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Normal scores of deep breathing tests: beware of dysrhythmia in transthyretin amyloidosis

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ABSTRACT

Background: The heart rate (HR) response to paced deep breathing (DB) is a common test of cardiac autonomic function, where high heart rate variability (HRV) is considered to reflect normal autonomic function. We evaluated the DB test in patients with hereditary transthyretin amyloid (ATTRm) amyloidosis, where autonomic dysregulation and atrial arrhythmias are common.

Methods: Paced DB was performed during one minute (six breaths/min) in 165 recordings in adult ATTRm amyloidosis patients with the TTR Val30Met mutation, 42 hypertrophic cardiomyopathy (HCM) patients and 211 healthy subjects. HRV was scored by traditional DB indices and by a novel regularity index, estimating the fraction of the HRV that was coherent with the breathing pattern.

Results: Twenty per cent of ATTRm amyloidosis patients presented with age-adjusted HRV scores within normal limits but poor regularity due to subtle atrial arrhythmias and cardiac conduction disturbances. Forty-seven per cent of ATTRm amyloidosis patients presented with HRV scores below normal limits, whereas HCM patients presented with higher HRV than ATTRm amyloidosis patients.

Conclusions: Reduced HRV is common in ATTRm amyloidosis patients during DB, however, autonomic function cannot be evaluated in patients presenting with the combination of “normal” scores and low regularity, since their HR responses often reflects dysrhythmias.

Abbreviations: ATTRm: mutated transthyretin amyloid protein; DB: deep breathing; DBI: deep breathing index (beats/min); FFT: fast Fourier transformation; FS: Fourier series; HCM: hypertrophic cardiomyopathy; HR: heart rate; HRV: heart rate variability; PTOT: total power of HRV; Rj: regularity index; TTR: transthyretin

Introduction

It is a well-recognized phenomenon that the heart rate is synchronized with respiration during deep breathing (DB), where the magnitude of the beat-to-beat fluctuations in the heart is considered to mirror the activity in the autonomic nervous system. Therefore, the DB test has been widely used to detect cardiovagal dysfunction in different diseases where neuropathies are common, e.g. in diabetes mellitus [1], as well as in healthy subjects [2–4]. The test is often performed with paced deep breathing at a rate of 6 breaths per minute during 40–60 s.

This study is focussed on the validity of the DB test in patients with hereditary transthyretin amyloid (ATTRm) amyloidosis. ATTRm amyloidosis is a severe disease where marked abnormalities in the cardiac autonomic regulation are common [5], as well as cardiac arrhythmias and conduction disturbances [6,7]. Since 1990, liver transplantation has been the only treatment available to halt the progression of ATTRm amyloidosis. However, the efficacy of new treatments is being investigated in on-going clinical trials, and the DB test was selected as one of the methods for scoring of autonomic function in the Tafamidis study [8]. DB is also recommended as one of the standard tests of autonomic function in ATTR amyloidosis [9].

We have not reported data from the DB test in our previous studies of cardiac autonomic function in ATTRm amyloidosis patients, which are based on analysis of heart rate variability (HRV). This is because we have questioned the reliability of this test for detection of cardiac autonomic dysfunction in this group of patients, which is mainly based on clinical observations of arrhythmias during DB. ATTRm amyloidosis patients often present with subtle atrial arrhythmias that may be difficult to separate from normal respiratory sinus arrhythmia. These arrhythmias can be noted both as small random variations in heart rate and as more complex heart rate patterns [10,11]. If such arrhythmias are undetected, HRV may be falsely increased and could lead to an incorrect scoring of the autonomic function [10,12].

Differences and similarities between ATTRm amyloidosis patients and hypertrophic cardiomyopathy (HCM) patients have been investigated in several previous studies of data
from other modalities. In echocardiographic examinations, ATTRm amyloidosis patients often present with increased myocardial thickness which resembles the hypertrophy found in HCM patients. Reduced HRV has also been found in HCM patients [13], but no previous study has compared HRV in ATTRm amyloidosis and HCM patients.

The aim of this study was to evaluate the ability of the DB test to detect cardiac autonomic dysfunction in ATTRm amyloidosis patients, focussing on the detection of autonomic dysregulation and subtle arrhythmias. Moreover, we also aimed to compare DB tests in ATTRm amyloidosis patients and patients with HCM. Our main hypothesis was that the majority of ATTRm amyloidosis patients would present with reduced HRV indicating cardiac autonomic dysfunction. However, we also hypothesized that subtle atrial arrhythmias would turn out to be a severe confounder when cardiac autonomic function is evaluated in ATTRm amyloidosis patients during the DB test, as it is in HRV recordings during spontaneous breathing. To detect arrhythmias, we also propose a novel regularity index, which is based on Fourier series analysis, to assess how well the heart rate follows the paced deep breathing pattern.

Materials and methods

This retrospective study is based on recordings from our clinical database, including 165 recordings in 89 ATTRm amyloidosis patients (46 men and 43 women, mean age 51 years, range 26–88 years). All subjects had been previously examined at the Department of Clinical Physiology, University Hospital, Umeå, Sweden. The recordings had been performed as part of their clinical evaluation before and after liver transplantation. All patients carried the TTR Val30Met mutation, and the diagnosis of ATTR amyloidosis had been verified histopathologically by the findings of ATTR deposits in skin, subcutaneous fat or intestinal biopsy specimens. In the majority of patients, no or only spurious extrasystolic beats were noted during DB, but four patients with frequent extrasystolic beats and two patients with atrial fibrillation were also included in the study.

We also evaluated recordings from 42 patients with hypertrophic cardiomyopathy (25 men and 17 women, mean age 53 years, range 17–80 years), including 20 patients on beta-blockade and 22 non-treated patients [13]. The control group consisted of recordings from 211 healthy individuals (107 men and 104 women, mean age 51 years, range 22–88 years), without any known autonomic or cardiovascular disease. All patients and healthy controls gave informed consent to participate, and the study was performed within the program for evaluation of ATTRm amyloidosis patients that has been approved by the Regional Ethical Review Board in Umeå, Sweden.

Study protocol

The subjects were instructed not to smoke, drink coffee, tea, or eat any larger meal 2 hours prior to the HRV recordings. After 10 minutes of supine rest, a continuous recording was started of a single-channel ECG and the breathing pattern. Free spontaneous breathing was continued for 6 minutes, followed by controlled deep breathing at a rate of six breaths per minute during one minute, where the operator instructed the patients when to inhale and exhale. The study protocol also included passive tilt to the upright position. HRV data during spontaneous breathing in the supine and upright positions have been published in previous studies in ATTR patients [12,14] and in HCM patients [13].

Data processing

All recordings were visually inspected to verify that the recorded ECG and respiration signals were of adequate quality and that the subject followed the paced breathing pattern. During the recording, the operator manually marked the start of the DB test, and the end-point was automatically marked 60 s after the start point. Heartbeats were automatically detected in the recorded ECGs, and the operator manually confirmed and edited all beats. The RR interval data were transformed into an evenly sampled (2 Hz) heart rate (HR) time series by cubic spline interpolation. The mean and linear trends were removed from all signals. The software used for recording and analysis was developed at our laboratory using the Matlab program (Mathworks Inc, Natick, MA).

Traditional indexes for evaluating the DB test

The overall response in heart rate was quantified by the commonly used deep breathing index (DBI), calculated as the average of the difference between the maximum and minimum heart rate within each of the six breathing cycles. This index is also referred to as the expiration/inspiration difference [3]. We also determined the variance of the HR data, which is equivalent to the total power ($P_{tot}$) of HRV.

Regularity analysis

In addition to the commonly used indices for scoring of autonomic function during DB, which are based on the amplitude of the heart rate response, we investigated a novel index based on Fourier series (FS) analysis to assess the regularity in the recorded signals. This index was designed to give a high value when heart rate follows the paced breathing pattern, whereas a low value indicates that the heart rate presents with a different pattern, which is the case when arrhythmias are present.

The DB test is performed with paced breathing during 60 s, where the duration of each of the six breathing cycles is 10 s, corresponding to a breathing frequency, $f_{cosp}$ equal to 0.1 Hz. Each signal, $x(n)$, was modelled as the sum of sinuses and cosines with different amplitudes and frequencies, according to

$$x(n) = \sum_{k=0}^{N-1} c_k e^{2\pi i k n / N}$$

(1)
\[ c_k = \sum_{n=0}^{N-1} x(n) e^{-j2\pi kn/N}, \tag{2} \]

where \( c_k \) are the FS coefficients, \( T \) is the sampling interval and \( N \) is the number of frequency components (\( N \to \infty \) for perfect reconstruction). By comparing the fitted model and the original data, we found that \( N = 18 \) components were sufficient to cover the expected frequency range of the signals (up to 0.3 Hz, see below), and used this number of components for all subjects. The length of the data sequence determines the fundamental frequency, i.e. the frequency of the first component in the model (1/60 Hz). Thus, the frequency of each component, \( f_k \), in the FS model is given by \( f_k = k/60 \) Hz.

The power of each signal component is given by \( P_k = |c_k|^2 \), which can be used to construct a line spectrum – a plot of power against component number (or component frequency). If the recorded signals are nearly sinusoidal, or present with a response which is nearly identical for all breathing cycles, the signals will have most power at the breathing frequency and its first two harmonics, i.e. in the 6th, 12th and 18th FS coefficients. This in turn corresponds to the frequencies 0.1 Hz, 0.2 Hz and 0.3 Hz.

As a measure of the cardiorespiratory interaction in the signals recorded during the deep breathing test, we defined a regularity index, \( R_I \), given by

\[ R_I = \frac{P_6 + P_{12} + P_{18}}{\sum_{k=1}^{18} P_k}. \tag{3} \]

Note that this corresponds to the fraction of the power of the signal that is coherent with the expected response, i.e. where the frequency components in the FS model appear at the paced breathing frequency and its harmonics.

For a signal with an identical cycle-by-cycle response, \( R_I \) will be equal to one, but normally we expect that \( R_I \) is somewhat lower than one. Similarly, if the recorded signals present with irregularities due to noise, arrhythmias or different types of modulation, such as amplitude or frequency modulation, FS components will appear at other frequencies resulting in a low value of \( R_I \).

\textbf{Statistical analysis}

All statistical analyses were performed using Matlab version 2016b (MathWorks Inc, Natick, MA) and IBM SPSS Statistics version 23.0 (IBM Inc. Armonk, NY). The agreement between the different HRV scores was assessed with Pearson’s correlation coefficient. Proportions between groups were compared using the Chi-squared test. A \( p \) values less than .05 was considered as statistically significant.

Age-adjusted HRV scores were determined based on linear regression analysis of logarithmically transformed data from controls, from which \( Z \)-scores were determined. DBI was age-corrected using the estimated age-dependency in controls as:

\[ \text{DBI}_{\text{AgeCorr}} = \log_{10}(\text{DBI}) - 0.0080 \times (50 - \text{age}), \tag{4} \]

where DBI is given in beats/min and age in years. \( Z \)-scores were then determined by subtracting the mean and dividing by the SD of age-corrected DBI for controls according to:

\[ \text{DBI}_{\text{Zscore}} = \frac{\text{DBI}_{\text{AgeCorr}} - 1.161}{0.213} \tag{5} \]

\textbf{Results}

Figure 1 shows examples of the recorded ECG and respiration signals in two ATTRm amyloidosis patients, where one presented with dysrhythmia. Patient A (DBI = 8.0 beats/min) presented the expected DB pattern with respiratory-related fluctuations in both the amplitude of the R waves and in the RR intervals. On the other hand, patient B (DBI = 26.1 beats/min) presented with intermittent decreases in RR intervals that were unsynchronized with the peaks in the respiration signal. After a close examination of the ECG, we concluded that patient B presented with varying p-wave morphology, reflecting a subtle multifocal atrial arrhythmia both before and during DB.

Figure 2 shows the corresponding HR tracings for these two and two other ATTRm amyloidosis patients as well as one control, where the results from the corresponding FS analysis are presented in Figure 3. As shown by the recorded respiration signals, all five subjects performed six complete

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Recorded ECG and respiration signals in two ATTRm amyloidosis patients during the first four cycles with paced deep breathing. Patient A presented the normal respiratory-related fluctuations in heart rate. Patient B presented a multifocal atrial arrhythmia, resulting in intermittent heart rate increases that were unsynchronized with the changes in the breathing signal.}
\end{figure}
breathing cycles. Since this study only included recordings with high quality of the recorded respiration signal, $R_t$ for the respiration signal was very high in all subjects, while $R_t$ for the HR signal varied from very low to very high values. Patient A showed a response that was considered to be normal: with high $R_t$ and a dominant component at the sixth harmonic, i.e. corresponding to the frequency 0.1 Hz. Patients B–D presented abnormal HRV patterns due to cardiac rhythm disturbances during the DB procedure, or also during spontaneous breathing as was the case for patient B. The dominant component was found at the fourth harmonic in patient B and C (Figure 3), where patient B presented with multifocal atrial arrhythmia both before and after DB, whereas patient C presented with second-degree atrio-ventricular block during DB. Patient D presented with low values of $R_t$ due to a broadband spectrum resulting from random fluctuations in heart rate during DB. The recording shown in panel E is from a subject in the control group who presented with intermittent episodes of nodal replacement beats.

There was a significant correlation ($r = 0.74$, $p < .001$) between DBI and $P_{tot}$. Therefore, we only present results in relation to DBI below. The overall relationship between DBI and $R_t$ is shown in Figure 4, where subjects were divided into two age groups since data showed a marked age dependency. Both DBI and $P_{tot}$ (not shown) decreased significantly with increasing age in controls ($p < .001$). A total of 55 recordings in ATTRm amyloidosis patients, nine HCM patients and seven controls presented with $R_t < 0.4$. Among those, DBI was higher than 10 beats/min in 26 ATTRm amyloidosis patients, three HCM patients and three controls – indicating marked heart rate responses where the dominating signal components appeared at other frequencies than the breathing frequency.

Table 1 summarizes the relation between the age-adjusted DBI scores and $R_t$. Considering age-adjusted DBI scores by themselves, reduced DBI ($z$-score$< -2$) were found in 78 recordings (47%) in ATTRm amyloidosis patients and in five (1%) controls ($p < .001$). The remaining 87 recordings (53%) in ATTRm amyloidosis patients presented with normal DBI scores, but when the regularity in the HR signal was taken into consideration, only 54 recordings (33% of all recordings) presented responses that can be considered as free of dysrhythmias, i.e. with $R_t > 0.4$. Reduced DBI was also found in 8 (19%) HCM patients ($p = .002$, HCM vs ATTR).

Correspondingly, low values of $R_t$ (<0.4) but normal age-adjusted DBI scores were found in 33 recordings in ATTRm amyloidosis patients. Twenty-three of these recordings presented with DBI in the upper normal region ($z$-score > 0), of which 18 recordings were performed in patients that were older than 50 years. Of these, six ATTRm amyloidosis patients had frequent extrasystolic beats or atrial fibrillation. A close inspection of the corresponding ECG recordings in the other 12 ATTRm amyloidosis patients, revealed that all had findings of more subtle arrhythmias, such as different types of cardiac conduction disturbances or atrial arrhythmias, resulting in heart rate fluctuations that were uncorrelated with the breathing pattern. Similar findings of subtle arrhythmias were noted in nine of the ATTRm amyloidosis patients with low regularity and where DBI was in the lower normal region. Several of those presented with high heart rate (>80 beats/min).

Recordings with reduced DBI and $R_t < 0.4$ in general presented with irregular heart rate patterns that could not be associated with arrhythmias. Two controls and two HCM patients also presented with low regularity and DBI scores in the upper normal region, where subtle arrhythmias were found in one control and one HCM patient. The control shown in Figure 2 (subject E) also presented with a subtle arrhythmia (intermittent nodal replacement beats, $R_t = 0.45$). Finally, the majority of recordings where $R_t$ was between 0.4–0.7 presented with amplitude modulated HR responses or baseline fluctuations. Amplitude modulation resulted in a dominating sixth component in the FS model, but with additional power in the sidebands, e.g. in the fifth and seventh coefficients. Baseline fluctuations in HRV, such as linear trends, resulted in a non-zero first coefficient in the FS model, also leading to a reduced $R_t$, in particular in subjects presenting low HRV.

**Discussion**

This study retrospectively analyzed HR responses during DB in a large cohort of recordings from ATTRm amyloidosis patients, HCM patients and healthy subjects. The DB test was able to detect cardiac autonomic dysfunction in 47% of the DB tests in ATTRm amyloidosis patients, as they presented with reduced HRV as compared to healthy controls. Although the other 53% of ATTRm amyloidosis patients presented DB scores within normal limits, only 33% were still considered as normal responses when the regularity in the HR signal was taken into consideration, whereas the other 20% presented with arrhythmias that precluded scoring of the autonomic function. Subtle arrhythmia was only found in one HCM patient and reduced HRV only found in few HCM patients.

**Deep breathing tests and subtle arrhythmias**

We have proposed an index based on Fourier series analysis that was useful to identify subjects where the scoring of autonomic function was precluded because of arrhythmias. Eleven patients with HRV scores in the upper normal region presented very low values of $R_t$, indicating that their HR fluctuations were uncorrelated with the breathing pattern. These patients had findings of atrial arrhythmias and conduction disturbances, but the conventional HRV index (DBI) was unable to distinguish these abnormal patterns from normal responses. Abnormal HR patterns due to frequent extrasystoles and atrial fibrillation could be detected directly after a visual inspection of the heart rate signal or the ECG recordings. However, the more complex HR responses of non-autonomic origin could only be detected after a careful inspection of the ECG recordings, which was performed by an operator with a solid experience in ECG interpretation. Thus, HR responses due to subtle
Figure 2. Deep breathing (DB) responses in (A–D) four ATTRm amyloidosis patients and (E) one control: recorded respiration (thin line, normalized) and heart rate (thick line, in beats/min). Dashed lines mark the start and end of the DB procedure. (A) normal response; (B) alternating bundle branch block both before and during DB; (C) second-degree atrio-ventricular block with onset during DB; (D) multi-focal atrial arrhythmia during DB; (E) a control subject presenting with alternating sinus beats and nodal replacement beats during DB.

Figure 3. Magnitude of Fourier series coefficients for the heart rate (left) and respiration (right) signals from the deep breathing test in the same five subjects as shown in Figure 2.
Arrhythmias could very well be missed in many subjects when only the traditional indices are used for scoring of the DB response, such as in subjects B, C and E in Figure 2. Thus, a more detailed analysis of the cardiorespiratory interaction is required. The proposed regularity index appears to meet this requirement since it is highly affected by arrhythmias. Thus, it serves as a complimentary index which helps to identify the subjects where autonomic function can be evaluated based on the DB test.

**The proposed regularity index**

Arrhythmias and other irregularities in the HRV signal generate signal components at other frequencies than at the breathing frequency. In this study, these additional signal components were detected by power spectrum analysis based on Fourier series analysis, which is well adapted for analysis of short recordings with repetitive patterns, such as signals with few cycles of the main oscillatory component. Our approach for determining the regularity index requires a recording with six breathing cycles, since we assume that only certain coefficients in the Fourier series model will be non-zero when HR is synchronized with respiration. Note that this approach also could be modified for other breathing frequencies and number of breathing cycles.

Another advantage with the Fourier series analysis is that the regularity in the HRV signal during DB can be analyzed without any additional recording of the respiration signal – provided that the pacing is performed in accordance with the hypothesized 10s breathing cycle pattern. In this study,

![Graph showing relationship between DBI and RI for different age groups](image)

**Figure 4.** Relationship between the deep breathing index (DBI) and the regularity index (RI) for subjects divided into groups according to age. Vertical lines indicate the thresholds used to divide data into different regularity regions: low regularity (RI < 0.4); moderate regularity (0.4 ≤ RI < 0.7); high regularity (RI ≥ 0.7). Horizontal lines show different reference levels of DBI. Shaded areas show subjects with high DBI but low regularity due to dysrhythmias.

<table>
<thead>
<tr>
<th>Table 1. Summary of age-adjusted HRV scores and regularity index (RI)</th>
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<tr>
<td>DBI*</td>
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<td>Upper normal</td>
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Data are number of subjects below/above 50 years. Bold numbers represent cases in regions where dysrhythmias were detected. High: > 0.7; Moderate: 0.4–0.7; Low: < 0.4.

*Z-score regions based on age-dependency in original DBI scores for controls. Upper normal: z > 0; Lower normal: −2 ≤ z ≤ 0; Reduced: −4 ≤ z < −2; Markedly reduced: z < −4.
we also analyzed the respiration signals to verify that subjects presenting with dysrhythmias had maintained a steady rhythm in breathing during the test.

**Interpretation of the regularity index**

By visual inspection of the HRV recordings, and in some cases also of the ECG, we found that the threshold \( R_I < 0.4 \) was suitable for defining abnormal non-autonomic responses, i.e. responses where HRV was unsynchronized with respiration. In these recordings, the sixth component in the FS model of the HR signals was very small. On closer inspection of the corresponding ECGs, we observed that these responses were found in subjects with cardiac conduction disturbances and atrial arrhythmias. Moreover, as we previously have noted during our clinical examinations, several ATTRm amyloidosis patients that developed cardiac arrhythmia during the DB test presented with markedly reduced HRV during spontaneous breathing.

Low values of \( R_I (<0.4) \) were also found in some patients that presented with markedly reduced HRV, which probably was due to severe parasympathetic dysregulation. There were also patients that presented with very low HRV scores but high values of \( R_I \). This could possibly reflect that respiration caused a pure mechanical modulation, such as stretching of the sinus node, or it could indicate that the patient had some small residual cardiovagal modulation.

Recordings with \( R_I \) in the range of 0.4–0.7 in general presented with a marked DB response, but with baseline fluctuations or different types of amplitude modulation that were found in the HRV signal but not in the recorded respiration signal. Other methods for analyzing the co-variation in the two signals could possibly enhance the differences between subjects with amplitude modulation in the breathing signal, who still have an HRV response that is synchronized with respiration, from those with dysrhythmias despite a regular breathing signal.

In the control group, the subjects that presented with somewhat reduced values of \( R_I \) (between 0.4 and 0.7) were mainly found among old subjects. Therefore, the more marked irregularity in HRV at older age could possibly also reflect a degradation in the parasympathetic nervous system, as also indicated by the successive reduction in HRV with increasing age. However, this finding needs to be investigated in further studies, where any eventual irregularity in the breathing signal is analyzed in more detail than in the present study.

**Deep breathing and autonomic responses**

Although DB mainly is a test of cardiovagal activity [15], HRV measured during deep breathing is relatively difficult to interpret. During spontaneous breathing, the breathing frequency normally is higher (0.2–0.3 Hz), and the power spectrum shows peaks in two or three different regions. The fraction of power of each spectral component has in turn been associated with activity in different parts of the autonomic nervous system [16]. During the DB test, the variability is concentrated to one peak in the HRV power spectrum (located at the frequency 0.1 Hz). Thus, the DB test cannot be used to separate the effects of parasympathetic and sympathetic modulation, or the effect of a pure mechanical modulation resulting from stretch of the sinus node. Still, our results showed that reduced HRV due to reduced cardiovagal modulation is a very common finding in ATTR patients during the DB test, which support previous findings in HRV recordings during spontaneous breathing [10,17,18]. We also found that subtle arrhythmia is a severe confounder also during DB, as it is during spontaneous breathing [10,12]. Moreover, the estimated age-dependency in HRV in the healthy controls was similar to previously published data [3,19]. Finally, we presented the majority of HRV results based on the DBI score, but the high correlation between \( P_{tot} \) and DBI indicate that these two indices can be regarded as almost interchangeable for scoring the overall HR response during DB.

**Additional methodological considerations**

In this study, the analysis of cardiorespiratory interaction was performed using FS analysis. We have evaluated other frequency domain methods in a preliminary study [20]. However, FS analysis is better-suited for modelling of short recordings than the fast Fourier transformation (FFT) method. One severe drawback with the FFT method is that data normally are windowed, i.e. multiplied with a bell-shaped function, which in turn introduces distortion if the analyzed segment only includes a few cycles of the signal, since the amplitude of signal’s first and last cycles will be close to zero after windowing. Autoregressive modelling is another commonly used method, but the selection of model order is crucial and also determines the number and location of spectral peaks. Therefore, in this study we considered the FS methodology to be superior to the other methods for analysis of the DB data.

**Conclusions**

Since the proportion of ATTRm amyloidosis patients with non-autonomic heart rate responses was so high, the DB test should not be used for scoring autonomic function in ATTRm amyloidosis patients, unless the corresponding ECG recordings are carefully scrutinized for signs of atrial arrhythmias and conduction disturbances. Reduced HRV during DB, indicating cardiac autonomic dysfunction, is a common finding in ATTRm amyloidosis patients. However, whenever an ATTRm amyloidosis patient present with DB scores within normal limits, there is still a very distinct possibility that the HR response is caused by subtle arrhythmias, which can be detected by the combination of a low value of the regularity index and a high DBI. Knowing that the deep breathing test is used for scoring of autonomic function in on-going studies for evaluation of the efficacy of new treatments for ATTR amyloidosis, these findings are very important.
Disclosure statement

The authors report no conflict of interest.

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