Abnormal Heart Rate Variability and Subtle Atrial Arrhythmia in Patients with Familial Amyloidotic Polyneuropathy

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Background: Cardiac autonomic dysfunction is a common complication of familial amyloidotic polyneuropathy (FAP), but cardiac arrhythmia and conduction disturbances are also common. We analyzed heart rate variability (HRV) in FAP patients using power spectrum analysis and Poincaré plot analysis.

Methods: HRV was analyzed in 24-hour ECG recordings (Holter) in 41 FAP patients.

Results: Power spectrum analysis showed reduced HRV in 21 FAP patients. A novel finding was that nine other patients with abnormal Poincaré plots had either very high power in the high-frequency region (0.15–0.50 Hz) or broadband HRV power spectra without any distinctive spectral peaks. Reanalysis of their ECGs showed a previously undetected intermittent atrial arrhythmia.

Conclusions: Subtle arrhythmias may be difficult to detect during analyses of Holter recordings. Patients with intermittent atrial arrhythmia were identified by broadband HRV spectra and abnormal Poincaré plots. High high-frequency power in HRV and irregular heart rate patterns may indicate the presence of subtle atrial arrhythmia. Consequently, such patients should be excluded from studies of cardiac autonomic modulation.

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Power spectrum analysis of heart rate variability (HRV) is used to assess the cardiac autonomic modulation in different groups of patients and in healthy subjects during different experimental conditions.¹ This study focuses on HRV patterns in 24-hour electrocardiographic (ECG) recordings in patients with familial amyloidotic polyneuropathy (FAP). It is well known that many FAP patients have marked reduced HRV, signifying pronounced dysfunction in the autonomic nervous system.^{2–5} A novel finding in this study is that high HRV can be a sign of abnormal heart rate fluctuations in FAP patients.

FAP is a rare hereditary systemic amyloidosis that is caused by a mutation in the transthyretin

(TTR) gene. The defect TTR has an increased tendency to dissociate and assemble into amyloid—an insoluble protein—in the nervous system and in various organs such as the heart, the kidneys, and the gastrointestinal tract. The mean age of onset of FAP is 56 years in Swedish patients, but cases with an early onset (<50 years of age) are also common.

Autonomic dysfunction can be identified early in the course of the disease using power spectrum analysis of short-term⁵ and long-term HRV recordings.^{3,4} Most FAP patients have parasympathetic dysfunction, resulting in low power of both the high-frequency component (HF) and the low-frequency component (LF). The HF component is normally reflecting respiratory related fluctuations.

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The LF component is often associated with baroreceptor-mediated blood-pressure control, reflecting both sympathetic and parasympathetic activity.¹ Although HRV normally is used to assess the cardiac autonomic modulation of the sinus node, HRV also mirrors heart rate fluctuations due to cardiac arrhythmia and conduction disturbances. If undetected, such abnormalities of the heart rhythm cause irregular fluctuations in heart rate which in turn results in increased HRV.⁶ To disclose abnormal HRV patterns, in this study we constructed Poincaré graphs-plots of each R-R interval against the previous value.⁷

The aim of this study was to analyze HRV patterns in 24-hour ECG recordings in Swedish FAP patients. Findings from power spectrum analysis of HRV were compared with those of Poincaré plots. Since FAP patients often have cardiac arrhythmia and conduction disturbances,⁸⁻¹¹ all recordings were carefully investigated using regular procedures for Holter analyses before HRV was analyzed. Nonetheless, the study shows that FAP patients with high HRV could have a subtle atrial arrhythmia and therefore should be excluded from studies of cardiac autonomic modulation.

METHODS

Study Group

Fifty-one FAP patients, 28 male and 23 female, with mean age 57 years (range 34–80 years) were included. All patients were evaluated at Umeå University Hospital, Sweden, during 1999 to December 2004. The examination was part of their clinical evaluation before liver transplantation, as well as for diagnosis and identification of complications of the disease. The patients were treated according to the Declaration of Helsinki, and the Ethical Committee of Umeå University accepted the study.

Forty-nine patients carried the ATTR Val30Met mutation, one carried the ATTR His88Arg and one carried the ATTRLeu33Phe mutation. In all cases, the diagnosis was verified by identification of a TTR mutation, clinical symptoms and findings of amyloid deposits in skin or intestinal biopsy specimens. The mean duration from onset of the disease to examination was 38 months, (range 6–108 months). At the time of the investigation, three patients were on beta-blocker treatment and one patient had calcium-inhibitors.

Holter-ECG Recordings

Cardiac conduction and rhythm disturbances were identified using standard 24-hour ambulatory ECG recordings (Holter), with a standard recorder unit (Braemar DL 700, Braemar Inc., Burnsville, MN, USA). Two channels of ECG data were digitized with a sampling rate of 128 Hz. The ECG recordings were analyzed using a PC-based Holter system (Aspect Holter System, GE Healthcare, Borlänge, Sweden).

Regular procedures for Holter analyses were performed to determine underlying rhythm, and to detect the presence and frequency of arrhythmic beats: atrial and ventricular premature beats, couplets, episodes of tachycardia, first or second degree atrioventricular block, left or right bundle-branch block and sinoatrial block/arrest. Heartbeats were classified as: normal, supraventricular extrasystolic beats, ventricular extrasystolic beats, or beats of uncertain origin. One investigator (R.H.) carefully examined and confirmed the classification of heartbeats. The editing time was between 1 hour and 3 hours depending on the quality of the ECG. The RR intervals and classification of heartbeats were exported from the Holter system for further analyses using Matlab (MathWorks Inc, Natick, MA, USA).

Filtering of RR-Interval Data

To remove possibly undetected arrhythmic beats or other spurious abnormal values, the series of all RR intervals related to normal-to-normal (N-N) interbeat intervals was filtered using a recursive procedure, similar to the approach suggested by Wichterle et al.¹² At each step, N-N intervals were removed if they differed more than 30% from the mean of the preceding and following value. The filtering was repeated on the remaining series of N-N intervals until no values were removed. The maximal number of iterations was set to twenty. With this approach, most values were removed in the first iteration.

Frequency Domain Analysis

Power spectrum analysis was performed using fast Fourier transformation (FFT) of filtered 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.¹³ N-N

intervals were converted to a time series by cubic spline interpolation, followed by re-sampling at two Hz. The mean N-N interval was removed, and data were smoothed using a Bartlett-window before calculating the 4096-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 recording's quality and the presence of arrhythmia. HRV was only analyzed in recordings with more than 70% used time.

The following HRV indices were calculated as averages over 24-hour records: total power in the frequency region 0.003–0.50 Hz (P_{tot}); power of the very low frequency (VLF; below 0.04 Hz); LF (0.04–0.15 Hz) and HF (0.15–0.50 Hz) components; and the ratio between the power of the LF and HF components. The average R-R interval value was calculated from N-N intervals (mean NN). Power spectra were also determined for each hour of the recording.

Poincaré Plots

Poincaré plots were constructed as scatterplots of all pairs of RR intervals with two successive heart cycles classified as normal.⁷ The following patterns are common in 24-hour recordings:⁷ (a) a comet, with an increasing variability with increasing inter-beat interval, corresponding to a "normal" HRV; (b) a torpedo, with the same dispersion along the diagonal irrespectively of mean N-N interval, typical for a subject with low HRV; (c) a fan-shaped, with a triangular or V-shaped dispersion along the diagonal, typical for a subject with frequent ectopic beats; (d) a complex pattern, with groupings of points off the diagonal, for example, reflecting variable atrioventricular conduction.

The geometric appearance of the Poincaré plot was described by defining a new coordinate axis rotated 45° counter clockwise to the normal axis. The standard deviation along new y-axis (SD1) describes the fast beat-to-beat (short-term) variability of the heart rate (HR). The standard deviation along the new x-axis (SD2) describes the long-term variability.¹⁴ High values of the ratio SD1/SD2 were used an indicator of abnormal Poincaré plots, as previously suggested.¹⁵

Statistical Analyses

All frequency-domain HRV indices were log-transformed (base 10) because of skewed distribution. Patients were divided into two age groups (≤ 50 years, and > 50 years, respectively). HRV parameters were compared using group-wise *t*-test. The level of statistical significance was defined as a 2-tailed *P* value < 0.05 . All statistical analyses were performed using SPSS version 15 (SPSS, Chicago, IL, USA).

RESULTS

Eleven FAP patients were excluded from further analysis of HRV: nine patients because of paroxysmal atrial arrhythmia, often combined with frequent ventricular extra systolic beats, which made it impossible to classify all heartbeats correctly; and two patients because less than 70% of the recording could be analyzed.

Table 1 summarizes HRV data based on edited and filtered N-N intervals in the remaining 40 FAP patients. Although total HRV, VLF power and LF power was reduced in the older patients, no significant differences were found in the indices reflecting the fast beat-to-beat fluctuations (HF power and SD1, respectively). Fifteen patients had LF power lower than 100 ms^2 (2.0 in log-transformed units); 23 patients had HF power lower than 100 ms^2 .

Table 1. Power Spectrum and Poincaré Plot Analysis Based on Carefully Edited and Filtered N-N Intervals

FAP patients	≤ 50 years (n = 14)	> 50 years (n = 26)	P value
Frequency-domain indices			
Ptot (ms^2 , log)	3.16 (0.43)	2.71 (0.56)	0.01
PVLF (ms^2 , log)	2.97 (0.37)	2.45 (0.55)	0.001
PLF (ms^2 , log)	2.49 (0.53)	1.91 (0.74)	0.02
PHF (ms^2 , log)	2.12 (0.55)	1.98 (0.56)	0.44
log PLF/PHF	0.37 (0.26)	-0.06 (0.42)	0.001
Poincaré plot indices			
SD1 (ms^2)	19.8 (12.3)	18.5 (12.2)	0.75
SD2 (ms^2)	176 (58)	136 (48)	0.03
SD1/SD2	0.11 (0.06)	0.14 (0.07)	0.25
NNmean (ms)	767 (90)	787 (93)	0.51

Data are given as mean (SD).

NNmean = mean N-N interval; P_{HF} = power of high-frequency component; P_{LF} = power of low-frequency component; P_{tot} = total power; P_{VLF} = power of very low-frequency component; SD1 and SD2 = Poincaré plot measures, see text for explanation.

Figure 1. Patient with normal HRV power spectrum with both a LF and HF peak and a comet-shaped Poincaré plot, where the variability increases with increasing N-N interval. Note the marked day-night variation in HF power. Left: 24-hour power spectra. Middle: three-dimensional plots of spectra for each hour of the recording. Right: Poincaré plot for the 24-hour recording.

Figures 1 and 2 show representative power spectra and Poincaré plots of patients with normal or reduced HRV. A broadband spectral pattern without any distinct peaks in the LF or HF region was found in the 24-hour spectra of eight patients (Fig. 3). In addition, one patient had very high HRV and a power spectrum with a sharp peak near 0.16 Hz (Fig. 4).

Twenty-seven patients had Poincaré graphs with the comet pattern ($n = 6$) or the torpedo pattern ($n = 21$). The Poincaré plot measure SD1/SD2 was below 0.15 in these 27 patients.

Thirteen patients had Poincaré graphs with either the fan pattern or the complex pattern. Four of these patients had very low SD2, that is, low total HRV, but where SD1 was affected by spurious undetected extrasystolic beats or scattered points due

to frequent ECG disturbances. One of these four patients had SD1/SD2 > 0.15 .

Findings in the remaining nine patients with the fan/complex pattern were as follows:

Eight patients had broadband power spectra with no or small LF and HF peaks, a result that was similar to the broadband power spectrum shown in Fig. 3. The ninth patient was the patient with very high HRV (Fig. 4). All nine patients had SD1/SD2 > 0.13 . A careful reexamination was performed of their series of N-N intervals, power spectra, 24-hour Poincaré graphs as well as hourly Poincaré plots, and P wave morphology. This analysis showed that they all had intermittent atrial arrhythmia, which had been undetected during the regular editing of Holter recordings. Figure 5 shows a typical ECG strip from patients with broadband

Figure 2. Patient with reduced HRV with no visible LF or HF peak, and a torpedo-shaped Poincaré plot, showing a low variability without any dependence of mean N-N interval.

Figure 3. Patient with a broadband HRV pattern, without any distinct peaks in the LF or the HF regions, and with a fan-shaped Poincaré plot, both typical findings in patients with slight intermittent arrhythmia.

power spectra, showing notable irregular changes in the RR interval as well as intermittent fluctuations in the P wave morphology.

Note that intermittent atrial arrhythmia was found in seven of the 11 patients with HF power higher than 200 ms² (Fig. 6). In total, paroxysmal or intermittent atrial arrhythmia was found in 18 FAP patients (45%): 14 of these patients were 60 years or older.

Finally, we compared the results from power spectrum analysis based on edited N-N intervals before (data not shown) and after additional filtering. The difference between spectral parameters before and after filtering was largest in patients > 50 years, where filtering reduced mean PHF with approximately 20%. Filtering reduced the width of fan-shaped Poincaré graphs, but the broadband spectral pattern was found in patients with intermittent atrial arrhythmia both before and after filtering.

DISCUSSION

This is the first study of power spectrum analysis of HRV combined with Poincaré plot analysis in FAP patients, where the analysis is based on 24-hours Holter-ECG monitoring. The study verifies previous findings of a pronounced reduced HRV in FAP patients,⁵ indicating a severe dysfunction in cardiac autonomic modulation. A novel finding was that several patients had intermittent atrial arrhythmia, undetected during the regular Holter analysis, but identified by a broadband HRV power spectrum or by high HF power. They also had a Poincaré plot exhibiting a fan-shaped or complex pattern. Since their HRV recordings were contaminated by subtle arrhythmia, the cardiac autonomic modulation may be difficult to assess in these patients with high HRV. Our findings show the importance of a careful arrhythmia analysis before HRV

Figure 4. Patient with extremely high HRV and a marked peak near 0.16 Hz. Note the different scale in the 3D-PSD for this patient, as compared to all other power spectra.

Figure 5. ECG strip from one patient with intermittent fluctuations in the N-N intervals, as well as fluctuations in the morphology of the P wave. Such ECGs were typical for patients with broadband HRV power spectra as shown in Figure 3.

is assessed, but our findings also illustrate the problem with detecting subtle arrhythmias during the analysis of Holter recordings.⁶ Poincaré diagrams can help disclose subtle arrhythmias.

We hypothesize that the broadband spectral pattern reflects an intermittent atrial arrhythmia. This hypothesis is mainly based on a close reexamination of ECG recordings, which revealed intermittent fluctuations in the morphology of the P wave and random changes in N-N intervals. The broadband spectral pattern indicates that these low-amplitude oscillations in heart rate are very irregular, mimicking the irregular heart rate fluctuations found in atrial fibrillation, but with lower amplitude. Although irregular breathing could have caused the broadband pattern in HRV, pronounced respiratory sinus arrhythmia was ruled out because these patients did not seem to have respiratory related fluctuations in N-N intervals, which are often noted as a peak in the HF region, in particular during the night.

Reduced power of different spectral components could be correlated with the severity of the autonomic dysfunction, as was found in a study of

24-hour HRV in 15 Japanese FAP patients.³ In particular, reduced HF power indicates reduced vagal modulation of the sinus node, which could be due to a parasympathetic dysfunction. Reduced LF power appears to be caused by a peripheral autonomic dysfunction, which is common in FAP patients. Many patients had reduced cardiac autonomic modulation because of severe autonomic dysfunction. This may be the main reason why we found the association between the broadband HRV spectrum and the presence of an intermittent atrial arrhythmia. Thus FAP patients, as well as other patients with reduced cardiac autonomic modulation, offer a possibility to study the influence of non-autonomic mechanisms on the HRV power spectrum.

We found intermittent atrial arrhythmia in nine patients based on findings during the HRV analysis. These patients were identified by high HF power and a broadband power spectrum, and also had an abnormal Poincaré plot, that is, with high values of SD1/SD2 and either the fan pattern or the complex pattern. Note that a few patients with almost no overall HRV also had relatively high values of SD1/SD2, but those patients had very low SD2. An important finding was that more than 60% of patients with HF power above 200 ms² had intermittent atrial arrhythmia. This shows that high HF power could be a sign of nonautonomic fluctuations in heart rate, such as rhythm and cardiac conduction disturbances. In fact, this could also be the case in other patient populations. In a recent study on elderly subjects, high values of HRV indices

Figure 6. HRV indices in FAP patients without (circles) and with intermittent atrial arrhythmia (dots). Left : LH/HF versus HF power; Right: SD1/SD2 versus HF power. Values were calculated after additional filtering of carefully edited N-N interbeat intervals.

were common in subjects with a significant degree of nonrespiratory sinus arrhythmia.⁶ Enhanced HF power (as compared to healthy subjects) has also been reported in old patients with hypertrophic cardiomyopathy, and was suspected to originate from undetected atrial arrhythmias.¹⁶ Note that subtle arrhythmia mainly will increase indices of short-term variability, for example, HF power and the time domain index RMSSD. Measures of long-term variability—such as ultra low-frequency power, SDNN and SDANN—will probably not be confounded by subtle arrhythmias.

One patient with intermittent atrial arrhythmia had a power spectrum with a distinct peak near 0.16 Hz and high total HRV (Fig. 4). Although we found signs of intermittent fluctuations in the P wave morphology, the high HRV could have been caused by pronounced respiratory sinus arrhythmia. However, a short-term HRV recording from this patient was analyzed in a recent study,¹⁷ where a simultaneous recording of respiration was performed. The patient also had high HRV with a distinct peak near 0.2 Hz in this recording, but it was shown that this peak was not associated with respiratory sinus arrhythmia. Moreover, a nonautonomic HF component was also found in a Japanese FAP patient and was assumed to reflect a compensatory rhythm because of a damaged autonomic nervous system.¹⁸

It is well known that subjects with severe cardiac arrhythmia, such as frequent nonsinus beats or alternating foci in the atria, have a distorted power spectrum. Therefore, all recordings were carefully edited for arrhythmic beats. We also performed automatic filtering of N-N intervals to remove undetected arrhythmic beats.^{6,12,19} This resulted in a small reduction of the HF power in patients with intermittent atrial arrhythmia, as compared to careful editing. Nonetheless, the broadband spectral pattern was still present in those patients after filtering. We also tested other thresholds in the automatic filter (20% and 10%, respectively, data not shown). Although more ectopic beats were removed in patients with low HRV, too many sinus beats were removed in patients with the comet pattern. Therefore, we consequently used the 30% threshold in this study.

In total, we found atrial arrhythmia in 45% of the FAP patients. A clinicopathological study in nine autopsy Swedish FAP patients showed heavy amyloid infiltrations in the atrium, particularly in the sinus node.²⁰ The authors hypothesized that amy-

loid infiltration accounted for electrophysiological disturbances in the atrium or the sinus node. Our findings support this hypothesis—the subtle atrial arrhythmia found in Holter recordings could have been caused by amyloid infiltration in local areas of the sinus node.

The time-consuming editing of data is one of the major problems with performing the HRV analysis on data from 24-hour recordings. Although one could argue that intermittent atrial arrhythmia would have been detected during an even more careful editing of the ECG-recordings, Stein et al. also found that it was very difficult to detect subtle cardiac arrhythmia during analyses of Holter recordings no matter how carefully they are edited.⁶ Another possible explanation of irregular heart rate fluctuations is nonuniform beat detection. We did not have detailed information on the algorithm used for beat detection (as often is the case for users of many Holter systems). Therefore, ECG data and R-R intervals were reanalyzed in Matlab, where we ruled out uneven beat detection by inspection of the time instants for detected heart beats in the ECG recordings. The reliability of the P wave analysis is somewhat reduced because of the low sampling frequency in the Holter system.

CONCLUSIONS

In summary, the most important finding in this study is that high power of the HF component in HRV could indicate rhythm disturbances instead of reflecting normal cardiac autonomic modulation. Patients with these highly irregular rhythms are probably undetected in many HRV studies. The presence of a broadband spectral pattern in HRV could be an early sign of multifocal atrial arrhythmia, which might develop to permanent atrial arrhythmia or even atrial fibrillation. These findings have important implications when the cardiac autonomic function is evaluated in patients that are expected to have low HRV because of autonomic dysfunction. Patients with high HF power in HRV could have a subtle atrial arrhythmia and therefore should be excluded from studies of cardiac autonomic modulation.

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