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RELIABILITY OF HEART RATE VARIABILITY MEASUREMENTS IN PATIENTS WITH A HISTORY OF MYOCARDIAL INFARCTION

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Abstract

Despite a well established prognostic value in cardiac patients, heart rate variability (HRV) indexes have been little used in the clinical setting. Poor reliability of the measurements might be a possible explanation. In this study we assessed the reliability of short-term HRV indexes in post myocardial infarction (MI) patients.

We studied 61 MI patients (50 males, mean age \pm SD: 59 \pm 8 yrs, LVEF: 46 \pm 6 %), who underwent a 5+5min ECG recording during spontaneous and paced breathing, on two consecutive days. Standard time- (SDNN, RMSSD) and frequency-domain (LF and HF power and LF/HF) indices of HRV were computed. Absolute and relative reliability were assessed respectively by the 95% limits of random variation and by the intraclass correlation coefficient (ICC). The agreement between the two measurements in classifying patients at low or high risk, according to different cut-points, and the sample size needed to detect a clinically relevant change, were also assessed.

During spontaneous breathing, individual changes in test-retest measurements ranged from -41% to +61% (SDNN, best case) and from -76% to +316% (LF/HF, worst case). The ICC ranged from 0.72 to 0.81. Most patients (79 – 90%) were assigned to the same class by the two measurements. Paced breathing did not improve reliability.

Short-term HRV parameters in MI patients may exhibit large day-to-day variations, making the detection of treatment effects in individual patients difficult. However, the ICC values and the analysis of consistency of classification between repeated tests indicate that HRV measurements fulfil the criteria required to be used for diagnostic or classification purposes.

INTRODUCTION

Although heart rate variability (HRV) has long been shown to provide independent prognostic information in patients after myocardial infarction [1, 2, 3, 4, 5, 6], and to be capable of detecting shifts in autonomic control induced by therapeutic interventions [7, 8], HRV measurements are not commonly used in the routine clinical management of individual patients and there is still little evidence that interventions based on these measurements improve clinical outcomes. Poor reliability of HRV indexes might be one of the reasons to explain this seeming paradox.

HRV indexes are commonly derived from either 24-hour ambulatory recordings or short term laboratory recordings [9]. The latter allow to assess autonomic cardiovascular regulation under standardized controlled experimental conditions [9]. While the reliability of 24-hour HRV measurements in post-myocardial infarction patients has been assessed in previous studies [10], investigations on short-term recordings are still lacking. Comprehensive studies on this subject are available only for healthy subjects [11, 12]; however, the obtained results cannot be generalized to patients with a history of myocardial infarction, since the abnormalities in autonomic regulatory mechanisms that occur in these subjects may affect the homeostatic control of cardiac activity and, as a consequence, the stability over time of spontaneous heart rate fluctuations. Moreover, some aspects of reliability are not a fixed characteristic of the parameter being measured, but change with the population of subjects under investigation [13].

A thorough evaluation of the reliability of HRV indexes should consider both absolute and relative reliability. Absolute reliability refers to the degree of random variability of the measurements in any given subject (i.e., intra-subject variability), and therefore is relevant to the assessment of individual changes in test-retest experiments (e.g., before and after a treatment). Relative reliability, on the contrary (on the other hand), refers to the magnitude of intra-subject variability relative to the variability of the measurements between subjects and is relevant to distinguish between subjects in a given population (i.e., to make diagnosis).

The aim of this study is to provide a comprehensive evaluation of absolute and relative reliability of standard short-term indexes of HRV in post-myocardial infarction patients and to derive practical implications for their clinical use.

METHODS

Subjects

We studied patients with a history of myocardial infarction, in sinus rhythm, stable clinical conditions without angina during the investigation, and < 5% of ectopic beats in the recorded ECG. Exclusion criteria were: pulmonary or neurological disease, including insulin dependent diabetes, atrio-ventricular conduction disturbances, implanted pacemaker or cardioverter defibrillator. Out of 69 patients screened, 5 patients were excluded because of atrial fibrillation or atrial flutter and 3 were excluded due to an ectopy rate > 5%. This led to a final study population of 61 patients.

The study was approved by the local Ethical Committee and all subjects gave their written informed consent before participation.

Study protocol

All tests were performed in a quiet and dimmed room, at a comfortable temperature, between 8.00 a.m. and 1.00 p.m., with subjects in the supine position after a 2-hour fast. Patients refrained from smoking or drinking caffeine or alcohol for 24 hours before the study. After instrumentation, they were instructed to perform the paced breathing protocol at a frequency of 0.25 Hz [14]. After 15 minutes for signal stabilization, subjects breathed spontaneously for 8 min, and then breathed at the paced breathing frequency for another 8 min. The ECG signal was recorded during both sessions. An identical session was repeated on the next day at the same hour.

Signal analysis and measurements

The ECG signal was processed by a custom software package [15] and the obtained RR interval time series (resolution 1 ms) was re-sampled at 2 Hz by cubic spline interpolation.

Following current standards for short-term HRV [16], the analysis was carried out in each recording on a 5-min window free from transients and artefacts. Isolated ectopic beats were corrected by linear interpolation. After trend removal via least-square second-order polynomial fitting, the power spectral density of RR time series was estimated by the Blackman-Tukey method (Parzen window, spectral bandwidth 0.015 Hz) [17]. The low frequency power (LF_BT) and high frequency power (HF_BT) were obtained by numerical integration of the power spectral density in the low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.45 Hz) bands respectively. The LF/HF ratio was computed as LF_BT/HF_BT.

We also computed two common short-term time-domain HRV parameters: the standard deviation of normal-to-normal beats (SDNN) and the root mean square of successive differences (RMSSD) [16]. Although mean RR interval is not, strictly speaking, an HRV parameter, it was included in the analysis as it is the simplest and most common index of cardiac autonomic control.

Statistical analysis

Since outliers may greatly affect the computation of reliability indexes, they were excluded from the analysis. After log-transformation of skewed variables (Shapiro-Wilk test for normality), an observed value was considered to be an outlier if it was greater/less than the upper/lower quartile plus/minus 1.5 times the interquartile range [18].

Plotting the difference between the measurements in the two consecutive days ($X_2 - X_1$) against their average (Bland-Altman plots), we assessed whether the examined variables were heteroscedastic (i.e. whether the magnitude of the difference increased with the magnitude of the variable). In case of heteroscedasticity, a log-transformation was applied [19]. Graphical analysis was substantiated by hypothesis testing (one-sample t-test on the difference between the two measurements) [19, 20].

Absolute reliability was assessed by the *95% limits of random variation for the ratio between two measurements* [11]. These limits express the range of values within which 95% of the ratios between the second and the first measurement are expected to lie due to pure random variation.

We also estimated the sample size needed to detect a clinically relevant change in the mean of HRV parameters after a treatment. Since there are no criteria as to what constitutes a “clinically relevant change”, we arbitrarily adopted the criterion of a change $\geq 30\%$ of between-subject standard deviation. This choice was based on the rationale that the larger the spread of values in a population, the greater the effect of a treatment should be in order to be clinically relevant. We used a significance level of 5% (two-tailed) and a power of 80%.

Relative reliability was assessed by the intraclass correlation coefficient (ICC) [13]. The ICC ranges from 0 to 1: the higher the value, the lower the intra-subject variability relative to inter-subject variability. An ICC >0.8 is usually considered as indicating good to excellent reliability, while an ICC between 0.6 and 0.8 may be taken to represent substantial reliability [20, 21].

Since HRV parameters are commonly coded as dichotomic variables to identify patients at low and high risk [1, 2, 5, 22], we did the same for the two measurements taken in each subject, using three different cut-off points: the 15-th, 20-th and 25-th percentile of the distribution. After dichotomization, we obtained a 2x2 cross-classification table relating the binary coding of the first and second measurement for each HRV parameter. The agreement between the two classifications was assessed as percentage of patients assigned to the same class by the two measurements.

RESULTS

Clinical and demographic characteristics of studied patients are given in table 1.

Spontaneous breathing

Two outliers were observed in SDNN, RMSSD and LF_BT and three in HF_BT and LF/HF. Accordingly, these values were excluded from analysis.

Representative Bland-Altman plots before and after log-transformation are depicted in fig. 1. It can be seen that raw data do not show any systematic change from the first to the second measurement; yet, the width of the scatter of points around the zero line shows a clearly increasing trend, indicating a progressive increase of the difference as the magnitude of the parameter increases (heteroscedasticity). A successful stabilization of random error was obtained after log-transformation (fig. 1 b). This behaviour was observed in all parameters.

Descriptive statistics of measured parameters in the two tests are shown in table 2. For completeness, both raw and log-transformed data are reported. Differences between the second and first measurement were non-significant for all variables.

Reliability indices and the proportion of patients assigned to the same class by the two measurements during spontaneous breathing are reported in table 3a and 4 respectively.

For spectral parameters, the 95% limits of random variation of the ratio between 2 measurements can be as large as 0.24 to 4.16 (LF/HF), while smaller intervals were found for time domain parameters. These limits are important to assess in a new subject from the same population whether the change in a HRV parameter after a treatment is real or may be due to pure random variation. To be 95% confident that a real change has occurred, the ratio between the two measurements (X_2/X_1) must lie outside the 95% limits of random variation. Hence, in the case of the LF/HF, the second measurement has to decrease more than 76% or increase more than 316%, compared to the first measurement. The plot in figure 2 for the ratio between HF_BT₂ and HF_BT₁ against their mean, clearly shows the magnitude of day-to-day random variability between the two measurements taken in the studied patients.

ICC values ranged from 0.72 (RMSSD) to 0.81 (LF_BT), indicating substantial to good relative reliability. For all considered HRV indices and dichotomization thresholds, the large majority of patients were assigned to the same class by the two repeated measurements, ranging from 79% to 90%. These values were only slightly lower than those found for mean RR (range: 92-95%).

Paced breathing

In paced breathing recordings, two outliers in SDNN and LF_BT and three in RMSSD, HF_BT and LF/HF were found. As in spontaneous breathing, all considered variables showed heteroscedasticity, and log transformation was successfully applied. Descriptive statistics are reported in table 5. Differences between the two measurements were largely non significant. Reliability indices for all variables are reported in table 3b. It can be seen that results from paced breathing are substantially similar to those from spontaneous breathing.

DISCUSSION

This is the first study to analyze the reliability of HRV measurements from short-term recordings in post-myocardial infarction patients, this being the population in which HRV indexes have mostly been used [12, 23]. We considered both absolute reliability (relevant to the assessment of individual changes in test-retest experiments) and relative reliability (relevant for diagnostic purposes). We found that HRV parameters are characterized by large day-to-day random variations. However, the observed values of ICC indicated that this intra-subject variability accounts for a limited portion of the overall variability across patients. Thus, HRV measurements apparently fulfil the criteria required for diagnostic or classification purposes.

The variability of HRV indexes

From the analysis of test-retest data we derived the 95% limits of random variation of the ratio between replicate measurements, which provide statistical inference about day-to-day intra-subject variability in the whole population. These results indicate that large random changes in HRV indexes are to be expected in the same subject from measurement to measurement, which could make difficult the detection of treatment effects in individual subjects. Indeed, measurements taken on the second day under the same experimental conditions, can be 2 to 4 times larger or 0.5 to 0.25 times smaller than the measurements taken on the first day. Only when the ratio between the measurements exceeds these limits of random variation, can the clinician confidently ascribe the observed change to a treatment effect. Reproducibility was lower for the spectral indices and markedly improved in the two time-domain indices, particularly in the SDNN.

Three major sources of variation are likely to contribute to intra-subject variability of HRV indexes. The first and most likely greatest source of variation is due to the intrinsic lability of HRV parameters, as autonomic regulation is under the continuous influence of such uncontrollable factors as, e.g., level of arousal and emotions. The second source is due to the sampling variability of estimated parameters, as they are nothing but statistics computed on a finite number of RR intervals [17]. The third source of variation is related to moment-to-moment changes in the frequency and depth of respiration, which have a direct effect on heart rate oscillations [14].

The ICC of HRV parameters ranged from 0.72 to 0.81, indicating substantial to good relative reliability [20, 21]. These values suggest that HRV measurements allow the detection of relevant differences between individuals and, therefore, they have the prerequisites to be used in diagnosis and as candidate predictors in prognostic studies. An indirect support to this interpretation was provided by assessing the agreement between the first and second measurement when they were used to classify patients according to depressed (high risk) or preserved (low risk) HRV (Table 5). We found that the two measurements yielded a concordant classification in a high percentage of cases, ranging from 79% to 90%, whatever the dichotomization threshold considered. These values are close to those found for mean RR, which is a clinical measurement commonly thought to be highly reliable. It is noteworthy that even HRV indices with very poor absolute reliability (e.g., LF/HF) showed a good classification capability, thus confirming the results obtained for their relative reliability.

Overall, both absolute and relative reliability were similar to those found in previous studies in healthy subjects [11, 24, 25]. We are aware of only one study in post-myocardial infarction patients, in which the reliability of 24-hour spectral indexes of HRV was assessed using a methodology similar to our investigation [10]. Limits of random variation (derived from tabulated SEMs) were narrower than ours, yet upper limits as high as 2.43 and 3.03 and lower limits as low as 0.41 and 0.33 were found for, respectively, the LF and HF power, thus indicating considerable variation between replicate observations in the same individuals.

A tenable explanation for the larger limits of random variation found in our study is that when 24-hour recordings are used, spectral estimators are more stable since the variance decreases as the record length increases [26]. However, short term recordings do have several advantages over

uncontrolled 24-hour ambulatory recordings. Firstly, they are quick to analyse, and each RR interval can be accurately edited. Secondly, short term recordings can be carried out in controlled standardized conditions, while HRV indexes from ambulatory recordings cannot. Thirdly, they can be made under a variety of physical or pharmacological stimuli allowing researchers to observe the autonomic responses to such stimuli.

At variance with our previous study on healthy individuals [11], we did not find an improvement of reliability of HRV measurements related to the LF band using paced breathing. Slow or irregular breathing patterns may occur in spontaneously breathing subjects and introduce a bias in the measurement of the spectral power in the LF band [14]. Paced breathing, by forcing respiratory components into the HF band, allows to avoid such possible bias [14]. We therefore argue that in some normal subjects the spontaneous breathing pattern changed between the first and second recording (e.g., breathing was slow or irregular in one recording and more regular and centered in the HF band in the other recording), thus worsening the repeatability of the measurements. Paced breathing stabilized the breathing pattern and repeatability therefore increased. On the contrary, the lack of improvement of reliability during paced breathing in post-MI patients suggests that their breathing pattern was regular and stable during both spontaneous breathing recordings. We do not have, however, an explanation for such increased stability in respiration.

Reliability and sample size estimation

We found that the sample size required to detect a clinically relevant treatment effect in the population under study varied from 40 to 72 patients, indicating that: i) sample size computation should be “tailored” to the specific index of interest, and ii) even for a relatively large change as the one used in our computations, the number of patients to be involved in the experiments is substantial. Greater sample sizes will obviously be needed in case smaller treatment differences are to be detected.

Conclusion

The data from this study indicate that HRV measurements, particularly those in the frequency domain, may largely and unpredictably vary from day to day in the same subject, making the assessment of the individual effect of treatments difficult. However, the ICC values and the analysis of consistency of classification between repeated tests, suggest that HRV measurements can be used to “locate” the patient in the full range of possible values of the considered population, and determine his/her diagnostic or risk class. As far as this aspect of reliability is concerned, HRV indexes appear comparable to such a common and trustworthy index of mean vagal and sympathetic outflow to the heart as mean RR.

Finally, our results highlight the need for large sample sizes to achieve adequate power in hypothesis testing.

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Figure legends

Fig. 1. Representative Bland-Altman plots of the difference between the two measurements ($X_2 - X_1$) against their average for the HF power (HF_BT, Blackman-Tukey method) before (a) and after (b) log-transformation. The scatter of points is symmetrical with respect to the zero line, indicating the absence of systematic change between the two tests. The width of the scatter around the same line, however, steadily increases as average HF_BT increases, indicating heteroscedasticity. Log-transformation (natural logarithm, ln) of the measurements was successful in stabilizing the magnitude of random changes between replicate measurements. Data are from recordings during spontaneous breathing.

Fig. 2. Plot of the ratio between the two measurements (X_2/X_1) against their mean value for HF_BT (HF power, Blackman-Tukey method). Dash-dotted lines represent the 95% limits of random variation for the ratio. Data are from recordings during spontaneous breathing

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Table 1. Demographic, clinical and functional characteristics of studied patients (N=61)

Age, years:	59 (8)
Sex, male/female	50/11
LVEF, %	46 (6)
Time since MI, months	31 (6)
Site of MI	
Anterior, %	56
Inferior, %	41
Other, %)	3
β -blockers, %	85
ACE inhibitors, %	95
Diuretics, %	10
Statins, %	97
Antiplatelet drugs, %	97

Data are expressed as mean (SD)

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Table 2. Descriptive results for HRV parameters during spontaneous breathing in the two tests taken one day apart from each other.

	Measurement 1	Measurement 2	Difference (2-1)	p*
Mean RR (ms)	1102 (162)	1119 (179)	17 (101)	
Ln Mean RR (ln ms)	7.0 (0.15)	7.0 (0.16)	0.01 (0.09)	0.244
SDNN (ms)	28 (11)	29 (10)	1 (9)	
Ln SDNN (ln ms)	3.26 (0.38)	3.31 (0.36)	0.04 (0.27)	0.226
RMSSD (ms)	26 (17)	25 (13)	-1 (13)	
Ln RMSSD (ln ms)	3.10 (0.52)	3.10 (0.53)	-0.01 (0.39)	0.761
LF_BT (ms ²)	267 (319)	268 (283)	1 (257)	
Ln LF_BT (ln ms ²)	5.2 (0.93)	5.1 (1.02)	-0.04 (0.60)	0.579
HF_BT (ms ²)	240 (359)	223 (249)	-17 (292)	
Ln HF_BT (ln ms ²)	4.93 (0.99)	4.93 (1.01)	0 (0.67)	0.991
LF/HF	2.08 (2.52)	2.04 (2.15)	-0.03 (1.88)	
Ln LF/HF (ln)	0.14 (1.15)	0.18 (1.12)	0.03 (0.73)	0.728

Data are expressed as mean (SD). Variables are also reported after log transformation.

SDNN=standard deviation of normal-to-normal beats; RMSSD=root mean square of successive differences; LF_BT = power in the low frequency band (0.04-0.15 Hz) according to the Blackman-Tukey (BT) method; HF_BT = power in the high frequency band (0.15-0.45 Hz) according to the Blackman-Tukey (BT) method; LF/HF= ratio between low frequency and high frequency power; Ln= natural logarithm.

*) p value for the test of no difference between the two measurements (one-sample t-test). The test was carried out after log-transformation.

Table 3. Reliability of heart rate variability (HRV) parameters.

a) Spontaneous breathing

HRV parameter	95% limits of random variation of the ratio between 2 measurements (X_2/X_1)	ICC (95% CI)	Required sample size (N)
Mean RR	0.84, 1.18	0.85 (0.75,0.91)	33
SDNN	0.59, 1.61	0.74 (0.60,0.84)	63
RMSSD	0.47, 2.14	0.72 (0.58,0.83)	69
LF_BT	0.31, 3.25	0.81 (0.70,0.88)	42
HF_BT	0.27, 3.72	0.77 (0.65,0.86)	53
LF/HF	0.24, 4.16	0.80 (0.68,0.88)	46

b) Paced breathing

HRV parameter	95% limits of random variation of the ratio between 2 measurements (X_2/X_1)	ICC (95% CI)	Required sample size (N)
Mean RR	0.83, 1.20	0.81 (0.70,0.88)	43
SDNN	0.55, 1.80	0.72 (0.57,0.83)	72
RMSSD	0.48, 2.10	0.77 (0.64,0.86)	54
LF_BT	0.31, 3.18	0.82 (0.71,0.89)	40
HF_BT	0.25, 3.98	0.80 (0.68,0.88)	45
LF/HF	0.24, 4.28	0.77 (0.64,0.86)	54

The legend of HRV parameters is given in table 2. The limits of random variation give the range of values within which 95% of the ratios between the two measurements are expected to lie due to pure random variability. ICC= intraclass correlation coefficient. CI= confidence intervals. The last column gives the estimate of the sample size needed to detect in a test-retest experiment a change in the mean $\geq 30\%$ of the between-subject standard deviation. A two-tail test with a significance level of 5% and a power of 80%. was assumed

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Table 4. Proportion of patients assigned to the same class by the two repeated measurements using three different cut-points (15-th, 20-th and 25-th percentile).

Spontaneous breathing			
HRV parameter	<i>% assigned to the same class (15-th percentile)</i>	<i>% assigned to the same class (20-th percentile)</i>	<i>% assigned to the same class (25-th percentile)</i>
Mean RR	92	92	95
SDNN	90	88	90
RMSSD	86	85	81
LF_BT	88	88	85
HF_BT	86	83	81
LF/HF	89	82	79

The legend of HRV parameters is given in table 2.

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Table 5. Descriptive results for HRV parameters during paced breathing in the two tests taken one day apart from each other.

	Measurement 1	Measurement 2	Difference (2-1)	p*
Mean RR (ms)	1088 (159)	1111 (170)	23 (107)	
Ln Mean RR (ln ms)	7.0 (0.15)	7.0 (0.16)	0.02 (0.09)	0.106
SDNN (ms)	30 (17)	30 (13)	-0.3 (11)	
Ln SDNN (ln ms)	3.31 (0.43)	3.32 (0.39)	0.01 (0.32)	0.729
RMSSD (ms)	28 (27)	27 (17)	-1.2 (17)	
Ln RMSSD (ln ms)	3.13 (0.56)	3.13 (0.55)	-0.01 (0.38)	0.915
LF_BT (ms ²)	207 (265)	202 (237)	-5.3 (160)	
Ln LF_BT (ln ms ²)	4.82 (1.00)	4.83 (0.96)	0.01 (0.59)	0.900
HF_BT (ms ²)	522 (1670)	387 (591)	-134 (1196)	
Ln HF_BT (ln ms ²)	5.3 (1.11)	5.3 (1.12)	0 (0.70)	0.967
LF/HF	0.93 (1.01)	0.94 (1.12)	0.02 (0.84)	
Ln LF/HF (ln)	-0.52 (1.06)	-0.66 (1.20)	-0.15 (0.78)	0.315

Data are expressed as mean (SD). Variables are also reported after log transformation. The legend of HRV parameters is given in table 2

*) p value for the test of no difference between the two measurements (one-sample t-test). The test was carried out after log-transformation.



