CIRCADIAN VARIATIONS OF BLOOD PRESSURE AND HEART RATE EARLY AND LATE AFTER HEART TRANSPLANTATION

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*Abbreviations: ACE, angiotensin-converting enzyme; HTx, heart transplantation.

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Abstract

Cardiac reinnervation late after heart transplantation has been reported in individual patients. As a measure for reinnervation, circadian changes in arterial blood pressure and heart rate have been used but not yet systemically evaluated in cardiac transplant recipients. Ambulatory blood pressure and heart rate monitoring was performed in 62 patients for 24 hr early (<6 months, mean 26 days, range 5-90 days, n=30) and late (≥6 months, mean 12 months, range 6-78 months, n=32) after heart transplantation. A loss of physiological nocturnal decline in blood pressure and heart rate was noted early after transplantation, whereas late after operation an improvement in circadian changes of blood pressure and heart rate was observed. The patients late after heart transplantation had a significant higher diastolic blood pressure. A pathological circadian blood pressure and heart rate pattern was observed in patients early after heart transplantation, which was improved late after operation. This could be explained by partial reinnervation of the heart. Diastolic hypertension late after transplantation may be due to cyclosporine treatment and/or neuroendocrine hyperactivity.

Heart transplant recipients under immunosuppressive therapy (e.g., cyclosporine, corticosteroids, azathioprine) develop systemic hypertension with a loss of the physiologic decline in blood pressure and heart rate at night (1-4). As a possible explantation for this abnormal response cardiac denervation and neurohumoral dysregulation have been discussed (5, 6). Heart transplantation is accompanied by a loss of afferent neural signal transmission from cardiac mechanoreceptors, leading to exaggerated neuroendocrine activity with an increase in plasma renin activity, atrial natriuretic peptide, norepinephrine, and vasopressine (7). The purpose of the present study was, therefore, to evaluate circadian variations in blood pressure and heart rate with regard to time after cardiac transplantation.

The measurements were performed with an oscillometric system (No. 90202, Spacelabs Inc., Redmond, WA). Blood pressure and heart rate were measured intermittently every 20 min during the day from 6 A.M. to 10 P.M. and every 60 min at night from 10 P.M. to 6 A.M. Median blood pressure and heart rate were calculated automatically for day and night, as

well as the difference in these parameters between day and night measurements.

A total of 62 patients (56 male, 6 female) with an average age of 45±6 years were included in the present analysis. These patients were divided into two groups depending on the interval after heart transplantation: group 1 consisted of 30 patients who were examined less than 6 months after HTx (early), and group 2 of 32 patients who were seen 6 months and more (late) after HTx. In the early group (26 males and 4 females, 45 years ±6) median follow-up was 26 days (range 5-90), and in the late group (24 males and 8 females, 43 years ±9) follow-up after heart transplantation was 12 months (range 6-78).

Concomittant medical therapy is summarized in Table 1. All patients received cyclosporine, which was adjusted according to the actual serum level. The total dose of cyclosporine was significantly higher in the late follow-up (group 2). This can be explained by the change in physical activity-95% of all patients received corticosteroids, which were lower during long-term follow-up, and 81% received azathioprine which was reduced late after HTx. Hypertension was treated individually accordingly to clinical practice. Approximately 50% of all subjects were on diuretics, but with increasing blood pressure during late follow-up ACE-inhibitors, calcium antagonists, and beta-blockers had to be administrated.

Patient characteristics are given in Table 1. Short-term and long-term patients had a similar age and gender distribution. The interval from operation to the study day was significantly different in the 2 groups according to the definition of the study.

Mean systolic blood pressure was similar in the two groups in the daytime. There was a tendency for nighttime systolic blood pressure to be slightly, although not significantly, lower in the patients late after transplantation. However, mean diastolic blood pressure in the daytime as well as heart rate during the whole day were significantly higher in the long-term than the short-term patients (Table 2).

Circadian changes in blood pressure and heart rate are summarized inTable 3. There were no circadian differences in blood pressure in patients early

after heart transplantation. Some patients showed a paradoxical increase in blood pressure and heart rate at night, resulting only in a small difference of 0.5 mmHg in systolic blood pressure between day and night and a small difference of 2 mmHg in diastolic pressure. The decrease in heart rate was also blunted (5 bpm).

Patients late after heart transplantation showed a return of circadian changes in systolic blood pressure and heart rate. There was also a trend toward a decrease in diastolic blood pressure at night but the differences did not reach statistical significance.

A loss of cardiac innervation, as in heart transplant recipients, has been associated with a loss of the normal nocturnal decline in blood pressure and heart rate as well as an acceleration of resting heart rate and an inadequate rise in heart rate during physical exercise(1-4).

Thus, the purpose of the present study was to evaluate the circadian changes of heart rate and blood pressure early and late after heart transplantation. There were three major findings in the present study:

Previous studies have shown a loss of the normal decline in blood pressure and heart rate at night in cardiac transplant recipients(1, 2). This phenomenon was attributed to the denervated state of the transplanted heart (6, 8). After cardiac transplantation, control of heart rate is dependent mainly on intrinsic stretch receptors and circulating catecholamines(2, 9). The reappearance of a circadian pattern in heart rate and blood pressure after transplantation suggests partial reinnervation of the transplanted heart(10-13). Wilson et al. determined that cardiac release of norepinephrine in response to tyramine(14). Tyramine causes degranulation of neuronal vesicles containing norepinephrine. These authors observed no release of norepinephrine. These authors observed no release of norepinephrine early after heart transplantation (within 5 months). However, late after heart transplantation (1 year and more) most patients revealed a significant tyramine-induced norepinephrine release, suggesting that limited reinnervation had occurred in these patients. In another study sensory reinnervation was suggested from the recurrence of angina pectoris in cardiac transplant recipients: two of these had typical angina pectoris and two did not(15). The two patients with pain were found to have substantial

release of norepinephrine after intravenous tyramine infusion, whereas the two others without chest pain had little or no norepinephrine release.

De-Marco and coworkers performed serial cardiac I-123 metaiodobenzylguanidine (MIBG) imaging in 23 cardiac transplant recipients early (<1 year) and late (>1 year) after operation(16). MIBG is taken up by myocardial sympathetic nerves and is proportional to myocardial sympathetic innervation of the heart. These authors observed no I-123 MIBG uptake early after transplantation. However, 11 of 23 subjects developed visible cardiac I-123 MIBG uptake 1 to 2 years after transplantation. These findings and our observation of the return of normal circadian variations of heart rate and blood pressure support the concept of partial reinnervation late (>6-12 months) after transplantation. Circadian variations in heart rate and blood pressure underline the ability of the heart to react to changes in circulating catecholamines, probably through the reappearance of catecholamine receptors, which have been documented by positron emission tomography (17-19).

In the late follow-up group the nocturnal decline of blood pressure and heart rate may also apply to the reduction of corticosteroids. In our study the steroid dose was significantly lower in group 2 than 1. Thus, the hormonal release from the pituitary respectively hypothalamus may be no longer inhibited and the circadian rhythm of cortisol release may reappear(20). Furthermore, neurohumoral factors like antidiuretic hormone and atrial natriuretic factor may be involved as well; it has been reported that these hormones may be increased in cardiac transplant recipients (7, 21, 22). It is possible that these hormones decrease over time with a normalization of neuroendocrine activity and a return of the circadian rhythm of neurohumoral release.

Most patients develop arterial hypertension after heart transplantation that increases over time (1, 22). In the present study, diastolic hypertension occurred in the late follow-up despite antihypertensive therapy. One of the reasons may be the administration of higher doses of cyclosporine in the late follow-up group. Cyclosporine is described as nephrotoxic and is associated with an increase in systemic vascular resistance (23, 24). Braith et al. suggested an ablation of cardiac mechanoreceptors, and consequently

an unopposed neuroendocrine stimulation (e.g., increased renin activity and vasopressin release) in heart transplant recipients (7). Since there is partial normalization of neuroendocrine hyperactivity, these factors cannot explain the occurrence of diastolic hypertension late after heart transplantation.

One limitation of the present study is that all measurements of blood pressure and heart rate were carried out under antihypertensive therapy. However, previous studies have shown that antihypertensive therapy does not influence the circadian pattern of blood pressure and heart rate variations(6).

The current study shows a reappearance of circadian blood pressure and heart rate in the long term after cardiac transplantation. This phenomenon can be explained by partial reinnervation of the transplanted heart. However, no data on reinnervation (positron emission tomography or histochemical examinations of the biopsies) are available, and thus no proof for this hypothesis can be given.

	Group 1 (n=30 [early follow-up])	group 2 (n=32 [late follow-up])
Age (years)	45±6	43±9
Gender (m)	4	8
(f)	26	24
Immunsuppressive medication (mg)		
Cyclosporine	194±60	292±102
Prednisolone	13±7	5±2
Azathioprine	82±28	36±21
Antihypertensive medication (count)		
Diuretics	18	16
ACE inhibitors	0	20
Calcium antagonists	0	9
Beta blockers	0	3

	Group 1 (n=30 [early follow-up])	group 2 (n=32 [late follow-up])
Daytime (6 A.M.–10 P.M.)		
SBP (mmHg)	131 (107 to 152)	129 (116 to 146)
DBP (mmHg)	79 (64 to 90)	84 (66 to 104)[b]
HR (bpm)	84 (53 to 107)	90 (72 to 117)[b]
Nighttime (10 P.M.–6 A.M.)		
SBP (mmHg)	132 (93 to 155)	122 (105 to 142)
DBP (mmHg)	78 (58 to 96)	78 (68 to 91)
HR (bpm)	71 (59 to 101)	82 (66 to 99)[b]

[a] Median values (range in parentheses).
[b] $P<0.05$ (group 1 versus group 2).

	Group 1 (n=30 [early follow-up])	group 2 (n=32 [late follow-up])
SBP (mmHg)	0.5 (−14 to +17)	−9.8 (−23 to +2)[b]
DBP (mmHg)	−0.2 (−10 to +11)	−7.8 (−19 to +2)
HR (bpm)	−5.6 (−13 to +6)	−10.0 (−20 to −2)[b]

[a] Median values (range in parentheses).
[b] $P<0.05$ (daytime versus nighttime).

Back to Top

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