr>
<td>24-Hour average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal change</td>
<td>-3±12</td>
<td>-5±9*</td>
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<tr>
<td>Heart rate, bpm</td>
<td></td>
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<tr>
<td>24-Hour average</td>
<td>87±14</td>
<td>93±12</td>
</tr>
<tr>
<td>Nocturnal change</td>
<td>-14±6†</td>
<td>-16±7‡</td>
</tr>
<tr>
<td>Nocturnal change, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-4±12</td>
<td>-5±8*</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-16±7†</td>
<td>-18±8‡</td>
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<tr>
<td>Stroke volume</td>
<td>7±9</td>
<td>3±10</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>-8±9</td>
<td>-15±13‡</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td>3±6</td>
<td>11±10‡</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute. Values are mean±SD. Differences between the various hemodynamic parameters of the two subgroups were not significant. *P<.05, †P<.01, ‡P<.001 for changes within groups.

In addition to the denervated state, the use of immunosuppressive therapy might also have contributed to the attenuated nocturnal fall in cardiac output. Cyclosporine is known to induce fluid retention; hence, it may increase venous return during nighttime recumbency, when extracellular fluid volume is shifted from peripheral to more central parts of the body. An attenuation of the circadian blood pressure variation in patients with Cushing's syndrome and in patients using glucocorticoids was reported by Imai and coworkers. However, in contrast to the present findings in cardiac transplant recipients, the attenuated circadian blood pressure variation in patients treated with glucocorticoids is hemodynamically characterized by a marked nocturnal increase in total peripheral vascular resistance, whereas the normally occurring nocturnal decrease in cardiac output appears to be completely preserved. It should also be remarked that the dose of glucocorticoids used by the patients studied by Imai and coworkers was several times higher than the dose of glucocorticoids used by the cardiac transplant recipients of this study.

Apart from the attenuated nocturnal decrease in cardiac output, another hemodynamic abnormality encountered in cardiac transplant recipients was a nocturnal increase in total peripheral vascular resistance. This nocturnal increase in vascular resistance is not easy to explain. To some extent, it may be related to the assumption, for the calculation of vascular resistance, that right atrial pressure remained stable at 0 mm Hg throughout the 24-hour period. Since in normal subjects, the diurnal variation of right atrial pressure compared with the diurnal variation of mean arterial pressure is very low, the bias introduced by omitting diurnal changes in right atrial pressure is relatively small. However, for a subject with a relatively small nocturnal decrease of mean arterial pressure, which is typical for the cardiac transplant recipient, an increase of 1 mm Hg of right atrial pressure during the night implies an overestimation of the nocturnal increase in vascular resistance by approximately 1%. Accordingly, the nocturnal increase in vascular resistance is probably overestimated in our patients.

Fig 3. Scattergrams showing percentage nocturnal change in cardiac output or total peripheral vascular resistance vs percentage nocturnal change in mean arterial pressure in cardiac transplant recipients (○) and control subjects (○). Nocturnal changes in cardiac output and mean arterial pressure were correlated: r=-.72 (P<.001) for cardiac transplant recipients and r=.45 (P=.03) for control subjects, whereas nocturnal changes in vascular resistance and mean arterial pressure were not correlated in either of the two groups.
Besides the attenuated nocturnal fall in blood pressure, the recordings of cardiac transplant recipients showed three prominent dips in blood pressure during the day. These dips in blood pressure coincided with the timing of meals and are probably a direct consequence of it. Since our subjects were in the hospital at the time of the blood pressure recording, the timing of meals was similar for each subject, thus synchronizing these postprandial dips in blood pressure in the groups. This may explain why the postprandial dips in blood pressure were so clearly visible on the blood pressure traces. Hemodynamically, the dips in blood pressure were associated with parallel decrements in total peripheral vascular resistance, most likely caused by arteriolar vasodilatation in the splanchnic circulation. In the control group, the most marked fall in blood pressure during daytime occurred in the early afternoon, whereas small dips in blood pressure were seen in the morning after breakfast and in the evening. The prolonged dip in blood pressure in the early afternoon was due to both the consumption of the principal meal and a postprandial nap, which is customary in our hospital.

Postprandial dips in blood pressure have been described in elderly subjects and in patients with autonomic insufficiency. In these subjects, the postprandial dips in blood pressure are sometimes symptomatic and may even cause syncope. As far as we know, symptomatic postprandial dips in blood pressure have not yet been reported in cardiac transplant recipients; also, our patients noticed no hypotensive symptoms in relation to ingestion of food.

Although average daytime blood pressure was lowered by the postprandial dips in blood pressure, this effect was far too small to account for the attenuated nocturnal fall in blood pressure. Without the dips in blood pressure, the estimated day-night difference in blood pressure increased from 5 to 7 mm Hg, which is still considerably smaller than the 20 mm Hg day-night difference in blood pressure observed in the control subjects.

The continuous recording of the intra-arterial blood pressure signal provided an opportunity to determine the “short-term” variability of blood pressure and heart rate in our subjects. In agreement with previous reports, short-term blood pressure and heart rate variability in control subjects, like blood pressure and heart rate, showed a clear diurnal variation, with lower values during the night than during the day. As expected, and related to the derenervated state of the transplanted heart, short-term heart rate variability was markedly lower in cardiac transplant recipients than in control subjects. However, as in control subjects, heart rate variability in cardiac transplant recipients also showed a diurnal rhythm with a significantly higher value during the day than during the night. Most likely, a greater fluctuation in circulating catecholamines during the day related to different levels of activity explains the observed higher level of daytime heart rate variability. Alternatively, and in accordance with studies showing evidence for regional structural sympathetic reinnervation late after orthotopic cardiac transplantation, it could be that some of our patients had partial reinnervation of their transplanted hearts. The short-term variability of blood pressure in cardiac transplant recipients was of the same magnitude as in the control subjects, and despite the attenuation of diurnal rhythm of blood pressure, its diurnal rhythm was comparable to that of control subjects. This finding indicates that to a certain extent, the tonic level of blood pressure and its variability are regulated independently, which is in line with the results of a previously reported study by our group.

In conclusion, the nocturnal fall in blood pressure in cardiac transplant recipients is markedly blunted because of an attenuation of the nocturnal fall in cardiac output as well as a moderate increase in total peripheral vascular resistance. Apart from the attenuated nocturnal fall in blood pressure, another peculiar finding in cardiac transplant recipients was marked postprandial dips in blood pressure. Finally, as opposed to the loss of long-term (day-night) blood pressure variability, “short-term” blood pressure variability is fully maintained in cardiac transplant recipients. “Unopposed” nocturnal increase in venous return may be one of the pathogenetic factors involved in the attenuated nocturnal fall in cardiac output and hence the attenuated nocturnal fall in blood pressure observed in cardiac transplant recipients. It seems worthwhile, therefore, to explore whether venodilatory treatment before patients go to sleep restores the abnormal diurnal rhythm. This is of interest not only from a theoretical but also from a clinical point of view. Cyclosporine-induced hypertension occurs in the vast majority of cardiac transplant recipients; an absent or attenuated nocturnal fall in blood pressure implies an important increase of the blood pressure load. This may contribute to the vascular and renal complications in these patients and plays a crucial role in the development of left ventricular hypertrophy. A better understanding of the hemodynamic abnormalities underlying the attenuated blood pressure profile in cardiac transplant recipients might prove to be of value in the development of pharmacotherapeutic strategies that favorably influence long-term prognosis in these patients.

References
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