Diurnal Variation in Blood Pressure in Patients With Biventricular Assist Devices and Retained, Nonpumping Native Hearts

Jens Sehested, MD, PhD; Egbert Happe, MD; Kozo Ishino, MD; Roland Hetzer, MD, PhD; Ulf Schiessler, MD; Søren Schifter, MD

Background Studies indicate that centrally mediated rhythms in sympathetic tone play a prominent role in diurnal cardiovascular variability. Recent evidence from heart transplant recipients, in whom blood pressure does not decline during sleep despite normal variability in plasma norepinephrine, however, suggests that afferent cardiac nervous traffic is necessary for the generation of diurnal variability. This implies that in the presence of an innervated heart excluded from the systemic circulation, blood pressure would still decrease during sleep. To assess this hypothesis, we studied 24-hour blood pressure, heart rate, and neuroendocrine variability in patients with biventricular assist devices in whom the retained native hearts had ceased to pump.

Methods and Results Eight patients were free of medication and were studied every 3 hours. Pump rates and output were kept constant throughout the study. Blood pressure showed a significant decline during sleep, as did norepinephrine and epinephrine (all \(P<.05\)). Atrial natriuretic factor showed a significant increase around midnight (\(P<.01\)). Significantly elevated levels were found for all hormones studied except for aldosterone and endothelin.

Conclusions Our results suggest that diurnal variations in cardiac function or in catecholamine levels (indicative of sympathetic activity) as found in heart transplant recipients alone are not responsible or sufficient for producing a nocturnal drop in blood pressure. The presence of an innervated heart appears crucial in this respect. This could be of importance for the understanding of circadian cardiovascular pathophysiology. (Circulation. 1994;89:2601-2604.)

Key Words • circadian rhythm • blood pressure • hormones • heart-assist device

The study of circadian rhythms has within recent decades evolved from a biological curiosity to a science with enormous implications for clinical medicine. The occurrence of several cardiovascular events, such as sudden cardiac death, stroke, and myocardial infarction, has been shown to follow a circadian pattern, being more frequent in the morning hours. These observations have generally been linked with the normally occurring circadian variations in cardiovascular dynamics, in particular with the morning increase in circulatory activity that follows the nocturnal reduction in blood pressure and heart rate. A recent study has further demonstrated a significant negative correlation between left ventricular mass index and the degree of nocturnal reduction in blood pressure in essential hypertension.

The physiological mechanisms behind this nocturnal drop in blood pressure and heart rate are still obscure. There is good evidence, however, that a reduction in sympathetic nervous activity during sleep plays a major role. Thus, plasma levels of catecholamines show a distinct diurnal variability, and conditions that affect autonomic nervous function, like autonomic failure and diabetic neuropathy, are generally associated with a loss of a nocturnal decline in pressure. Furthermore, results of a recent study extend and support those of an older one showing a circadian rhythm in basal vascular tone, which is highest at times that correspond to elevated plasma levels of catecholamines, probably because of diurnal variations in \(\alpha\)-sympathetic vasoconstrictor activity. At the same time, arterial baroreceptors show an increase in sensitivity during the hours of sleep, suggesting a central sleep-induced modification of baroreceptor influence on autonomic neurons modulating cardiovascular activity. Taken together, present information thus indicates that circadian cardiovascular variability in humans has its origin in the central nervous system.

A series of observations, however, suggest that the heart itself could play an important role in the establishment of diurnal variations in blood pressure, independently of variations in heart rate: (1) patients with a fixed heart rate still maintain a nocturnal pressure drop; (2) patients with congestive heart failure show a basically preserved nocturnal reduction in blood pressure, whereas the same type of patients, on restoration of normal cardiac function through a denervated heart transplant, do not; despite normal baroreceptor function, preserved circadian variability in heart rate, and normal variations in plasma norepinephrine; and (3) a patient without a biological heart but served by an implanted totally artificial heart does not present any circadian variations in pressure.

These observations thus suggest that a normally innervated heart is a prerequisite for the generation of diurnal variations in blood pressure. If this is a decisive prerequisite, it follows that in a patient whose native...
heart is excluded from the circulation but remains connected with the central nervous system, a nocturnal drop in pressure would still occur.

This hypothesis was tested in patients in whom the circulation was maintained by a biventricular assist device but whose native heart was left in situ. Blood pressure, heart rate, and neuroendocrine plasma levels were recorded over a 24-hour period of supine rest.

Methods

Study Population

We studied eight patients (four women and four men) who had received a biventricular assist device (BVAD) because of irreversible cardiogenic shock and the unavailability of suitable donor hearts. The mean age of the patients was 38 years (range, 22 to 55 years). Heart failure was due to dilated cardiomyopathy in six and to ischemic cardiac disease in two patients. All patients were clinically stable at the time of study and did not receive cardiovascular medication. Diuretics (two patients) were stopped 24 hours before the study, during which only low doses of heparin were administered to prevent clotting in the pumps. The patients were studied for an average of 3.5 weeks (range, 1 to 8 weeks) after the BVAD was implanted. The BVAD used was the Berlin Artificial Heart (Berlin Heart Co), a two-chamber artificial heart of the membrane type equipped with four pivoting disk valves with each chamber separately driven by a pneumatic drive unit (Heimes). The BVAD was connected to the heart of the patients via canulas through which blood was drawn from the right atrium into the right chamber and from there pumped into the main stem of the pulmonary artery. On the left side, blood was drawn from the left atrium and pumped into the ascending aorta via the left chamber. This procedure involves minimal dissection at the atria and thus, combined with longitudinal incisions in the pulmonary artery and the aorta, should leave the vast majority of cardiac nerves intact. The BVAD, placed on top of the abdomen, was connected to the intravascular canulas via transcutaneous silicon tubes, thus allowing visual inspection of both pump chambers. Repeated echocardiography showed that the aortic valves remained closed in the hearts. Thus, systemic circulation was maintained by the BVAD in all patients. The same was true for the pulmonary circulation in four patients with arrested hearts. In the other four patients, movements of the pulmonary valves could not be visualized with certainty because of interference from the BVAD tubes.

All patients had normal renal function based on levels of serum creatinine (mean±SD, 0.64±0.07 mg/dL; normal range, 0.5 to 1.1 mg/dL) and serum urea (mean, 23.4±8.7 mg/dL; normal range, 10 to 50 mg/dL). Serum Na\(^+\) and K\(^+\) were at the lower border of normal (135±2 and 4.0±0.2 meq/L; normal ranges, 138 to 147 and 4.0 to 4.7 meq/L for Na\(^+\) and K\(^+\), respectively). Hematocrit was low in all patients (mean, 0.27±0.07; normal range, 0.37 to 0.52), which is believed to be primarily an effect of the four mechanical valves. The study was approved by the hospital's ethics committee, and all patients gave their consent after thorough information on the aim and risks of the study, which was completed without any early or late adverse effects.

Study Protocol

Patients were studied during 24 hours of supine rest. During this period, pump rate and output were kept constant to avoid pump-induced variations in blood pressure. The rate was 88±6 beats per minute, and left chamber output was 3230±390 mL·min\(^{-1}\)·m\(^{-2}\). Intra-arterial blood pressure was recorded in the left radial artery in four patients by use of optimally vented and calibrated catheter-transducer lines. In the other four, who did not have an arterial line, pressure was measured every third hour with a sphygmomanometer on the left upper arm by a single, trained person not informed about the purpose of the study. To avoid systematic bias, the study began at different times of the day. Central venous pressure (CVP) was measured in half of the patients. Continuous ECG recordings were done in all patients.

Peripheral venous blood drawn every 3 hours into prechilled tubes containing EDTA, heparin, and aprotinin as appropriate was immediately centrifuged for 10 minutes at 3000 rpm and 4°C, and supernatants were stored at −80°C for later analysis. Determinations were done for plasma catecholamines, renin activity (PRA), aldosterone, atrial natriuretic factor (ANF), endothelin 1 and 2, and serum calcitonin gene–related peptide (CGRP), the latter centrifuged and stored after 2 hours of coagulation. Laboratory procedures for determination of catecholamines, PRA, aldosterone, ANF, and CGRP\(^\#\) have been described previously. Endothelin 1 and 2 were measured with a radioimmunoassay kit from Amersham after extraction on Sep-Pak C-18 cartridges (Waters Chromatography Division). Sensitivity was 1.3 pg/mL. Intra-assay and interassay variabilities were 6% and 7%, respectively.

Statistical Analysis

Friedman's test was used for the analysis of series of matched observations, followed by Wilcoxon's test for the comparison of peak and trough levels with the method of Bonferroni. The Mann-Whitney test was used to compare mean values from different groups, and Pearson's test was used for the correlation analyses. The level of statistical significance was set at P=.05. Results are given as mean±SD unless otherwise indicated. NS indicates statistical insignificance.

Results

Diurnal Changes in Hemodynamics

The patients generally slept from around 10 PM until 7 AM. During this period, all but one patient showed a decline in systolic blood pressure (P<.05) followed by a rise on awakening (Fig 1). There were no significant variations in diastolic pressure. Mean pressures over 24 hours were 114±7.5 and 58±5 mm Hg for systolic and diastolic pressures, respectively. There were no differences in the magnitude of systolic pressure changes between patients with beating and nonbeating hearts or between patients measured by phgymomanometry and intra-arterially. Half of the patients had cardiac arrest; heart rate in the other half (fast sinus rhythm) varied in parallel to systolic blood pressure and showed a strong tendency for significant diurnal variability (P=.06). Mean heart rate was 120±20 beats per minute (Fig 1). CVP was slightly elevated (8.8±4.6 mm Hg) and did not vary over time.

Diurnal Changes in Hormone Levels

Both plasma norepinephrine (P<.05) and epinephrine (P<.03) showed a significant diurnal variation, with trough levels around 4 AM (Fig 2), whereas dopamine did not. Plasma aldosterone also showed a significant increase from 4 AM (P<.05), contrary to the nonsignificant variations in PRA. ANF levels varied significantly during the 24-hour period and peaked around midnight (P<.01, Fig 2). Endothelin showed a modest but significant peak at 10 AM (P<.05). CGRP did not vary significantly over time.

Compared with our laboratory values from 20 supine, age-matched healthy control subjects (Table), significantly higher levels in our patients were found for norepinephrine, epinephrine, dopamine, PRA, ANF, and CGRP. Levels of endothelin and aldosterone did
not differ from normal. There was a positive correlation between mean values in the individual patients for PRA and aldosterone ($r = .93$, $P < .01$). We did not find any correlation between CVP and levels of ANF or between levels of serum Na$^+$ and ANF or aldosterone ($P = \text{NS}$). There was a weak negative correlation between left pump chamber output and PRA ($r = -.61$, $P = .09$).

**Discussion**

We find it natural to discuss the results of the present study in relation to those obtained from similar groups of patients with end-stage congestive heart failure but treated with a denervated heart transplant. The results thus confirm the hypothesis that in the presence of an innervated heart that is excluded from the systemic circulation, diurnal reduction in blood pressure does occur. This is in contrast to numerous reports on failure of blood pressure to decrease during sleep in patients with denervated cardiac transplants. Since current data suggest that sleep-induced decline in blood pressure primarily reflects a centrally controlled reduction in sympathetic drive to the peripheral vascular tree, as indicated by a nocturnal drop in catecholamines both in the present study with bypassed hearts and in our study of patients with heart transplants and normal control subjects,7 it may be argued that such a control is compromised after cardiac transplantation and institution of immunosuppressive medication. The surgical technique applied for heart transplantation, however, does not affect peripheral vascular innervation; thus, arterial baroreflex sensitivity is normal in heart transplant recipients,16 as well as the vascular response to the cold pressor test,20 ie, results indicating intact autonomic function. Although cyclosporine, the principal drug for immunosuppression, has been shown to interfere with the contractile response in isolated vessels,21,22 the capacity for peripheral vasodilation (reactive hyperemic blood flow) normalizes after heart transplanta-

**Levels of Circulating Hormones In 8 BVAD Patients Compared With 20 Age-Matched Control Subjects**

<table>
<thead>
<tr>
<th>BVAD Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>510±210</td>
<td>219±54</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>43.6±32.9</td>
<td>11.8±9.8</td>
</tr>
<tr>
<td>Dopamine, pg/mL</td>
<td>32.8±41</td>
<td>ND</td>
</tr>
<tr>
<td>PRA, ng · mL$^{-1}$ · h$^{-1}$</td>
<td>6.8±8.5</td>
<td>0.8±0.4</td>
</tr>
<tr>
<td>ANF, pg/mL</td>
<td>162±107</td>
<td>42±17</td>
</tr>
<tr>
<td>CGRP, pmol/L</td>
<td>66±21.3</td>
<td>36.4±13.1</td>
</tr>
<tr>
<td>Endothelin, pg/mL</td>
<td>40±10.1</td>
<td>46±11.6</td>
</tr>
<tr>
<td>Aldosterone, nmol/L</td>
<td>0.21±0.17</td>
<td>0.27±0.18</td>
</tr>
</tbody>
</table>

BVAD indicates biventricular assist device; PRA, plasma renin activity; ANF, atrial natriuretic factor; CGRP, calcitonin gene-related peptide; and ND, not detectable, ie, < 20 pg/mL. Values are mean±SD.
tion. This, together with the finding of a normal vascular response to α-adrenergic stimulation by phenylephrine, probably excludes major functional defects in the vasculature as the cause of diurnal abnormalities in blood pressure regulation in cardiac transplant recipients. On the other hand, a series of studies have demonstrated abnormalities in neurohumoral and vascular reactivity in response to modulation of cardiopulmonary receptor activity in humans with heart transplants, probably causally related to cardiopulmonary deafferentation and of potential importance for diurnal blood pressure regulation.

The hormone levels found in this study are in accordance with those repeatedly found in patients with congestive heart failure and probably include the effects of reduced baroreceptor stimulation and renal perfusion pressure, as indicated by the tendency for a negative correlation between left chamber output and PRA. Of interest, however, is the finding of a significant circadian variability in ANF that closely resembles that of normal subjects but at levels corresponding to those of heart transplant recipients. Since ANF in these patients is considerably increased and shows a highly irregular 24-hour profile, this finding adds further evidence to the concept of a neural control of ANF release.

In conclusion, available information from humans with a denervated heart (or without a biological heart) and from patients with a heart no longer active in the circulation but still innervated thus suggests that afferent cardiac traffic to the central nervous system is necessary for establishing diurnal reduction in blood pressure. The results further indicate that neither variations in sympathetic activity (as suggested by significant circadian variations in circulating catecholamines in heart transplant recipients) nor variations in cardiac output and pump rate (kept constant in the present study) are alone responsible or sufficient for producing nocturnal variations in blood pressure. The results of this study may thus provide further insight into the linkage between diurnal blood pressure variations and the heart, which could be of importance also for the "cause-and-effect" concepts in cardiovascular pathophysiology.

Acknowledgments

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References

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