Elsevier Editorial System(tm) for Journal of Electrocardiology
Manuscript Draft

Manuscript Number:

Title: Discrimination of coronary artery disease patients by heart rate variability analysis during exercise stress testing. STAFF.

Article Type: Research Paper

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Abstract: In this study the dynamics of the autonomic nervous system (ANS) regulation on the heart during exercise stress testing (EST) have been compared between a group of coronary artery disease patients and a group with Framingham risk index lower than 5%. The ANS activity has been assessed using a methodology which comprises estimation of the ANS modulating signal dividing the HRV signal by the time-varying mean HR and redefinition of the classical high frequency (HF) band to include respiratory frequencies above 0.4 Hz. Indices related to the ANS activity obtained a moderate discrimination accuracy of 76%, which increased to 86% when other HF components non-related to respiratory sinus arrhythmia were considered. The main conclusion of this work is that care should be taken in the interpretation of HRV parameters and their diagnostic performance if information on the time-varying mean HR and respiratory frequency during EST are not taken into account.

Dr. Galen Wagner,
Editor-in-Chief of Journal of Electrocardiology

Dear Galen,
I submit the enclosed manuscript for you consideration to be published in the Journal of Electrocardiology. This is an original research paper presented in the STAFF meeting and conducted via the collaboration between the Aragon Institute of Engineering Research and the School of Medicine of the University of Zaragoza.
The aim of the present manuscript is to assess whether autonomic nervous system activity measured from heart rate variability analysis during exercise stress testing is capable of discriminating between coronary artery disease (CAD) patients and low CAD-risk subjects referred for stress testing.

I'm looking forward to your news.
Best regards,
Raquel Bailón
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Discrimination of coronary artery disease patients by heart rate variability analysis during exercise stress testing. STAFF.

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Short title: Discrimination of CAD by HRV during stress testing

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ACKNOWLEDGMENTS

This study was supported by Ministerio de Ciencia e Innovación, Spain, under Project TEC2010-21703-C03-02 and TRA2009-0127, by the Diputación General de Aragón (DGA), Spain, through Grupos Consolidados GTC ref:T30, and by ISCIII, Spain, through CIBER CB06/01/0062.

Abstract

In this study the dynamics of the autonomic nervous system (ANS) regulation on the heart during exercise stress testing (EST) have been compared between a group of coronary artery disease patients and a group with Framingham risk index lower than 5%. The ANS activity has been assessed using a methodology which comprises estimation of the ANS modulating signal dividing the HRV signal by the time-varying mean HR and redefinition of the classical high frequency (HF) band to include respiratory frequencies above 0.4 Hz. Indices related to the ANS activity obtained a moderate discrimination accuracy of 76%, which increased to 86% when other HF components non-related to respiratory sinus arrhythmia were considered. The main conclusion of this work is that care should be taken in the interpretation of HRV parameters and their diagnostic performance if information on the time-varying mean HR and respiratory frequency during EST are not taken into account.

Introduction

Impairment of autonomic cardiac regulation has been observed in many diseases including ischemic coronary artery disease (CAD), which has been suggested to destroy cardiac receptors resulting in altered autonomic regulation (1). The activity of the autonomic nervous system (ANS) on the heart is usually assessed noninvasively by means of spectral analysis of heart rate variability (HRV), which, in resting conditions, reveals the existence of three main components: a very low frequency (VLF) component in the range between 0 and 0.04 Hz, a low frequency (LF) component between 0.04 and 0.15 Hz, and a high frequency (HF) component between 0.15 and 0.4 Hz (2). The power in the HF band is considered to be a measure of parasympathetic activity, mainly due to respiratory sinus arrhythmia (RSA). The power in the LF band is considered to be a measure of sympathetic and parasympathetic activity, together with other regulatory mechanisms such as the rennin-angiotensin system and baroreflex (3), although its interpretation is still controversial.

It has been reported that HRV is altered among patients with stable CAD, even before the development of symptoms (1). It has also been reported that alterations in HRV correlates with the development and severity of CAD (1, 4). Exercise stress testing (EST) is routinely used for the diagnosis of CAD. Heart rate (HR) response to exercise and HR recovery from exercise have been shown to predict cardiovascular prognosis (5, 6), and HR profile during exercise has been associated with the severity of CAD (7). However, the prognostic value of HRV during EST is controversial and has not been elucidated yet. Some studies have reported indices obtained from stress testing HRV having added value in the diagnosis of CAD (8), and in cardiovascular and all-cause mortality prognosis (9). On the contrary, HRV during exercise did not exhibit mortality prognostic value in the Finnish Cardiovascular study (FINCAVAS) (10).

There are three main concerns in the analysis of HRV during EST which, if not taken into account, may lead to erroneous interpretation of the evolution of the ANS activity: i) local mean HR is time-varying; ii) HRV during EST is highly non-stationary; iii) respiratory frequency increases with workload and may exceed the upper limit of the classical HF band, 0.4 Hz.

The fact that local mean HR is time-varying during EST makes it necessary to correct HRV before the evolution of the ANS activity is assessed from it. The reason is that mean HR influences HRV measurements as markers of autonomic function (11). Recently, an approach for HRV analysis during EST has been proposed based on the integral pulse frequency modulation (IPFM) model where a time-varying threshold is included to account for the time-

varying mean HR (12). The proposed approach estimates the ANS modulating signal dividing the HRV signal by the time-varying mean HR.

Several approaches to non-stationary analysis of HRV have been proposed in the literature (13), of which time-frequency (TF) methods are the most common. The smoothed pseudo Wigner-Ville distribution (SPWVD) has been widely used due to its good time-frequency resolution and independent control of time and frequency filtering, using different approaches to reduce the effect of cross terms (14).

Finally, the fact that respiratory frequency is not restricted to the classical HF band during EST makes it necessary to redefine the HF band (15). The HF band can be extended to include the whole range of possible respiratory frequencies, or it can be centered on the respiratory frequency, if an estimate of it is available.

The purpose of this study is to assess whether ANS activity measured from HRV analysis during EST is capable of discriminating between CAD patients and low CAD-risk subjects referred for EST. The methodological approach used to assess ANS activity comprises: i) estimation of the ANS modulating signal dividing the HRV signal by the time-varying mean HR, ii) non-stationary analysis of the estimated ANS modulating signal by means of the SPWVD, iii) redefinition of the HF band to include respiratory frequencies above 0.4 Hz.

Methods and Materials

Study population and acquisition

A database recorded in the University Hospital Lozano Blesa of Zaragoza, Spain, consisting in the standard 12-lead ECG of patients referred for a treadmill exercise test following Bruce protocol, was analyzed. The usual pharmacologic treatment was not varied before any exercise test. Antianginal medications were not taken prior to exercise test. The ECG leads were recorded at 1 kHz sampling rate with an amplitude resolution of 0.6 μV. The investigation conformed to the principles outlined in the Declaration of Helsinki. The procedures and protocols used in this study were approved by the Ethics Committee of the Hospital. Informed consent was obtained from all subjects prior to data collection.

Patients were classified into two different groups:

1) *Ischaemic*: patients with significant stenoses in at least one major coronary artery, as revealed by coronary angiography (used as gold standard).
2) *Low-risk:* patients with Framingham risk index lower that 5%. Framingham risk algorithm computes the 10 year predicted risk of developing manifest CAD using data relating to several risk factors (age, total and HDL cholesterol, blood pressure,

diabetes and smoking) (16). Only patients with information of at least four risk factors were considered. Three of the patients classified as *low-risk* by Framingham index were indeed *ischaemic*, as revealed by coronary angiography, and were then excluded from this group. All patients in this group presented a negative clinical and electrical exercise test.

Since the purpose of the study was to analyze HRV evolution during exercise and recovery, only patients presenting no arrhythmias nor excessive number of ectopic beats, with at least 3 minutes of exercise and 3 minutes of recovery, were considered. Moreover, since one of the redefinitions of the HF band is centered on the respiratory frequency, only patients for which respiratory frequency could be estimated more than 50% of the total duration of the recording and with successive respiratory frequency estimates separated no more than 3 minutes, were considered.

Some study population characteristics are shown in Table 1. More information on the database can be found in (8).

The integral pulse frequency modulation model with time-varying threshold (TVIPFM)

In order to estimate the dynamic changes of the ANS activity from the available information, which are the QRS detection marks, obtained in this study by ARISTOTLE (17), the TVIPFM model proposed in (12) was used. First, an instantaneous HR signal $d_{HR}(n)$ is estimated from the QRS detection marks following a method based on the IPFM model which accounts for the presence of ectopic beats (18), and it is sampled at a sampling rate of F_s = 4 Hz. Then, a time-varying mean HR signal $d_{HRM}(n)$ is obtained by low-pass filtering $d_{HR}(n)$ with a cut-off frequency of 0.03 Hz. The HRV signal is computed as $d_{HRV}(n) = d_{HR}(n) - d_{HRM}(n)$. Finally, the ANS modulating signal $m(n)$ is obtained correcting the HRV signal by the time-varying mean HR, as proven in (13) to be necessary, $m(n) = d_{HRV}(n) / d_{HR}(n)$.

Signals $d_{HR}(n)$, $d_{HRM}(n)$ and $m(n)$ are displayed in Figure 1 for an *ischaemic* and in Figure 2 for a *low-risk* patient.

The smoothed Pseudo Wigner-Ville distribution

The non-stationary analysis of the ANS modulating signal $m(n)$ was performed by means of the SPWVD

$$P_m(n,v) = 2\sum_{k=-K+1}^{K-1} h(k)\left[\sum_{n'=-N+1}^{N-1} g(n')a_m(n+n'+k)a_m^*(n+n'-k)\right]e^{-j2\pi\frac{v}{M}k}$$

where *n* represents time index, *v=-M+1,..., M* frequency index, $a_m(n)$ is the analytic signal of *m(n)*, and *h(k)* and *g(n)* represent the time and frequency smoothing windows, respectively. In this study, *g(n)* was chosen as a rectangular window of length *2N-1* and *h(k)* as an exponential window with damping factor γ. Used parameters values (12) are reported in Table 2.

Finally, the power of the LF and HF components were computed at each time instant *n* integrating $P_m(n,v)$ over the LF and HF bands, respectively.

Frequency bands definition

In this study the LF band is defined in its standard way, i.e. from 0.04 to 0.15 Hz, while two approaches are considered in the definition of a time-varying HF band (15):

1) *HF1*: the HF band is extended to include the whole range of potential respiratory frequencies, being the upper limit given, at each time instant, by half the time-varying mean HR, which is the maximum frequency with physiological meaning.
2) *HF2*: the HF band is centered on the respiratory frequency, derived from the ECG using the method in (19), and has a bandwidth of 0.14 Hz, being the bandwidth reduced when required to avoid the lower limit to be lower than 0.15 Hz and the upper limit to be higher than half the time-varying mean HR.

Figure 3 displays the SPWVD of the ANS modulating signal *m(n)* for an *ischaemic* patient, where the limits of the LF and HF (*HF1*and *HF2*) bands are shown.

Clinical indices

In order to compare the dynamics of the ANS activity during EST in the *ischaemic* and *low-risk* patients, the power in the LF band, $P_{LF}(n)$, and in the HF band, considering definitions HF1 and HF2, $P_{HF1}(n)$ and $P_{HF2}(n)$, respectively, were evaluated at different time instants: the first minute of the recording (n_1), three minutes before stress peak (n_{3p}), one minute before stress peak (n_{1p}), stress peak (n_p), one minute after stress peak (n_{p1}), and three minutes after stress peak (n_{p3}). Stress peak was defined as the instant of maximum time-varying mean HR. Time-varying mean HR $d_{HRM}(n)$ as well as the ECG-derived respiratory frequency $F_R(n)$ were also evaluated at n_1, n_{3p}, n_{1p}, n_p, n_{p1} and n_{p3}.

Figures 4 and 5 display $P_{LF}(n)$, $P_{HF1}(n)$ and $P_{HF2}(n)$ for an *ischaemic* and a *low-risk* patient, respectively; time instants n_1, n_{3p}, n_{1p}, n_p, n_{p1} and n_{p3} have been marked.

Statistical analysis and classification

First, the non-parametric Kruskal-Wallis approach was applied to the clinical indices to compare their medians between the *ischaemic* and *low-risk* patients.

Then, multivariate discriminant analysis was used to identify the clinical indices which best classify patients into the *ischaemic* and *low-risk* groups. Feature selection was performed using the stepwise approach based on Wilk's lambda minimisation criterion. The number of selected features was truncated, when necessary, to follow the criterion of *number of variables* < *(smallest group size)*$^{1/2}$. Classification results (sensitivity *SE*, specificity *SP*, positive predictive value *P+*, negative predictive value *P-*, and exactness *EX*) were obtained by *leave-one-out* cross-validation.

Discriminant analysis assumes that variables are normally distributed. However, clinical indices based on the power of the LF and HF bands did not satisfy the normality assumption, as revealed by the Kolmogorov-Smirnov test (p<0.05). For that reason indices $P_{LF}(n_i)$, $P_{HF1}(n_i)$, and $P_{HF2}(n_i)$, with $n_i \in \{n_1, n_{3p}, n_{1p}, n_p, n_{p1}, n_{p3}\}$, were logarithmically transformed prior to the discriminant analysis.

Results

Table 3 displays mean, SD and median of the clinical indices in the *ischaemic* and *low-risk* groups as well as those indices which were significantly different in both groups (p < 0.05, 0.01) as revealed by the Kruskal-Wallis test.

The power of the LF band evaluated at the first minute was significantly lower in the *ischaemic* group with respect to the *low-risk* group, while it was significantly higher when evaluated at stress peak. The power of the HF band centered on the respiratory frequency (*HF2*) evaluated three minutes before stress peak and one and three minutes after stress peak was significantly higher in the *ischaemic* group with respect to the *low-risk* group. Note that the power of the HF band extended from 0.15 Hz to half the time-varying mean HR (*HF1*) is higher than the power of *HF2* since it may include, besides RSA, other components (14), as depicted in Figure 6, which displays the SPWVD of an excerpt of the ANS modulating signal corresponding to a *low-risk* patient. The power of *HF1*evaluated at the first minute and at stress peak was significantly higher in the *low-risk* group with respect to the *ischaemic* group. Respiratory frequency evaluated at one minute before and at stress peak was significantly lower in the *ischaemic* group with respect to the *low-risk* group, as it happened with the time-varying mean HR evaluated at every time instant except for the first minute.

Multivariate discriminant analysis was applied independently to different subsets of features: i) ANS-related indices, i.e. the power in the LF and HF band (*HF1* and *HF2* were studied

separately), ii) respiratory frequency indices, iii) time-varying mean HR indices, iv) all clinical indices. Classification results are displayed in Table 4. Classification features used in each case are listed in the same order as selected by the stepwise method, together with the standardized canonical discriminant function coefficients.

Discussion

Methodological aspects

The shortcomings of extending interpretation of classical HRV analysis at rest to the setting of dynamic exercise have been already pointed out (3, 9), and may explain the differences found in different studies both in healthy subjects (20) and in patients (9, 10).

In this paper the dynamics of the ANS activity during EST have been assessed using a method which comprises: i) estimation of the ANS modulating signal based on the TVIPFM model which takes into account the time-varying mean HR, ii) non-stationary analysis based on the SPWVD, iii) redefinition of the HF band to include respiratory frequencies above 0.4 Hz.

It has been shown that mean HR influences HRV parameters as markers of autonomic activity (11, 12), for example, if the power of the LF and HF components are obtained from the HR signal (heart period signal), an increase in mean HR leads to an overestimation (underestimation) of the ANS modulating signal (12). This justifies the necessity of correcting the HRV signal during EST with the time-varying mean HR before the evolution of the ANS activity is assessed from it. This is extremely important in our study, not only because the mean HR is time-varying during EST, but also because mean HR during exercise and recovery is significantly higher in the *low-risk* group with respect to the *ischaemic* group (see Table 3).

To overcome the limitation that respiratory frequency during EST may exceed the upper limit of the classical HF band, 0.4 Hz, two approaches have been considered in this study. Approach *HF2* requires the knowledge of respiratory frequency, which can be obtained either from a simultaneous recorded respiratory signal or from an ECG-derived respiratory signal, using e.g., as in this study, the method described in (19). This method is not applicable in some situations, e.g. when respiratory signal does not exhibit a unimodal pattern or when HR is lower than twice the respiratory frequency. On the other hand, approach *HF1* does not rely on any prior information, but may include not only the RSA but also other HF components which may be unrelated to the parasympathetic system activity. For example, a component synchronous with the pedalling, most likely unrelated to parasympathetic activity, is sometimes present in EST performed on bicycle ergometer (21, 22). Although the presence of

a similar component in treadmill exercise testing has not been reported in literature, the fact is that in our study population power in *HF1* was significantly higher ($p < 0.001$) than in *HF2* for all time instants considered, which suggests the presence in *HF1* of other components besides RSA (see Figure 6).

CAD diagnostic performance of the clinical indices was evaluated using multivariate discriminant analysis. However, other classification methods, such as support vector machine, may obtain better classification results than discriminant analysis, as reported in (23).

Physiological aspects

In this study the dynamics of the ANS activity during EST have been compared in two groups of patients referred for treadmill EST: *ischaemic* and *low-risk*.

The power in the LF band evaluated at the first minute of the recording was significantly lower in the *ischaemic* group with respect to the *low-risk* group, while it was significantly higher when evaluated at stress peak. In FINCAVAS lower LF power during the first minute of exercise was associated with increased risk of mortality (10), and in (9) lower LF power during recovery was significantly associated with increased all-cause and cardiovascular mortality. In our study, the LF power evaluated at three minutes after stress peak was lower in the *ischaemic* group, but the difference with respect to the *low-risk* group was not significant.

Regarding the power in the HF band, higher power in *HF2* evaluated three minutes before stress peak and one and three minutes after stress peak was significantly higher in the *ischaemic* group with respect to the *low-risk* group. This result is in agreement with (9), where higher HF power during recovery turned out to be significantly associated with increased all-cause and cardiovascular mortality (9). However, these results contrast with those obtained at rest, where decreased HF power has been observed in CAD patients (1, 4), and with those obtained in FINCAVAS, where none of the HRV parameters at peak exercise or during the recovery phase were associated with mortality (10).

If the power in *HF1* is considered, it turns out that at the first minute and at stress peak it was significantly higher in the *low-risk* group, suggesting a higher presence of HF components non-related to RSA in this group. In fact, when classification performance of ANS-related indices was assessed, using the power in *HF1* instead of in *HF2* increased both SE and SP (from 75% to 85% and from 79% to 90%, respectively). These HF components non-related to RSA have an uncertain origin, but they may be related to the pedalling component found in EST performed on bicycle ergometer, which originates from a dynamic modulation of venous return by rhythmic limb muscles contractions, and whose power increases with workload

(21). The venous return modulation is likely to induce a rhythmic stretching of the sinus node, which modulates HR. There are some works in running subjects reporting a blood pressure modulation at the stride rate (24), which may be the origin of the HF components non-related to RSA. If our hypothesis that the HF components non-related to RSA observed in our study are similar to the pedalling component found in bicycle stress testing is true, the increase in classification accuracy obtained by *HF1* with respect to *HF2* may be justified by the higher workloads supported by the *low-risk* group, as revealed by the minutes of exercise (12.1±13.6 in the *low-risk* and 6.2±2.7 in the *ischaemic*) and the percentage of the theoretical maximum HR achieved in the EST (95±3% in the *low-risk* and 79±18% in the *ischaemic*).

In (8) classical HRV frequency indices obtained a classification accuracy over the same database of this study of 89%, and up to 93% when HRV time and frequency indices were combined. However, there is a limitation in the interpretation of those indices as ANS activity markers. First, as the influence of the mean HR was not corrected, those indices may include information on the mean HR changes during EST, which, as displayed in Table 4, achieves a classification accuracy of 90%. Then, classical HF band (0.15-0.4 Hz) was used in conjunction with a new band, the very high frequency band (VHF) which extended from 0.4 to 1 Hz. In Table 3 it can be observed that respiratory frequency exceeds the upper limit of the classical HF band during exercise and recovery in both groups, making the interpretation of the classical HF and VHF power difficult. Finally, one of the classification variables which was included and selected in the analysis was the slope of the linear detrending of the HRV signal in each analyzed period, which, in fact, is accounting for the changes in the mean HR which, as previously stated, showed high classification accuracy.

The classification performance of the respiratory frequency and the time-varying mean HR was also evaluated. Respiratory frequency one minute before stress peak obtained a classification accuracy of 74%, which may also be related to the different workloads supported by the *ischaemic* and *low-risk* groups. A combination of the mean HR at the first minute and at stress peak obtained a SE=88% and a SP=93%, and when information of the power in *HF1* and respiratory frequency is included SE increased to 93%. However, the power in *HF2* did not add any classification improvement to the time-varying mean HR indices. The high classification accuracy achieved by the time-varying mean HR indices is in agreement with (7), where it was shown that decreased HR increment and decreased HR decrement during exercise and recovery is strongly associated with the severity of CAD. However, in our study population, the classification accuracy of time-varying mean HR

indices may be justified by the difference in mean ages between the *ischaemic* and *low-risk* groups, as well as the negative chronotropic drugs taken by some patients.

Limitations.

One of the limitations of this study is that there exists a bias in the study population since the traditional interpretation of EST influence the decision to perform a coronary angiography. This limitation is unavoidable in studies which use coronary angiography as gold standard since it is unviable to perform a coronary angiography to all patients independently of the EST results.

Conclusions

In this study the dynamics of the ANS regulation on the heart during EST have been assessed using a methodology which comprises: i) estimation of the ANS modulating signal dividing the HRV signal by the time-varying mean HR, ii) non-stationary analysis of the estimated ANS modulating signal, iii) redefinition of the HF band to include respiratory frequencies above 0.4 Hz, either extending the HF band from 0.15 Hz to half the mean HR or centering the HF band on the respiratory frequency.

Then, it was assessed the ability of indices related to the ANS activity during EST to discriminate two groups of patients referred for treadmill exercise test: a group of CAD patients and a group with Framingham risk index lower than 5%. Indices related to the ANS activity at rest (power in the LF band and RSA) obtained a moderate discrimination accuracy of 76%, which increased to 86% when other HF components non-related to RSA were considered. When indices related to the mean HR were considered classification accuracy reached 95%, although a 90% was already achieved using only the mean HR at the first minute and at stress peak. The main conclusion of this work is that care should be taken in the interpretation of HRV parameters and their diagnostic performance if information on the time-varying mean HR and respiratory frequency are not taken into account, since, otherwise, HRV itself indirectly includes HR and other extra components non-related to the ANS.

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TABLE CAPTIONS

Table 1. Study population characteristics.

Table 2. Parameter values used in the SPWVD.

Table 3. Mean SD and p-*value of the clinical indices in the* ischaemic *and* low-risk *groups.*

Table 4. Classification results: ischeamic *versus* low-risk *groups*

FIGURE CAPTIONS

Figure 1. Signals (a) $d_{HR}(n)$, (b) $d_{HRM}(n)$ and (c) m(n) for an ischaemic *patient. Time instants n_1, n_{3p}, n_{1p}, n_p, n_{p1} and n_{p3} are marked.*

Figure 2. Signals (a) $d_{HR}(n)$,(b) $d_{HRM}(n)$ and (c) m(n) for a low-risk *patient. Time instants n_1, n_{3p}, n_{1p}, n_p, n_{p1} and n_{p3} are marked.*

Figure 3. SPWVD of m(n) corresponding to an ischaemic *patient, limits of the LF and* HF1 *bands are shown in dashed lines, and of* HF2 *in dotted line.*

Figure 4. (a) $P_{LF}(n)$, (b) $P_{HF1}(n)$ and (c) $P_{HF2}(n)$ for an ischaemic *patient.*

Figure 5. (a) $P_{LF}(n)$, (b) $P_{HF1}(n)$ and (c) $P_{HF2}(n)$ for a low-risk *patient.*

Figure 6. SPWVD of m(n) during the exercise phase corresponding to a low-risk *patient, , limits of the LF and* HF1 *bands are shown in dashed lines, and of* HF2 *in dotted line.*

Figure(s)

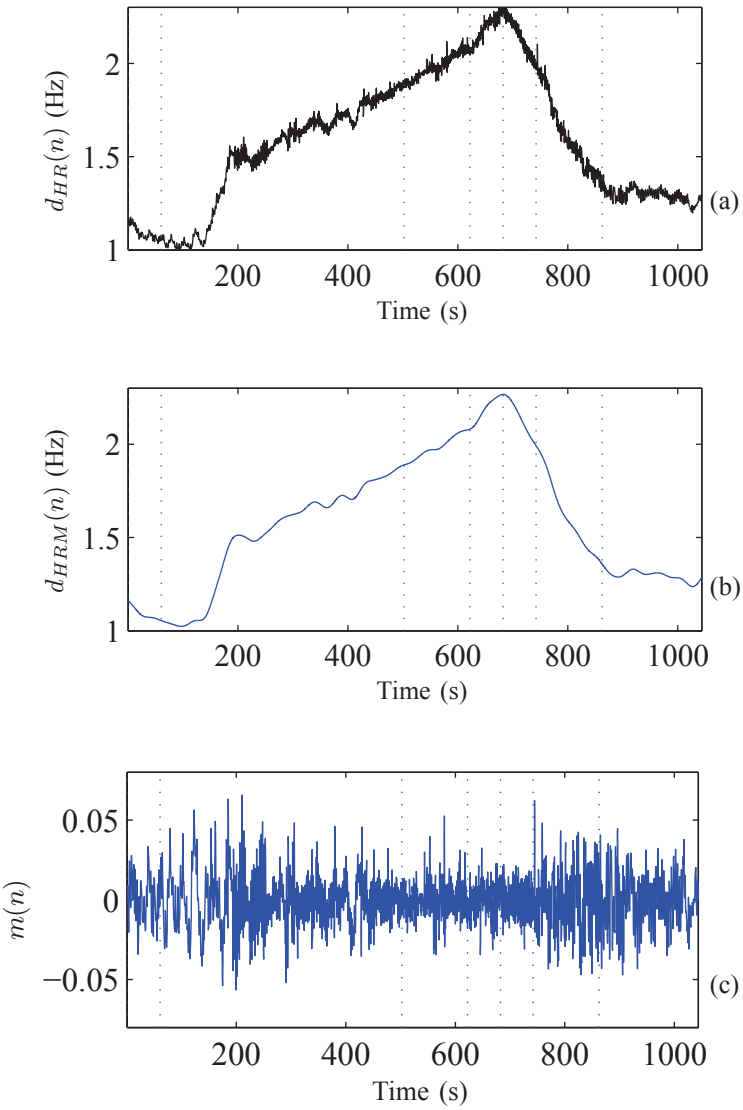

Fig. 1.

Figure(s)

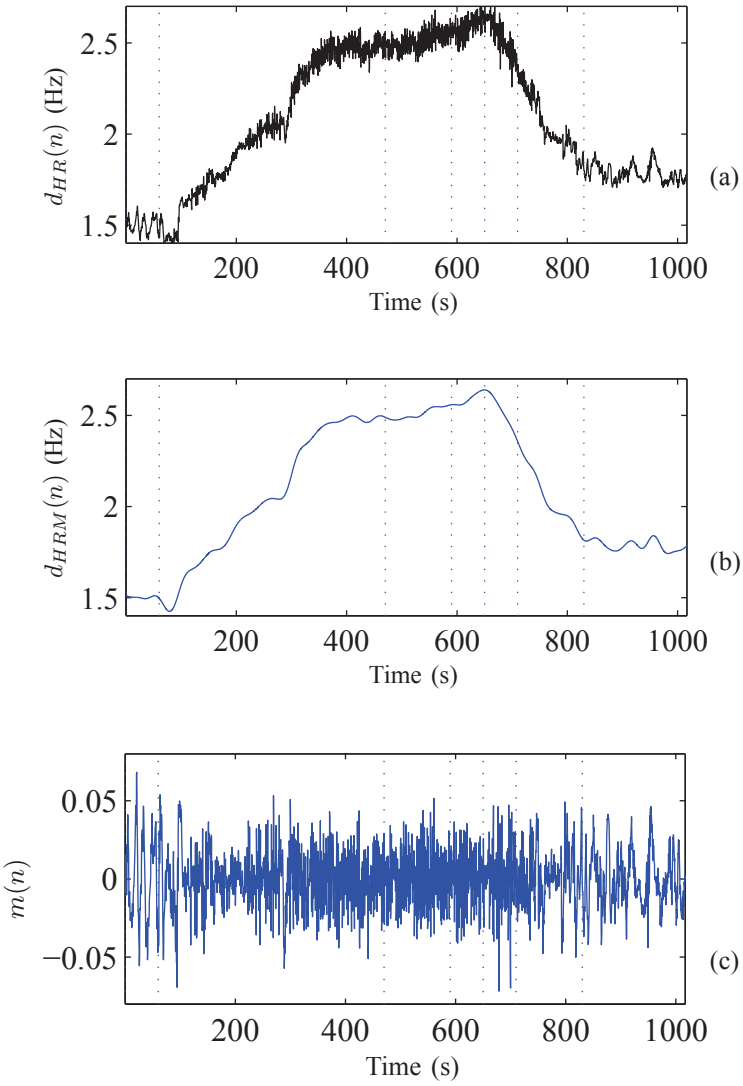

Fig. 2.

Figure(s)

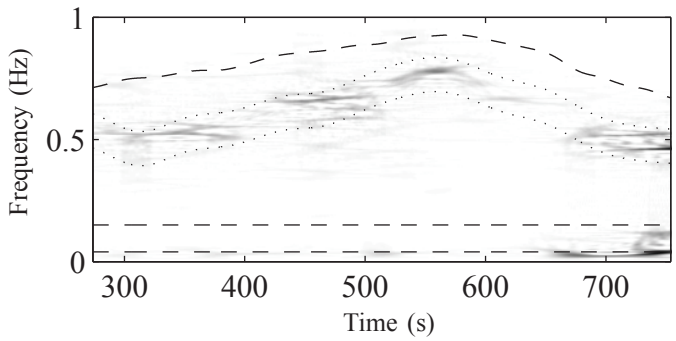

Fig. 3.

Figure(s)

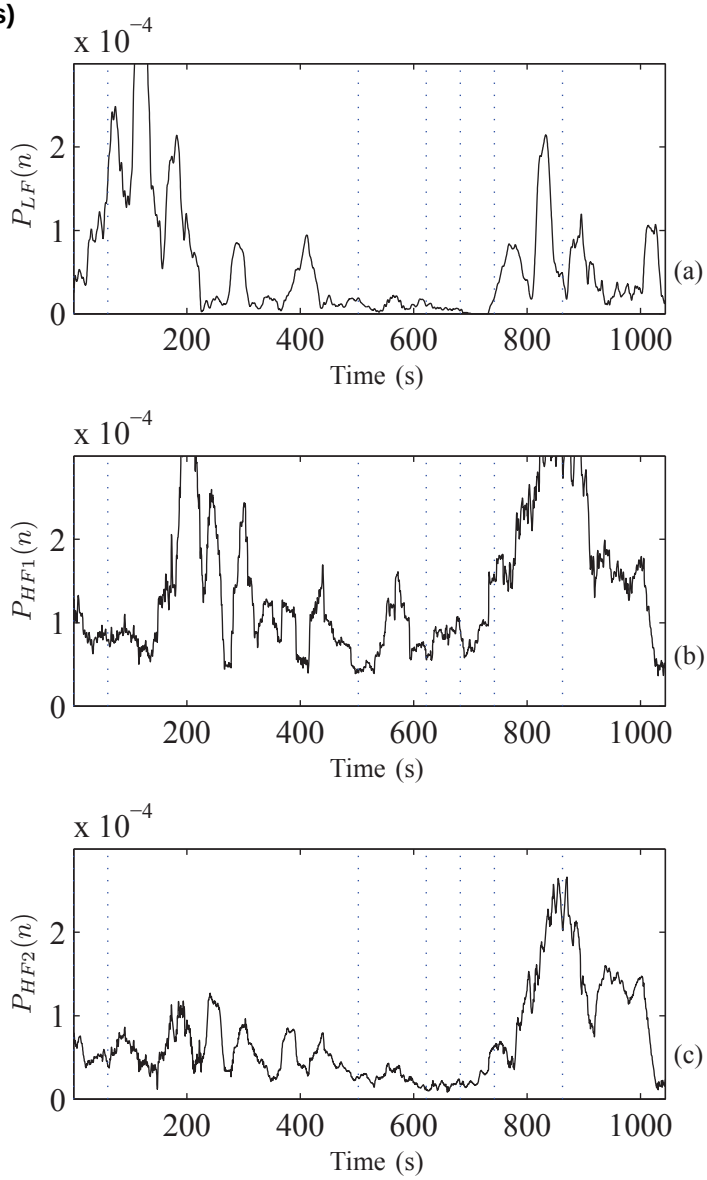

Fig. 4.

Figure(s)

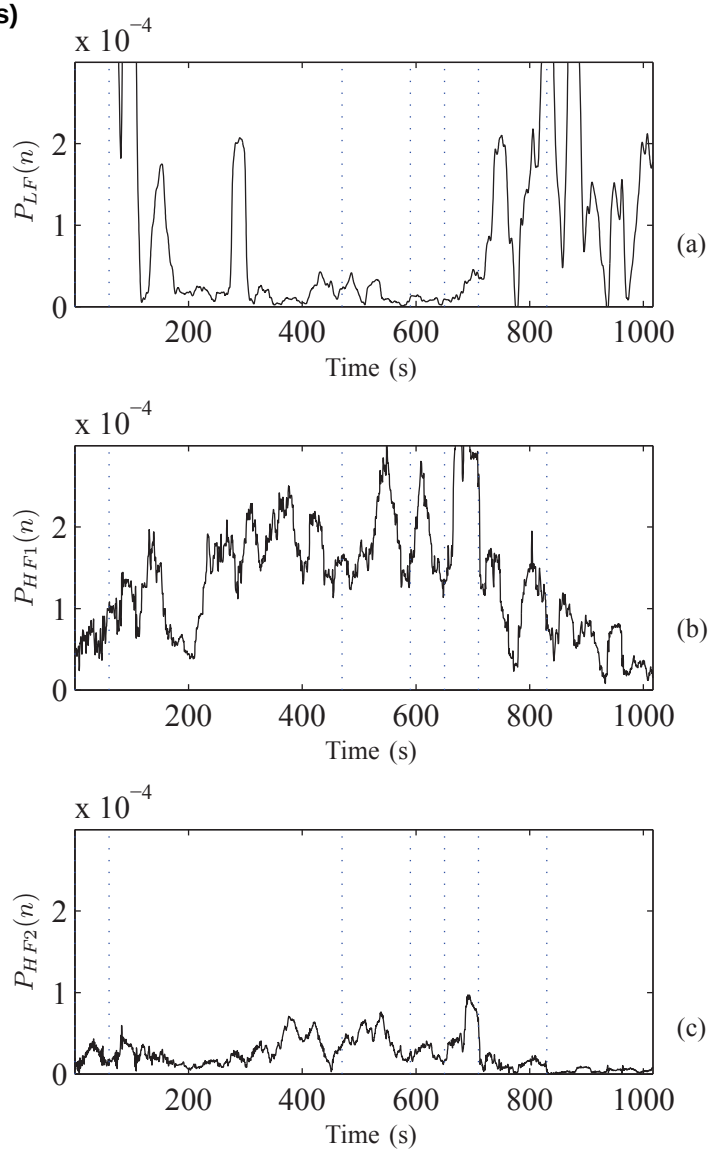

Fig. 5.

Figure(s)

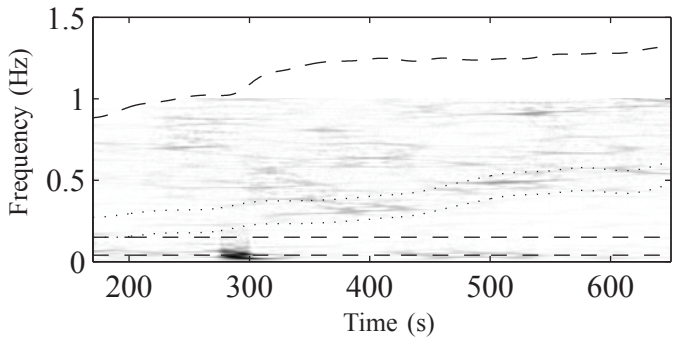

Fig. 6.

Table(s)

Table 1. Study population characteristics

Characteristic	Ischaemic	Low-risk
Number	52	29
Age (year)*	59±10	40±12
Sex (male/female)*	50/2	20/9
MaxHR (bits/min)*	133±19	174±12
PerMaxHR (%)*	79±18	95±3

*Mean±SD,
MaxHR: maximum heart rate achieved,
PerMaxHR: percentage of maximum heart rate achieved

Table 2. Parameter values used in the SPWVD

Parameter	2M	2K-1	2N-1	γ
Value (units)	1024 (samples)	1023 (samples)	101 (samples)	1/128 ($samples^{-1}$)

Table 4. Classification results: *ischaemic* versus *low-risk* groups

Feature subset Classification variables[†] (Standarized coefficients)[*]	SE (%)	SP (%)	P+ (%)	P- (%)	EX (%)
ANS-related indices (HF1) $P_{LF}(n_p)$, $P_{HF1}(n_p)$, $P_{LF}(n_1)$, $P_{HF1}(n_{p3})$, $P_{HF1}(n_{3p})$ (0.623, -1.015, -0.618, 0.518, 0.539)	85	90	94	76	86
ANS-related indices (HF2) $P_{HF2}(n_{3p})$, $P_{LF}(n_1)$, $P_{LF}(n_p)$, $P_{HF2}(n_{p3})$ (0.605, -0.606, 0.431, 0.433)	75	79	87	64	76
Respiratory frequency indices $F_R(n_{1p})$ (1)	75	72	83	62	74
Time-varying mean HR indices $d_{HRM}(n_p)$, $d_{HRM}(n_1)$ (1.135, -0.454)	88	93	96	82	90
All clinical indices (HF1) $d_{HRM}(n_p)$, $d_{HRM}(n_1)$, $P_{HF1}(n_p)$, $F_R(n_{p1})$ (1.084, -0.397, 0.338, 0.334)	96	93	96	93	95
All clinical indices (HF2) $d_{HRM}(n_p)$, $d_{HRM}(n_1)$, $F_R(n_{p3})$ (1.153, -0.497, 0.330)	88	90	94	81	89

[†]listed in the same order as selected by the stepwise method

[*]Standarized canonical discriminant function coefficients

Table(s)

Table 3. Mean, SD and median of clinical indices in the *ischaemic* and *low-risk* groups

Clinical indices mean (SD) median	*Ischaemic*						*Low-risk*					
	n_1	n_{3p}	n_{1p}	n_p	n_{p1}	n_{p3}	n_1	n_{3p}	n_{1p}	n_p	n_{p1}	n_{p3}
$P_{LF}(n_i)$	6e-4 (12e-4) 2e-4*	6e-5 (12e-5) 2e-5	4e-5 (9e-5) 9e-6	2e-4 (9e-4) 9e-6*	2e-4 (4e-4) 7e-5	7e-4 (11e-4) 2e-4	11e-4 (13e-4) 6e-4*	2e-5 (2e-5) 1e-5	9e-6 (10e-6) 5e-6	5e-6 (4e-6) 5e-6*	7e-5 (7e-5) 4e-5	8e-4 (12e-4) 4e-4
$P_{HF1}(n_i)$	2e-4 (3e-4) 1e-4*	1e-4 (1e-4) 6e-5	8e-5 (6e-5) 6e-5	8e-5 (8e-5) 5e-5*	2e-4 (3e-4) 1e-4	4e-4 (6e-4) 2e-4†	6e-4 (9e-4) 3e-4*	6e-5 (4e-5) 5e-5	1e-4 (7e-5) 8e-5	1e-4 (2e-4) 1e-4*	1e-4 (6e-5) 8e-5	2e-4 (2e-4) 9e-5†
$P_{HF2}(n_i)$	1e-4 (1e-4) 4e-5†	3e-5 (4e-5) 2e-5*	2e-5 (3e-5) 1e-5	2e-5 (3e-5) 1e-5	8e-5 (11e-5) 4e-5*	1e-4 (2e-4) 8e-5*	4e-4 (7e-4) 1e-4†	1e-5 (1e-5) 7e-6*	1e-5 (1e-5) 1e-5	1e-5 (9e-6) 1e-5	2e-5 (3e-5) 1e-5*	5e-5 (7e-5) 3e-5*
$F_R(n)$ (Hz)	0.30 (0.09) 0.29	0.39 (0.10) 0.39†	0.45 (0.12) 0.44*	0.48 (0.12) 0.47*	0.46 (0.10) 0.45†	0.40 (0.08) 0.39	0.29 (0.08) 0.29	0.45 (0.13) 0.43†	0.55 (0.12) 0.55*	0.57 (0.12) 0.59*	0.52 (0.11) 0.53†	0.43 (0.13) 0.44
$d_{HRM}(n_i)$ (Hz)	1.4 (0.3) 1.4	1.9 (0.3) 1.9*	2.1 (0.3) 2.1*	2.2 (0.3) 2.2*	1.9 (0.3) 1.9*	1.5 (0.3) 1.5*	1.5 (0.3) 1.4	2.5 (0.3) 2.5*	2.7 (0.3) 2.7*	2.9 (0.2) 2.9*	2.5 (0.3) 2.5*	1.8 (0.2) 1.8*

† $p < 0.05$, * $p < 0.01$