International Journal of Cardiology 155 (2012) 273–278

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Left ventricular dyssynchrony is associated with reduced heart rate variability in familial amyloidotic polyneuropathy

Ying Zhao [a,e], Rolf Hörnsten [a,c], Per Lindqvist [a,b,c], Urban Wiklund [d], Ole B. Suhr [b], Michael Y. Henein [a,b,*]

[a] Heart Centre, Umeå University Hospital, Sweden
[b] Department of Public Health and Clinical Medicine, Umeå University, Sweden
[c] Department of Surgical and Perioperative Science, Umeå University, Sweden
[d] Biomedical Engineering, Umeå University Hospital, Sweden
[e] Ultrasound Department, Beijing AnZhen Hospital, Capital Medical University, Beijing, China

ARTICLE INFO

Article history:
Received 23 July 2010
Received in revised form 8 September 2010
Accepted 10 October 2010
Available online 5 November 2010

Keywords:
Familial amyloidotic polyneuropathy
Heart rate variability
Left ventricular dyssynchrony

ABSTRACT

Background: Cardiac complications are common in familial amyloidotic polyneuropathy (FAP), in which heart rate variability (HRV) is reduced. Although autonomic disturbances are well-established, mechanisms for reduced HRV, their relationship with left ventricular (LV) function in FAP are not well understood.
Methods: Twenty-nine FAP patients and 29 healthy controls were studied using Doppler echocardiography. Patients' and controls' HRV were studied using power spectral analysis from 24-hour Holter-ECG recordings.
Results: In FAP patients, all HRV parameters were lower ($p<0.01$ for all) than those in controls. Echocardiography showed a normal LV systolic function in patients. Relative filling time (FT/RR) was shorter ($p<0.01$) and total isovolumic time (t-IVT) was longer ($p<0.01$) in patients than in controls. E/Em was higher ($p<0.01$), as was Tei index ($p=0.02$) as compared to controls. T-IVT and Tei index correlated with stroke volume (SV) ($r=-0.54$, $p<0.01$ and $r=-0.44$, $p<0.05$, respectively) in patients.
HRV was reduced in 9/29 (31%) patients, who had shorter FT/RR ($p<0.01$), longer t-IVT ($p<0.01$), higher Tei index ($p=0.05$), A wave ($p<0.01$) and E/Em ($p<0.05$) than in subjects without reduced HRV. FT/RR and t-IVT correlated with HRV spectral parameters ($p<0.05$ for all). The correlation between t-IVT and SV was stronger in patients with reduced HRV ($r=-0.80$, $p<0.01$) than in those without. QRS duration was not different in the two subgroups of patients.
Conclusions: In a subset of patients with FAP, HRV was significantly reduced and appeared to be associated with shortened LV filling time and prolonged t-IVT, which reflect ventricular dyssynchrony, despite normal QRS. Thus, in addition to autonomic disturbances in FAP, ventricular dyssynchrony is another factor associated with reduced HRV. Correction of such disturbed ventricular function by cardiac resynchronization therapy may control patients' symptom.

© 2010 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Familial amyloidotic polyneuropathy (FAP) is a rare hereditary disorder which is caused by mutated transthyretin (TTR) [1]. Among the over 100 documented amyloid TTR mutations [2], the most common mutation is the exchange of valine for methionine at position 30 (ATTR Val30Met), which is often found in endemic areas in Portugal, Japan, and Sweden. The typical symptom of FAP is peripheral sensori-motor polyneuropathy, often accompanied by autonomic neuropathy that causes a defective autoregulation of blood pressure and heart rate [3].

Cardiac complications, e.g. arrhythmia, are described in FAP patients who develop increased left ventricular (LV) wall thickness, diastolic dysfunction and enlarged atria [4,5]. FAP patients develop autonomic system dysfunction during the disease process which is progressive in nature. This can easily be assessed by heart rate variability (HRV) studies [4–6]. Although autonomic disturbances are a well-established mechanism for reduced HRV [7], we hypothesize that cardiac function disturbances by themselves may have an additional impact on HRV — in a way similar to what was previously found in dilated cardiomyopathy [8,9]. The aim of this study was, therefore, to assess the relationship between LV function and HRV in a cohort of Swedish patients with FAP.

2. Methods

2.1. Study population

Thirty-five consecutive FAP patients were evaluated at Umeå University Hospital, Sweden. Twenty-four hour Holter-ECG recordings and Doppler echocardiographic studies were performed within 3 days of each other. Six patients were excluded because of poor quality of the ECG recordings. Of the studied FAP cohort, 29 patients

* Corresponding author. Department of Public Health and Clinical Medicine, Umeå University, Sweden. Tel.: +46 90 7850000; fax: +46 90 137633.
E-mail address: michael.henein@medicin.umu.se (M.Y. Henein).

0167-5273/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2010.10.015

(mean age 60.3 ± 12.5 years, 12 females) constituted the study population, five of whom had prior liver transplantation. All patients proved to be carriers of the ATTR Val30Met trait and the diagnosis of FAP was histopathologically confirmed in all, based on biopsy evidence for amyloid deposits in the skin or intestine. One patient was on β-blockers for hypertension. All patients were managed according to the Declaration of Helsinki. All examinations were performed as part of their clinical evaluation before and after liver transplantation, as well as for diagnosis and identification of complications of the disease. The control group consisted of twenty-nine sex and age-matched healthy subjects (age 55.2 ± 11.2 years, 13 females) selected from the Swedish population registry, none of whom had any cardiac or systemic disease. All patients and controls gave informed consent to participate in the study, which was approved by the Local Ethics Committee of Umeå University. Patients were followed up for 1.1–7.1 years, average 4.5 ± 2.2 years. At the end of the follow-up period, cardiac events were documented including cardiac death, hospital admission with uncontrolled heart failure symptoms or pacemaker implantation.

2.2. Echocardiography

Echocardigraphy was performed using a Vivid 7 digital ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a phased array transducer (1.5–4 MHz), and standard Doppler echocardiography was obtained as well as myocardial tissue pulsed Doppler imaging (TDI). The echocardiographic examination was performed with the subject in the left lateral decubitus position and recordings were made during quiet expiration. Parasternal and apical projections were studied according to the recommendations of the American Society of Echocardiography [10]. All recordings were made with a simultaneously superimposed electrocardiogram (ECG) [11] and at a sweep speed of 100 mm/s.

2.2.1. Echocardiographic measurements

The following M-mode echocardiographic measurements were made: LV internal diameter (LVd), septal (IVS) thickness, and posterior wall (PW) thickness, all measured at end-diastole (onset of the Q wave of the ECG), using leading edge methodology. End-systolic dimension (LVs) was also measured as the shortest distance between the septal and the posterior wall endocardial border, and LV fractional shortening (LVFS) was calculated as the percentage fall in cavity dimension during systole with respect to that at end-diastole [12]. LV long-axis M-mode recordings were obtained with the cursor placed at the lateral and septal angles of the mitral annulus from the apical four-chamber view. LV long-axis amplitude of motion was measured as the distance between the innermost point and the outermost point of the motion display. Left atrial dimension (LAd) was measured at end-systole. The stroke volume (SV) was calculated from the LV outflow tract cross sectional area (LV outflow tract radius$^2 \times \pi$) multiplied by blood flow velocity time integral (VTI).

Conventional diastolic LV function was assessed from the filling pattern. Peak LV early (E) and late (A) filling velocities were measured from the pulsed wave Doppler recordings of the transmitral forward flow and E/A ratio was calculated [13]. E wave deceleration time (DT) was measured from the time of peak velocity to the point when the left atrial and left ventricular pressures equalised. LV filling time (FT) was measured as the time interval between the onset of the E wave and the end of A wave. LV ejection time was taken from the onset to the end of aortic flow velocity signal. Relative ejection and filling times with respect to R–R interval were calculated and expressed as (%). In addition, they were both multiplied (in seconds) by heart rate and then expressed as total ejection and filling times (s/min). From these measurements global dyssynchronous LV function was assessed using the following parameters: a) total isovolumic time (t-IVT), calculated as 60 − [total ejection time + total filling time] and was expressed in s/min [14]; and b) Tei index, calculated as the ratio between t-IVT and ejection time [15,16]. Finally, E/Em (a marker of LV filling pressure) was also measured, where Em was the peak early diastolic myocardial velocity at the basal septal segment obtained from the apical 4 chamber view [17].

2.3. HRV recordings

2.3.1. Ambulatory 24-hour HRV recording

A continuous ECG was recorded during a 24-hour period using a two-channel ambulatory Holter recorder (Braemar DL 700, Braemar Inc., Burnsville, MN). The ECG data were digitized with a sampling rate of 128 Hz and analyzed using the Aspect Holter System (GE Healthcare, Borlänge, Sweden). Pathological events were automatically detected, which were then manually edited and confirmed. Conventional methods of Holter analysis were performed to determine the underlying rhythm, presence and frequency of atrial and ventricular extra beats, couplets, episodes of tachycardia, atrio-ventricular block, left or right bundle-branch block, sino-atrial block or arrest. Supra-ventricular tachycardia (SVT) was defined as a series of more than five consecutive supra-ventricular beats at a heart rate more than 100 beats/min. Ventricular arrhythmia was defined as more than two consecutive ventricular beats at a heart rate less than 100 beats/min and/or more than 10 ventricular beats/h. Ventricular tachycardia was defined as three or more ventricular successive beats with a rate more than 100 beats/min [18].

2.3.2. Power spectral analysis of HRV

R–R intervals and the classification of heart beats were exported from the Holter software for further analyses using Matlab (Mathworks Inc., Natick, Mass., USA) as previously described [19]. Before HRV was analyzed, undetected ectopic beats were removed by additional filtering, where R–R intervals were removed if they differed more than 30% from the mean of the preceding and following R–R intervals. Power spectrum analysis was performed using fast Fourier transformation (FFT) of N–N interval data. Data from the 24-hour recording were divided in 300-second segments, and averaged spectra were calculated using the Welch method [19]. Each data segment was preprocessed by removal of the mean value and eventual linear trends in the series of R–R intervals. Data were then converted to a time series by cubic spline interpolation, followed by re-sampling at 2 Hz. Finally, data were smoothed using a Bartlett-window before calculating the 2048-point FFT. Ectopic beats and episodes with poor signal quality were replaced by interpolation, but segments with more than 4% interpolated data were discarded. The percentage of segments used for frequency domain HRV analysis was used as an indicator of the quality of the recording and the presence of arrhythmia. All recordings with less than 70% used time were discarded. The averaged R–R interval value was calculated from N–N intervals (mean NN). The following HRV indices were calculated as averages over the 24-hour recording: total power in the frequency region 0.003–0.50 Hz (PTOT), power of the very low-frequency (VLF; 0.003–0.04 Hz); low-frequency (LF; >0.04–0.15 Hz) and high-frequency (HF; >0.15–0.50 Hz) components. Total power and the power of each spectral component were log transformed (base 10) because of skewed distributions.

2.4. 12 lead electrocardiogram (ECG)

Standard 12 lead resting ECG was recorded and analyzed using the GE Mac 5000 instrument (General Electric, Milwaukee, USA). The QRS duration, PR interval and QRS + PR interval were measured using the built-in software.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 13.0 (SPSS, Chicago, IL, USA). All data were presented as mean ± SD. Unpaired Student's *t*-test was used to compare values between groups. Pearson's correlation and linear regression analysis were performed to display the relations between HRV and echocardiographic parameters. For subgroup comparisons non-parametric Mann–Whitney U test was used because of the small number of patients. A p value less than 0.05 was considered statistically significant.

3. Results

Patients had a higher heart rate (HR) as compared to controls (76.1 ± 12.5 vs. 64.3 ± 7.6 beats/min, $p<0.05$).

3.1. LV structure and function (Table 1)

In FAP patients, IVS and PW were thicker ($p<0.01$ for both). LV systolic function, assessed by LVFS, was maintained despite the smaller LV end-diastolic dimension ($p=0.01$). LV septal and lateral long-axis amplitude of motion were not different from controls, neither was LAd. SV was maintained in patients (Table 1).

LV E and waves were higher ($p<0.01$ for both) and E/A ratio was lower ($p=0.02$) in patients than in controls. Patients had lower Em ($p<0.01$), resulting in rasied E/Em ($p<0.01$). LV dyssynchronous function was quite different in patients, with t-IVT ($p<0.01$) significantly longer and Tei index raised ($p=0.02$) as compared to controls. These findings were caused by the shortened relative FT in patients ($p<0.01$). T-IVT and Tei index correlated modestly with SV in patients ($r=-0.54$, $p<0.01$; $r=-0.44$, $p<0.05$, respectively), but not in controls.

3.2. ECG and HRV vs. LV function

All patients and controls were in sinus rhythm. Fourteen (48%) patients had abnormal findings in the Holter-ECG recordings, commonly shown as various combinations of recurrent supra and ventricular ectopic beats (n = 8), but only one patient had recurrent non-sustained ventricular tachycardia. Patients also had various degrees of electrical blocks varying between first and second degree AV-block, sino-atrial block and bundle-branch block (n = 2). Only one patient had non-conducted supra-ventricular beats for a maximum of 2.4 s.

Patients' HRV parameters (PTOT, PVLF, PLF, and PHF) were all lower than in controls ($p<0.01$ for all). Spectral analysis showed reduced total HRV (PTOT<300 ms^2) in 9/29 (31%) patients. Both FT/RR and t-IVT modestly correlated with HRV spectral parameters in patients ($p<0.05$

Table 1
Echocardiographic and heart rate variability (HRV) data in patients with familial amyloidotic polyneuropathy (FAP) and controls.

	Controls (n = 29)	FAP (n = 29)	*p* value
Echocardiography			
M-mode			
LAd (mm)	35.8 ± 4.9	36.3 ± 8.0	0.75
LVd (mm)	50.0 ± 4.4	46.9 ± 4.8	0.01
LVs (mm)	30.9 ± 3.4	30.0 ± 4.6	0.39
LVFS (%)	38.2 ± 4.1	36.2 ± 5.7	0.14
IVS thickness (mm)	10.2 ± 1.6	11.9 ± 3.6	0.02
PW thickness (mm)	8.6 ± 1.4	9.9 ± 2.2	0.01
LxS(cm)	11.7 ± 2.6	11.0 ± 2.2	0.24
LxL(cm)	13.4 ± 3.0	12.4 ± 2.6	0.19
Doppler			
SV (ml)	73.2 ± 14.1	79.0 ± 24.2	0.10
E (cm/s)	58.0 ± 14.0	70.6 ± 13.8	0.002
A (cm/s)	51.7 ± 11.5	68.8 ± 20.5	0.001
E/A	1.17 ± 0.38	0.96 ± 0.29	0.02
Em (cm/s)	10.5 ± 3.3	7.2 ± 2.8	0.001
E/Em	6.1 ± 2.6	11.7 ± 6.5	0.001
DT(ms)	188 ± 50	218 ± 76	0.09
FT/RR(%)	52.2 ± 6.3	46.1 ± 7.6	0.002
t-IVT(s/min)	8.69 ± 3.23	11.22 ± 3.88	0.009
Tei index	0.44 ± 0.18	0.56 ± 0.20	0.02
Heart rate variability			
PTOT (ms^2, log)	3.43 ± 0.24	2.84 ± 0.55	0.001
PVLF (ms^2, log)	3.22 ± 0.21	2.59 ± 0.57	0.001
PLF (ms^2, log)	2.86 ± 0.35	2.08 ± 0.72	0.001
PHF (ms^2, log)	2.32 ± 0.31	1.95 ± 0.51	0.002

All values are presented as mean ± SD.
LAd: left atrial dimension; LVd: left ventricular end-diastolic dimension; LVs: left ventricular end-systolic dimension; LVFS: left ventricular fractional shorting; IVS: interventricular septum; PW: posterior wall; LxS: long-axis amplitude (septal); LxL: long-axis amplitude (lateral); SV: stroke volume; E: early diastolic velocity; A: late diastolic velocity; E/A: diastolic early and late velocity ratio; Em: early diastolic myocardial velocity; DT: deceleration time; FT/RR: relative filling time (to RR interval); t-IVT: total isovolumic time. PTOT: total power; PVLF: power of the very low-frequency component; PLF: power of the low-frequency component; PHF: power of the high-frequency component.

for all), whereas controls only presented a significant correlation between FT/RR and PVLF (Table 2). There was no relationship between HRV indices and the rest of the systolic and diastolic LV function measurements in the two groups.

3.3. Reduced HRV and LV function

The relationship between HRV and LV function was further studied by dividing the patients in two subgroups: a) patients with reduced HRV, defined as PTOT<300 ms^2 (n = 9); and b) patients with relatively preserved HRV, defined as PTOT>300 ms^2 (n = 20) (Fig. 1). This limit was selected because it is difficult to distinguish any low- and high-frequency peaks in the power spectrum when total HRV becomes lower than 300 ms^2. As shown in Table 3, LV size and systolic function were not different between the two subgroups, but the long-axis amplitude of motion was significantly lower in patients with reduced HRV (septal: $p<0.01$ and lateral: $p<0.05$, respectively), as compared to those without reduced HRV. Patients with reduced HRV also had shorter FT/RR ($p<0.01$), longer t-IVT ($p<0.01$), higher Tei index ($p=0.05$), higher A wave ($p<0.01$) and higher E/Em ($p<0.05$), as compared to patients without reduced HRV. E/A was not different between groups (p = ns). T-IVT correlated with SV in the two subgroups ($r=-0.80$, $p<0.01$ and $r=-0.41$, $p<0.05$), but to a much stronger extent in those with reduced HRV(Fig. 2).

Table 2
The correlation between heart rate variability (HRV) and echocardiographic parameters in patients with familial amyloidotic polyneuropathy (FAP) and controls.

	PTOT	PVLF	PLF	PHF
FAP (n = 29)				
FT/RR, r(*p*)	0.53(0.003)	0.44(0.02)	0.48(0.009)	0.54(0.003)
t-IVT, r(*p*)	−0.45(0.02)	−0.41(0.03)	−0.41(0.03)	−0.38(0.04)
Controls (n = 29)				
FT/RR, r(*p*)	0.31(0.11)	0.46(0.01)	0.18(0.35)	0.13(0.49)
t-IVT, r(*p*)	−0.22(0.26)	−0.32(0.09)	−0.14(0.49)	−0.11(0.58)

FT/RR: relative filling time (to RR interval); t-IVT: total isovolumic time; PTOT: total power; PVLF: power of the very low-frequency component; PLF: power of the low-frequency component; PHF: power of the high-frequency component.

3.4. Clinical outcome

During the follow-up period (4.5 ± 2.2 years), 8 of 29 patients had cardiac events: two patients died; three developed significantly thickened LV and RV walls (two of them required pacemakers); two patients received pacemaker treatment because of cardiac conduction disturbances; and the remaining patient developed heart failure. Four of these 8 patients were in the subgroup with reduced HRV (2 died and 2 received pacemakers). The incidence of cardiac events was significantly different in the two subgroups ($p<0.05$).

3.5. 12 lead ECG in the two subgroups of patients

There was no difference between reduced HRV and preserved HRV subgroup in QRS (97 ± 17 ms vs. 88 ± 15 ms), PR interval (186 ± 38 ms vs. 192 ± 21 ms) and QRS + PR interval (283 ± 48 ms vs. 280 ± 39 ms) (p = ns for all).

4. Discussion

4.1. Findings

Familial amyloidotic polyneuropathy is a multi-system disease which involves many organs with the heart commonly affected. In the present study, conventional LV structure measurements showed normal cavity size and systolic function in patients, including long-axis function and SV, whereas wall thickness was significantly increased. However, markers of LV dyssynchronous function clearly differentiated patients from controls, showing prolonged t-IVT and raised Tei index as well as high E/Em, the latter was consistent with high left atrial pressure. Only t-IVT correlated with HRV measurements, because of the significantly shortened relative LV filling time. Almost one third of our studied patients had reduced HRV. Although LV size and FS were preserved in this subgroup, long-axis amplitude of motion was significantly reduced, t-IVT was longer, and Tei index and E/Em were both higher than in those with preserved HRV. QRS and PR interval were not different in the two subgroups of patients. Moreover, in patients with reduced HRV,
t-IVT correlated with the SV to a much stronger degree, as compared to patients with preserved HRV. Finally, the incidence of cardiac events occurring in our patients was significantly higher in FAP with reduced HRV as compared to those without.

4.2. Data interpretation

The most prominent finding in this study was the significant LV dyssynchronous function which correlated with markers of HRV, particularly in the subgroup of patients with reduced HRV. Also the same disturbances were the only ones profoundly found among patients who developed cardiac events as compared to those who did not. It is well documented that cardiac involvement in FAP is a recognized complication, with phenotypic picture of thickened walls and mainly reduced diastolic function [20]. This study is the first to demonstrate clear evidence for significant LV dyssynchrony in such patients, even in the absence of overt systolic dysfunction or electrical

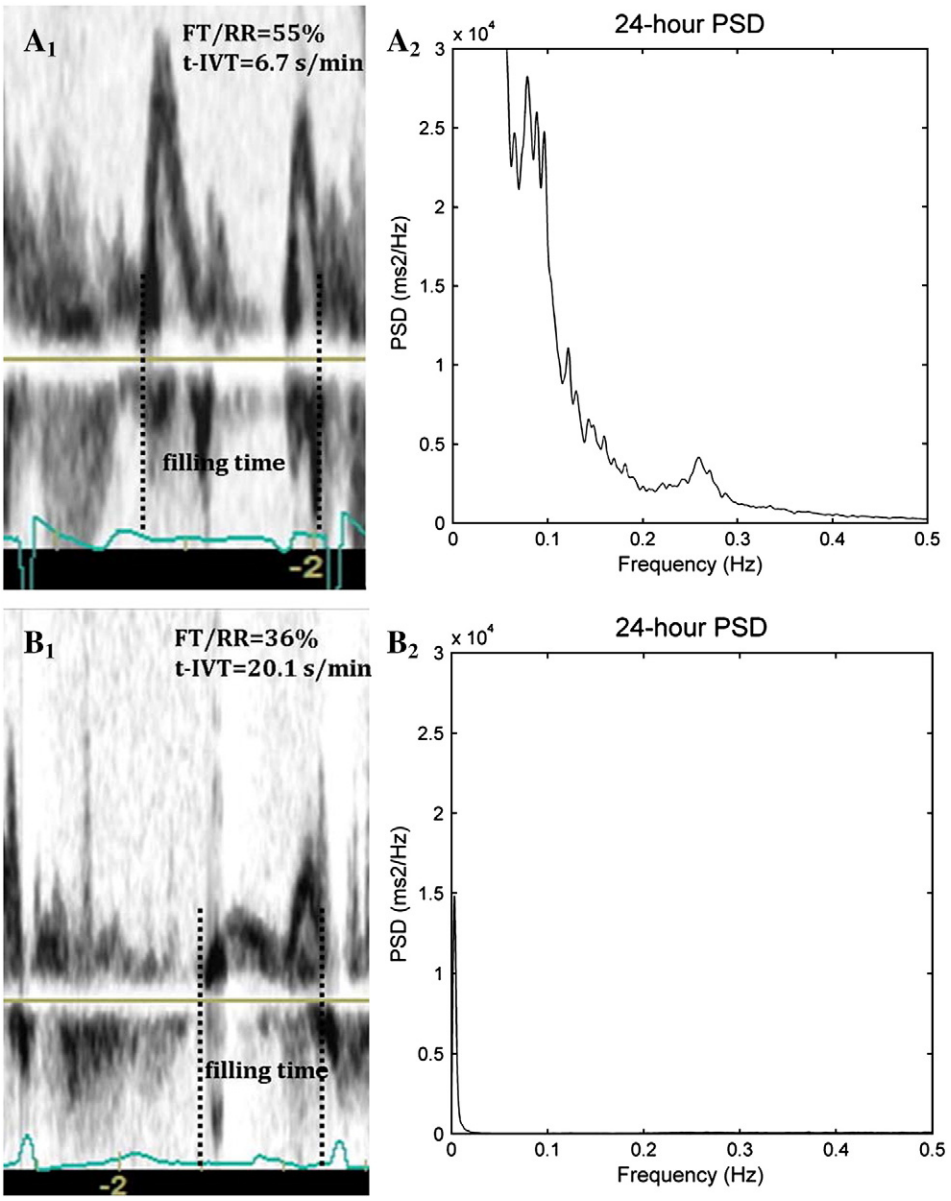


Fig. 1. A_1 and A_2: examples of LV Doppler filling (between dotted line) and spectral HRV from a normal control, respectively. B_1 and B_2: respective recording from a patient with reduced HRV. Note the significant shortening of LV filling and poor HRV in the patient. FT/RR: relative filling time; t-IVT: total isovolumic time; PSD: power spectral density.

abnormalities. It was only the subgroup of patients with reduced HRV who, in addition, had reduced long-axis function which represents subendocardial dysfunction, again despite having preserved overall systolic function. The strong association that we found between markers of ventricular dyssynchrony and stroke volume as well as the prevalence of cardiac events in patients with reduced HRV, suggests a serious clinical impact of those abnormalities rather than pure academic interest. These findings also demonstrate that in such patients with reduced HRV, the stroke volume has become dependent on the degree of LV dyssynchrony as shown by t-IVT, a pattern that is not physiological. Indirect indices of raised left atrial pressure, i.e., E/Em, were higher in the patients' cohort as a whole. The same indices also differentiated the subgroups, being higher in patients with reduced HRV. T-IVT represents the time in the cardiac cycle when the LV is neither filling nor ejecting, generally caused by cavity dyssynchrony. These disturbances have been shown to have serious implications on overall ventricular performance, as they determine cardiac output [21] and exercise tolerance [22] in patients with heart failure. They have also been shown to determine clinical outcome in patients with systolic heart failure, in particular [23]. Our patients did not have significant evidence for systolic dysfunction, neither had clinical evidence for fluid retention. However, they had profound evidence for dyssynchronous LV with prolonged t-IVT and raised Tei index. Whether these disturbances represent a picture of diastolic heart failure, knowing that patients limited exercise tolerance perceived to be contributed to by other pathologies, this remains to be challenged. The further supportive evidence for severity of cardiac abnormalities was the association of those markers of dyssynchrony with HRV and clinical outcome.

Despite the deeply rooted belief that autonomic nervous system abnormalities are the main cause for abnormal HRV in these patients, it seems that dyssynchronous LV function is another important factor. LV dyssynchrony limits filling time and hence stroke volume, thus is bound to dictate changes in heart rate, according to body needs. An alternative argument could be that the autonomic disturbances themselves are the ones which dictate LV filling time and hence measurements of dyssynchrony. This is an unlikely explanation since our findings show an additional clear evidence

Table 3
Echocardiographic parameters in familial amyloidotic polyneuropathy (FAP) patients with reduced and preserved heart rate variability (HRV) subgroups.

	Preserved HRV (n = 20)	Reduced HRV (n = 9)	*p* value
M-mode			
LAd (mm)	36.0 ± 8.0	37.2 ± 8.4	0.56
LVd (mm)	47.3 ± 4.2	46.2 ± 5.8	0.46
LVs (mm)	30.2 ± 4.6	29.7 ± 5.0	0.74
LVFS (%)	36.3 ± 6.0	35.9 ± 5.4	0.96
IVS thickness (mm)	11.6 ± 3.5	12.8 ± 3.9	0.22
PW thickness (mm)	9.4 ± 1.8	10.9 ± 2.8	0.14
LxS (cm)	**11.9 ± 1.9**	**9.0 ± 1.6**	**0.001**
LxL (cm)	**13.2 ± 2.1**	**10.8 ± 3.0**	**0.03**
Doppler			
SV (ml)	82.8 ± 25.4	70.7 ± 20.4	0.19
E (cm/s)	69.2 ± 13.4	73.9 ± 14.8	0.38
A (cm/s)	**70.9 ± 17.6**	**91.8 ± 10.5**	**0.008**
E/A	1.03 ± 0.32	0.80 ± 0.10	0.06
Em (cm/s)	7.8 ± 2.6	5.9 ± 2.9	0.15
E/Em	**9.7 ± 3.0**	**16.0 ± 9.7**	**0.027**
DT(ms)	225.4 ± 80.3	200.1 ± 67.0	0.57
FT/RR(%)	**49.1 ± 6.5**	**39.5 ± 4.1**	**0.002**
t-IVT(s/min)	**9.86 ± 3.42**	**14.24 ± 3.19**	**0.005**
Tei index	**0.50 ± 0.17**	**0.68 ± 0.22**	**0.05**

All values presented as mean ± SD.
Abbreviations are the same as Table 1.

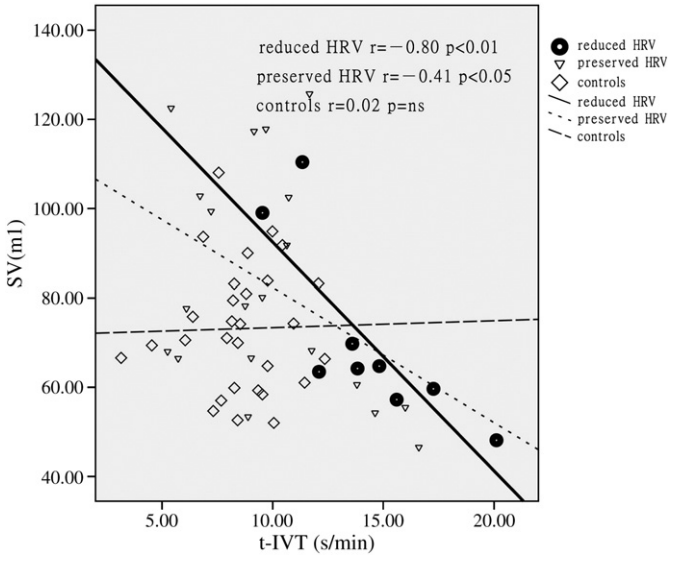


Fig. 2. Correlation between stroke volume (SV) and total isovolumic time (t-IVT) in FAP patients and controls.

for compromised LV subendocardial long-axis function in patients with reduced HRV. This confirms the presence of intrinsic myocardial involvement with the amyloid pathology, despite being at a subendocardial level, and hence the dyssynchronous function, as previously shown in other systemic diseases involving the myocardium [24,25].

4.3. Clinical implications

Familial amyloidotic polyneuropathy patients have evidence for significant LV dyssynchrony, particularly those with reduced HRV. These findings may explain the failure of blood pressure response to fluid loading during general anaesthesia, known in these patients. A detailed preoperative assessment with view of cardiac resynchronization therapy may improve clinical as well as the surgical outcome of these patients.

4.4. Limitations

Five of the 29 FAP patients were investigated after liver transplantation, but we did not subgroup these patients because of the small number. We did not have strain and strain rate measurements in these patients, which might have assisted in identifying segmental myocardial dysfunction of relevance [20]. All time measurements were corrected for R–R interval to eliminate any element of influence of heart rate on the accuracy of our data interpretation. Finally, we did not have myocardial biopsies which might have confirmed the pathological nature of the subendocardial abnormalities.

5. Conclusion

In familial amyloidosis with polyneuropathy, HRV correlates with markers of global left ventricular dyssynchrony. Such relationship is most powerful in patients with reduced HRV suggesting that dyssynchrony might hold an important role in controlling cardiac function and stroke volume. These findings should have significant clinical implications for optimum management of FAP patients, particularly those who may benefit from resynchronization therapy.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [26]. This study was supported by grants from the patient's associations FAMY and FAMY North, and the Swedish Heart and Lung Foundation.

References

[1] Saraiva M, Costa P, Birken S, Goodman S. Presence of an abnormal transthyretin (prealbumin) in Portuguese patients with familial amyloidotic polyneuropathy. Trans Assoc Am Physicians 1983;96:261–70.
[2] Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants. Amyloid 2003;10:160–84.
[3] Ando Y, Suhr OB. Autonomic dysfunction in familial amyloidotic polyneuropathy (FAP). Amyloid 1998;5:288–300.
[4] Backman C, Olofsson BO. Echocardiographic features in familial amyloidosis with polyneuropathy. Acta Med Scand 1983;214:273–8.
[5] Olofsson BO, Backman C, Boman K. Familial amyloidotic polyneuropathy in northern Sweden. A cross-sectional and longitudinal study of cardiac function with echocardiography. Arctic Med Res 1988;47(Suppl 1):423–5.
[6] Wiklund U, Hornsten R, Karlsson M, Suhr OB, Jensen SM. Abnormal heart rate variability and subtle atrial arrhythmia in patients with familial amyloidotic polyneuropathy. Ann Noninvasive Electrocardiol 2008;13:249–56.
[7] Morelli S, Carmenini E, Sgreccia A, Francia A. Heart rate variability and familial amyloidosis. Int J Cardiol 2002;83:295–7.
[8] Mbaissouroum M, O'Sullivan C, Brecker SJ, Xiao HB, Gibson DG. Shortened left ventricular filling time in dilated cardiomyopathy: additional effects on heart rate variability? Br Heart J 1993;69:327–31.
[9] Bellavia D, Pellikka PA, Abraham TP, et al. 'Hypersynchronisation' by tissue velocity imaging in patients with cardiac amyloidosis. Heart 2009;95:234–40.
[10] Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
[11] Garcia-Fernandez MA, Azevedo J, Moreno M, et al. Regional diastolic function in ischaemic heart disease using pulsed wave Doppler tissue imaging. Eur Heart J 1999;20:496–505.
[12] Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
[13] Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
[14] Duncan AM, Lim E, Clague J, Gibson DG, Henein MY. Comparison of segmental and global markers of dyssynchrony in predicting clinical response to cardiac resynchronization. Eur Heart J 2006;27:2426–32.
[15] Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. J Am Coll Cardiol 1996;28:658–64.

[16] Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357–66.
[17] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.
[18] Engel G, Beckerman JG, Froelicher VF, et al. Electrocardiographic arrhythmia risk testing. Curr Probl Cardiol 2004;29:365–432.
[19] Oppenheim AV, Schafer RW. Digital Signal Processing. Englewood Cliffs, NJ: Prentice-Hall; 1975.
[20] Lindqvist P, Olofsson BO, Backman C, Suhr O, Waldenstrom A. Pulsed tissue Doppler and strain imaging discloses early signs of infiltrative cardiac disease: a study on patients with familial amyloidotic polyneuropathy. Eur J Echocardiogr 2006;7:22–30.
[21] Duncan A, Wait D, Gibson D, Daubert JC. Left ventricular remodelling and haemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: sub-study of the MUSTIC (Multisite Stimulationin Cardiomyopathies) trial. Eur Heart J 2003;24:430–41.
[22] Duncan AM, Francis DP, Gibson DG, Henein MY. Limitation of exercise tolerance in chronic heart failure: distinct effects of left bundle-branch block and coronary artery disease. J Am Coll Cardiol 2004;43:1524–31.
[23] Duncan AM, Lim E, Gibson DG, Henein MY. Effect of dobutamine stress on left ventricular filling in ischemic dilated cardiomyopathy: pathophysiology and prognostic implications. J Am Coll Cardiol 2005;46:488–96.
[24] Lindqvist P, Morner S, Olofsson BO, et al. Ventricular dysfunction in type 1 myotonic dystrophy: electrical, mechanical, or both? Int J Cardiol 2010;143:378–84.
[25] Morner S, Lindqvist P, Mellberg C, et al. Profound cardiac conduction delay predicts mortality in myotonic dystrophy type 1. J Intern Med 2010;268:59–65.
[26] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.