Multiscale entropy analysis of heart rate variability in heart failure, hypertensive, and sinoaortic-denervated rats: classical and refined approaches

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Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil; Department of Electronic Engineering, University San Buenaventura, Cali, Colombia; Department of Computing and Mathematics, School of Philosophy, Sciences and Letters, University of São Paulo, Ribeirão Preto, São Paulo, Brazil; Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; and Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, Milan, Italy

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Silva LEV, Lataro RM, Castania JA, da Silva CAA, Valencia JF, Murta LO, Jr., Salgado HC, Fazan R, Jr., Porta A. Multiscale entropy analysis of heart rate variability in heart failure, hypertensive, and sinoaortic-denervated rats: classical and refined approaches. Am J Physiol Regul Integr Comp Physiol 311: R150–R156, 2016. First published May 25, 2016; doi:10.1152/ajpregu.00076.2016. — The analysis of heart rate variability (HRV) by nonlinear methods has been gaining increasing interest due to their ability to quantify the complexity of cardiovascular regulation. In this study, multiscale entropy (MSE) and refined MSE (RMSE) were applied to track the complexity of HRV as a function of time scale in three pathological conscious animal models: rats with heart failure (HF), spontaneously hypertensive rats (SHR), and rats with sinoaortic denervation (SAD).

Results showed that HF did not change HRV complexity, although there was a tendency to decrease the entropy in HF animals. On the other hand, SHR group was characterized by reduced complexity at long time scales, whereas SAD animals exhibited a smaller short- and long-term irregularity. We propose that short time scales (1 to 4), accounting for fast oscillations, are more related to vagal and respiratory control, whereas long time scales (5 to 20), accounting for slow oscillations, are more related to sympathetic control. The increased sympathetic modulation is probably the main reason for the lower entropy observed at high scales for both SHR and SAD groups, acting as a negative factor for the cardiovascular complexity. This study highlights the contribution of the multiscale complexity analysis of HRV for understanding the physiological mechanisms involved in cardiovascular regulation.

Heart failure; baroreflex; hypertension; heart rate variability; complexity; refined multiscale entropy; cardiovascular control; autonomic nervous system

THE CARDIOVASCULAR SYSTEM is acknowledged to be complex, with nonlinear properties and regulatory mechanisms acting at several time scales (13, 18, 33). Therefore, the cardiovascular variability, i.e., the oscillation of variables such as arterial pressure or cardiac interval over a beat-by-beat basis, encompasses relevant information about the complexity of cardiovascular function and its control. Methods designed to evaluate nonlinear dynamics of heart rate variability (HRV) are gaining more and more attention in the study of cardiovascular variability due to their ability to extract information about nonlinearity and complexity of cardiovascular control (31, 36, 41).

As complex signals, the oscillations of cardiovascular parameters are better characterized when multiscale properties are taken into account. Within entropy-based methods, multiscale entropy (MSE) proposed by Costa et al. (7) is certainly one of the most important in the field of complex signals analysis. Since its proposal, MSE has been successfully applied to physiological signals such as recordings from electroencephalogram (19, 42), electrocardiogram (2), postural control (10, 25), HRV (3, 11, 15, 37), and others (26, 40, 43).

Nevertheless, some studies considered MSE biased because it keeps the similarity criteria constant over all scales, even though variance decreases with scale (27, 39) and the procedure for the selection of time scales explored a poorly designed filtering process (39). Refined MSE (RMSE) is an approach recently proposed by Valencia and co-workers (39), aiming at refining MSE. Despite the methodological differences between MSE and RMSE, there are few studies comparing practical differences between those approaches (1, 14).

In this context, the aim of the present study was to study the multiscale entropic properties of HRV, using both MSE and RMSE, in three distinct experimental conscious animal models of cardiovascular diseases; i.e., rats with heart failure (HF), spontaneously hypertensive rats (SHR), and rats with sinoaortic-denervation (SAD). The groups were considered together because they all exhibited a dominant sympathetic activity. However, while SAD and SHR groups featured an increased sympathetic modulation, the HF group presented a reduced ability of varying sympathetic activity about its mean value. These peculiar features of the chosen groups will enlarge the possibility to correlate changes of entropy to pathophysiological mechanisms and allow us a deeper comparison between MSE and RMSE.

MATERIALS AND METHODS

This is a study whose data were obtained from the original recordings from previously published papers involving rats with congestive HF (23), or SAD (20), but also SHRs especially planned for this study. Previous studies (23) characterized the cardiovascular function and autonomic profile of the considered animal models without assessing the complexity of the cardiovascular control.

All experimental procedures adhered to the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health (National Institute of Health 1985). The authors are grateful to the reviewers for their valuable comments on previous versions of this manuscript and to A. D. C. for improving the language.
and Wistar-Kyoto (WKY) counterparts (21). Briefly, common carotid arteries and the vagal nerves were isolated, and the aortic depressor fibers either traveling with the sympathetic trunk or as an isolated nerve were cut. Aortic baroreceptor fibers traveling with the inferior laryngeal nerve were interrupted by resection of the superior laryngeal nerve after stripping the carotid bifurcation. SAD was performed by cutting the sinus nerve as well as all carotid branches and the carotid body. Male Wistar control rats (N = 7) underwent the same surgical procedures, but the nerves and carotid sinus were left intact. A polyethylene catheter was inserted into the femoral artery and exteriorized in the back of the neck after SAD or sham surgery.

On the following day, the rats were taken to the recording room and arterial pressure (AP) line was connected to a pressure transducer (Statham, P23 XL, Valley View, OH). Basal AP was sampled (2 kHz) for 180 min using an IBM/PC equipped with an analog-to-digital interface (D1220 Data Instruments, Akron, OH).

Animal model of HF. HF was produced by myocardial infarction (MI) according to the method described elsewhere (29). Briefly, male Wistar rats (250–300 g) were anesthetized with ketamine and xylazine (50 and 10 mg/kg ip), and, under mechanical ventilation, the animal’s chest was opened and the heart quickly exteriorized. The left anterior descending coronary artery was ligated with polyester suture between the pulmonary artery outflow tract and the left atrium. The heart was returned to the chest cavity, and the thorax incision was closed. Male Wistar control rats underwent the similar surgical procedure without coronary ligation. The infarct size was confirmed by postmortem examination, and only rats with an infarct size >40% of the left ventricle wall were used in the study. The average infarct size was 57 ± 1 expressed as a percentage of the left ventricle size (means ± SE).

Four weeks after MI (N = 9) or sham surgery (N = 9), the rats were anesthetized (tribromoethanol, 250 mg/kg ip) and submitted to mechanical ventilation. Common carotid arteries and the vagal nerves were isolated, and a polyethylene catheter into its lumen was firmly sutured to the underlying tissue. Animals were left to recover for 3 days before recordings were initiated. The ECG from the implantable unit was received via a dedicated receiver (Telemetry Research) and sampled (2 kHz) using a PowerLab data acquisition system, associated LabChart software (model ML870, ADInstruments, Castle Hill, NSW, Australia).

Data analysis. AP or ECG recordings were analyzed off-line using AP or ECG analysis module for LabChart software (ADInstruments), respectively. Beat-by-beat series of pulse interval (PI) or RR intervals were generated respectively from AP or ECG. The average length of all PI and RR series was 20,904 cardiac beats, whereas the shortest series considered was composed by 10,126 values and the longest by 36,955 values.

Multiscale entropy and refined multiscale entropy. MSE was originally proposed by Costa et al. (7, 8) and is intended to measure the irregularity of a time series as a function of time scale. Given u(i) a N-length time series, i = 1, . . . , N, and scaled versions of u(i) are first created by a coarse-graining procedure that calculates a windowed (size τ) average, without overlap, taking each mean value as a point for the scaled time series. Each scaled series u(i, j), j = 1, . . . , N/τ, represents the dynamics of u(i) in a different time scale, where slower time scales are represented by greater values of τ. Next, sample entropy (34) is calculated for each scaled series, resulting in a curve of conditional entropy as function of τ.

The calculation of sample entropy requires two parameters to be set, namely the length of patterns whose probability of occurrence will be estimated, usually referred to as embedding dimension m, and the pattern similarity criterion, usually referred to as tolerance r. Usually, r is chosen as a percentage of the time series standard deviation (SD), thus allowing the comparison of entropy between series with different variance (22). This kind of choice is equivalent to normalize the time series by the SD. It is important to notice that, in MSE, the similarity criterion is kept fixed for all scales. Even though the SD decreases with the coarse-graining procedure, entropy is calculated using the same tolerance criterion for all scales, defined as a percentage of the original time series SD.

After the MSE proposal, a criticism was raised about the use of a fixed similarity criterion for all scales (27). As the variance of scaled signals decreases, it was argued that MSE would measure both regularity and variation. In response, Costa et al. (9) still maintained their first position, arguing that subsequent changes of SD over scale contain information about the temporal structure of the original time series, and therefore, should be accounted for the entropy measurement.

The RMSE, proposed by Valencia et al. (39), supports the arguments of Nikulin and Brismar (27, and 27) that entropy converge for each scale. Moreover, Valencia et al. (39) disagrees with the coarse-graining procedure of MSE that did not safely control aliasing due to the use of a poorly designed low-pass filter. The limitation comes from the fact that MSE coarse graining is performed via a moving average low-pass filter (i.e., the plain mean), which is characterized by a very poor frequency response, a slow roll-off of the main lobe, a large transition band, and considerable side lobes in the stopband, causing aliasing during downsampling (39). In RMSE, the poorly designed low-pass filter was replaced by a Butterworth filter of order 6, which is characterized by a faster roll-off, that passband, and no side lobes in the stopband. Aliasing during down-sampling produces effects that depend on the relation between the frequency of the original oscillation and the downsampling rate, thus generating spurious oscillations even at frequencies slower than that of the original component. Therefore, the use of an antialiasing filter with better performance is mandatory to limit as much as possible the generation of spurious oscillations due to aliasing that artificially might alter the complexity of the signal in an unpredictable and variable way with the frequency content of the series.

Calculation of sample entropy, definition of global indexes, and mapping the time scales from beat-to-beat domain to frequency domain. In this study, sample entropy was computed with m = 2, r = 15% of SD of the rescaled version and a maximum scale τ = 20 for both MSE and RMSE. In addition, we computed the following
compact descriptors: the scale at which entropy is minimum, the sum of entropy over short (from 1 to 4) and long (from 5 to 20) time scales, as well as the sum of entropy over all scales (from 1 to 20).

Considering the cut-off frequency of the low-pass filters utilized by MSE and RMSE and the period of the main rhythmicities characterizing HRV in rats, we associated MSE and RMSE time scales expressed in beats to spectral bands (4, 5). We propose that values of the entropy computed at the short time scales (1 to 4) are more under parasympathetic control, whereas longer time scales (5 to 20) should be more under sympathetic control. However, this mapping should not be considered as a one-to-one association due to several reasons: the low-pass characteristic of the filters, the variable heart rate of the animals, the contributions of the vagal modulation in the low frequency band, and the influence of noise, especially at scale 1. Our mapping is similar to that proposed by Bari et al. (1), given that humans and rats have the same scaling of frequencies when their

Fig. 1. Comparison between multiscale entropy (MSE, solid squares) and refined MSE (RMSE, open squares) in the three animal models of cardiovascular disease. Right, results relevant to rat with heart failure (HF), spontaneously hypertensive rats (SHR), and rat with sinoaortic denervation (SAD). Left, results relevant to control animals: sham Wistar [heart failure (HF) and SAD controls] and Wistar-Kyoto (WKY). Values are expressed as means ± SE. SampEn, sample entropy. *P < 0.05.
cardiac frequency is normalized to the mean heart rate and, thus, expressed in cycles per beat in the beat-to-beat domain (35).

Statistical analysis. Comparisons between MSE and RMSE among the same population were performed with Wilcoxon signed rank test, whereas the comparisons between control and pathological groups were performed with Mann-Whitney rank sum test. Significant differences were considered when $P < 0.05$.

RESULTS

Figure 1 shows mean entropy values for MSE and RMSE within the same group. Overall, RMSE tended to decrease faster than MSE for the first scale factors followed by a steeper increase. The major differences between MSE and RMSE were found in larger scales and in the sharpness of transitions from high entropy.

Fig. 2. Comparison between control animals (solid circles) and the 3 animal models of cardiovascular disease (open circles). The control animals are sham Wistar (HF and SAD controls) and WKY. The 3 animals models are rats with HF, SHR, and rats with SAD. Right, results of multiscale entropy (MSE); left, results relevant refined MSE. Values are expressed as means ± SE. SampEn: sample entropy. *$P < 0.05$. 

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values to small ones and vice versa (i.e., MSE profile appeared to be more smoothed than the RMSE one). However, marked similarities between MSE and RMSE did exist.

Figure 2 compares different groups of rats for both MSE (first column) and RMSE (second column). Results for MSE and RMSE were similar, except only for the significant difference between SHR to WKY found by RMSE at scale 3.

Surprisingly, rats with HF were not significantly different from the sham group at any scale factor. Curves of either MSE or RMSE were markedly different in rats with SAD compared with intact rats, whereas the differences between SHR and control animals were significant from scales larger than 3 (RMSE) or 4 (MSE).

Table 1 shows global indices extracted from MSE and RMSE. The majority of the indices indicated that the MSE and RMSE were different. These global indices confirmed the steeper decrease of RMSE, the smaller values of RMSE at short time scales and the larger at long scales. When comparing populations, no index was found different when HF rats are compared with sham animals. Moreover, the scale at the minimum entropy did not detect any difference with control animals. The sum of entropy over short time scales (from 1 to 4) was found different only in the comparison between SAD and sham group, whereas the sum of entropy over long time scales (from 5 to 20) was different for both SHR versus WKY animals and SAD versus sham group. The sum of the entropy over all the scales (from 1 to 20) was always higher in control animals than in pathological groups, except in the case of HF rats.

**DISCUSSION**

**Multiscale entropy and refined multiscale entropy.** Comparison between MSE and RMSE suggests that: 1) MSE and RMSE are significantly different, especially at long time scales, in the position of the minimum as a function of the time scale and in the sharpness of transition from high entropy values to small ones and vice versa; 2) despite these differences they show similar tendencies with scale factor; and 3) overall, RMSE is lower than MSE for the first few scales and larger for high scales, RMSE has minimum entropy at shorter time scales, and MSE profiles appear to be smoother compared with those of RMSE indicating a reduced ability to detect rapid changes of entropy with scales. It is worth noting that those properties were not detected in simulated signals (39), thus suggesting that the observed differences between methods are linked to nontrivial features present in our data.

The coarse-graining procedure of both MSE and RMSE attenuates the variance of the scaled signals. Updating $r$ parameter at each scale in RMSE aims at reducing the dependence of entropy on the variance. Indeed, keeping $r$ fixed for all scales, as in MSE, will confine more and more patterns inside a single phase space cell, as patterns will become less scattered, and entropy will tend to decrease. Interestingly, results showed that keeping $r$ fixed (MSE) or varying (RMSE) induces significant differences in the two types of entropy, but there is no global relationship between MSE and SD. Again, this feature was not detected in simulated signals, such as 1/f and white noise (27, 39), thus indicating that the captured differences cannot be simply explained in terms of trivial dynamics and can involve nonlinear properties of the time series.

As previously highlighted, RMSE tends to decrease faster than MSE for the first scales and increase steeper for large ones. The lower values of RMSE at low scales might be associated with the procedure for the selection of the time scales. The spurious effects of RMSE at low scales might be associated with the correction of the tolerance factor ($r$), which naturally tend to limit the dependence of entropy on the modifications of variance due to the filtering procedure necessary to focus different time scales.

**Control versus experimental models of diseases and SAD.** Although MSE and RMSE are significantly different within groups, results showed that they give the same information when comparing different groups. Therefore, the following discussion is valid for both methods.

It has been reported that MSE and RMSE for time series derived from healthy subjects is low on short time scales, increasing from scale 1 to 5, and then stabilizing at a relatively constant value (7, 8, 39, 40). This behavior can be attributed to the relatively regular action of respiration and short-term regulatory mechanisms (32) and the higher complexity of the cardiovascular control at long time scales. For rats, those profiles seem to be different. The shape of MSE and RMSE curves for control animals is high at scale 1, decreases for the next few scales, reaching a minimum at approximately scale 3 or 4, and then monotonically increases. This result is compatible with a larger influence of the measurement noise at scale 1 in rats than in humans, to a reduction of entropy at short time scales (above 1 but smaller than 4) due to the regular, periodic action of respiratory rhythm and to a more complex cardiovascular control at long time scales.

The increased sympathetic activity plays a significant role in the development and maintaining of high levels of arterial pres-

Table 1. Parameters extracted from MSE and RMSE curves as a function of the animal model

<table>
<thead>
<tr>
<th>Group</th>
<th>Scale at MSE Minimum</th>
<th>Scale at RMSE Minimum</th>
<th>MSE$_{1–4}$</th>
<th>RMSE$_{1–4}$</th>
<th>MSE$_{5–20}$</th>
<th>RMSE$_{5–20}$</th>
<th>Total MSE</th>
<th>Total RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Wistar controls</td>
<td>5.9 ± 1.4</td>
<td>4.0 ± 0.8†</td>
<td>4.1 ± 0.4</td>
<td>3.8 ± 0.4‡</td>
<td>13.8 ± 1.4</td>
<td>14.7 ± 1.5‡</td>
<td>18.0 ± 1.6</td>
<td>18.5 ± 1.8</td>
</tr>
<tr>
<td>HF rat</td>
<td>6.8 ± 1.8</td>
<td>5.0 ± 1.2†</td>
<td>3.6 ± 0.3</td>
<td>3.5 ± 0.6</td>
<td>11.0 ± 1.3</td>
<td>12.6 ± 1.7†</td>
<td>14.6 ± 1.7</td>
<td>16.1 ± 2.2</td>
</tr>
<tr>
<td>WKY controls</td>
<td>3.5 ± 0.7</td>
<td>3.0 ± 0.6</td>
<td>2.9 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>13.8 ± 1.1</td>
<td>14.5 ± 1.1†</td>
<td>16.7 ± 1.2</td>
<td>17.3 ± 1.3‡</td>
</tr>
<tr>
<td>SHR</td>
<td>4.1 ± 0.4</td>
<td>3.3 ± 0.4†</td>
<td>2.5 ± 0.2</td>
<td>2.3 ± 0.2‡</td>
<td>9.1 ± 0.7†</td>
<td>9.5 ± 0.8‡</td>
<td>11.6 ± 0.9*</td>
<td>11.8 ± 0.9‡</td>
</tr>
<tr>
<td>SAD rat</td>
<td>4.9 ± 1.2</td>
<td>4.7 ± 1.6</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.2</td>
<td>17.0 ± 1.1</td>
<td>17.8 ± 1.2†</td>
<td>20.7 ± 1.1</td>
<td>21.6 ± 1.2†</td>
</tr>
</tbody>
</table>

Values are means ± SE. The scales at the MSE and RMSE minimum were expressed in beats. HF, heart failure; WKY, Wistar-Kyoto; SHR, spontaneously hypertensive rat; SAD, sinoaortic denervation; MSE$_{1–4}$, sum of MSE from scales 1 to 4; RMSE$_{1–4}$, sum of RMSE from scales 1 to 4; MSE$_{5–20}$, sum of MSE from scales 5 to 20; RMSE$_{5–20}$, sum of RMSE from scales 5 to 20; Total MSE, sum of all MSE values (1 to 20); Total RMSE, sum of all RMSE values (1 to 20). *Significant difference from control group; †significant difference from MSE. $P < 0.05$. 

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sure in SHR (38). As stated before, the sympathetic control to the heart is more likely to operate at longer time scales. For this reason, the higher influence of sympathetic modulated mechanisms in SHR compared with control animals may contribute to the slower recovering phase of entropy with temporal scales. The higher sympathetic drive might reduce HRV complexity by limiting fast (vagal) oscillations and by producing synchronized, highly regular behaviors. Moreover, it is well established that humoral mechanisms as nitric oxide, adrenal catecholamines, and the renin-angiotensin system are involved in arterial pressure regulation (30) and are modified in SHR. These humoral factors, usually associated with the genesis of very slow rhythms observed in HRV (24, 28), are also likely to be involved in limiting entropy at high time scales in SHR.

SAD breaks down the feedback loop of cardiac baroreflex, which is a fast arterial pressure regulatory reflex mainly under vagal control. A few days after SAD surgical procedure, where both inhibitory (baroreceptors) and excitatory influences (chemoreceptors) on the arterial pressure are removed, the impairment of the cardiac baroreflex led to an increase in arterial pressure (12). As a result, it was expected that short-term control was altered in SAD animals. Indeed, we found that the sum of entropy over short time scales (MSE1–4 and RMSE1–4) decreased in SAD compared with sham animals. Moreover, our results suggest that long-term mechanisms are affected by SAD as well. Indeed, the sum of entropy over long time scales (MSE5–20 and RMSE5–20) are also decreased in SAD animals compared with sham animals. Those results on the complexity of the cardiac control indicate that both short- and long-term mechanisms are impaired in SAD. This finding denotes that, even though being a short-term mechanism, cardiac baroreflex also affects mechanism operating over longer temporal scales. This result highlights the presence of cross-talking phenomena among cardiovascular control mechanisms operating over different time scales.

HF is characterized by an increased sympathetic activity (12, 33, 39), a decreased sympathetic modulation (34), and an impaired cardiac baroreflex control (39). The decrease of sympathetic modulation is the main factor responsible for the insignificant decline of MSE and RMSE in HF animals compared with controls and for the different behavior of the HF group compared with the SAD and SHRs. Indeed, in SAD and SHR groups, in presence of increased sympathetic activity, sympathetic modulation is raised as well, thus reducing the complexity of cardiac control through its powerful synchronizing and regularizing action. In conclusion, MSE and RMSE analyses suggest that the breakdown of complexity of the cardiac control occurs by eliminating or depressing one of the main short-term control reflexes (i.e., cardiac baroreflex) and by increasing sympathetic modulation. Variations of the sympathetic activity about its mean value, more than the mean value itself, seem to be responsible for the decline of HRV complexity.

It is still a challenge to quantify the complexity of the cardiovascular control based on HRV analysis. In this regard, methods that account for multiscale properties of signals, such as MSE and RMSE, have become very important (1, 37). Indeed, control and pathological groups might be distinguished at time scales longer than the fastest one (i.e., $\tau = 1$). In addition, not only specific values of the entropy but also their dependence on time scale factor need to be taken into account because the course of entropy with temporal scales depends on the pathological condition (8).

Extended comparison with different MSE approaches. There are several approaches proposed to improve the performance of MSE (16). Those techniques suggested modifications of the coarse graining procedure with the final aim to avoid the reduction of the length of the series with the scale factor (44–46) or proposed changes of the filtering procedure with the final purpose to be more adaptive and circumvent the strict definition of the filter cut-off (17). Some of the recently proposed procedures deviated from the original approach by focusing quantities that are not the result of a selection of the time scales according to a low-pass filtering procedure (6). In the present study we limited our comparison to RMSE because it is straightforward and interpretation of the findings is direct. Indeed, MSE and RMSE use exactly the same logic of coarse graining, select time scales according to the definition of the filter cut-off, and monitor comparable quantities. A full comparison considering all MSE approaches present in literature requires a more complex methodological framework to be addressed properly.

Perspectives and Significance

Even though RMSE seems to be more appropriate than MSE from a signal processing standpoint and the differences between MSE and RMSE reported in this study are remarkable, the two measures of multiscale complexity give virtually the same information when between-population differences are assessed. Both methods suggest that the impairment of baroreflex as well as a dominant sympathetic modulation reduces HRV complexity, and this reduction occurs at any time scales longer than one. In addition, findings indicate that having a high sympathetic driver does not imply necessarily a significant reduction of the complexity of the cardiovascular control and highlight the presence of cross-talking phenomena among cardiovascular control mechanisms operating over different time scales. Those findings are important to guide future studies of multiscale properties of HRV, both in the methodological aspect as in the interpretation of results.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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