Temporal asymmetries of short-term heart period variability are linked to autonomic regulation

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Porta A, Casali KR, Casali AG, Gneecchi-Ruscone T, Tobaldini E, Montano N, Lange S, Geue D, Cysarz D, Van Leeuwen P. Temporal asymmetries of short-term heart period variability are linked to autonomic regulation. Am J Physiol Regul Integr Comp Physiol 295: R550–R557, 2008. First published May 21, 2008; doi:10.1152/ajpregu.00129.2008.—We exploit time reversibility analysis, checking the invariance of statistical features of a series after time reversal, to detect temporal asymmetries of short-term heart period variability series. Reversibility indexes were extracted from 22 healthy fetuses between 16th to 40th wk of gestation and from 17 healthy humans (aged 21 to 54, median = 28) during graded head-up tilt with table inclination angles randomly selected inside the set {15, 30, 45, 60, 75, 90}. Irreversibility analysis showed that nonlinear dynamics observed in short-term heart period variability are mostly due to asymmetric patterns characterized by bradycardic runs shorter than tachycardic ones. These temporal asymmetries were 1) more likely over short temporal scales than over longer, dominant ones; 2) more frequent during the late period of pregnancy (from 25th to 40th week of gestation); 3) significantly present in healthy humans at rest in supine position; 4) more numerous during 75 and 90° head-up tilt. Results suggest that asymmetric patterns observable in short-term heart period variability might be the result of a fully developed autonomic regulation and that an important shift of the sympathovagal balance toward sympathetic predominance (and vagal withdrawal) can increase their presence.

heart rate variability; autonomic nervous system; head-up tilt; fetal maturation; nonlinear dynamics

The variability of heart period (usually approximated as the temporal distance between two consecutive R peaks on the ECG, R-R) has been proven to be nonlinear in healthy fetuses between 38th and 40th week of gestation (8) and in healthy humans (1, 4), mostly during experimental conditions periodically forcing cardiovascular regulation (i.e., controlled breathing) (15, 16). However, this finding has not been translated yet into a notion actually helpful in pathophysiology. The main reason is that, until now, the detection of nonlinear dynamics has not been linked to a clear temporal correlate (i.e., a pattern associated with nonlinear dynamics).

Time irreversibility analysis checks the invariance of the statistical properties of a time series after time reversal. This analysis might be helpful to translate the involved concept of nonlinear dynamics into a simple, comprehensible notion useful in pathophysiology, since it clearly indicates a time domain scheme responsible for nonlinear dynamics. Indeed, time irreversibility analysis is capable of detecting a specific class of nonlinear dynamics, that is, those characterized by a temporal asymmetry. In other words, when a series is detected as irreversible using simple tests in the two-dimensional phase space (6, 9, 17), it can be stated that the nonlinear behavior is the result of the presence of asymmetric patterns (i.e., waveforms characterized by the upward side shorter or longer than the downward side), thus directly linking the abstract concept of nonlinear dynamics to a clear, easily imaginable, feature (17).

The aim of this study is twofold. The first aim is to link the presence of temporal asymmetries of short-term R-R variability, as detected from irreversibility analysis, to the autonomic regulation. A set of R-R variability data recorded from healthy fetuses in different periods of maturation (12, 24) will allow us to elucidate the role of autonomic nervous system in generating these temporal asymmetries. The second aim is to link the presence of these asymmetric patterns to the amplitude of sympathetic modulation. R-R variability series recorded from healthy humans during graded head-up tilt will be utilized to assess whether the contemporaneous increase of sympathetic modulation and decrease of vagal one (3, 7, 13, 18) is responsible for a more pronounced presence of these temporal asymmetries.

In this study, we will exploit three indexes devised to detect irreversible dynamics (6, 9, 17). In the Appendix, we will derive them according to a unique framework based on the representation of the dynamics in the two-dimensional phase space (R-R(i),R-R(i+τ)), and we will summarize the relationship between time irreversibility, pattern asymmetry, and nonlinear dynamics.

METHODS

Experimental protocols. The data belong to two historical databases designed to evaluate R-R variability of the autonomic nervous system (12, 24) and 2) in healthy humans, the effects of a graded orthostatic challenge (head-up tilt) on the cardiovascular regulation (18), as assessed from short-term analysis of heart period variability. We report below a brief description of both experimental protocols. A detailed description of the population

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and a comprehensive description of the experimental setup can be found in Refs. 12, 18, and 24. The study adheres to the Declaration of Helsinki and protocols have been approved by independent local review boards.

Recordings from healthy fetuses. We investigated 66 recordings of 22 healthy fetuses in singleton pregnancies recorded using fetal magnetocardiography (MCG). Ten fetuses were male, ten were female, and for two fetuses, the information on gender was not available. Full information relevant to mothers’ age, gravidity, birth weight and 10 min Apgar scores can be found in Ref. 12. Fetuses underwent recordings between 16th and 40th wk of gestation (WoG). All the 22 fetuses had three recordings, and one fell in each of the following periods of gestation (PoG): 1) PoG1: from 16th to 24th WoG; 2) PoG2: from 25th to 32nd WoG; and 3) PoG3: from 33rd to 40th WoG. IMCG was recorded using a 61-channel biomagnetometer (Magnes 1300C; 4D Neuroimaging, San Diego, CA) for 5 min at rest at a sampling rate of 1 kHz. In each recording, after a digital subtraction of the maternal components from the signal, fetal QRS complexes were identified in a channel with high-amplitude signal using a template-matching approach. Fetal heart period was derived as the time interval between two consecutive fetal R peaks (R-R interval), with an accuracy of 1 ms. Sequences of 256 beats were randomly chosen from the 5-min recordings. If the randomly selected sequence included evident nonstationarities such as slow drifting of the temporal distance between two consecutive fetal R peaks (R-R), the sequence was discarded, and a new random selection was performed.

Recordings from healthy humans during graded head-up tilt. We studied 17 healthy humans (aged 21 to 54, median = 28; 7 females and 10 males). A complete description of the experimental protocol can be found in Ref. 18. Briefly, we recorded surface ECG (lead II) and respiration via thoracic belt at rest (R) in supine position and the mean value or sudden changes of the variance, the sequence included evident nonstationarities such as slow drifting of the temporal distance between two consecutive fetal R peaks (R-R interval), and respiration via thoracic belt at rest (R) in supine position and the mean value or sudden changes of the variance, the sequence was discarded, and a new random selection was performed.

RESULTS

Irreversibility analysis. Given the series R-R=[R-R(i), i = 1, . . . , N = 256], R-R is irreversible if the probability distribution of R-R2 = [R-R2(i) = (R-R(i), R-R(i+τ)], i = 1, . . . , N−τ] is different from that of R-R2 = [R-R2(i) = (R-R(i), R-R(i+τ)], i = 1, . . . , N−τ]. The parameter τ is the time lag utilized for the reconstruction of the dynamics in the plane [R-R(i), R-R(i+τ)]. The distributions of R-R2 and R-R2 are different if the scatterplot in the plane (R-R(i), R-R(i+τ)) is asymmetric with respect to the line R-R(i) = R-R(i+τ), i.e., the main diagonal of the plane (R-R(i), R-R(i+τ)). Since the distance of the point R-R(i) with respect to the main diagonal is equal to kΔR-R(i) = k[R-R(i)−R-R(i)] with k = 2−1/2, testing the asymmetry of the scatterplot in the plane (R-R(i), R-R(i+τ)) with respect to the main diagonal is equivalent to evaluating the asymmetry of the distribution of kΔR-R (or ΔR-R) with respect to 0 (17). We exploited three traditional irreversibility indexes (see Appendix for a detailed description), checking the asymmetry of the distribution of R-R2 via the analysis of ΔR-R. The considered indexes are 1) Porta’s index (17), based on the evaluation of the percentage of negative ΔR-R with respect to the total number of ΔR-R ≠ 0 (this index will be indicated as P% in the following); 2) Guzik’s index (9), based on the evaluation of the cumulative distance between the points R-R above the main diagonal and the main diagonal normalized by the cumulative distance between all the points R-R and the main diagonal (this index will be indicated as G% in the following); and 3) Ehlers’ index (6), based on the evaluation of the skewness of the distribution of ΔR-R (this index will be indicated as E hereafter).

Values of P% and G% significantly larger than 50 and values of E significantly larger than 0 indicate that the number of negative ΔR-R (ΔR-R < 0) is larger than that of positive ΔR-R (ΔR-R > 0) (i.e., brady-cardiac runs are shorter than tachycardic ones), as detected by P% or, equivalently, that the averaged magnitude of |ΔR-R| was larger than that of |ΔR-R−1| (i.e., ascending side of an R-R pattern is steeper than the descending side) as detected by G% and E. Values of P% and G%, which are significantly smaller than 50, and values of E, which are significantly smaller than 0, indicate the opposite.

Surrogate data approach. We used a surrogate data approach to check irreversibility of the R-R series. Surrogates are series that preserve only specific statistical properties of the original data, according to a null hypothesis. We set as a null hypothesis that the series is a linear process with Gaussian distribution, possibly distorted via a nonlinear static invertible transformation, thus being reversible. Accordingly, we built surrogate series with the same second-order statistical properties (i.e., with preserved power spectrum) and the same distribution (i.e., with preserved histogram) as the original ones (25). Amplitude-adjusted Fourier transform (AAFT) surrogates have been constructed according to Theiler et al. (22). To achieve the best approximation of the original power spectrum with the exact distribution of values of the original series, the procedure for generating AAFT was iterated several times (up to 100 times), thus obtaining the so-called iteratively refined AAFT surrogates (I-FAFT) (19, 20). We constructed a set of 500 I-FAFT surrogates, and we implemented a two-sided nonparametric test. As test parameter χ in the surrogate data approach, we utilized a reversibility index among those previously defined. The test parameter χ was calculated over the surrogate series (χs) and over the original series (χo). If χo was smaller than the 2.5th percentile of the χs distribution or larger than the 97.5th percentile, the null hypothesis was rejected and the original series was said to be irreversible. Otherwise, the original series was found consistent with the null hypothesis. In both protocols, we calculated the percentage of irreversible series as indicated by each index (IPE%, IGE%, and IIE). If χo was larger than the 97.5th percentile of the χs distribution, the number of ΔR-R was significantly larger than that of |ΔR-R| as detected by P% or, equivalently, the averaged magnitude of |ΔR-R| was significantly larger than that of |ΔR-R−1|, as detected by G% and E. The fraction of this specific irreversible pattern with respect to the overall amount of irreversible dynamics will be indicated as IPE%, IGE%, and IIE in the following.

Selection of the time lag. If the time lag τ is quite small with respect to the dominant temporal scale of the dynamics, R-R(i) and R-R(i+τ) are strongly correlated, and the points R-R lay along the main diagonal R-R(i) = R-R(i+τ). On the contrary, if the time lag τ is comparable with the temporal scale of the dominant feature (τ approximately equal to T/4 where T is the period of the dominant pattern), R-R(i) and R-R(i+τ) are linearly uncorrelated, and the points R-R form a large cloud laying on the main diagonal R-R(i) = R-R(i+τ). We adopted two strategies for the selection of the time lag τ. In the first strategy, τ was equal to 1. This selection is more helpful in describing temporal asymmetry over short timescales. The second strategy was based on the calculation of the autocorrelation function and on the evaluation of τ in correspondence of its first zero (11). In the case that the autocorrelation function did not decrease below 0 when τ was varied from 0 to 45, we selected τ in correspondence of the global minimum. This choice is more suitable for the evaluation of temporal asymmetries over longer dominant scales where the linear correlation is 0.

RESULTS

Irreversibility analysis is described over a specific example in Fig. 1. Figure 1 shows an R-R series (Fig. 1A) obtained from...
a healthy, young subject at R. The scatterplot in the plane (R-R(i),R-R(i+1)) with $k = 2^{1/2}$ (E and F, respectively). Scatterplot in the plane (R-R(i),R-R(i+1)) and distribution of $k \Delta R-R$ relevant to the original series are clearly asymmetric (C, E), while those relevant to the surrogate series are symmetric (D, F).

null hypothesis of reversibility. Indeed, the values of $P\%$, $G\%$, and $E$ derived from the original series were outside the intervals defined by the 2.5th and 97.5th percentiles derived from surrogates (i.e., 46.66 and 53.33 for $P\%$, 45.50 and 54.33 for $G\%$. $-0.023$ and 0.022 for $E$).

The results of irreversibility analysis in healthy fetuses as pregnancy progresses are described in Fig. 2. The analysis was carried out with a time lag $1$ (Fig. 2, A, C, E) and with a time lag $\tau$ optimized according to the first zero of the autocorrelation function [Fig. 2, B, D, F: $\tau = 30.7 \pm 12.3, 18.3 \pm 7.2, 25.9 \pm 12.1$ beats during PoG1, PoG2, and PoG3, respectively, means $\pm SD$]. Box-and-whiskers plots reporting the 10th, 25th, 50th, 75th, and 90th percentiles of all the irreversibility indexes (i.e., $P\%$, $G\%$, and $E$) as a function of the PoG are shown in Fig. 2, A and B. Assigned $\tau = 1$, $P\%$ and $G\%$ exhibited a tendency to be larger than 50 and $E$ to be larger than 0 (Fig. 2A). This tendency was significant (i.e., 95% of the $P\%$ and $G\%$ values were larger than 50, and 95% of the $E$ values were larger than 0) in the case of $P\%$ during PoG2 and PoG3, in the case of $G\%$ during PoG1, PoG2, and PoG3 and in the case of $E$ during PoG3. These significant differences are marked with the symbol * in Fig. 2A. On the contrary, when the time lag $\tau$ was optimized (Fig. 2B), $P\%$ and $G\%$ were
around 50 and E was around 0 in all PoGs. The comparison of indexes calculated during PoG2 and PoG3 with those calculated during PoG1 based on Friedman repeated-measures ANOVA on ranks (Dunn’s test with \( P < 0.05 \)) indicated that P% was larger during PoG2 and PoG3 (Fig. 2A). These significant differences are marked with the symbol # in Fig. 2A. On the contrary, when \( \tau \) was optimized, all the indexes calculated during PoG2 and PoG3 were not significantly different from those calculated during PoG1. Individual detections of irreversible dynamics based on surrogate approach confirmed the statistical analysis carried out on pooled P%, G%, and E values. Indeed, with \( \tau = 1 \), we found that during PoG1, \( I_{P^+}, I_{G^+}, \) and \( I_E \) are significant (32%, 55%, and 50%, respectively) and increased during PoG2 and PoG3 (Fig. 2C). On the contrary, when the time lag \( \tau \) was optimized (Fig. 2D), \( I_{P^+}, I_{G^+}, \) and \( I_E \) were close to 0 during PoG1 (i.e., 9%, 5%, and 9%) and constant as pregnancy progressed. During any PoG, irreversible dynamics were completely due to the presence of bradycardic runs shorter than tachycardic ones. Indeed, the fraction of irreversible dynamics characterized by a number of \( \Delta R-R^- \) larger than that of \( \Delta R-R^+ \) (i.e., \( I_{P^+} \)) or, equivalently, by an averaged amplitude of \( \Delta R-R^- \) larger than that of \( \Delta R-R^+ \) (i.e., \( I_{G^+} \) and \( I_E \)) were close to 100% (Fig. 2E). Within the small amount of irreversible dynamics detected when the time lag \( \tau \) was optimized, according to the first zero of the autocorrelation function, the large majority was characterized by the presence of bradycardic runs shorter than tachycardic ones (Fig. 2F).

Results of irreversibility analysis in healthy humans during graded head-up tilt are described in Fig. 3. The analysis was carried out with a time lag \( \tau = 1 \) (Fig. 3, A, C, E) and with a time lag \( \tau \) optimized according to the first zero of the autocorrelation function [Fig. 3, B, D, F; \( \tau = 8.4 \pm 7.3, 14.2 \pm 12.1, 13.9 \pm 8.9, 13.0 \pm 7.2, 14.7 \pm 13.4, 15.3 \pm 11.4 \) and 10.3 \( \pm 8.7 \) at R and during T15, T30, T45, T60, T75, and T90, respectively, means \( \pm SD \)]. Box-and-whiskers plots reporting the 10th, 25th, 50th, 75th and 90th percentiles of P%, G%, and E as a function of the tilt table inclination are shown in Fig. 3, A and B. Assigned \( \tau = 1 \) P% and G% exhibited a tendency to be larger than 50 and E to be larger than 0 (Fig. 3A), but this tendency was insignificant for all the indexes in all the experimental conditions. When the time lag \( \tau \) was optimized (Fig. 3B), this tendency was even weaker. The comparison of indexes calculated during T with those calculated at R based on Friedman repeated-measures ANOVA on ranks (Dunn’s test with \( P < 0.05 \)) indicated that G% and E were significantly larger during T75, whereas P% became significantly larger during T75, whereas P% became significantly larger during T90 (Fig. 3A). On the contrary, when \( \tau \) was optimized, all the indexes during T were not significantly different from those calculated at R. With \( \tau = 1 \), individual detections of
irreversible dynamics based on surrogate approach indicated that at R, the series were irreversible in a significant percentage of subjects ranging from 41% as detected by P% to 59% as detected by G% and E (Fig. 3C). Given a specific index, during T60, T75, and T90, the percentage of irreversible dynamics was larger than that found at R (Fig. 3C). When the time lag $\tau$ was optimized (Fig. 3D), $I_p$, $I_G$, and $I_E$ were low at R (i.e., 12%, 29%, and 35%, respectively), and no clear trend was observable as a function of the tilt table inclination. Both at R and during T, irreversible dynamics were mostly due to the presence of bradycardic runs shorter than tachycardic ones. Indeed, the fraction of irreversible dynamics characterized by a number of $R-R$ larger than that of $\Delta R-R$ (i.e., $I_{p\%}$) or, equivalently, by an averaged amplitude of $\Delta R-R$ larger than that of $[\Delta R-R]$ (i.e., $I_{G\%}$ and $I_E$) were high at R (Fig. 3E, $I_{p\%}$ = 60, $I_{G\%}$ = 73, $I_E$ = 80) and increased during T60, T75, and T90 with respect to R (Fig. 3E). When the time lag $\tau$ was optimized and during T $I_{p\%}$, $I_{G\%}$, and $I_E$ were even larger than those observed at $\tau = 1$ (Fig. 3F).

DISCUSSION

The major findings of this study are as follows: 1) simple time irreversibility indexes enable the detection of temporal asymmetries in short-term heart period variability series in healthy fetuses and humans and permit the identification of temporal features responsible for nonlinear dynamics; 2) temporal asymmetries are the result of bradycardic runs shorter than tachycardic ones and are more likely over short time scales than over longer dominant ones, 3) the increased presence of temporal asymmetries in healthy fetuses as a function of the maturation of the autonomic regulation suggests that a fully developed cardiac control is a prerequisite for their generation; 4) these temporal asymmetries are more frequent during the increase of sympathetic modulation (and activity) produced by 75° and 90° head-up tilt, whereas less important sympathetic modulations, such as those produced by smaller tilt table inclination angles fail to increase their presence.

Several recent studies have applied irreversibility analysis to heart period variability (1, 4, 9, 17). Because time irreversibility is incompatible with a linear Gaussian process, possibly transformed via a static nonlinear invertible transformation (25), time irreversibility analysis has been mainly utilized to detect nonlinear dynamics (1, 4). This interest is related to the conjecture that the presence of nonlinearities is a hallmark of the complex dynamics.
creases as pregnancy progresses. This result confirms the gestation and that the presence of irreversible patterns in the age of healthy fetuses between the 25th and 40th wk of heart period variability is irreversible in a significant percentage of healthy young humans (15, 16). In addition, we found that period variability is nonlinear in a significant percentage of nonlinear dynamics, we can confirm that short-term heart variability, thus translating the involved concept of nonlinear dynamics into a clear, easily imaginable, temporal pattern, and links the presence of these temporal asymmetries to the cardiac regulation.

Since all the proposed irreversibility indexes are based on the calculation of the R-R variations, $\Delta R-R$, and on the separate evaluation of positive and negative variations (i.e., $\Delta R-R^+$ and $\Delta R-R^-$), they are intrinsically capable of detecting temporal asymmetries. Indeed, $P%$ and $G%$ significantly larger than 50 or $E$ larger than 0 suggest that dynamical features are asymmetric with the averaged magnitude of $|\Delta R-R^+|$ larger than that of $|\Delta R-R^-|$ (i.e., with the upward side of the waveform steeper than the downward side). In addition, simply by changing the time lag $\tau$, it is possible to differentiate temporal asymmetries related to dynamical structures characterized by different temporal scales. Indeed, $\tau = 1$ allows the characterization of the asymmetries over short timescales, whereas the value of $\tau$ corresponding to the first zero of the autocorrelation function allows the description of asymmetries over longer, dominant timescales, when the linear correlation is 0.

We confirm that heart period variability in healthy young humans is irreversible at rest in supine position (1, 4, 9, 17). Since the detection of time irreversibility implies the presence of nonlinear dynamics, we can confirm that short-term heart period variability is nonlinear in a significant percentage of healthy young humans (15, 16). In addition, we found that heart period variability is irreversible in a significant percentage of healthy fetuses between the 25th and 40th wk of gestation and that the presence of irreversible patterns increases as pregnancy progresses. This result confirms the observation that heart period variability in healthy fetuses is nonlinear between the 38th and 40th week of gestation (8) and that nonlinear dynamics are more frequent as pregnancy progresses (12). However, none of the studies about humans or fetuses was able to identify the temporal scheme responsible for the nonlinear behavior. We suggest that asymmetric patterns with bradycardic runs shorter than tachycardic ones are responsible for the nonlinear behavior. Figure 4B clearly shows this nonlinear pattern. The asymmetry between ascending and descending sides of the waveforms is obvious; indeed, the upward part is shorter than the downward part, and the ascending side is steeper than the descending side. Figure 4D indicates that this peculiar asymmetry is lost when nonlinear dynamical features are destroyed by phase randomization procedure. Indeed, in an example of IAAFT surrogate (Fig. 4B) created from the original series (Fig. 4A), the durations of the ascending and descending sides are similar, and the averaged $|\Delta R-R^+|$ is not significantly different from the averaged $|\Delta R-R^-|$.

The increased presence of irreversible dynamics as pregnancy progresses supports the conclusion that the observed temporal asymmetries are related to a more developed cardiovascular control. Because it is well known (14) that the para-sympathetic-cholinergic control of the fetal heart becomes functional at weeks 15–17 and earlier than the sympathetic-adrenergic regulation (at weeks 23–28), the increased percentage of irreversible might be linked to the full cardiac regulation or to the development of the sympathetic control. However, the correlation between the presence of irreversible dynamics and maturation of the cardiac regulation does not imply any cause-and-effect link, and many other factors can play a role (e.g., the increased fetal activity as pregnancy progresses). Data on healthy humans indicate that these temporal asymmetries are affected by head-up tilt, but the correlation with the
amplitude of the sympathetic modulation (i.e., with the degree of tilt table inclination) is weak. Indeed, these temporal asymmetries are more frequent during the increase of the sympathetic modulation (and activity) produced by head-up tilt at the highest inclination angles (i.e., 75° and 90°), but their incidence is not influenced by smaller changes of the sympathetic modulation produced by lower inclination angles. In addition, irreversibility indexes (i.e., P%, G%, and E) are not linearly correlated with tilt angles as derived from Spearman rank-order correlation with \( P < 0.05 \).

The comparison between the results obtained with \( \tau = 1 \) with those derived after the optimization of \( \tau \) suggests that short-term heart period variability is more likely to be asymmetric over short temporal scales. Indeed, the percentage of irreversible dynamics with asymmetric patterns found when the time lag \( \tau \) is optimized according to the first zero of the autocorrelation function is insignificant and independent of the period of gestation in the case of healthy fetuses and small and independent of the table inclination angle in the case of healthy humans. Therefore, it can be suggested that asymmetric features over short time scales can coexist with more symmetric patterns over longer, dominant scales.

It is worth noting that, in contrast to the present study, recent investigations aiming at detecting nonlinearities based on local nonlinear prediction have not found a large percentage of nonlinear dynamics during 90° head-up tilt (15, 16). This puzzle might be solved by considering that the coarse graining procedure used by methods based on local nonlinear prediction (15, 16) may smooth asymmetric features responsible for the increase of the percentage of nonlinear dynamics over short temporal scales during 90° head-up tilt. If this observation were confirmed, the use of a technique that does not need any coarse graining procedure like the irreversibility analysis would become mandatory for the detection of nonlinear dynamics over short-term heart period variability.

In the literature, several groups have dealt with the scatterplot in the plane \((R-R(i), R-R(i+\tau))\) more commonly referred to as two-dimensional return map or Poincare plot [see e.g., 10, 21, 23]. These studies analyzed the shape of the Poincare plots and related it to pathology. For example, in healthy subjects the Poincare plot was found to be fan-shaped as a result of an increasing beat-to-beat R-R dispersion with increasing R-R interval duration (10, 23), while in pathological subjects the shape is more complex (21). Quantitative analysis of the Poincare plots is based on indexes that are essentially correlated with the area occupied by the cloud of points in the plane \((R-R(i), R-R(i+\tau))\) (10, 23). These indexes do not quantify the asymmetry of the Poincare plot with respect to the main diagonal. The present study suggests that indexes of asymmetry of the Poincare plot might provide helpful and insightful information about cardiovascular regulation and, thus, these indexes should be added to more conventional descriptors of the Poincare plot.

**Perspectives and Significance**

This study suggests that the nonlinear behavior of short-term heart period variability is the result of asymmetric patterns with bradycardic runs shorter than tachycardic ones (i.e., the heart decelerates more rapidly than it accelerates). This pattern is more likely when sympathetic control can play a role in the overall regulation of the fetal cardiac function and when sympathetic regulation is predominant, such as during head-up tilt at highest degrees of the table inclination. The detection of this nonlinear pattern might stimulate a more insightful interpretation of the cardiovascular regulation, the development of more precise models of short-term cardiac control and pharmacological studies to better clarify the mechanisms producing this nonlinear pattern.

**APPENDIX**

This appendix describes in detail the irreversibility indexes exploited in this study and summarizes the relationship between irreversibility, pattern symmetry, and nonlinear dynamics. To better compare them, indexes will be derived based on a representation of the R-R dynamics as points \( R-R_2 = [R-R_2(i) | R-R_2(i+\tau)] \), \( i = 1, \ldots, N-\tau \) in the two-dimensional phase space \( (R-R(i), R-R(i+\tau)) \). Let us define with \( R-R_2^-(i) \) a point above the main diagonal and with \( R-R_2^+(i) \) a point below it. In the case of \( R-R_2^{-}(i) \), \( \Delta R(R^-) = R-R_2(i+\tau)-R-R_2(i) > 0 \) [i.e., \( \Delta R-R^+(i) \)], while in the case of \( R-R_2^{+}(i) \), \( \Delta R(R^+) = R-R_2(i)-R-R_2(i+\tau) < 0 \) [i.e., \( \Delta R-R^-(i) \)].

**Porta’s index.** Porta et al. (17) assessed the asymmetry of the distribution of \( R-R_2 \) with respect to the main diagonal by evaluating the number of points below the main diagonal, \( R-R_2^- \), with respect to the overall amount of points \( R-R_2 \) outside the main diagonal. This index can be calculated as

\[
P% = \frac{N(\Delta R-R^-)}{N(\Delta R \neq 0)} \cdot 100,
\]

where \( N(\Delta R-R^-) \) is the number of \( \Delta R-R^- \) and \( N(\Delta R-R \neq 0) \) is the number of \( \Delta R-R \) different from 0 [i.e., \( N(\Delta R-R \neq 0) = N-\tau \cdot N(\Delta R-R = 0) \)]. \( P% \) ranges from 0 to 100. Irreversible series are characterized by values of \( P% \) significantly larger (or smaller) than 50. Under the hypothesis of stationarity and reversibility \( N(\Delta R-R^-) = N(\Delta R-R^+) = (N-\tau \cdot N(\Delta R-R = 0))/2. \) As a consequence \( P% > 50 \) implies that the number of \( \Delta R-R^- \) is larger than that of \( \Delta R-R^+ \), or, equivalently, that the averaged magnitude of \( \Delta R-R^+ \) is larger than that of \( \Delta R-R^- \). Therefore, the distribution of \( \Delta R-R \) is skewed toward positive values. The reverse situation is observed with \( P% < 50 \).

**Guzik’s index.** In the attempt to take into account even the position of \( R-R_2 \) with respect to the main diagonal, Guzik et al. (9) evaluated the asymmetry of the distribution of \( R-R_2 \), with respect to the overall diagonal as the ratio of the sum of the squared distances between \( R-R_2^+ \) and the main diagonal to the sum of the squared distances between \( R-R_2 \) and the main diagonal (multiplied by 100). Thus, the Guzik’s index is defined as

\[
G% = \frac{\sum_{i=1}^{N(\Delta R-R^+)} (\Delta R-R^+(i))^2}{\sum_{i=1}^{N(\Delta R-R^-)} (\Delta R-R^-(i))^2} \cdot 100. 
\]

This index ranges from 0 to 100. Irreversible series are characterized by values of \( G% \) significantly larger (or smaller) than 50. It is worth noting that, if \( G% > 50 \), the averaged magnitude of \( |\Delta R-R^+| \) is larger than that of \( |\Delta R-R^-| \). Therefore, the distribution of \( \Delta R-R \) is skewed toward positive values. The reverse situation is observed with \( G% < 50 \).

**Ehlers’ index.** Since \( R-R_2^+ \) are characterized by \( \Delta R-R^+ \) and \( R-R_2^- \) by \( \Delta R-R^- \), Ehlers et al. (6) utilized the skewness of distribution of \( \Delta R-R \).
irreversible. If \( E \geq G\% \), but a significant departure from 0 indicates that the series is irreversible. This index has not a predefined range like \( P\% \) and \( G\% \), but a significant departure from 0 indicates that the series is irreversible. However, if irreversibility is detected by the above-reported indexes devised according to a two-dimensional biological system that generates the nonlinear dynamics is high time irreversibility and more specific tests (2) are needed to discover the direct consequence of this result is as follows: If the series is a realization of a Gaussian autoregressive moving average process (ARMA) then it is reversible (25). The same finding holds even when the Gaussian ARMA process is distorted by a nonlinear static invertible transformation (e.g., \( I/\Delta R \) transformation that converts the heart period series into a heart rate series). The direct consequence of this result is as follows: If the series is irreversible, then the series is not completely described by a Gaussian ARMA process or it is nonlinear. If the series is nonlinear, this feature does not necessarily imply that it is irreversible (5). Indeed, irreversible dynamics are a small subset of the possible nonlinear dynamics.

\[
E = \frac{\sum_{i=1}^{N(RR)} \Delta R(i)^3}{\left( \sum_{i=1}^{N(RR)} \Delta R(i)^2 \right)^{\frac{3}{2}}}
\]

(3)

to evaluate the asymmetry of the distribution of \( R-R \) with respect to the main diagonal. This index has not a predefined range like \( P\% \) and \( G\% \), but a significant departure from 0 indicates that the series is irreversible.

**REFERENCES**
