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Decreased Circadian Blood Pressure Variation Up to Three Years After Heart Transplantation

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The normal circadian blood pressure (BP) variation has been reported to be attenuated or completely abolished in cardiac transplant recipients.[1–3] The reason for this attenuation is not clear, but it has been suggested to be related to the force-fed pump characteristics of the denervated heart or the use of glucocorticoids, or both.[1,4] A consequence of the attenuation or abolishment of the nocturnal reduction in BP is an increase in the 24-hour BP load, which may be especially injurious in cardiac transplant recipients, because of the development of cyclosporine-induced hypertension in a large proportion of these subjects. Recently, evidence was provided that attenuation of the circadian BP variation soon after cardiac transplantation disappears within 1 year and that a normal circadian rhythmicity of BP is restored.[5,6] In the present study, we report the results of invasive 24-hour BP recordings obtained in cardiac transplant recipients 11 to 36 months after transplantation. The findings indicate that >1 year after cardiac transplantation, an attenuation of the circadian BP variation remains in most subjects.

Invasive 24-hour ambulatory BP recordings were obtained in 17 cardiac transplant recipients 17 months (range 11 to 36) after transplantation. Clinical characteristics of patients, the time intervals between transplantation and BP recording, and the dosages of cyclosporine and prednisone are listed in Table I. No patient received any antihypertensive agent at the time of the BP recording. Invasive 24-hour ambulatory BP recordings were obtained also in 17 subjects who were

matched for age and average 24-hour mean BP. Recordings in subjects were obtained as part of the assessment of their hypertension. No subject used any medication for ≥3 weeks before the BP recording. All subjects gave informed consent to participate in the study, which was approved by the Medical Ethical Committee of the University Hospital "Dijkzigt." All subjects were in the hospital at the time of the BP recording to standardize environmental conditions. During the recordings, subjects were free to move within the hospital, but had their meals at fixed times, went to bed at 10:30 P.M. and were awakened at 7 A.M.

Ambulatory BP was measured according to previously described methods.[7] Using the Seldinger tech-

TABLE I Age, Sex, Time After Transplantation, and Dosages of Cyclosporine and Prednisone in 17 Cardiac Transplant Recipients

Patient	Age (yr) & Sex	Time After Transplantation (mo)	Cyclosporine (mg/kg)	Prednisone (mg/kg)
1	18M	13	5.3	0.18
2	22M	12	14.9	0.15
3	30F	21	5.4	0.11
4	32F	36	9.1	0.15
5	32M	33	6.3	0.13
6	38M	12	7.1	0.14
7	38M	12	6.1	0.15
8	42M	24	3.3	0.11
9	43M	12	5.5	0.11
10	44M	12	4.6	0.09
11	44M	24	7.6	0.12
12	44M	12	7.3	0.15
13	48M	11	7.9	0.13
14	49M	36	8.2	0.26
15	49M	12	6.6	0.13
16	56M	11	6.6	0.13
17	56F	12	9.7	0.16
Mean	40	17	7.1	0.14

TABLE II Average Day and Night Values of Systolic, Diastolic and Mean Arterial Pressures, Pulse Pressure and Heart Rate, and the Difference Between These Values in Cardiac Transplant Recipients and Control Subjects

	Cardiac Transplant Recipients			Control Subjects		
	Day	Night	Night–Day Difference	Day	Night	Night–Day Difference
Systolic arterial pressure (mm Hg)	142 ± 17	132 ± 18	−10 ± 12*	154 ± 18	124 ± 17	−31 ± 12‡§
Mean arterial pressure (mm Hg)	108 ± 13	103 ± 15	−5 ± 9†	114 ± 15	93 ± 13	−21 ± 9‡§
Diastolic arterial pressure (mm Hg)	90 ± 11	86 ± 12	−4 ± 7†	91 ± 12	74 ± 10	−18 ± 8‡§
Pulse pressure (mm Hg)	51 ± 10	46 ± 9	−6 ± 6*	63 ± 11	50 ± 10	−13 ± 8*§
Heart rate (beats/min)	105 ± 13	83 ± 13	−16 ± 7‡	82 ± 11	65 ± 7	−15 ± 8‡

*p <0.01, †p <0.05, ‡p <0.001 for within-group differences.
§p <0.001 for between-group differences.
Values are mean ± SD.

nique, a 10 cm long, 1 mm diameter Teflon catheter was inserted into the brachial artery of the nondominant arm after local anesthesia with a 2% lidocaine solution. The catheter was connected to a miniature transducer-perfusion device which was fitted in front of the chest at the level of the heart. The transducer signal was recorded on magnetic tape with a portable tape recorder (Medilog Recorder II, Oxford Medical Instruments, Oxford, United Kingdom).

The BP signals were scrutinized for artifacts off-line by a computer program that calculated systolic, diastolic and integrated mean BP, pulse pressure and pulse interval of individual beats. The diurnal variations of BP and heart rate were quantitated as the differences between average day and night values. Transient periods between day and night were removed from the calcula-

tions by defining night as the period from 12 to 6 A.M. and day as that from 8 A.M. to 8 P.M.

Values are presented as mean ± SD. Student's t test was used for comparison. A p value <0.05 was considered statistically significant.

The mean age of the 17 control subjects (1 woman and 16 men) was 42 ± 11 years. Average 24-hour mean BP was 107 ± 14 mm Hg in cardiac transplant recipients and 107 ± 13 mm Hg in control subjects. The profiles of 24-hour ambulatory mean BP and heart rate of cardiac transplant recipients and control subjects are shown in Figure 1. In the control group, BP markedly decreased during the night, whereas only a small, nocturnal reduction was observed in the transplant group (Table II). In contrast to this attenuated day–night fluctuation, BP in cardiac transplant recipients fluctuated
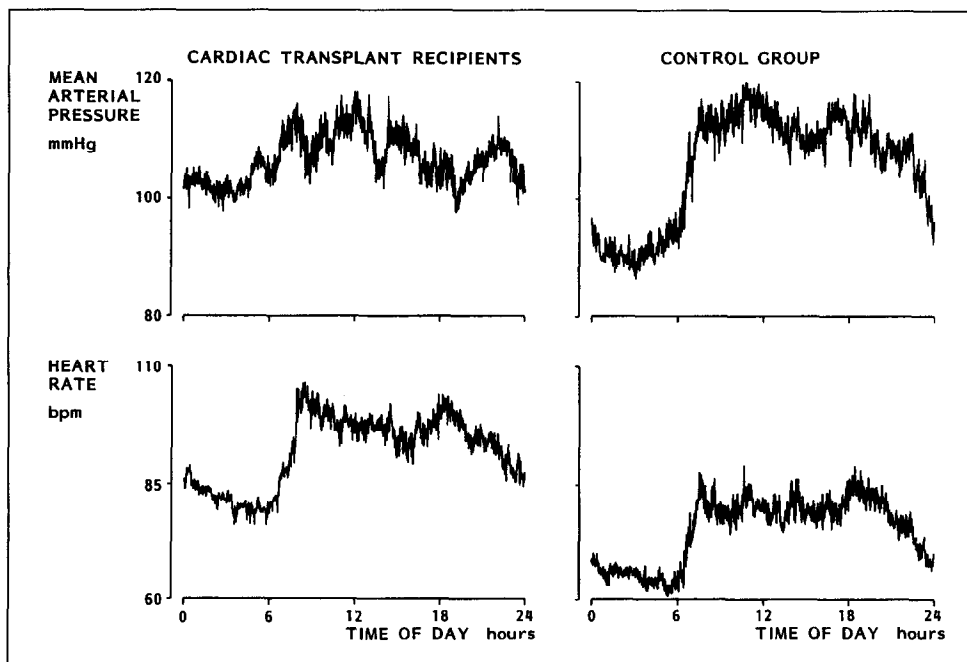
FIGURE 1. Profiles of invasive 24-hour ambulatory blood pressure recordings in 17 cardiac transplant recipients and 17 control subjects. Group means of 1-minute averages of mean arterial pressure and heart rate are depicted.

more during the day than in control subjects. In the transplant group, 3 short-lasting but prominent reductions in BP occurred at 8 A.M., noon and 6 P.M. (i.e., soon after meals). To quantify the effects of these decreases on daytime BP, and hence on the difference in BP between day and night, the beginning and end points of the decreases were identified visually, and an artificial BP profile without the decreases was constructed by interpolation. As a result of this procedure, average daytime BP increased by 2.2 mm Hg.

In regard to the BP data of individual subjects, only 1 cardiac transplant recipient had a nocturnal reduction in BP that was greater than the average nocturnal decrease in control subjects (Figure 2).

Heart rate was significantly higher in cardiac transplant recipients than in control subjects, but the day–night difference in the 2 groups was of similar magnitude (Table II).

The principal finding of this study is the persistence of an abnormally low diurnal variation of BP in most patients 1 to 3 years after cardiac transplantation. The findings confirm some previous studies using noninvasive ambulatory BP recording techniques,[1–3] but are at variance with those of van de Borne et al[5] and von Pölnitz et al.[6] Those investigators found a reappearance of the normal circadian variation of BP after long-term cardiac transplantation. They both speculated that a reduction in the dose of glucocorticoids after chronic cardiac transplantation could explain their observation. This explanation remains questionable because the average daily dose of glucocorticoids in the present study was similar to those used in the 2 aforementioned studies.

In regard to medical treatment, the present subjects differed from those studied by van de Borne et al[5] and

von Pölnitz et al,[6] in 2 important aspects. First, the average daily dose of cyclosporine of 7.1 mg/kg of body weight in the present subjects was much higher than that of 4.2 mg/kg of body weight in those of the other 2 studies. The subjects needed this higher dose of cyclosporine, because they did not use the immunosuppressant azothioprine. Cyclosporine is associated with an increase in BP. Although the mechanism responsible for this increase is not completely clear, cyclosporine has been reported to cause fluid retention[8] and an increase in sympathetic nerve activity.[9] If these effects of cyclosporine are dose-dependent, then the attenuation of the nocturnal BP reduction observed in the present study may be related to the relatively high dose of cyclosporine, although we were unable to show a relation between the daily dose of cyclosporine used in cardiac transplant recipients and the nocturnal reduction in BP. Second, the present subjects, in contrast to most of those in the aforementioned 2 studies, did not use antihypertensive medication. The antihypertensive medication used by subjects in the aforementioned 2 groups predominantly consisted of calcium antagonists, angiotensin-converting enzyme inhibitors and diuretics. There is no evidence that these agents have important influences on the 24-hour BP profile in normal hypertensive subjects, but their effect on diurnal BP variation in heart transplant recipients is unknown. However, no relation between antihypertensive drug therapy and absence of a nocturnal reduction in BP was found in cardiac transplant recipients studied by Reeves et al.[1]

Although the present cardiac transplant recipients did not use antihypertensive medication, this does not mean that their BP was not increased. Average daytime ambulatory BP in cardiac transplant recipients was 142/90 mm Hg. Using the same technique of BP recording as in the present study and in a comparable environmental setting, Pomidossi et al[10] reported an average daytime ambulatory BP in a group of normotensive and borderline hypertensive subjects of 120/64 mm Hg (i.e., a considerably lower value than in cardiac transplant recipients).

A phenomenon that to the best of our knowledge has not been reported in cardiac transplant recipients was 3 prominent decreases in BP during the day occurring soon after eating. Ingestion of food is associated with vasodilatation in the splanchnic circulation.[11] In healthy subjects, this vasodilatation is usually not accompanied by a reduction in BP, because of an increase in cardiac output and reflex-vasoconstriction in other vascular beds.[12,13] Presumably owing to the absence of cardiac sympathetic innervation, the increase in cardiac output in response to postprandial vasodilatation is insufficient after heart transplantation and explains why ingestion of food in this condition is associated with a reduction in BP. Although average daytime BP was lowered by the postprandial reductions in BP, this effect was insufficiently large to significantly influence the day–night difference in BP. We estimated that without the postprandial reductions, the day–night difference in mean BP would increase from 5.3 to 7.5 mm Hg, which is markedly lower than the average 20.5 mm Hg day–night difference observed in the control group.
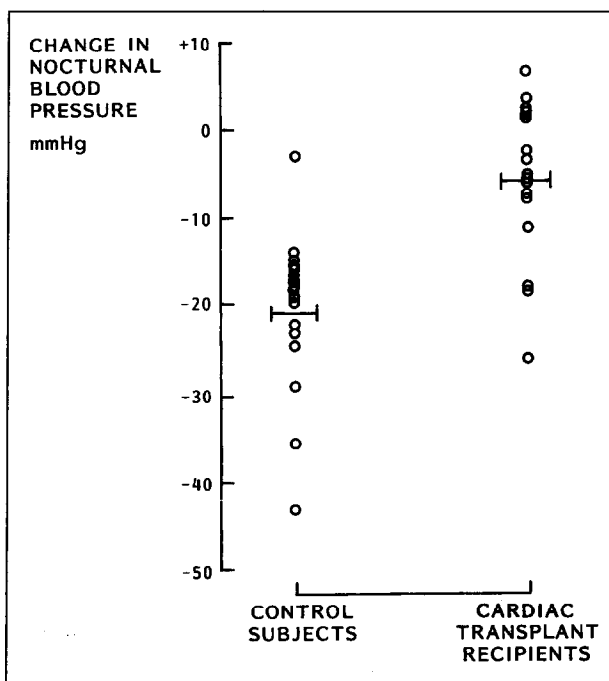
FIGURE 2. Individual changes in nocturnal mean arterial pressure compared with average daytime values in cardiac transplant recipients and control subjects.

Heart rate in cardiac transplant recipients is increased owing to the denervated state, particularly the absence of vagal tone. In the present study, heart rate in cardiac transplant recipients was almost 20 beats/min higher than in control subjects. This higher heart rate was observed during both the day and night periods; therefore, the absolute day–night difference of heart rate in cardiac transplant recipients was similar to that in control subjects. The higher heart rate after heart transplantation explains why, notwithstanding similar values of 24-hour mean BP, pulse pressure was significantly lower in cardiac transplant recipients than in control subjects.

Thus, attenuation of the normal circadian variation of BP may occur up to 3 years after heart transplantation. In addition, cardiac transplant recipients may have marked postprandial reductions in BP, which because of their relatively short duration have only a small effect on the day–night difference of BP.

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Frequency and Significance of Right Bundle Branch Block After Cardiac Transplantation

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Arrhythmias and conduction abnormalities are a frequent sequela of orthotopic cardiac transplantation, with many studies describing sinus node dysfunction,[1,2] atrial arrhythmias[3] and bradycardia.[4] The appearance of a new intraventricular conduction defect leading to new QRS morphology on the surface electrocardiogram after surgery is also a frequent occurrence. Recently, there were reports of the new appearance of right bundle branch block (RBBB) QRS morphology in up to 46% of patients.[5–7] The etiology of this finding and its clinical importance have not been determined. To investigate this issue, we reviewed the records of 85 consecutive patients who underwent cardiac transplantation and had been followed for ≥1 year.

Between June 1, 1988 and March 1, 1992, 85 patients underwent orthotopic cardiac transplantation for end-stage congestive cardiomyopathy. All patients had abnormalities on the electrocardiogram before transplantation. The 12-lead surface electrocardiograms of all 85 cardiac donors were reviewed, and none had evidence of any conduction abnormality before transplantation. All donors were evaluated by the surgical team

at the time of procurement and were thought to be hemodynamically suitable. Most donors were evaluated also with echocardiography, and no significant cardiac abnormality was defined.

Donor hearts were harvested with a technique using topical cooling and the infusion of cold hyperkalemic Stanford cardioplegia in the aortic root immediately after aortic cross-clamping. Grafts were then stored in a cold Plasmalyte solution and transported to the recipient facility. Each recipient underwent orthotopic cardiac transplantation using standard techniques. During the procedure, the durations of aortic clamping, cardiopulmonary bypass and total graft ischemia were recorded. The graft ischemic time was the total time from cross-clamping the aorta of the donor to unclamping that of the recipient after implantation.

All patients returned to the intensive care unit after surgery. A 12-lead surface electrocardiogram was obtained within the first postoperative hour and daily during the hospital stay. All patients received intravenous infusions of lidocaine (usually 2 mg/min) and isoproterenol (0.03 to 0.05 μg/kg/min) for the first 24 to 48 hours after surgery. Measurements of serum creatine kinase-MB fraction were obtained at 8-hour intervals for the first 48 hours after surgery using an immunoradiometric technique. Patients were observed during follow-up at regular intervals after transplantation. Twelve-lead electrocardiograms were obtained biweekly for the first