Circadian Variation of Heart Rate But Not of Blood Pressure After Heart Transplantation

G.J. Wenting, A.H. v.d. Meiracker, M.L. Simoons, E. Bos, H.J. Ritsema v. Eck, A.J. Man in 't Veld, W. Weimar, and M.A.D.H. Schalekamp

ALTHOUGH the survival with cyclosporine (Cs) treatment has increased markedly after cardiac allografting, one of the most notable adverse effects of Cs administration is hypertension. Blood pressure is a continuous variable, depending on the intricate balance between output of the heart and resistance to flow in the vascular system. The ultimate level of blood pressure is determined by the interplay of a host of factors, which all have their impact on the nervous drive to the heart, on filling pressures and on vascular tone.

The transplanted heart is and remains denervated. The consequences of interruption of vagal afferents, vagal efferents, and of sympathetic outflow to the heart with respect to blood pressure regulation are not known. Intraarterial blood pressure was therefore continuously monitored over 24 hours in 10 Cs-treated recipients of orthotopic heart transplants. Not only the 24 hour blood pressure profile was studied, but the recordings were also analyzed, beat by beat, by a computer to get insight into blood pressure and heart rate variabilities.

PATIENTS AND METHODS

Observations were made in 10 heart transplant recipients (9 men, 1 woman; age 37 to 51 years) who represented the total number of patients transplanted in our center between July 1984 and December 1985. At the time of monitoring, 8 to 12 weeks after surgery, all patients were capable of moderate exercise and none showed clinical or radiological evidence of heart failure. They were also free of histological evidence of endomyocardial tissue rejection for at least 4 weeks. All patients were immunosuppressed with Cs combined with low dose prednisone.

Antihypertensive drugs, if any, were discontinued a few days before the study but diuretics were continued. Absence of cardiac reinnervation was demonstrated by abnormal responses to tilt, Valsalva maneuver, carotid sinus massage, atropine, and exercise.

Nine patients with mild essential hypertension (7 men, 2 women; age 42 to 58 years) who had been monitored as part of the assessment of their hypertension served as controls. They were selected from a larger series to match the heart transplant recipients for degree of day-time blood pressure. They had stopped antihypertensive treatment for at least 2 weeks. Informed consent was obtained from all patients and no complications resulted from the procedure. Blood pressure and heart rate monitoring was performed in the hospital setting in order to standardize conditions like physical activity, timing of meals, rest, and morning rise. After cannulation of the brachial artery, the blood pressure signal, measured by a portable transducer-perfusion unit (Northwick Park Hospital device) was registered by an Oxford-Medilog 2 recorder. Computer processing of the digitized pressure signal and of the ECG enabled us to determine 24-hour histograms of systolic, diastolic, mean pressures, and of heart rate. Long-term blood pressure and heart rate variabilities were expressed as the standard deviation of the 24-hour frequency histogram. Short-term variabilities were assessed by the standard deviation and variation coefficients of hourly means. Data are expressed as mean ± standard error of the mean.

Two-tailed P values < 0.05 are used to express significance of the results.

RESULTS AND DISCUSSION

Circadian blood pressure patterns in the heart transplant recipients did not show the normal fall at night (Fig 1, upper panel). Mean blood pressure was 105 ± 5 mmHg during the day (8 AM to 8 PM) *v* 107 ± 3 mmHg at night (0 to 6 AM). In the transplant

From the Department of Internal Medicine and the Thorax Center, University Hospital Dykzigt, Erasmus University, Rotterdam, The Netherlands.

Address reprint requests to G.T. Wenting, Department of Internal Medicine and the Thorax Center, University Hospital Dykzigt, Erasmus University, Rotterdam, The Netherlands.

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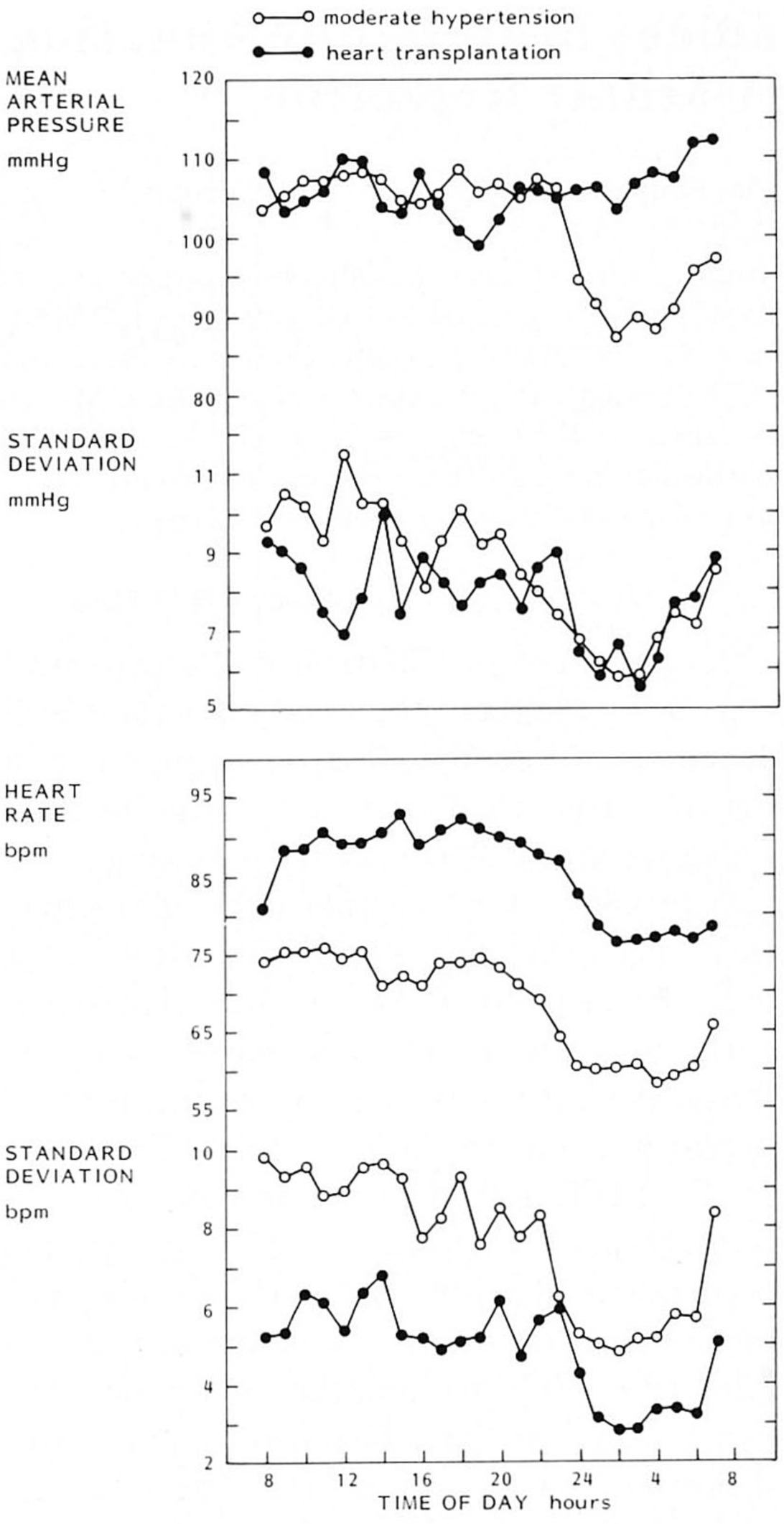

Fig 1. Circadian patterns of blood pressure, heart rate and variability of blood pressure and heart rate in ten heart transplant recipients and nine patients with moderate hypertension.

group heart rate was higher during the whole 24-hour period than in the controls ($P < 0.01$). But in contrast to blood pressure heart rate fell at night; 90 ± 5 beats per minute during the day *v* 79 ± 4 beats per minute at night ($P < 0.01$).

Hourly blood pressure and heart rate variabilities were reduced at night (Fig 1, lower panel), a phenomenon that was also observed in the controls. Probably as a consequence of the denervated state of the heart, hourly heart rate variability was much lower than in the control subjects. This contrasted with hourly blood pressure variability, which was more or less equal in both groups. Long-term blood pressure and heart rate variabilities were smaller in the transplant group than in the controls.

Our results suggest that at night redistribution of fluid together with the force-fed pump characteristics of the denervated heart counteracted the blood pressure lowering effect of diminished sympathetic drive to heart (via circulating catecholamines) and blood vessels (via neurotransmitter catecholamine). This will increase the "pressure load" to the heart and other vital organs and may aggravate the hypertensive damage of chronic CsA administration in these patients. In addition, the discrepancy between diminished heart rate variability and normal blood pressure variability in patients with denervated hearts, makes it unlikely that the former is an important determinant of the latter, as proposed in patients with normal hearts.