Original article

Heart rate variability after heart transplantation: A 10-year longitudinal follow-up study

Véronique A. Cornelissen (PhD) a,∗, Johan Vanhaecke (MD, PhD) b, André E. Aubert (PhD) c, Robert H. Fagard (MD, PhD) d

a Research Centre for Cardiovascular and Respiratory Rehabilitation, Department of Rehabilitation Sciences, University of Leuven, K.U. Leuven, Leuven, Belgium
b Cardiology Unit, Department of Cardiovascular Diseases, University of Leuven, K.U. Leuven, Leuven, Belgium
c Laboratory of Experimental Cardiology, Department of Cardiovascular Diseases, University of Leuven, K.U. Leuven, Leuven, Belgium
d Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, University of Leuven, K.U. Leuven, Leuven, Belgium

Received 15 September 2011; received in revised form 5 December 2011; accepted 12 December 2011

KEYWORDS
Transplantation;
Heart rate variability;
Autonomic nervous system;
Re-innervation

Summary
Background: Cross-sectional studies suggest, by use of heart rate variability (HRV), that partial re-innervation of the sinus node may occur after heart transplantation (HTx). Our aim was to test this hypothesis by examining HRV in long-term longitudinal follow-up study of HTx recipients.
Methods and results: 14 HTx recipients (11 men) were studied 1–48 (median 13) months (baseline) and 119–172 (median 141) months after HTx (follow-up). At baseline and follow-up, electrocardiographic RR interval was continuously recorded in the supine position for 20 min. The signals were analyzed in the time domain and in the frequency domain by means of power spectral analysis. RR-interval decreased significantly from baseline to follow-up (p < 0.05). This was associated with an increase of total power (p < 0.001), absolute low frequency (p < 0.001), and high frequency power (p < 0.001), but unchanged relative low frequency and high frequency power.
Conclusions: The observed changes in HRV during long-term follow-up after HTx are compatible with partial re-innervation of the cardiac sinus node, as has been suggested by cross-sectional studies.
© 2012 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.
Introduction

Orthotopic heart transplantation (HTx) results in complete cardiac denervation, including the donor sinus node which usually controls the heart rate (HR) after transplantation [1]. Re-innervation of the heart may be clinically important resulting in improved exertional HR response, contractile function, increased peak oxygen uptake, and may permit angina pectoris to occur in the presence of myocardial ischemia [2–4]. Power spectral analysis (PSA) of HR variability (HRV) is a non-invasive method to assess autonomic cardiac modulation and provides information on sympathetic and parasympathetic modulation of the sinus node [5,6]. Compared to healthy controls, the HR of the cardiac graft is rigid and HRV is nearly absent soon after HTx [7]. Cross-sectional studies by our group [8–10] and several others [11–14] have in general shown an increase of HRV with time after transplantation, suggesting the occurrence of re-innervation. However, this observation should be confirmed by longitudinal longer-term follow-up of HTx patients, which would be more appropriate to investigate time-related phenomena. To the best of our knowledge, only Überfuhr et al. [15] performed serial investigations after HTx using HRV to investigate re-innervation. However, the longest observation time after HTx was 3.5 years, so no information about the development of re-innervation over longer periods is currently available.

Therefore, the objective of this study was to assess HR and the spectral components of its variability, as indices of autonomic nervous activity of the sinus node, at baseline shortly after HTx and at least 10 years after HTx in the same patients.

Materials and methods

Study population

HTx patients who were initially evaluated for our cross-sectional study [8] and were alive and willing to participate ≥10 years after HTx were included in this follow-up study. Further, patients had to be in good physical condition without signs of acute rejection, heart failure, or left ventricular dysfunction on echocardiography, at the time of measurements. All patients gave their written informed consent, which received approval by the Ethics Committee of the Faculty of Medicine of the University of Leuven.

Measurements

Protocol

All patients were investigated in the morning between 8 A.M. and 12 A.M. After 20 min of supine rest, data collection consisted of 20 min of continuous recording of the RR-interval (electrocardiogram monitor 78353A, Hewlett Packard, Philips Medical, Amsterdam, the Netherlands) whilst lying down on the examination table.

Data analysis

Off-line signal processing was performed to analyze the records. After RR peak detection and visual inspection by the investigator, a file containing the consecutive RR-intervals was exported. The tachogram of each recording was displayed on a computer screen and a stationary section from the tachogram, free of ectopic beats and artefacts and as close to the end of each recording as possible, was chosen for further analysis. Analyses were performed on segments of 512 consecutive beats, unless only shorter periods appeared suitable for analyses; a previous study showed that the results from power spectral analysis (PSA) were similar when periods of 512, 256, or 128 beats were used [16]. Premature supraventricular and ventricular beats, missed beats, and pauses were filtered and replaced by an interpolated value. Subsequent analysis was performed using methods published previously by Aubert and colleagues [17]. PSA of HRV was performed by Fast Fourier Transform algorithm. PSA allowed estimating the power in the low frequency (LF) and the high frequency (HF) range. The total power in the frequency range from 0.04 to 0.4 Hz was divided according to the guidelines of the European Society of Cardiology and the North American Society of Pacing Electrophysiology of 1996 into a LF (0.04–0.15 Hz) and a HF (0.15–0.4 Hz) band [6]. Signal powers of each band were calculated as integrals under the respective power spectral density functions. Next, we expressed the LF and HF powers also in normalized or relative units, that is the absolute power divided by the partial power (0.04–0.4 Hz). In addition the ratio between LF and HF power content was calculated. All software was developed in house by the Laboratory of Experimental Cardiology using Labview 6.1 (National Instruments, Austin, TX, USA) for Windows.

Statistical analysis

Statistical analyses were done using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were calculated on all study variables. Data are reported as (logarithmic) means ± standard deviation (SD) and their geometric means when appropriate. Parameters with skewed distribution were analyzed statistically only after logarithmic transformation. Paired Student’s t-tests were performed to investigate whether variables differed over time (baseline versus follow-up). Statistical tests were two-sided; a p-value of 0.05 or less was considered statistically significant.

Results

A total of 14 patients (11 men) with standard orthotopic HTx were studied at a median time of 13 months (range 1–48) after transplantation and then again at 141 months (range 119–172) after HTx. Time between the two measurements was 125 months (range 95–137). The underlying heart disease was ischemic cardiomyopathy in 7 patients and dilated cardiomyopathy in the other 7 patients. All were operated using the classical Shumway technique. Median age was 59 years (range 13–66) at baseline, and 70 years (range 23–76) at the time of follow-up measurements. Both at baseline and follow-up, all patients were on various immunosuppressive regimens which included cyclosporine, azathioprine, and/or tacrolimus. Beta-blocker therapy was part of the treatment in one patient at baseline and three patients at follow-up.
Heart rate variability after heart transplantation: A 10-year longitudinal follow-up study

Table 1  Heart rate variability parameters in the supine position at baseline and follow-up.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR (ms)</td>
<td>711.7 ± 103.0</td>
<td>655.8 ± 66.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total power, In ms² (geometric mean)</td>
<td>3.30 ± 0.58 (27.1)</td>
<td>4.94 ± 0.31 (139.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF-component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute power, In ms² (geometric mean)</td>
<td>1.20 ± 1.24 (3.32)</td>
<td>3.00 ± 0.72 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative power, %</td>
<td>16.5 ± 13.7</td>
<td>16.0 ± 7.66</td>
<td>NS</td>
</tr>
<tr>
<td>HF-component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute power, In ms² (geometric mean)</td>
<td>2.08 ± 0.68 (8.00)</td>
<td>3.72 ± 0.31 (41.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative power, %</td>
<td>32.3 ± 13.0</td>
<td>30.4 ± 8.14</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF ratio, ln (geometric mean)</td>
<td>−0.89 ± 1.13 (0.41)</td>
<td>−0.72 ± 0.65 (0.49)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD (geometric mean). LF, low frequency; HF, high frequency; NS, not significant.

Results of mean RR-interval and HRV parameters in supine position are given in Table 1. Mean RR-interval decreased significantly from baseline to follow-up. This was associated with an increase of total HRV in all patients (Fig. 1) and an increase in both LF and HF power, when expressed in absolute units. However, both LF and HF-power remained unchanged when expressed in normalized units, as did the LF/HF ratio. Exclusion of patients on beta-blocker therapy did not change the results (data not shown).

Discussion

The primary findings of our long-term longitudinal study, involving 14 HTx patients, confirm a significant increase in HRV after transplantation suggesting partial re-innervation of the sinus node. To the best of our knowledge, this is the first prospective study that investigates HRV parameters (absolute and relative units) in the same adult heart transplant recipients starting after a median of 13 months after HTx (range 1–48 months) and following these patients for at least 10 years (range 119 and 180 months) after HTx.

HRV is a widely used non-invasive technique to investigate cardiac autonomic modulation. It is suggested that the efferent vagal activity is the major contributor to the HF-component of HRV whereas the interpretation of the LF component is more controversial and complex and includes most likely both vagal and sympathetic influences [5]. As expected HRV of our patients was low at baseline when compared to normal data [18], confirming disruption of innervations [8,14]. At follow-up, we observed an increase of total HRV compared to baseline values. It is of note that the increase was observed in each individual patient without exception. Further, the increase in total HRV was associated with a parallel increase in LF and HF components when expressed in absolute units, but unchanged relative LF and HF. Whether this means that there is sympathetic and/or vagal re-innervation of the donor heart remains controversial, but the presence of increased frequency components in all our patients suggests at least partial functioning of the autonomic cardiac nervous system.

Our results are in line with previous cross-sectional studies that investigated the evolution of HRV in transplanted patients and reported similar time-related signs of re-innervation of the sinus node [8,9,11,12,14]. Überfuhr et al. [12] investigated the absolute LF-component of HRV as a measure of sympathetic activity in 38 patients, 4.6 years (range 0.2–13.6 years) after HTx. They showed that the average time of the measurement after HTx was 7.4 years in the innervated patients and 3.7 years in the not innervated patients, indicating that time was a significant factor in sympathetic re-innervation of the sinus node. Likewise, Beckers et al. [9] and Dalla Pozza et al. [14] reported a significant increase in absolute LF oscillations [9] and LF to HF ratio [14], respectively, starting slowly from 4 years after transplantation. Further, van de Borne et al. [11] compared the HRV spectrum of early (5 months) versus late (138 months) adult HTx patients and found increased absolute and relative LF-values in the late group. Moreover they showed that the reappearance of LF oscillations in RR were linked to those of muscle sympathetic nerve activity suggesting the restoration of a functional link between the sympathetic outflow of the recipient and the sinus node of the donor, which may support cardiac sympathetic re-innervation. Whereas, Bernardi et al. [19] found no LF component in HTx patients early after transplantation (6–18 months), later, they did detect an LF component in patients at least 20 months after transplantation [20]. Finally, in cross-sectional studies, time-related signs of sympathetic re-innervation have also been proposed for the myocardium by use of other techniques such as:


Fig. 1  Total power [ln(ms²)] at baseline and follow-up for each of the individual patients. Htx, heart transplantation.
as positron emission tomography (PET) and metaiodobenzylguanidine (MIBG) [12,21,22] and significant correlations have been revealed between sympathetic activity detected using MIBG scintigraphy [23] or PET [12] and the absolute LF component of HRV.

Although less conclusive, increasing evidence also suggests vagal re-innervation. Previously we assessed short term HRV in 62 patients divided in 4 groups according to time after HTx, i.e. 1 month, 1 year, 2 years, and 3–5 years after transplantation [8]. Intergroup comparison showed significantly higher values of LF and HF components in patients studied 3–5 years after surgery than in patients studied within one month. Moreover, a positive correlation was observed between time since HTx and LF and HF components [8]. Concordant with our results Halpert et al. [13] reported in 37 HTx patients that only those beyond 3 years of HTx exhibited a significant increase of sympathetic (LF) and parasympathetic (HF) activity. Further, in the only study which prospectively followed patients for 4 years after HTx, Überfuhr et al. [15] confirmed that LF power increases 4 years after transplantation, suggesting a possible sympathetic re-innervation of the heart. On the other hand they also observed an increase of the HF band and concluded that there is also increasing vagal influence 4 years post HTx. However, only absolute values were reported and the LF/HF ratio was not assessed, which hampers the interpretation of the findings. Finally, the degree of vagal modulation of the sinus node as measured with HRV (rmsSD and absolute HF) has also been shown to correlate well with the development of nerve fibers in the subendocardium of the interventricular septum constituting evidence of reinnervation in the cardiac graft [23].

It is important to note the limitations of our study. First of all, the small number of included patients may have limited the statistical power. On the other hand, the fact that the increase in HRV is a consistent pattern in all our patients between baseline and at least 10 years after HTx does strengthen the finding. Next, it should be noted that the study of HRV only allows conclusion of re-innervation of the sinus node. In this regard, today, debate continues on the physiological meaning of the LF and HF powers of HRV in normal subjects [24]. Moreover, Bernardi et al. [20] previously reported that the HF component may not be such a reliable marker of vagal re-innervation in HTx patients. However, the observed decrease in mean RR or increase in HR and the trend to a higher LF/HF ratio in our study may be indicative of a certain degree of sympathetic re-innervation. However, since formal assessment of autonomic re-innervation in either a clinical or investigational protocol was not performed, our findings are supportive rather than a direct proof of cardiac autonomic re-innervation. Future prospective studies in a larger population using different techniques to confirm re-innervation and its functional consequences are warranted.

Acknowledgments

V.A.C. is supported as a Postdoctoral Fellow by Research Foundation Flanders (F.W.O.). The authors have no conflicts of interest to declare.

References

Heart rate variability after heart transplantation: A 10-year longitudinal follow-up study


