Cardiorespiratory Coherence Analysis of Abnormal Heart Rate Responses during Deep Breathing

Urban Wiklund, Amir Kadkhodaee, Kennet Andersson

Radiation Sciences, Biomedical Engineering,
Umeå University, Umeå, Sweden

Abstract

Although the heart rate variability (HRV) normally is highly synchronised with respiration during deep breathing, in patients with transthyretin amyloidosis we occasionally observe abnormal heart rate responses due to subtle arrhythmias. This study evaluates the use of cardiorespiratory coherence analysis for automatic detection of these abnormal patterns.

1. Introduction

In healthy subjects, paced deep breathing (DB) with six breaths/min causes a marked response in the heart rate variability (HRV). On the other hand, patients with autonomic dysfunction often present reduced HRV during deep breathing. Therefore, the overall variation in heart rate during the DB test is often used as an index of autonomic function, e.g., in patients with diabetes mellitus [1], and in healthy subjects [2].

Progressive autonomic dysfunction is common in patients with the hereditary and fatal disease transthyretin amyloidosis (ATTR), or as it is also known, familial autonomic polyneuropathy (FAP) [3]. ATTR is caused by a mutation in the transthyretin gene, which causes widespread deposition of amyloid fibrills, e.g., causing organ dysfunction and neuropathies and ultimately, death. Transthyretin is mainly produced by the liver, and liver transplantation has been the only available treatment to stop the progress of the disease. The efficacy of new medical treatments are currently evaluated in clinical trials, where the DB test has been selected as one of the tests for scoring of autonomic function [4].

At our clinic, the first HRV recordings were performed around 1990, as part of the clinical evaluation of the autonomic function in ATTR patients before eventual liver transplantation. DB is included as part of our study protocol, but ATTR patients often present arrhythmias due to atrioventricular blocks or other irregular heart rate responses during the test [3]. Therefore, we have questioned the reliability of the DB test in this group of patients. Instead, in previous studies we have evaluated autonomic function in ATTR patients based on recordings during spontaneous breathing before and after passive tilt, or based on data from 24-hour ECG recordings. However, the HRV analysis is often difficult to evaluate, since subtle atrial arrhythmias are common in many patients [5, 6]. This study aimed to evaluate if cardiorespiratory coherence analysis could be used to detect abnormal HRV patterns during the DB test.

2. Methods

One-minute sequences from paced DB (6/min) were obtained from 131 recordings in adult ATTR patients and 176 healthy subjects. The recorded signals, respiration and the beat-to-beat variability in heart rate, were converted to equidistantly sampled data (using f_s=5 Hz for re-sampling). Data were taken from previously performed clinical investigations. Power spectrum analysis was used to validate the quality of the respiration signals. In this study, we only included recordings where >70% of the power of the respiration signal was found at the breathing frequency (at 0.1 Hz).

The total power of HRV (P_{TOT}) and the power in the low-frequency region (P_{LF}; 0.04-0.15 Hz) were estimated. Linear regression analysis was used to estimate the age-dependency in HRV for controls with corresponding 95% confidence intervals.

The coherence function is defined as:

$$c_{12}(f) = \frac{|p_{12}(f)|^2}{p_1(f)\,p_2(f)} \quad (1)$$

where $p_1(f)$ and $p_2(f)$ are the power spectral density function of $x_1(t)$ and $x_2(t)$, and $p_{12}(f)$ is the cross-power spectrum of the two signals.

The magnitude-squared coherence was determined with the nonparametric Welch (averaged periodogram) method and by bivariate autoregressive (AR) modelling. We investigated the effect of two central parameters for each method: the length of the analysis window, or

equivalently the number of segments (N_{seg}) used for averaging of power spectra in the Welch method, and the model order in the bivariate autoregressive model. The coherence function was sampled at 0.1 Hz. To obtain an index for the overall co-variation in the two signals, we calculated the fraction of the total power of $x_1(t)$ that was coherent with $x_2(t)$ as follows:

The product of the coherence and the power spectrum is referred to as the coherent output power spectrum,

$$p_c(f) = p_1(f) \cdot c_{12}(f) \quad (2)$$

This gives a measure of how much of the power of the output signal is caused by the input signal at different frequencies. Then, the fraction of the total power of $x_1(t)$ that is coherent with $x_2(t)$ is given by the coherent power index (CPI)

$$\mathrm{CPI} = \frac{\int_{f=0}^{f_s/2} p_1(f) \cdot c_{12}(f) df}{\int_{f=0}^{f_s/2} p_1(f) df} \quad (3)$$

Non-parametric statistical methods were used in all comparisons, where a p-value <0.05 was considered statistically significant.

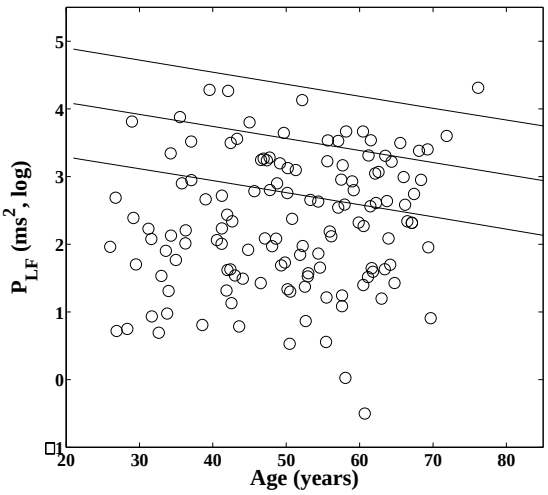


Figure 1. Low-frequency (LF) power in HRV during deep breathing. Solid lines show the regression line and 95% confidence intervals for the age-dependency in controls, and symbols (o) show individual values in patients.

3. Results

Figure 1 shows results from the "traditional" HRV analysis, where 58 (44%) patients presented P_{LF} within normal limits. Note that data for controls are only presented as the regression line for the age-dependency in controls, together with the corresponding 95% confidence intervals. For P_{TOT}, HRV scores were within normal limits in 55 patients (42%).

Figure 2 shows results from the coherence analysis. the mean of AR-based coherence increased from 0.67/0.87 in patients/controls for AR(2), to 0.86/0.96 for AR(8). The Welch-based coherence decreased markedly with increasing number of segments used for averaging. Both methods showed significantly lower coherence and CPI in patients than in controls; except for the trivial case where only one segment was used in the Welch method, since the coherence then will be equal to one at all frequencies. For AR(8) mean CPI was 0.57 in patients vs. 0.79 in controls ($p<0.001$, Mann-Whitney test).

The relation between coherence and coherent power index is shown in Figure 3 (for N_{seg}=4 and AR(8), respectively). Among subjects with high coherence (>0.80), CPI was below 0.50 in 21 subjects (4 controls/17 patients) for AR, and in 14 subjects (4 controls/10 patients) for Welch.

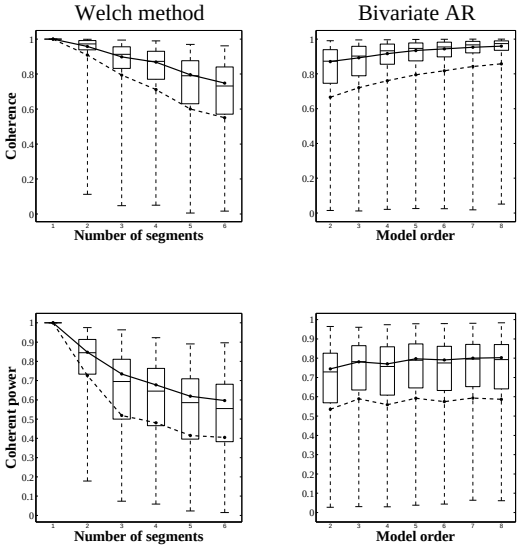
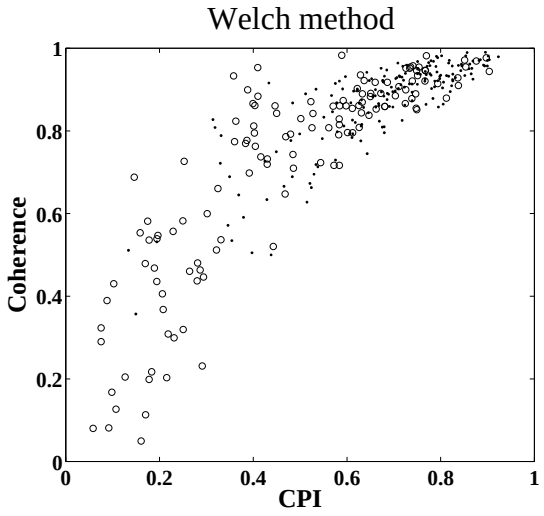


Figure 2. Changes in coherence and coherent power index for different analysis parameters. Coherence between the HRV and respiration signals was determined based on the Welch method and bivariate autoregressive modeling (AR). Boxes show range, interquartile range and median for all subjects. Solid line show mean values for controls, and dashed lines show means for patients.



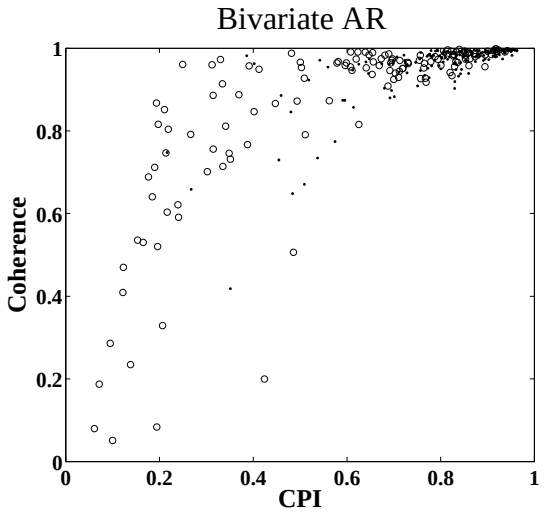
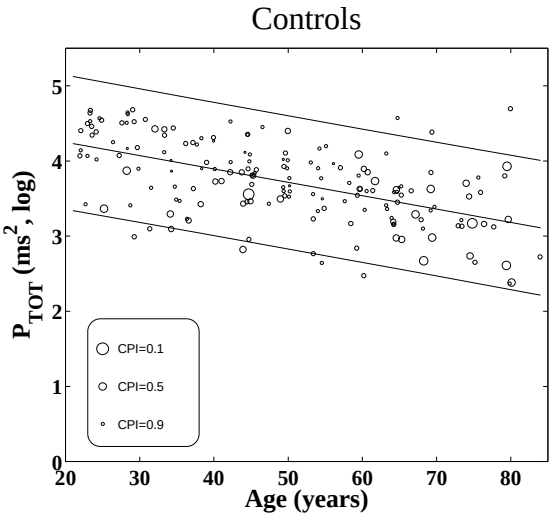


Figure 3. Relation between coherence and coherent power index for patients (o) and controls (•). Top: Welch method. Bottom: bivariate autoregressive modeling (AR).



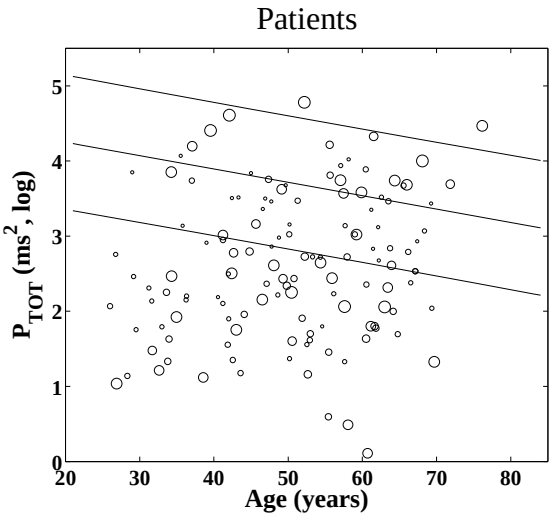


Figure 4. Total power (P_{TOT}) in HRV during deep breathing. Solid lines show the regression line and 95% confidence intervals for the age-dependency in controls. Symbols are scaled according to 1-CPI (CPI=coherent power index).

To further illustrate the additional information given by CPI, Figure 4 shows the age-dependency in HRV for all subjects presented as the regression line for controls together with the 95% confidence intervals. Symbols show individual values but are scaled proportionally to 1-CPI. Thus, a large circle represents a lower CPI indicating a more irregular HRV pattern. Among the subjects with normal HRV scores (58 patients and 170 controls), AR-based CPI was lower than 0.50 in 29% of patients and in 5% of controls (for Welch the corresponding proportions for patients/controls were 40%/11%).

4. Discussion and conclusion

This study analysed HRV patterns during deep breathing in a cohort of patients where both severe autonomic dysfunction and cardiac arrhythmia are common findings. We started with the traditional HRV analysis, where the focus is on the magnitude of the heart rate responses. This analysis verified the expected finding that HRV was reduced during the DB test in the majority of ATTR patients, as shown in Figure 1. However, among those patients (and to some extent controls) that presented

HRV scores within normal limits, the cardiorespiratory coherence analysis could identify a significant number of subjects that presented more irregular HRV patterns than expected. These irregularities partly originated from cardiac conduction disturbances and subtle atrial arrhythmias, but also from different types of amplitude modulation that were found in the HRV signal, but not in the recorded respiration signal. There were also patients that presented very regular responses in HRV, but where the magnitude of these fluctuations was very low. This could possibly reflect a pure mechanical modulation, such as stretching of the sinus node, or it could indicate that the patient had some small residual cardiac autonomic modulation.

Low values of CPI were found among patients with HRV scores both within and below normal limits (Figure 4). Older controls also tended to present lower CPI (larger circles) than younger controls. One explanation for the latter is that older subjects probably have more difficulties in keeping a steady breathing pattern during the test than younger subjects. Another possibility is that the more marked irregularity in HRV at older age reflects degradation in the parasympathetic nervous system, as also indicated by the well-known successive reduction in HRV with increasing age. However, further studies are needed, where any eventual irregularities in the breathing signal are analysed in more detail than in the present study.

Coherence, by itself, provided information that helped to identify some, but not all, subjects with abnormal HRV patterns. The Welch-based estimates were successively reduced when the number of segments used for averaging was increased, which also reduces the resolution in frequency in the estimated coherence spectrum as shown in Figure 2. Thus, the threshold for defining a significant coherence was dependent on N_{seg}, but the difference in mean values for the two groups remained relatively unchanged for $N_{seg} > 3$.

On the contrary, the coherence at the breathing frequency increased with increasing model order in the bivariate AR model (Figure 2). The lowest model order that we investigated was two, since this is the lowest order where a frequency component with a non-zero central frequency can be modelled. However, to obtain an estimated coherence spectrum with a peak near 0.1 Hz, a model order of four or higher was needed in most subjects. When the model order becomes high, over-fitting may cause problems with the interpretation of the results.

In particular for the coherence estimated using the AR model, there was a substantial number of subjects that presented coherence values above 0.8, but where CPI was below 0.5, see Figure 3. Therefore, for AR, a high coherence close to one probably means that there is at least some power at the breathing frequency, but if CPI is low then the HRV signal is dominated by signal components at other frequencies than respiration. The recorded signals must then be carefully inspected, e.g. to detect cardiac arrhythmia or other factors that could explain the lack of the expected heart rate response.

Conclusion: To evaluate the reliability of the deep breathing test for detection of cardiac autonomic dysfunction in ATTR patients, we determined the coherent power index, CPI, as the fraction of HRV that was coherent with respiration. The study showed that CPI provided additional information to the conventionally used HRV indices, which can be used to identify subjects with "falsely" increased HRV scores due to non-autonomic responses during deep breathing.

Acknowledgements

This study was supported by the Swedish Research Council.

References

[1] Ewing DJ, Martyn CN, Young RJ, et al: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985, 8:491-498.

[2] May O, Arildsen H, Moller M: Parasympathetic function during deep breathing in the general population: relation to coronary risk factors and normal range. J Intern Med 1999, 245:287-294.

[3] Suhr OB, Gustavsson S, Heldestad V, et al: New insights into the clinical evaluation of hereditary transthyretin amyloidosis patients: a single center's experience. Degenerative Neurological and Neuromuscular Disease 2012, 2012:93-106.

[4] Coelho T, Maia LF, da Silva AM, et al: Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol 2013.

[5] Wiklund U, Hornsten R, Karlsson M, et al: Abnormal heart rate variability and subtle atrial arrhythmia in patients with familial amyloidotic polyneuropathy. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc 2008, 13:249-256.

[6] Hornsten R, Suhr OB, Olofsson BO, et al: Arrhythmia--a pitfall in tests of cardiac autonomic function after liver transplantation for familial amyloidotic polyneuropathy: a long-term follow-up of Swedish patients. Amyloid 2012, 19:81-86.

Address for correspondence:
Urban Wiklund, Department of Biomedical Engineering, Umeå University Hospital, SE-90185 Umeå, Sweden.
urban.wiklund@radfys.umu.se