Heart Rate Variability Fraction—A New Reportable Measure of 24-Hour R-R Interval Variation

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Background: The scatterplot of R-R intervals has several unique features. Its numerical evaluation may produce a new useful index of global heart rate variability (HRV) from Holter recordings.

Methods: Two-hundred and ten middle-aged healthy subjects were enrolled in this study. The study was repeated the next day in 165 subjects. Each subject had a 24-hour ECG recording taken. Preprocessed data were transferred into a personal computer and the standard HRV time-domain indices: standard deviation of total normal R-R intervals (SDNN), standard deviation of averaged means of normal R-R intervals over 5-minute periods (SDANN), triangular index (TI), and pNN50 were determined. The scatterplot area (0.2–1.8 second) was divided into 256 boxes, each of 0.1-second interval, and the number of paired R-R intervals was counted. The heart rate variability fraction (HRVF) was calculated as the two highest counts divided by the number of total beats differing from the consecutive beat by <50 ms. The HRVF was obtained by subtracting this fraction from 1, and converting the result to a percentage.

Results: The normal value of the HRVF was $52.7 \pm 8.6\%$. The 2–98% range calculated from the normal probability plot was 35.1–70.3%. The HRVF varied significantly with gender (female $48.7 \pm 8.4\%$ vs male $53.6 \pm 8.6\%$, $P = 0.002$). The HRVF correlated with RRI ($r = 0.525$) and showed a similar or better relationship with SDNN (0.851), SDANN (0.653), and TI (0.845) than did the standard HRV measures with each other. Bland-Altman plot showed a good day-by-day reproducibility of the HRVF, with the intraclass correlation coefficient of 0.839 and a low relative standard error difference (1.8%).

Conclusion: We introduced a new index of HRV, which is easy for computation, robust, reproducible, easy to understand, and may overcome the limitations that belong to the standard HRV measures. This index, named HRV fraction, by combining magnitude, distribution, and heart-rate influences, might become a clinically useful index of global HRV.

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heart rate; scatterplot; healthy subjects; reproducibility; ambulatory ECG monitoring

Heart rate variability (HRV) analysis, especially in the time-domain, has been studied extensively during the last two decades following the observation that this analysis may provide important prognostic information for risk stratification after myocardial infarction (MI) and in heart failure.^{1–3}

Several time-domain approaches have already been introduced, which describe different aspects of HRV. One of them is the scatterplot of R-R intervals (also referred to as a scatterplot, Lorenz plot or Poincaré map), which is a plot of the duration

of any given R-R (or normal N-N) interval against the duration of the next or preceding R-R (N-N) interval.⁴ This method offers the optimum way for visually assessing HRV itself and the quality of the ECG recording. In healthy subjects, the scatterplot is usually a fan-like or comet-like in shape.⁴

On the basis of pattern recognition, Woo et al. described an association between the complex pattern of the scatterplot and sudden death in congestive heart failure.⁵ These authors found a correlation between the scatterplot's shape and serum

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norepinephrine levels.⁶ There have been several studies of developmental changes in the HRV of normal infants and of sudden infant death syndrome based on the quantitative evaluation of the return plot shape.^{7,8} All these studies brought proof of the prognostic value of the shape of the scatterplot itself.

An attempt to quantify the scatterplot of R-R intervals in healthy subjects from short-term recordings was described by Sosnowski et al. who calculated the coefficient of correlation between successive R-R intervals in patients after MI.⁹ Numerical processing of the scatterplot from long-term ECG recordings was described by Hnatkova et al.¹⁰ They calculated the Compactness Index of scatterplots and showed that the prognostic power of this index was better than that of standard time-domain HRV measures in a large population of MI-patients over a 2-year follow-up. Other quantitative descriptors of the scatterplots are now available in order to detect parasympathetic influences^{11,12} or to study the effects of drugs.^{13,14}

The concept of processing scatterplots is based on the assumption that the density of paired R-R intervals might be different despite the same overall two-dimensional shape. Indeed, Hnatkova et al. showed an example of two patients matched for age, gender, site of MI, ejection fraction, and medications, but with different outcomes, who had seemingly the same shape of scatterplots in the two-dimensional approach, while the density indicated by the Compactness Index was different.¹⁰

We have developed a method of global HRV evaluation, which is based on the same assumptions as the Compactness Index, but which introduces a simple, reproducible, and easy to understand index, namely the fraction of the density of selected areas of the scatterplot in relation to the total number of R-R intervals differing from another by less than 50 ms.

MATERIALS AND METHODS

Study Population

The study population consisted of 210 seemingly healthy subjects, recruited from local government. There were 173 men and 37 women, of mean age 49.5 ± 6.0 years. All were nonobese and nonsmokers. All were examined by a physician and presented neither symptoms nor signs of cardiovascular diseases. All had normal ECGs.

The two-dimensional echocardiographic examinations in majority of them revealed normal anatomy and function of the heart.

Methods

In each subject a 24-hour ambulatory ECG recording was obtained using a two-channel tape recorder. In 165 subjects, an ambulatory ECG was repeated the next day. The data of this subset of population were used for the evaluation of reproducibility. The ECG recordings were processed with standard precision on a Medilog Excel 2 System (Oxford Instruments, Abingdon, UK). Careful manual editing was performed and, after visual corrections, data with labeled R-R intervals were stored in the files and transferred into a personal computer for further processing using an in-house software package. This program determined the standardized time-domain indices of HRV, including standard deviation of total normal R-R intervals (SDNN, ms), standard deviation of averaged means of normal R-R intervals over 5-minute periods (SDANN, ms), and the triangular index (TI, dimensionless).¹⁵

The scatterplot and its evaluation were obtained using an algorithm written in MATLAB (Version 4, The MathWorks, Inc., Natick, MA), implemented on a personal computer. The scatterplot is a plot of a given R-R interval ($R-R_i$) against the next R-R interval ($R-R_{i+1}$). In such a way, a graphic two-dimensional presentation of beat-to-beat R-R interval changes is obtained. The scatterplot area (from 0.2 to 1.8 second by 0.2 to 1.8 second) was divided into 256 boxes each of 0.1-second interval (16×16 , from 0.2 to 0.3, 0.3 to 0.4, and so on up to 1.7 to 1.8) (Fig. 1). In each box, the number of paired R-R intervals was counted. In such a way the matrix of numbers over 256 boxes was obtained. Absolute and relative counts of normal R-R intervals differing by more than 50 ms from the preceding normal R-R interval (absNN50, pNN50) were obtained.

Calculation of Heart Rate Variability Fraction

The index was calculated according to the formula:

$$\text{HRVF} = \left(1 - \frac{N1 + N2}{\text{Total NN} - \text{NN50}}\right)100,$$

Figure 1. Simplified view of a scatterplot of R-R interval variation. Each square indicates the number (N) of pairs of successive R-R intervals in a box of $0.1 \text{ s} \times 0.1 \text{ s}$ grouped at different R-R interval lengths (from 0.2 s up to 1.8 s). The two highest are easily seen as two black boxes, containing more than 20,000 pairs of R-R intervals. These two counts are taken as figures N1 and N2 for the HRVF calculation.

where, N1 and N2 are the two highest numbers of counts in all the boxes, total NN is the number of all normal R-R intervals, and NN50 is the number of normal RRIs that differ from the successive RRI by more than 50 ms.

An algorithm to calculate the counts and this index is easy for computation and the time needed for its evaluation is only few seconds.

Statistical Analysis

Means and standard deviations, as well as the normal limits, defined as 2–98 percentile values from the probability plots, were calculated for each parameter. Linear correlations and their coefficients were calculated among all measured parameters (both for raw values and for values transformed to decimal logarithm). Reproducibility was assessed using the calculation of intraclass correlation coefficients, Bland-Altman plots, and standard error differences (absolute and relative). Age and gender effects were evaluated using one-way analysis of variance.

RESULTS

The mean and standard deviation values of the HRVF in the 210 middle-aged subjects, who were

examined, were $52.7 \pm 8.6\%$. The range of normality, calculated as the range between the 2nd and 98th percentile, was between 35.1 and 70.3%. The mean, SD, and range of normality for R-R intervals were $799 \pm 94 \text{ ms}$, and 626–1005 ms, respectively. The mean and SD values of the commonly used HRV measures were: for SDNN 142 ± 33 , for SDANN 135 ± 39 , for TI 35.7 ± 8.1 and for pNN50 $7.002 \pm 6.160\%$. The ranges of normality were 86–221 ms, 74–230 ms, and 19.2–52.2 for SDNN, SDANN, and TI, respectively. For pNN50 the range was 0.142–27.394%.

Because of the small range of age within the studied population, an effect of age was not observed for any parameter, including the HRVF.

Gender significantly influences all variables, except pNN50. Both RRI and HRV measures were lower in female than male subjects (Table 1), despite similar mean age ($F 51 \pm 6$, $M 49 \pm 6$).

Linear regression analysis showed that the HRVF was moderately correlated with RRI (Pearson's $r = 0.524$), while for standard measures these correlations were slightly lower (Table 2). The HRVF showed a similar or better relationship with SDNN ($r = 0.855$), SDANN ($r = 0.753$), and TI ($r = 0.834$) than did the standard HRV measures to each other (Table 2). These correlations became closer after logarithmic transformation of SDNN ($r = 0.872$) or of SDANN ($r = 0.718$) (Fig. 2). Correlation between the HRVF and pNN50 was rather weak, but improved slightly after logarithmic transformation of pNN50 ($r = 0.395$ and $r = 0.501$, respectively, Fig. 2).

Table 1. Effect of Gender on HR and its Variability in a Middle-Aged Population

Gender Parameter	Female N = 38	Male N = 172	P Value
RRI	750 ± 80	810 ± 934	<0.001
SDNN	128 ± 30	145 ± 33	0.004
SDANN	122 ± 38	138 ± 39	0.022
TI	31.8 ± 8.8	36.5 ± 7.7	0.001
pNN50	6.210 ± 4.907	7.177 ± 6.403	0.382
HRVF	48.7 ± 8.4	53.6 ± 8.4	0.002

Results presented as means ± 1 standard deviation. A one-way ANOVA was used for statistical comparisons. Abbreviations: RRI = mean of all normal R-R intervals, SDNN = standard deviation of all R-R intervals, SDANN = standard deviation of averaged 5 minute means of R-R intervals, TI = triangular index, pNN50 = percent of R-R intervals that differ from another by more than 50 ms, HRVF = heart rate variability fraction.

Table 2. The Correlation Coefficients among Standard HRV Measures and HRVF in Healthy, Middle-Aged Subjects

	RRI	SDNN	SDANN	TI	NN50	HRVF
RRI	–	0.494	0.326	0.453	0.395	0.524
SDNN		–	0.870	0.723	0.462	0.855
SDANN			–	0.527	0.335	0.723
TI				–	0.437	0.834
PNN50					–	0.395
HRVF	0.535	0.875	0.770	0.828	0.501	–

The numbers represent Pearson's moment correlation coefficients. The numbers in bold represent correlation coefficients between HRVF and log-transformed RRI and standard HRV measures. See Table 1 for abbreviations.

The reproducibility of the HRVF, RRI, and standard HRV measures was evaluated in 165 subjects. The results are shown in Table 3. Bland-Altman plots of reproducibility of all measures are presented in Figure 3. The intraclass correlation coefficient between the day-by-day HRVF reached 0.839 ($P < 0.001$), while for SDNN, SDANN, TI, and pNN50, the coefficients were, respectively, 0.889, 0.816, 0.780, and 0.943 (all $P < 0.001$). Day-by-day RRI means were also closely correlated (ICC = 0.912, $P < 0.001$). However, RRI and HRVF showed the smallest relative standard error differences (Table 3).

DISCUSSION

With the introduction of any new index, the question may always arise as to whether it is necessary since several indices are already commonly used and their clinical utility has been proved over several years. The answer should be positive if previous indices suffer from several limitations that could be overcome by a new index.

Several time-domain measures of HRV, including statistical, counts, and geometrical indices, de-

scribe different properties of R-R interval variation. The overall magnitude of R-R variations is usually expressed as the standard deviation of all R-R intervals (sinus beats or so-called normal beats). Standard deviation itself, as well as other measures that are based on this formula, suffer from sensitivity to the quality of R-R interval data.^{16,17} Therefore, statistical methods can be reliable only for high-fidelity R-R data that are sometimes difficult to sustain in clinical settings. In addition, these indices quantify one aspect of HRV, i.e., its magnitude, while distribution may be different at the same magnitude of HRV.

Counts and relative counts methods are used to separate changes between consecutive R-R intervals that are different from a threshold value, usually 50 ms.¹⁸ Despite theoretical arguments for counting, these methods possess peculiar statistical properties owing to their discrete nature and high abnormal distribution in normal and clinical populations.

By considering the sensitivity of SDNN and SDANN, as well as pNN50 to sudden and large changes in RRI, caused either by physiologic reflexes or by artefacts, it was shown that geometrical methods are better for quantifying 24-hour HRV from imperfect long-term recordings. Geometric methods are based on the sample density histogram of R-R intervals or differences between consecutive intervals, and on the scatterplot. The simplest method commonly used is the so-called TI, which is based on the triangular shape of the normal R-R intervals density histogram, while the distribution of incorrect measurements fall outside the major peak of the histogram. The TI method is especially suitable for in-hospital clinical studies, with a stable environment and limited physical activity.¹⁵

Table 3. Reproducibility of RRI and HRV Variables in the Subgroup of 165 Healthy Subjects

	Day 1	Day 2	Mean	SEM Diff	Relative SEM Diff	ICC	P Value
RRI	792 (88)	810 (91)	801 (90)	9.87	1.2%	0.912	<0.001
SDNN	140 (31)	137 (33)	138.6 (32.3)	3.55	2.6%	0.889	0.063
SDANN	132 (35)	128 (34)	129.8 (34.4)	3.78	2.9%	0.816	<0.05
TI	35.6 (7.7)	35.5 (7.6)	35.6 (7.7)	0.85	2.4%	0.780	ns
PNN50	6.57 (5.91)	7.37 (6.70)	6.97 (6.32)	0.70	10.0%	0.943	<0.001
HRVF	52.5 (8.4)	51.9 (9.0)	52.2 (8.7)	0.96	1.8%	0.839	ns

Numerical values represent mean values, unless otherwise depicted. Their standard deviation values are seen in parentheses. One-way ANOVA was used for statistical comparisons. Abbreviations: SEM = standard error of mean, ICC = intra-class coefficient; for other abbreviations see Table 1.

Figure 2. Relationship between HRVF and standard HRV measures. Raw HRVF data and log-transformed standard HRV measures were drawn for plots and calculations.

The TI method is less sensitive to artifacts and large inter-beat changes, while it is strongly dependent on the distribution of RRI in the density histogram. Therefore, in cases with bimodal distribution, calculation of the TI may lead to incorrect assessment of HRV from a 24-hour ECG. The bimodal distribution of RRI histograms is commonly seen in healthy subjects and in patients during out-of hospital 24-hour ambulatory ECG recordings. It is the result of day-night difference, as well as physical and mental activity, which is usually greater in not-controlled out-of hospital conditions.

The formula for the HRVF calculation is based on several assumptions. First, two boxes with highest counts were chosen on the basis of day-night difference in the mean heart rate. In ambulatory subjects bimodal distribution of RRIs is common, reflecting diurnal variation of heart rate. Thus, two boxes are necessary and enough to gain these dominating frequencies. Second, the denominator used in the HRVF formula includes only normal sinus beats that differ by less than 50 ms, thus short-term variation of RRIs is filtered. So, the denominator includes control mechanisms other than purely

Figure 3. Bland-Altman plots of reproducibility of all analyzed measures. Mean values shown in plots indicate mean difference between two day-by-day measurements, $+1.96 \times \text{SD}$ and $-1.96 \times \text{SD}$ values are also shown.

vagally mediated. Consistently, the HRVF expresses normalized RRIs variation that sustain after subtraction of two dominating frequencies related to day-night rhythm. The size of the boxes ($0.1 \text{ s} \times 0.1 \text{ s}$) was chosen empirically in a way that allows to gain dominating frequencies and prevent dissipation of the data.

The index described in this study has properties that may allow it to overcome several of the limitations of the HRV time-domain measures discussed

above. First, since the HRVF calculation is based on the scatterplot, this index possesses properties similar to those of the TI. This similarity is indicated by the close correlation to the TI in the normal population. But this index is independent of the distribution because a sum is taken from the two boxes with the highest number of counts, not necessarily lying close to each other. Thus, bimodal distribution, which may influence the calculation of the TI, does not affect the calculation of the HRVF.

Moreover, this index takes such a distribution into account. It is the only HRV measure to do so, in contrast to all commonly used indices.

Second, with the use in the equation of the total number of beats that differ by less than 50 ms, this index is robust to the beats that are other than normal (i.e., either premature beats or artifacts mistakenly taken as normal beats), which usually fall into the outer boxes of the scatterplot.⁴ These abnormal R-R intervals affect the calculation of statistical measures, and may bring overestimation of global HRV. In these terms, the HRVF is similar to the TI.

Third, the calculation of HRVF takes into account the influence of HR itself. Thus, at the same level of HRV variability indicated by the value of SDNN, but faster HR, the HRVF is lower. At the same time, for the same level of HR, this index properly indicates magnitude and distribution of R-R interval changes. This unique property of the new index is the result of calculating a sum from whichever two boxes have the greatest number of counts, while the interval (side) of each box is the same irrespective of R-R interval length. Therefore, the probability of finding the highest number of counts is greater for boxes lying in the area of short R-R intervals in the scatterplot and, because of this, the probability is greater at a faster heart rate, and consequently, the HRVF is lower. In this way, the HRVF combines both heart rate and its variability. It is of special importance because previous methods, despite moderate relationships with R-R interval values, do not bring information regarding the R-R interval itself. In a study by Tsuji et al.,¹⁹ the conclusion was drawn that age and heart rate must be taken into account while assessing HRV using standard measures. However, it was proved that increased heart rate itself is an independent predictor of cardiac mortality. Increased 1-year mortality was found in the postinfarction patients with HR > 90 bpm (on admission or at discharge) in a large study by Hjalmarson et al.²⁰ Copie et al. showed that a shorter mean RR interval itself was a better predictor of total, cardiac, and sudden death mortality than a depressed left ventricular ejection fraction in a large population of survivors from MI.²¹ The sensitivity, specificity, and positive predictive accuracy of an RR interval <700 ms was practically the same as of the TI < 17.²¹

Fourth, the reproducibility of the HRVF is good and the mean and standard deviation of this in-

dex was virtually identical between 2 days measurements. The intraclass correlation coefficient of HRVF was similar to that of SDNN or SDANN, and somewhat greater than that of TI. Moreover, the relative SE difference is the lowest of all the HRV measures. Therefore, smaller day-by-day changes might be considered significant, while the same changes in other HRV measures are still within limit of reproducibility.

It is worth noticing that our study is a relatively large attempt to evaluate reproducibility of HRV measures in healthy subjects. Until now, there were several studies that included rather small numbers of subjects (33 subjects—Van Hoogenhuyze et al.,²² 14—Kleiger et al.,²³ 18—Pitzalis et al.,²⁴ 19—Nolan et al.,²⁵ 17—Klingenheden et al.²⁶). The greatest reproducibility observed in the present study for heart rate (mean RR intervals) is in agreement with the result of previous studies. Day-by-day changes of HRV measures were larger than usually described, except in the study of Ponikowski et al.²⁷ of 16 heart-failure subjects, in which he found the variation coefficient of time-domain measures between 25 and 139% and the study of Van Hoogenhuyze et al.²² who reported individual variation of standard HRV time-domain measures of up to 46% in 33 normal subjects and 51% in 22 patients with congestive heart failure secondary to coronary artery disease.

Fifth, the value of the standard deviation of the HRVF is relatively lower (16% of mean value) than that of other HRV measures (23% for SDNN and TI, 29% for SDANN). It indicates a smaller interindividual variability of this index. A high interindividual variability of previous HRV measures is a main reason for the absence of normal limits for any common measure. The limits of normal values of time-domain HRV measures we provided are almost identical to those described by Molgaard et al.²⁸ However, a relatively less wide limit of normality of the proposed index (49% of upper limit), as opposed to a larger relative limit of the remaining HRV measures (63% for SDNN, 73% for SDANN, and 62% for TI, incalculable for pNN50) may help to overcome this unresolved problem. This is a result of the better statistical properties of the new index, while the lower limit of normality for others allows low HRV (for instance 80 ms for SDNN) to be recognized as a normal value.

Sixth, it is important for any measure to be easy to understand. For different HRV commonly used measures, one has to know the limits of normality

(to recognize an abnormal result) and its meaning. As mentioned earlier, the limits are still lacking. In spite of this, an expression of HRV as a fraction (%) of total HR variations makes this as easy to understand as the expression of the ejected volume of blood as a fraction of the total endiastolic volume of the ventricle. This is another unique property of the proposed index. According to this, a statement that the HRVF is about 20% indicates, in itself, a low value. Thus, an interpretation of global HRV from 24-hour ECGs may be close to practitioners as well as to clinicians or researchers. A need for such an index has been raised in a review by Huikuri et al.²⁹

Seventh, the close relationships of the HRVF with standard HRV measures resulted in a similar finding of gender differences in HRV. As previously shown by different authors, HRV variability was found to be lower in women than in men.^{30,31} This study, like others, would suggest that gender-dependency should be taken into account while interpreting the results of HRV analysis. The relatively small number of women in this study, however, did not allow separate normal limits for women and men to be calculated.

The presented study has several limitations. The most important is that this study was performed in a healthy population only. Therefore, the prognostic importance of the proposed new index is unknown. Prospective study is necessary to prove whether this index is as good a predictor of cardiac mortality as standard HRV measures. The small age-range of the studied population did not allow the age-dependency of any HRV measures to be shown, although it has been clearly seen in several previous studies.^{19,30}

As a global HRV index, it is not applicable to short data, like 5-minute periods, since a reliable calculation of the scatterplot is not possible in such cases.

In summary, our study introduces a new simple index of HRV, easy for computation, robust, reproducible, easy to understand, and which may overcome the limitations that belong to the standard HRV evaluation from 24-hour ECG recordings. Because of these limitations, the recent study of Voss et al.³² stressed the necessity of combining the four parameters of HRV from all domains to find a better predictor of high risk for malignant arrhythmia. However, the best-fit parameter set included a mean R-R interval value from a 30-minute stationary stage within a 24-hour tachogram.³² Our index combining magnitude, distribution, and heart-rate

influences, might become a clinically useful index of global HRV. However, several prospective studies are necessary to show the clinical utility of the HRVF.

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