Sympathetic reinnervation after heart transplantation, assessed by iodine-123 metaiodobenzylguanidine imaging, and heart rate variability

Silvia Samarin Lovric a,*, Viktor Avbelj c, Roman Trobec c, Darko Zorman a, Peter Rakovec a, Sergej Hojker b, Borut Gersak d, Metka Milcinski b

a Department of Cardiology, University Medical Centre, Zaloska 7, Ljubljana, SI 1000, Slovenia
b Department of Nuclear Medicine, University Medical Centre, Ljubljana, Slovenia
c Department for Communication and Computer Networks, Jožef Stefan Institute, Ljubljana, Slovenia
d Department of Cardiovascular Surgery, University Medical Centre, Ljubljana, Slovenia

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Abstract

Objective: Complete allograft denervation occurs during heart transplantation. Partial ventricular sympathetic reinnervation may develop one year or later after transplantation and can be measured with iodine-123-meta-iodobenziylguanidine (MIBG) uptake. Aim of this study was to assess sinus node sympathetic reinnervation measured with heart rate variability and ventricular sympathetic reinnervation evaluated with MIBG. Methods: Twelve patients and 14 healthy controls were included. In patients, MIBG scintigraphy with early and late imaging was performed. Heart to mediastinum ratio (HMR) was calculated and patients were divided in groups with (HMR > 1.3) and without left ventricular reinnervation (HMR < 1.3). Bipolar ECG with high sampling rate and resolution was recorded over 8.5 min in supine position and in upright position after 10 min interval. R–R intervals in time domain and heart rate variability in frequency domain through spectral power analysis of R–R intervals were analysed to evaluate sinus node reinnervation. Spectral power in low frequency range (0.04–0.15 Hz) above 4.5 ms² was considered as sinus node sympathetic reinnervation. Results: Six (50%) patients had evidence of left ventricular sympathetic reinnervation on scintigraphy. Sinus node sympathetic reinnervation based on heart rate variability was detected in 6 (50%) patients in supine, and in 4 (33%) patients in upright body position. Four patients groups were discerned: (1) with ventricular and sinus node sympathetic reinnervation, (2) with sinus node sympathetic reinnervation, (3) with ventricular sympathetic reinnervation and (4) without atrial or ventricular sympathetic reinnervation. Ventricular reinnervation process was time dependent and sinus node reinnervation was not. Conclusions: Simultaneous ventricular sympathetic reinnervation assessed by MIBG and sinus node sympathetic reinnervation assessed by heart rate variability in supine as in upright position were detected only in two patients (17%). The results of our study show that eventual sinus node sympathetic reinnervation and left ventricular sympathetic reinnervation do not occur simultaneously.

Keywords: Heart transplantation; Sympathetic reinnervation; Heart rate variability; MIBG

1. Introduction

A cardiac allograft is completely denervated as a consequence of harvesting dissection. Previous studies demonstrated that sympathetic reinnervation can occur one or more years after transplantation (HTx). This process is very slow and time dependent and may still not be complete up to 15 years after transplantation [1]. Studies regarding sympathetic reinnervation extent and localization showed that the process is heterogeneously distributed [1–4].

Sympathetic nerve terminal growth was demonstrated first in anterior and septal parts of the left ventricle, than in the lateral parts, but inferior segments were frequently shown to have no substantial reinnervation [1].

The major clinical consequence of sinus node sympathetic reinnervation is partial restoration of normal heart rate at rest and chronothropic responsiveness to exercise [5]. Restoration of sympathetic reinnervation to the left ventricle can improve blood flow regulation, exercise performance and ventricular function [6,7]. It is also connected to chest
pain sensation resulting from allograft coronary obstructive disease [8].

Different methodologies have been used to investigate sympathetic reinnervation, either for sinus node or for ventricular reinnervation. Sinus node sympathetic reinnervation was most frequently shown by studies with tyramine (an agent that causes norepinephrine release from intact sympathetic nerve terminals) injection into the artery that perfuses the sinus node and with heart rate variability analysis (HRV) [5,9–13]. The most convincing biochemical and spatial evidences of ventricular sympathetic reinnervation are from studies with radiolabeled norepinephrine analogues, such as iodine-123-meta-iodobenzylguanidine scintigraphy (MIBG) and positron emission tomography (PET) with C-11 Hydroxyephedrine (HED), which are taken up by myocardial sympathetic nerves [1–4,13].

However, the relation between sinus node sympathetic reinnervation and left ventricular sympathetic reinnervation is not clear. The aim of this study was to estimate spatial differences of left ventricular sympathetic reinnervation after HTx and to evaluate if sinus node sympathetic reinnervation occurs simultaneous with left ventricular sympathetic reinnervation.

2. Methods

2.1. Patients

Twelve HTx patients, 12 months or more after orthotopic heart transplantation, were included in the study. Patient data are shown in Table 1. Inclusion criteria were: sinus rhythm and no evidence of transplant rejection or congestive heart failure. No patient received any medication known to interfere with catecholamine uptake in presynaptic nerve terminals. Beta blocking agents were withdrawn 24 h before the study.

For comparison, a control group of 14 healthy volunteers (3 w, 11 m; mean age 49.7±9.6 years, range 31–70 years) with presumably normal cardiac innervation was enrolled in this study. None of those subjects was receiving any medications or have history of cardiovascular disease.

The study was approved by Slovenian ethical committee. Written informed consent was obtained from all the subjects before the study.

2.2. Iodine-123 metaiodobenzylguanidine imaging (MIBG)

Stress-rest myocardial perfusion scintigraphy was performed prior to MIBG studies to evaluate possible allograft fibrosis as a result of transplant vasculopathy. A standard two day protocol was used as follows: pharmacological stress testing with 0.56 mg diprydiamole/kg/body weight administered intravenously was used and separate day rest imaging, both after 370 MBq of 99 m-Tc-MIBI injection. Tomographic gamma camera (General Electric, Mil lenium), equipped with all purpose low energy collimator, was used. Data analysis was performed with camera’s built in software. Gated post-stress study was acquired, 8 frames per cardiac cycle, 64 steps, 20 s each. Butterworth filter of 5th order and 0.4 cut of frequency were used for reconstruction.

Seven days after myocardial perfusion scintigraphy, MIBG imaging was performed. Thirty minutes after thyroid blockade with 500 mg of potassium perchlorate, 370 MBq/1.73 m2 MIBG was administered intravenously. Early (15–30 min) and late (4 h) planar images were taken in anterior and left anterior oblique (LAO) projection. Regions of interest (ROI) were used for semiquantitative evaluation of MIBG uptake in left ventricular myocardium (heart, H) and in the mediastinum (M). Heart to mediastium ratio (HMR), was calculated as index of MIBG uptake in the myocardium. In healthy subjects HMR is >1.8. In our study, an HMR >1.3 was selected for allograft left ventricular sympathetic reinnervation [3]. After HMR calculation, HTx patients were divided in two groups: patients with left ventricular sympathetic reinnervation and without left ventricular sympathetic reinnervation.

Examples of MIBG planar imaging in early and late phase of a patient with reinnervated heart (HMR 1.42, 66 months after HTx) and a patient with denervated heart (HMR 1.25, 52 months after HTx) are shown on Fig. 1A and 1B, respectively. MIBG and 99 m-Tc MIBI studies were not performed in control subjects.

2.3. ECG and heart rate variability (HRV)

The surface electrocardiogram, using bipolar lead CM5, was recorded with a high sampling rate (1800 Hz) and resolution (2 μV). An 8.5-min ECG recording was obtained first with a patient in the supine position. Ten minutes later, the second recording of the same length was obtained from the same patient in standing position. Immediately after ECG, MIBG scintigraphy was performed. Each patient was breathing autonomously. The recordings were analysed offline. After the low-pass filtering (40 Hz cutoff) and linear baseline correction, the time of each R-wave peak was identified by an automated computer-based peak detection algorithm. To improve the time resolution, quadratic
2.4. Statistical analysis

The results are given in mean value ± SD. The nonparametric Mann–Whitney test was used to compare the results between different groups and the Wilcoxon test was used for explorations within groups. Values with $P < 0.05$ were considered as statistically significant. Pearson correlation coefficient $r$ was used to measure the correlation between HMR and LF with the time after HTx.

3. Results

3.1. Left ventricular sympathetic reinnervation assessed by iodine-123 metaiodobenzylguanidine imaging (MIBG)

On myocardial perfusion scintigraphy, 2 of 12 patients had minor inferior wall myocardial perfusion defects; remaining 10 patients had normal myocardial perfusion.

Six (50%) of 12 HTx patients had evident myocardial MIBG uptake and HMR > 1.3. MIBG uptake was detected in anterior myocardial region in 4 patients, and in anterolateral myocardial region in 2 patients. Based on HMR threshold 1.3, HTx patients were divided in group with left ventricular reinnervation (HMR 1.47 ± 0.13, $n = 6$) and group without left ventricular reinnervation (HMR 1.17 ± 0.08, $n = 6$). Mean HMR of two groups was significantly different $P < 0.001$. Patients with left ventricular reinnervation have longer time interval after HTx than denervated patients. HMR has tendency to increase with time after HTx ($r = 0.531$). This is presented on Fig. 2.
3.2. Sinus node sympathetic reinnervation assessed by heart rate variability (HRV)

HRV parameters LF power, normalized LF power (nLF) and R–R interval were analysed within groups in upright and supine position. Results are given in Table 2. R–R intervals were significantly shorter in upright position for control and both groups of patients (LV reinnervated, LV denervated), nLF is different for control and LV denervated, while LF power was different only for LV denervated.

The same HRV parameters have also been analysed among all groups. R–R intervals were different between control and LV reinnervated group only in the supine position. nLF is different for all tree possible combinations of groups (control, LV reinnervated, LV denervated) only in upright position. Significant difference for LF power was detected between control-LV denervated ($P<0.005$ in both positions) and control-LV reinnervated ($P<0.005$ for supine position, $P<0.05$ for upright position).

Six (50%) of 12 HTx patients had LF power more than 4.5 ms$^2$ in supine position and 4 (33%) in upright position. Graphic presentation of sympathetic reinnervation assessed by MIBG and HRV is presented on Fig. 3.

3.3. Patient groups

From the results given, our study confirms existence of 4 groups of HTx patients: (1) group with ventricular and sinus node sympathetic reinnervation, (2) group with sinus node sympathetic reinnervation only, (3) group with ventricular sympathetic reinnervation only and (4) group without any sympathetic reinnervation. The results are schematically shown on Fig. 4.

Weak positive correlation between LF power and time after HTx was detected (supine position $r=0.276$; upright position $r=0.221$).

4. Discussion and conclusions

The major finding of this study is that sympathetic reinnervation of the sinus node after HTx does not predict left ventricular sympathetic reinnervation and might have a different occurrence in time pattern. Sympathetic reinnervation was evaluated with two independent methods; MIBG was used to evaluate left ventricular sympathetic reinnervation and HRV to assess reinnervation of sinus node.

The results of our study are in concordance with other studies that had shown, that ventricular sympathetic reinnervation begins from the base of the heart toward to the apex [13]. In our study, MIBG uptake was observed in the anterior and anterolateral regions. MIBG uptake was not present in the posterior or inferior myocardial region, as seen also in other studies [4]. Our study also confirms, that ventricular sympathetic reinnervation progressively increase over time, as shown also in other studies [3]. Complete ventricular sympathetic reinnervation was not observed. All patients with ventricular sympathetic reinnervation had only partial MIBG uptake up to 97 months after HTx.
These observations are in concordance with previous studies on the ventricular sympathetic reinnervation process [1–4].

Ventricular sympathetic reinnervation assessed by MIBG coincided with sinus node sympathetic reinnervation assessed by HRV only in two patients (17%), both in supine and in upright position.

Upright body position was used as simple manoeuvre to increase sympathetic tone and to test sinus node function after sympathetic load. In normal subjects physiological answer to upright position is increase in LF power and nLF power and decrease in R–R interval what was seen also in our control group (Table 2). Our finding that HTx patients do not respond to standing with similar changes in HRV parameters, may be explained with non-uniform groups of sympathetic reinnervation (Fig. 4) and other possible causes of sinus node dysfunction, known to appear after HTx. We also found, that sinus node sympathetic reinnervation occurrence and magnitude varies greatly between the patients, what also suggest intrinsic sinus node disease.

As example of unpredictability of these findings we describe two patients. In LV reinnervated group we had one patient with extremely high R–R interval variability, higher than the mean R–R interval in control group (HTx patient: R–R SD = 36 ms, HMR = 1.42; control group: R–R SD mean = 31 ms). In LV denervated group we had one patient with higher R–R variability as other patients in the same group (R–R SD = 21 ms, HMR = 1.2). All other HTx patients (except the two just mentioned) have essentially lower R–R intervals variability (R–R SD < 10 ms).

Limitations of our study: first, the small number of included patients. Unfortunately, from all transplanted patients in our small country, all that met the inclusion criteria were enrolled in our work. Furthermore, due to known time-related ventricular reinnervation process, patients up to one year after transplantation were not included. Due to small number of patients, statistical analysis was limited. Second major limitation is the diversity of factors, influencing both sinus node function in transplanted heart, so in early postoperative period as those occurring later. It is reported, that prolonged ischemic time, surgical trauma to the sinus node, perinodal atrial tissue, or sinoatrial artery, postoperative use of amiodarone, accelerated atherosclerosis and immunologic processes such as rejection [16–18], alone or in combination may contribute to sinus node dysfunction. All this factors, causing sinus node disfunction, could mask possible sinus node sympathetic reinnervation after HTx. Standard atrial anastomosis transplantation technique, performed in all but one patients in our study, is known to result in higher incidence of sinus node dysfunction then the bicaval anastomosis [19] and could be one of possible explanation for low number of sinus node reinnervated patients in our group. Our patient with with bicalval anastomosis has the highest HMR value (HMR = 1.63). Although, with present study we cannot clearly elucidate the reason for sinus node dysfunction in our patients, because its etiology is multifactorial and need further evaluation.

In conclusion, studies of sympathetic reinnervation after HTx based on investigation of sinus node function by HRV parameters, based on our results considered unreliable and possibly influenced by not well understood factors. Assessment of sympathetic ventricular reinnervation investigated by MIBG imaging seems to be more reliable. The results of our study show that eventual sinus node sympathetic reinnervation and left ventricular sympathetic reinnervation do not occur simultaneously. Regarding to previous studies on clinical consequences of allograft sympathetic reinnervation, our opinion is, that the optimal benefit of sympathetic reinnervation would be in patients with both, nodal and ventricular sympathetic reinnervation. Namely, higher stroke volume can be mediate also through forcefrequency relationship, where higher heart rate increased left ventricle contraction. Although the survival outcome is not connected with sympathetic reinnervation rate [20], higher exercise capacity in patients with sympathetic reinnervation would provide them better quality of life.

References


