Autonomic Neuroscience: Basic and Clinical 156 (2010) 124–130

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Cardiac autonomic function does not improve after liver transplantation for familial amyloidotic polyneuropathy

Urban Wiklund [a,b,*], Rolf Hörnsten [c], Bert-Ove Olofsson [d], Ole B. Suhr [d]

[a] Department of Biomedical Engineering & Informatics, University Hospital, SE-901 85 Umeå, Sweden
[b] Centre of Biomedical Engineering & Physics, Umeå University, Umeå, Sweden
[c] Clinical Physiology, Heart Centre, University Hospital, Umeå, and Department of Surgical and Perioperative Sciences, Clinical Physiology, Umeå University, Umeå, Sweden
[d] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

ARTICLE INFO

Article history:
Received 16 March 2010
Received in revised form 21 April 2010
Accepted 21 April 2010

Keywords:
HRV
Heart rate variability
Amyloid
FAP

ABSTRACT

Objective: Liver transplantation is the only potentially curative treatment for familial amyloidotic polyneuropathy (FAP). We investigated cardiac autonomic function in 63 transplanted Swedish FAP patients.
Methods: Heart rate variability (HRV) was recorded between 1–17 (mean 8) months before, and 10–40 (mean 20) months after transplantation. HRV was analysed by power spectrum analysis, but only in patients without arrhythmia ($n=38$).
Results: Patients with moderate cardiac autonomic dysfunction showed a statistically significant reduction in HRV after transplantation, as compared to the pre-transplant recording. Patients with severe cardiac autonomic dysfunction presented unchanged HRV after liver transplantation. Twenty patients were excluded because they presented cardiac arrhythmia, five of these presented increased HRV after transplantation but had developed subtle arrhythmias, thus, they had not improved cardiac autonomic control. Five patients were excluded because they were pacemaker-treated.
Conclusions: The reason why HRV decreased after transplantation remains unclear, but there are several possibilities: 1) liver transplantation did not stop the deterioration in cardiac autonomic function; 2) the deterioration continued until transplantation and was then halted; or 3) a sudden reduction in HRV occurred in connection with the transplantation procedure. Nonetheless, this study failed to disclose any improvement in cardiac autonomic function after liver transplantation for FAP.

1. Introduction

Familial amyloidotic polyneuropathy (FAP) is a hereditary amyloidosis, characterized by systemic depositions of amyloid fibrils resulting in multiple organ dysfunction (Andersson, 1976; Andrade, 1952). The salient feature of the disorder is a progressive sensorymotor and autonomic polyneuropathy (Ando et al., 1992; Benson, 1995; Olofsson et al., 1994). More than 100 amyloidogenic transthyretin (TTR) mutations are described (Connors et al., 2003), but the most common neuropathic mutation consists of an exchange of valine for methionine at position 30 (ATTR Val30Met) (Benson, 1995), a mutation found in endemic areas of Portugal, Japan, and Sweden. Liver transplantation interrupts the production of mutated amyloidogenic TTR, which is mainly produced in the liver, and is the only present treatment to stop the progression of FAP (Yamamoto et al., 2007). The first liver transplantation for TTR FAP was performed in Sweden in 1990 (Holmgren et al., 1993). Today, approximately 100 FAP patients are yearly transplanted worldwide (Familial Amyloidotic Polyneuropathy World Transplant Register, available at http://www.fapwtr.org).

Analyses of heart rate variability (HRV) have shown that Swedish FAP patients develop autonomic nervous dysfunction early after onset of the disease, progressing to a severe autonomic dysfunction (Olofsson et al., 1994; Suhr et al., 1997b). In addition to HRV impairment, cardiac arrhythmias and conduction disturbances are common in Swedish FAP patients both before and after transplantation (Beckman et al., 1992; Hörnsten et al., 2004, 2006). The outcome of cardiac autonomic function after liver transplantation is still not settled: does autonomic dysfunction progress or do patients improve their cardiac autonomic function after liver transplantation? Previous studies of HRV after liver transplantation have shown inconsistent results, but most studies were follow-ups based on a low number of patients or were performed relatively shortly after transplantation (Ando et al., 1995; Shimojima et al., 2008; Suhr et al., 2000; Suhr et al., 1997a).

If the cardiac autonomic neuropathy is presumed to be an indicator of systemic involvement in FAP, increased HRV after

Abbreviations: ATTR, Amyloidogenic transthyretin; ECG, Electrocardiogram; FAP, Familial amyloidotic polyneuropathy; HF, High frequency; HRV, Heart rate variability; LF, Low frequency; MET, Methionine; TTR, Transthyretin; VAL, Valine.

* Corresponding author. Department of Biomedical Engineering & Informatics, University Hospital, SE-901 85 Umeå, Sweden. Tel.:+46 90 7852718; fax: +46 90 12 76 30.
E-mail address: urban.wiklund@vll.se (U. Wiklund).

1566-0702/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.autneu.2010.04.007

transplantation could indicate systemic improvement. However, a recently identified confounder in HRV assessments is that many FAP patients have subtle arrhythmias that may be difficult to separate from normal respiratory sinus arrhythmia (Wiklund et al., 2008). These subtle arrhythmias reflect underlying abnormalities in cardiac control, and are noted as small random variations in heart rate as well as more regular but complex heart rate patterns (Abe et al., 1996; Ostlund et al., 2007). Thus, the occasional findings of seemingly increased HRV after liver transplantation might indicate a type of previously overlooked primary cardiac arrhythmia, which could be falsely interpreted as improved autonomic function (Hörnsten et al., 2008). This observation is taken under further consideration in the present study.

This study evaluates cardiac autonomic function in all available Swedish FAP patients where short-time HRV recordings (up to 30 min) have been performed both before and after liver transplantation — performed as a pre-transplant investigation and as a post-transplant (up to 30 months) follow-up recording.

2. Materials and methods

2.1. Liver transplanted patients

This study comprises a total of 63 liver transplanted FAP patients, 33 men and 30 women, who were evaluated at Umeå University Hospital, Sweden from 1991 to 2009. All patients carried the ATTR Val30Met trait, and the diagnosis of FAP was in all cases verified histopathologically by the findings of amyloid deposits in skin or intestinal biopsy specimens. The mean age at liver transplantation was 48 years (range 25–68 years), and the mean duration from diagnosis to transplantation was 4.0 years (range 0.8–12.0 years). Details of the transplantation procedure and associated complications have been reported previously (Suhr et al., 1995; Suhr et al., 1997b). After transplantation all patients were given immunosuppressive treatment with calcineurin inhibitors (CNIs): cyclosporine ($n=22$) or tacrolimus ($n=41$). This was combined with cortisol in a majority of the cases. Five patients were treated with beta-blockers after transplantation, but two of these were excluded from the HRV analysis (see below). No other patient was treated with any other medication that could have any significant effect on the results.

All HRV examinations were performed as part of the clinical evaluation before liver transplantation and during scheduled controls after liver transplantation. The mean waiting time between the pre-transplant recordings and transplantation was 8 months (range 1–17 months), and the mean time between transplantation and the post-transplant recordings was 20 months (range 10–40 months). The study was approved by the Ethics Committee of Umeå University.

2.2. Healthy controls

The patients were compared with previously recorded data from 90 controls, (45 men and 45 women, mean age 50 years, range 20–80 years). Controls older than 50 years were randomly selected from the population register, whereas controls below the age of 50 years were recruited from the hospital staff. None of the controls exhibited any cardiac arrhythmia or neurological disorders and were not treated with drugs known to affect HRV.

2.3. Non-transplanted patients

To study the natural course of the development of cardiac autonomic dysfunction in non-transplanted FAP patients, we also analysed data from two different recordings in 23 patients (11 men and 12 women, mean age 51 years, range 24–72 years), where the mean time between the first and second recording was 22 months (range 6–42 months). Twelve of these patients were not transplanted for various reasons, and eleven patients were repeatedly evaluated before they were transplanted.

2.4. Study protocol

This study is based entirely on short-time HRV recordings, where a single-channel ECG is recorded for up to 30 min while the subjects is placed on a manually operated tilt-table. The subjects were instructed not to smoke, drink coffee, tea, or eat any larger meal 2 h before the HRV recordings. After 10 min of supine rest, the blood pressure was measured with a sphygmomanometer, and a continuous recording was started using a single-channel ECG and respiration (using a thoracic belt or a nasal thermistor). The subjects remained in the supine position and performed free spontaneous breathing for 6 min, followed by two short sequences with controlled breathing (data not analysed). After passive tilting to 70° in the head-up position, the recording continued for 4 min with free breathing, after which the blood pressure was measured again.

2.5. Analysis of HRV

R–R interval data were transformed into an evenly sampled (2 Hz) heart rate time series by cubic spline interpolation. After the mean value had been removed, the power spectral density was estimated by auto-regressive modeling using the Burg algorithm, consequently using the Burg algorithm with 30 parameters (Marple, 1987). The mean heart rate, the total spectral power (P_{tot}, 0.003–0.50 Hz), and the power in the low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.50 Hz) regions were calculated. The power of the LF component (P_{LF}) has been related to baroreceptor mediated blood pressure control, reflecting both sympathetic and parasympathetic activity (Weise et al., 1987). The power of the HF component (P_{HF}) is normally related to the respiratory rate and was used as an estimate of parasympathetic activity (Anonymous, 1996). The ratio P_{LF}/P_{HF} was calculated as an indicator of sympathovagal balance. The recording and analysis software was developed at our laboratory using the Matlab program (MathWorks Inc, Natick, Ma.).

Power spectrum analysis was performed on heart rate data from 2-minute sequences in the supine and upright positions, but only if both sequences were free of arrhythmic beats and artifacts. Spurious extrasystolic beats were replaced by interpolation, but sequences with more than five extrasystolic beats were excluded from further HRV analysis. To verify that all subjects were in sinus rhythm, we compared the power spectrum for HRV with the power spectrum for respiration. This method enables detection of subtle arrhythmias in subjects who have a marked high-frequency component in HRV at frequencies other than respiration. To detect subtle atrial arrhythmias, we also inspected the morphology of p-waves in the ECG. Finally, we excluded all recordings where patients were on pacemaker-treatment.

2.6. Statistical analysis

Before statistical analysis, spectral indices were log-transformed (base 10) and age-corrected to age 50 years using the linear regression model for healthy controls. Non-parametric methods were used for all statistical analyses, using the SPSS software (SPSS Inc., Chicago, Il). A p-value less than .05 was considered statistically significant.

3. Results

HRV was analysed in the 38 liver transplanted patients that did not present any signs of arrhythmia in any of the four sequences (supine and upright, before and after) that were selected for power spectrum analysis. Twenty-five liver transplanted patients were excluded from