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Clinical Investigations

Heart Rate Variability in Patients with Orthotopic Heart Transplantation: Long-Term Follow-Up

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Summary: To evaluate heart rate variability (expressed as the standard deviation of RR intervals) within 5 years of follow-up, we studied 20 patients (14 males, 6 females, mean age 44 ± 12 years) who underwent orthotopic heart transplantation. Six measurements were taken: one in the first 3 weeks after transplantation, and the others once annually, for 5 years. Twenty healthy subjects (mean age 44 ± 7 years) constituted the control group. Heart rate variability increased significantly in the first 3 years of follow-up (7.2 ± 1 vs. 11.1 ± 4, $p < 0.001$; 11.1 ± 4 vs. 15.2 ± 4, $p < 0.01$; 15.2 ± 4 vs. 18.9 ± 5, $p < 0.05$); in the following years this trend slackened and values did not reach a statistically significant difference (18.9 ± 5 vs. 21.4 ± 5; 21.4 ± 5 vs. 22.5 ± 5). The mean standard deviation was invariably greater in the control group (63.6 ± 12). These findings show that sinus rhythm variability in the denervated heart progressively increased over 5 years of follow-up. The absence of presynaptic uptake, which is responsible for adrenergic hypersensitivity to circulating catecholamines and intrinsic cardiac reflexes, does not appear to cause this phenomenon, since these mechanisms are not able to evolve in time after cardiac transplantation. Therefore, an enhanced beta-adrenergic receptors density or affinity to circulating catecholamines or a limited sympathetic reinnervation may be the more probable underlying mechanism.

Key words: Heart transplantation, autonomic nervous system, heart rate variability

Introduction

Recent studies have reported the development of a sinus node responsiveness related to different stimuli in cardiac transplant patients.[1–3] However, despite the evidence that transplanted hearts in animals reestablish efferent neural connections, there is no direct indication that anatomic reinnervation occurs in humans; functional reinnervation was suggested by means of different indirect methods in only two recent studies.[4, 5]

Moreover, to explain the increase in heart rate variability (HRV) over time, beta-receptor density or sensitivity was evaluated in these patients, but results to date are controversial.[6–8]

Different methods of HRV analysis were also employed to discern changes in the neurovegetative influences on the denervated heart,[9–12] and the most appropriate procedure for long-term assessment seems to be time domain analysis by means of Holter recording.

The purpose of this study was to characterize HRV importance and the evolution by measuring the standard deviation of the RR interval in 20 patients who underwent orthotopic heart transplantation over a 5-year follow-up.

Patients and Methods

Patients

We studied 20 patients (14 males, 6 females) who underwent orthotopic cardiac transplantation. At the time of surgery, their mean age was 45 ± 14 years (range 14–59). The preoperative disease was idiopathic dilated cardiomyopathy in 13 cases, ischemic heart disease in 3, valvular heart disease in 3, and restrictive cardiomyopathy in 1. The mean age of donors was 25 ± 10 years (range 13–48) (Table I). All patients received immunosuppressive therapy with cyclosporine A and azathioprine; no patient was receiving corticosteroids.

During follow-up, patients were always clinically stable and had normal cardiac function with no atrioventricular conduc-

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TABLE I Clinical data on transplant patients

Donor		Recipient		Underlying
Age	Sex	Age	Sex	pathology
48	M	56	M	DCM
14	M	21	F	RCM
27	F	59	F	DCM
25	M	55	M	DCM
13	F	14	F	DCM
18	M	56	M	VHD
18	M	39	M	DCM
29	F	43	M	IHD
18	M	32	M	DCM
41	M	38	M	VHD
16	M	56	M	DCM
30	F	33	M	DCM
16	F	46	M	IHD
22	M	43	F	DCM
35	M	55	M	DCM
21	M	45	M	DCM
31	F	36	M	DCM
25	M	52	M	IHD
19	F	48	F	VHD
36	M	56	F	DCM

Abbreviations: DCM = dilated cardiomyopathy, IHD = ischemic heart disease, RCM = restrictive cardiomyopathy, VHD = valvular heart disease, F = female, M = male.

tion disturbances. Endomyocardial biopsies showed mild rejection just once in only two cases; findings in the other patients were always classified as no rejection.

Our control group consisted of 20 healthy subjects, free of organic heart disease, with a mean age of 44 ± 7 years (range 35–47).

Methods

Six tape recordings of 24-h Holter monitoring were obtained from each patient by means of a two-channel recorder (ICR recorder). The first recording was taken within the first 3 weeks after transplantation and the others at 1-year intervals up to 5 years. A commercially available system for long-term electrocardiographic analysis (Del Mar Avionics 750) was used to obtain the sequence of the duration of the intervals between adjacent QRS complexes of normal supraventricular morphology. HRV was expressed in ms as the standard deviation (SD) of the 24-h RR intervals. Periods with atrial or ventricular premature beats, artifacts, and postprandial or physical exercise periods were excluded from the measurements. Moreover, to evaluate circadian variations in SD, two windows corresponding to daytime (from 9 A.M. to 1 P.M.) and nighttime (from 1 A.M. to 5 A.M.) were distinguished on each 24-h recording, and the SDs relative to these periods were then calculated.

TABLE II Standard deviation of RR intervals in transplant patients

Years	Day	Night	p	24-Hours	p
Patients (n = 20)					
0	7.2 ± 0.5	7 ± 0.6	NS	7.2 ± 1	—
1	10.6 ± 4	10.7 ± 3	NS	11.1 ± 4	<0.001
2	14.1 ± 4	14.7 ± 5	NS	15.2 ± 4	<0.01
3	18.5 ± 5	18.3 ± 7	NS	18.9 ± 5	<0.05
4	20.6 ± 6	21.1 ± 5	NS	21.4 ± 5	NS
5	22.1 ± 5	22.3 ± 5	NS	22.5 ± 5	NS
Control group (n = 20)				63.6 ± 12	—

Abbreviation: NS = not significant.

Statistical Analysis

Using the Student's *t*-test, mean SDs were compared during follow-up and between patients and controls. A p value < 0.05 was considered significant.

Results

Mean SDs for all patients at each follow-up are summarized in Table II.

Mean nighttime and daytime SD values for each period did not show significant differences in study groups. All patients had a lower SD value than the control group in the early period after transplantation (7.2 ± 1 vs. 63.6 ± 12 $p < 0.001$), with slight variations among the patients. In the subsequent 3 years, a progressive but slow increase in SD was evidenced in the patients; during the fourth and fifth years the increase in SD was lower, with a trend toward stabilization. In fact, the differences between mean SD in these last years were not significant compared with the previous year (Fig. 1).

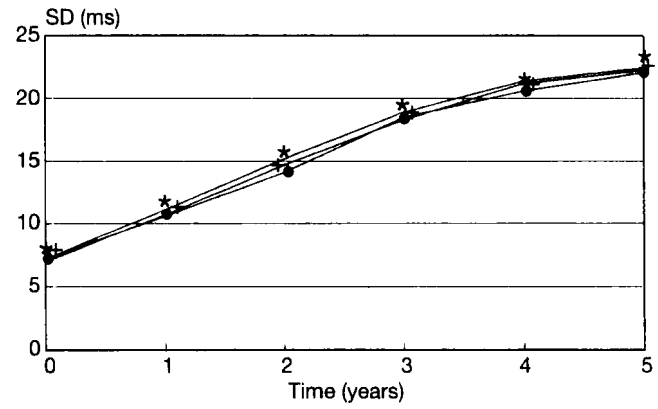

FIG. 1 Relation of time after transplantation and mean SD of RR intervals in all patients. • = SD day, + = SD night, * = SD 24-h.

Discussion

Different methods of analyzing heart rate variability provide an indirect evaluation of the influence of the autonomic nervous system in transplant patients. Power spectral analysis showed a random or broad band pattern, different from that of the normal subjects who presented well characterized oscillations at specific frequencies.[4, 9, 10] The SD of the RR intervals has been reported to provide an indirect estimate of the level of vagal cardiac efferent activity.[13] Smith *et al.*[11] applied this method (SD of 120 RR intervals) to assess baseline parasympathetic activity during supine rest periods in patients who underwent heart transplantation. However, modifications in methods of sampling and analysis performed in the presence of several clinical conditions, such as congestive heart failure, acute myocardial infarction, inducible complex ventricular arrhythmias, and in patients at high risk for sudden death, showed that the SD of the RR intervals is influenced by both the sympathetic and parasympathetic nervous systems.[14, 15–21]

Bearing these results in mind, we followed the SD of RR intervals in patients who underwent orthotopic heart transplantation to assess the evolution of this index in the first 5 years after transplantation. A comparison with the control group disclosed an invariably much higher SD value than in transplant patients. Moreover, our results showed a reduced heart rate variability early after transplantation, followed by a slow and statistically significant increase in SD in the first 3 years; a lower increase in this trend was evidenced over the fourth and fifth years. In addition, a comparison between the mean SD obtained during day and night show no circadian changes in this index in transplanted patients (Table II).

Several authors have studied transplant patients to characterize neurovegetative influences on the denervated heart.[1, 9, 10, 11] From these data it was demonstrated that the donor heart appears to remain denervated indefinitely.[22–25] Despite evidence of reinnervation in animals,[26–29] ultrastructural studies on human myocardial biopsy tissue confirmed these findings.[30] Only one case of functional reinnervation was described by use of power spectral analysis.[4] More recently, Wilson *et al.*[5] evaluated sympathetic reinnervation in human transplant patients by measuring cardiac release of norepinephrine in response to tyramine or sustained handgrip, and concluded that a limited sympathetic reinnervation occurs in most patients after orthotopic cardiac transplantation.

However, the transplanted heart seems to be nearly completely dependent on circulating catecholamines for homeostatic regulation of the sinus rhythm, particularly during the first years after surgery. Other influences seem to be due to intracardiac reflexes induced by local mechanoreceptor stimulation.[31–35]

It is well recognized that the transplanted heart with postganglion denervation shows an increased sensitivity to circulating catecholamines.[6, 36–39] This supersensitivity is due to the absence of neuronal uptake which removes epinephrine from the synaptic interstitial space. The mechanism involved in presynaptic supersensitivity was explained by studies that showed selective hypersensitivity to epinephrine but not to isoproterenol infusion in the transplanted heart.[31] On the other hand, observations consistent with an increase in beta-receptor density in the denervated heart have often been reported in animals, but were not always confirmed in humans.[8, 14, 36, 38–40]

Finally, an increase in beta-receptor affinity was also proposed to explain heart rate variability in the denervated heart.[7]

Heart rate changes secondary to orthostasis or exercise were recently demonstrated in transplant patients.[1] In fact, subjects studied for 3 or more years after transplantation showed a significant increase in heart rate during exercise, which was particularly rapid just within the first minute, and then a complete and rapid recovery after exercise. These rapid changes cannot account for circulating catecholamines, which increase within 2–5 min[41] and continue to increase after exercise.[42] To explain this behavior intracardiac reflexes have been proposed; this mechanism could also influence variations in SD.

The low SD values evidenced early after transplantation in our patients seem to be due both to absence of autonomic neurologic control and a nearly complete dependence on circulating catecholamines. The increase in SD observed in the first 3 years indicates that different mechanisms overlap, with a consequent enhanced responsiveness of the receptorial system.

In conclusion, a progressive increase in beta-adrenergic receptor density or affinity, as well as a limited sympathetic reinnervation associated with intracardiac reflexes, might be the main factors involved. A combination of these mechanisms, in a different way for each patient, would thus better explain the heart rate variability changes during the first 5 years after transplantation. To clarify these adaptative mechanisms better, long-term sequential ultrastructural studies will be necessary.

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