# Assessment of the Autonomic Control of Heart Rate Variability in Healthy and Spinal-Cord Injured Subjects: Contribution of Different Complexity-Based Estimators

Giampiero Merati, Marco Di Rienzo, *Member, IEEE*, Gianfranco Parati, Arsenio Veicsteinas, and Paolo Castiglioni*

***Abstract*—We investigated how complexity-based estimators of heart rate variability can detect changes in cardiovascular autonomic drive with respect to traditional measures of variability. This was done by analyzing healthy subjects and paraplegic patients with different autonomic impairment due to low (vascular impairment only) or high (cardiac and vascular impairment) spinal cord injury, during progressive autonomic activations. While traditional techniques only quantified the effects of the autonomic activation, not distinguishing the effects of the lesion level, some recently proposed complexity estimators could also reveal the pathologic alterations in the autonomic control of heart rate. These estimators included the detrended fluctuation analysis coefficient (sensitive to both low and high autonomic lesions), sample entropy (sensitive to low-level lesions) and the largest Lyapunov exponent (sensitive to high-level lesions). Thus complexity-based methods provide information on the autonomic function from the heart rate dynamics that cannot be obtained by traditional techniques. This finding supports the combined use of both complexity-based and traditional methods to investigate the autonomic cardiovascular control from a more comprehensive perspective.**

***Index Terms*—DFA, entropy, heart rate variability, Hurst, Lyapunov exponents, self-similarity, spinal cord injury.**

## I. Introduction

HEART RATE variability (HRV) is increasingly used to assess autonomic dysfunction in different pathological conditions, either of cardiac (myocardial infarction, congestive heart failure, life threatening arrhythmias) [1]–[4] or noncardiac origin (diabetes, neuropathies, obesity, etc.) [5]–[9].

Currently, the assessment of cardiovascular autonomic impairment is mostly based on statistical indexes of variability derived from heart rate variance or power spectrum [10], whereas complex and nonlinear components of heart rate dynamics are largely neglected to this aim, although several authors provided evidence of their clinical importance and potential ability to identify cardiac autonomic dysfunction [11]–[18]. The limited attention to complexity-related components of HRV in the assessment of autonomic control of circulation is possibly due to the lack of a general consensus on the validity and reliability of these components. This scenario may be determined by a poor knowledge of the settings in which estimators of complex dynamics can be applied to physiologic data. It may also be determined by the lack of an unequivocal biological interpretation of the results obtained from the complexity-based analyses.

In an effort to provide a contribution to clarify these issues, this study investigated the ability of different complexity-based estimators of HRV to detect changes in the autonomic drive of the cardiovascular system in health and disease. This was done under three behavioral conditions which are known to induce progressively increasing degrees of autonomic activation (supine rest, sitting at rest and mild physical exercise). Recordings have been performed in healthy subjects and in patients with various degree of autonomic impairment due to traumatic spinal cord injury (SCI). The performances of the complexity estimators in detecting autonomic changes have been also compared with the performances of some frequency-domain and time-domain parameters traditionally derived from HRV analysis.

Given that each estimator offers a particular perspective on the HRV phenomena, our study was aimed at investigating whether the new complexity-based perspectives are more suitable than the traditional approaches to explore autonomic control of circulation in conditions characterized by different degrees of autonomic activation and/or different levels of autonomic dysfunction.

## II. Methods

First, the rationale behind the methodological choices made in designing the experimental protocol is briefly described.

### A. Experimental Conditions

We considered three behavioral conditions because they are characterized by a progressive increase in autonomic cardiovascular activation: supine rest (baseline "tonic" autonomic activation); sitting rest (mild autonomic activation caused by blood

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G. Merati and A. Veicsteinas are with the Institute of Physical Exercise, Health and Sports (IEFSAS), University of Milan, I-20148 Milan, Italy (e-mail: giampiero.merati@unimi.it).

M. Di Rienzo is with the Centro di Bioingegneria of the Fondazione Don C. Gnocchi ONLUS, I 20148, Milan, Italy (e-mail: mdirienzo@cbi.dongnocchi.it).

G. Parati is with the Istituto Scientifico Ospedale San Luca, Istituto Auxologico Italiano and University of Milano-Bicocca, I–20126 Milan, Italy (e-mail: gianfranco.parati@unimib.it).

*P. Castiglioni is with the Centro di Bioingegneria of the Fondazione Don C. Gnocchi ONLUS, via Capecelatro 66, I 20148, Milan, Italy (e-mail:pcastiglioni@cbi.dongnocchi.it).

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redistribution associated with the posture change); light physical exercise while sitting (further increase in autonomic tone due to muscle activity).

### B. Selection of Patients

We selected patients with SCI at different levels of impairment because SCI represents a suitable pathophysiological model of cardiovascular autonomic impairment, the degree of which depends on the lesion level [19]. In particular, if the SCI is below the fourth thoracic vertebra, $T_4$, the autonomic innervation of the heart is preserved, whereas the vascular innervation of the splanchnic and lower limb areas are compromised. In this case, resting heart rate is usually higher than that observed in healthy subjects, possibly because of an activation of the sympathetic system compensating for the lack of venous return secondary to the inefficient vascular innervation of splanchnic and lower limbs regions. When the SCI level is above or equal to $T_4$, the sympathetic innervation of the heart is also compromised, and thus the possible sympathetic hyper-activation caused by the vascular denervation cannot affect heart rate through the physiological neural channels (cardiac sympathetic control can still be exerted through circulating cathecolamines). The consequence of this is a prevalence of parasympathetic cardiac modulation, as shown by a resting heart rate usually lower than that observed in healthy subjects.

### C. Complex Dynamics Properties and Estimators

Since the spinal cord lesion produces a partial decoupling of several interconnected physiological systems, it is likely that this sequence may alter the overall complexity of cardiovascular regulation and the correlation properties over multiple time scales as quantified by fractal methods. Such a decoupling may also affect the overall stability of the cardiovascular system as quantified by the Lyapunov exponent. Furthermore, a spinal cord lesion may be responsible also for a reduction in the number of independent neural input reaching the heart, thus modifying the rate of new information, or entropy, in the heart rate time series. On this basis, we selected estimators that were capable of quantifying fractal properties, entropy and system stability and that could be applied on short data segments (about 10 minutes) because this is the typical time span used for heart rate recordings in clinical settings.

*Subjects, Measurements and Experimental Procedure:* Twenty healthy subjects, seven SCI subjects with lesion level at $C_6 - T_4$, and nine SCI subjects with lesion level at $T_5 - L_4$ were enrolled. Healthy and SCI subjects were age matched. All SCI patients were in a stable clinical condition (the traumatic event occurred more than 5 years before the time of the study). Prior to data collection, all subjects underwent a clinical examination, including the measurement of resting arterial blood pressure. None of the subjects showed symptoms of cardiorespiratory disease or of other pathological conditions that might affect autonomic cardiovascular control (e.g., diabetes, hypertension, etc.). The anthropometric features of recruited subjects are shown in Table I.

For each subject, three separate 10-min ECG recordings were obtained in the following experimental conditions: 1) supine rest; 2) sitting rest; 3) light (5 W) exercise by an arm ergometer

TABLE I
ANTHROPOMETRIC FEATURES OF THE ENROLLED SUBJECTS ($M \pm SD$)

| | SCI ($C_6$-$T_4$) | SCI ($T_5$-$L_4$) | HEALTHY CONTROLS |
|---|---|---|---|
| Number of subjects | 7 | 9 | 20 |
| Gender, M/F | 7/0 | 9/0 | 15/5 |
| Age, yrs | 25.6 ±4.1 | 28.0 ±2.3 | 27.4 ±3.4 |
| Body mass index, kg/m$^2$ | 22.3 ±2.0 | 23.3 ±4.2 | 23.5 ±3.2 |

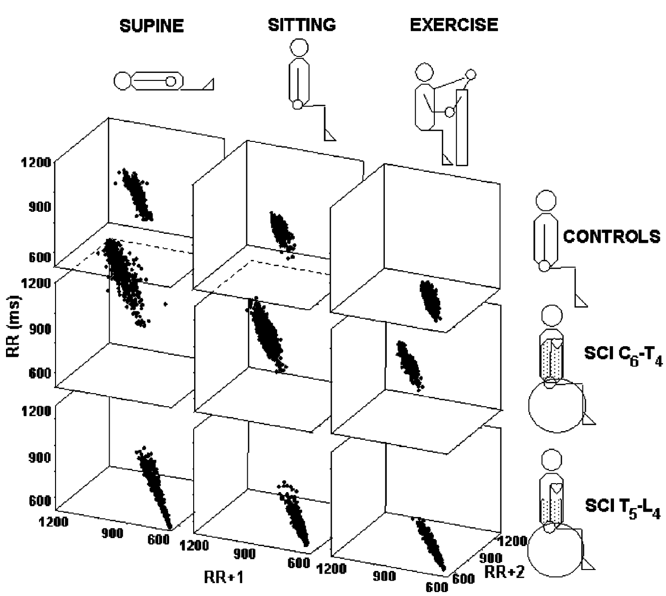


Fig. 1. Scheme of the experiment. The R-R interval series was derived in each subject during three conditions: supine at rest; sitting at rest; and during a light exercise in sitting position; three groups of subjects were enrolled: healthy controls; SCI subjects with lesion level below $T_4$ (SCI $T_5 - L_4$: compromised sympathetic vascular innervation, but intact sympathetic efferences on the heart); and SCI subjects with lesion between $C_6$ and $T_4$ (SCI $C_6 - T_4$: impaired sympathetic efferences on the heart and vessels). Three-dimensional plots represent R-R interval variability in one typical subject for each group.

(Monark 881, Sweden). Each recording was preceded by a period of adaptation of few minutes to allow the stabilization of the heart rate after the change of posture or the start of exercise. The ECG was sampled at 200 Hz, and edited to remove artifacts and ectopic beats. R-R intervals were derived beat by beat from the edited signals. The experimental protocol, approved by the local Ethics Committee (Don C. Gnocchi Foundation), is summarized in Fig. 1.

*Data Analysis:* The following complexity-based characteristics of R-R interval time series were assessed: self similarity and fractal dimension, entropy, and the largest Lyapunov exponent. Definitions and interpretation of each characteristic are reported in Table II. In order to create a reference benchmark, we also estimated frequency-domain and time-domain parameters traditionally employed in the assessment of the autonomic tone from HRV [10]: the heart rate powers over the high frequency (HF) and low-frequency (LF) bands, the LF/HF power ratio, and the RMSSD and pNN50 indexes. Details of these analyses are reported hereafter.

*Traditional HRV indexes:* For the estimation of frequency-domain indexes, the Welch periodogram was computed by interpolating and evenly re-sampling each R-R interval series at 10 Hz, by splitting each interpolated series into 120-s

TABLE II
DEFINITION, INTERPRETATIVE KEY AND ESTIMATORS OF COMPLEX CHARACTERISTICS OF TIME SERIES

| CHARACTERISTIC | DEFINITION | MEANING | ESTIMATORS |
|---|---|---|---|
| Self-similarity | A process x(t) is self-similar when it has the same statistical distribution of the process $a^{-H}x(at)$. H is called self-similarity coefficient. | Any sub-set of the time series can be rescaled to the size of the original series maintaining the original statistical properties. If H>0.5, self-similarity implies long-range correlation. | Analysis of Aggregated Variances, $H_{AV}$ [20]; Detrended Fluctuation Analysis, $H_{DFA}$ [21] |
| Fractal Dimension | Geometric dimension of the time series considered as a fractal object | Measure of the characteristics of convolutedness and space filling of the time-series plot | Fractal Dimension, FD [23] |
| Entropy | Negative logarithm of the probability that two segments of the time series which are similar for m points remain similar at the next point. | Measure of regularity closely related to the rate of generation of new information; low entropy reflects a high degree of regularity in the time series. | Approximate Entropy, ApEn [25]; Sample Entropy, SampEn [26] |
| Lyapunov Exponents | Rate of exponential divergence of neighboring trajectories into directions of the phase space. | Chaos is generated by the exponential growth of small perturbations, together with folding mechanisms. Positive Lyapunov exponents generate such instability characterizing a dynamic system as chaotic. | Largest Lyapunov Exponent $\lambda_{LLE}$ [28] |

long, 50% overlapped Hann windows, by computing an FFT spectrum over each window and by averaging the spectra over all the windows. The resulting power spectral densities were integrated over the HF (0.15–0.50 Hz) band, with the HF power being considered an index of cardiac vagal modulation. The spectrum was integrated also over the LF (0.05–0.15 Hz) band, and the LF/HF powers ratio, which is usually taken as an indirect measure of sympatho-vagal balance, was also computed. Two time-domain indexes, RMSSD (root-mean square of successive differences in R-R interval) and pNN50 (fraction of successive intervals which differ more than 50 ms), were also estimated as a further indirect measure of cardiac vagal modulation.

*Complexity-based analyses: Self-similarity and fractal-related measures*—We first calculated the Hurst coefficient by the method of aggregated variances [20]. The Hurst coefficient is a self-similarity index ranging between 0 and 1, and equal to 0.5 for white noise. The method is based on the observation that if $\sigma_0^2$ is the variance of a self-similar series, then when $k$ consecutive values are averaged, the variance decreases to $\sigma_k^2 = k^{2H-2}\sigma_0^2$ with $H$ being the Hurst coefficient. In case of white noise ($H = 0.5$) we obtain the well known formula for the variance of the mean of $k$ uncorrelated values: $\sigma_k^2 = \sigma_0^2/k$. From each R-R interval series $RR(i)$ we derived the aggregated series

$$RR_k(i) = \frac{1}{k}\sum_{m=1}^{k} RR\left((i-1)k+m\right) \quad \text{with} \quad i = 1,\ldots,\frac{N}{k} \tag{1}$$

and calculated

$$\sigma_k^2 = \frac{1}{\frac{N}{k}}\sum_{i=1}^{\frac{N}{k}}\left(RR_k(i)-\mu\right)^2 \tag{2}$$

with $\mu$ the mean of $RR(i)$. From the slope of the regression line between $ln(k)$ and $ln(\sigma_k^2)$ we derived an estimate of the Hurst exponent, $H_{\mathrm{AV}}$. The aggregated variance $\sigma_k^2$ was computed for 21 values of $k$ homogeneously distributed over the $ln(k)$ axis between $k = 2$ and $k = 100$.

We also estimated a self-similarity coefficient by means of detrended fluctuation analysis (DFA) as described in [21]. While the Hurst exponent is defined between 0 and 1, the coefficient estimated by detrended fluctuation analysis, $H_{\mathrm{DFA}}$, is defined and can be estimated even for values greater than 1 (e.g., $H_{\mathrm{DFA}} = 1.5$ for Brown noise). To evaluate $H_{\mathrm{DFA}}$, we computed the integral of the series after subtraction of its mean value

$$y(k) = \sum_{i=1}^{k}\left(RR(i)-\mu\right) \tag{3}$$

with $\mu$ being the mean of $RR(i)$. The integrated series was divided into boxes of equal length, $n$, and in each box a least-square line $y_n(k)$ (representing the trend in that box) was fit to the data. Then the integrated series was detrended by subtracting the local trend. The root-mean square $F(n)$ of the detrended series

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}\left(y(k)-y_n(k)\right)^2} \tag{4}$$

was measured in each box and plotted against the box size $n$ on a log-log scale. The slope of the regression line between $ln(n)$ and $ln(F(n))$ gave the scaling exponent $H_{\mathrm{DFA}}$.

The concept of self-similarity is tightly related to another measure of the complex dynamics of a time series: the "temporal" fractal dimension. In fact, if a time series is self-similar, its generating process does not have a characteristic scale of time, similarly to a fractal object that lacks a characteristic scale of length [22]. Therefore, the concept of geometrical fractal dimension, introduced to measure the length of irregular geometric objects in which the number of visible details increases with the measuring resolution, can be extended to self-similar time series.

We estimated the fractal dimension (FD) of each R-R interval series by applying a method based on the definition of the Hausdorff dimension of a set in a metric space [23]. Briefly, the time series of $N$ beats is mapped into a unit square by normalizing the vertical and horizontal axes by two linear transformations.

The length $L$ of the transformed waveform is computed and the FD is estimated as

$$\mathrm{FD} = 1 + \frac{ln(L)}{ln(2N-2)}. \tag{5}$$

The relation between fractal dimension and self-similarity is shown analytically by the following equation which holds if the process generating the time series is a fractional gaussian noise with Hurst exponent $H$:

$$\mathrm{FD} = \mathrm{E} + 1 - \mathrm{H} \tag{6}$$

where $E$ is the Euclidean dimension [24].

*Entropy*—To compute the approximate entropy (ApEn) [25], from a R-R interval series of $N$ beats, $RR(i)$, one should first create the series of $N-m+1$ vectors of $m$ components $\mathrm{R}_m(i) = [RR(i),\ RR(i+1), \ldots,\ RR(i+m)]^{\mathrm{T}}$. The vector $\mathrm{R}_m(i)$ represents the sequence of $m$ consecutive R-R intervals starting at the beat $i$. Two vectors $\mathrm{R}_m(i)$ and $\mathrm{R}_m(j)$ are similar if the absolute difference between each couple of corresponding scalar components is less than the distance $r$. Calling $n_i^m(r)$ the number of $N-m+1$ vectors $\mathrm{R}_m(j)$ similar to $\mathrm{R}_m(i)$, then

$$C_i^m(r) = \frac{n_i^m(r)}{(N-m+1)} \tag{7}$$

is the probability to find a sequence of $m$ beats similar to the sequence represented by $\mathrm{R}_m(i)$, and $C^m(r)$, defined as the mean of all $C_i^m(r)$, quantifies the prevalence of similar strings of $m$ beats. Since each vector at least matches itself, $n_i^m(r)$ is always greater or equal to 1, and this implies that $C^m(r) > 0$. ApEn is defined as

$$\mathrm{ApEn}(m,r) = -ln\left[\frac{C^{m+1}(r)}{C^m(r)}\right]. \tag{8}$$

A high degree of regularity means that sequences which are similar for $m$ points are likely to be similar also for the next $m+1$ point, while this is unlikely to occur for irregular time series. Thus low values of ApEn reflect high regularity. Following the suggestion of [25], we estimated ApEn by choosing $m = 2$ and $r$ equal to 20% the standard deviation of $RR(i)$.

Since each $\mathrm{R}_m(i)$ sequence matches itself, ApEn is a biased estimator and it is lower than expected for short records. This also implies that it lacks relative consistency, making it difficult to interpret the comparison of different datasets. Sampling entropy (SampEn) is a variation of ApEn, in which the self-comparison between vectors is avoided to reduce the bias. In other words, when SampEn is evaluated, $n_i^m(r)$ is the number of $N-m$ vectors $\mathrm{R}_m(j)$ similar to $\mathrm{R}_m(i)$ with $j \neq i$. According to [26], this leads to a more accurate and reliable evaluation of the signal entropy. However, if self-matches are removed, it is no more guaranteed that $n_i^m(r) > 0$, and thus that entropy can be calculated as $-ln[C^{m+1}(r)/C^m(r)]$. For this reason, the quantities $B^m(r)$ and $A^m(r)$ are respectively computed as the average of

$$B_i^m(r) = \frac{n_i^m(r)}{(N-m-1)} \tag{9}$$

and

$$A_i^m(r) = \frac{n_i^{m+1}(r)}{(N-m-1)} \tag{10}$$

with $i$ ranging from 1 to $N-m$. If both $B^m(r)$ and $A^m(r)$ differ from 0, then SampEn is defined as

$$\mathrm{SampEn}(m,r) = -ln\left[\frac{A^m(r)}{B^m(r)}\right]. \tag{11}$$

Similarly to ApEn, we estimated SampEn with $m = 2$ and $r = 20\%$ the standard deviation of $RR(i)$.

Because of its bias, ApEn depends on the signal length. When two time-series are compared, care must be taken to estimate ApEn on the same signal durations. All our recordings had the same duration (10 min.), but the number of beats N was greater during exercise than at rest. In order to evaluate the effects of different heart rates on entropy estimates, we also measured ApEn and SampEn on the first 500 beats of each recording, $\mathrm{ApEn}_{500}$ and $\mathrm{SampEn}_{500}$, and compared the results with those obtained estimating ApEn and SampEn on a fixed signal duration of 10 minutes.

*Lyapunov Exponents*—We estimated the largest Lyapunov exponent, $\lambda_{\mathrm{LLE}}$, by using the Tisean implementation [27] of the algorithm proposed by Rosenstein *et al.* [28]. Briefly, the $RR(i)$ series of $N$ beats is considered as a trajectory in the embedding space. The algorithm locates the nearest neighbor of each point $j$ of the trajectory, and considers the distance between these two close points as a small perturbation, $\Delta_{\mathrm{j}}(0)$. It is assumed that the $j$-th pair of nearest neighbors diverges in time at the exponential rate given by the largest Lyapunov exponent $\lambda_{\mathrm{LLE}}$, which means that $ln\Delta_{\mathrm{j}}(i) = \mathrm{C_j} + \lambda_{\mathrm{LLE}} i$. This equation, evaluated for all the $j$ pairs, represents a set of parallel lines. To reliably estimate $\lambda_{\mathrm{LLE}}$ from short and noisy data, the average of the parallel lines is computed. In general, the average line shows a long linear region after a short transition, and $\lambda_{\mathrm{LLE}}$ is estimated as the slope of the regression line fitting the average line. In our application, where the duration of the recording is relatively small, we found that the length of the linear region which should be used to extract $\lambda_{\mathrm{LLE}}$ can sometimes be comparable with the initial transition. In this case, the slope of the regression line tends to overestimate the slope of the linear portion of the average line. For this reason, we first identified the linear segment of the average line as the line portion with the more stable slope, and estimated $\lambda_{\mathrm{LLE}}$ as the mean slope in the identified linear segment.

*Statistics:* Before any statistical evaluation, the hypothesis of normality was evaluated by the Kolmogorov-Smirnov goodness-of-fit test, and accepted for $p$-values greater than 20%. The normality hypothesis was accepted for all estimators except pNN50, HF power and LF/HF power ratio. However, these three indexes passed the normality test after a logarithmic transformation.

In the first part of the study we focused on the effects of the experimental maneuver (supine, sitting at rest, exercise) on the group of healthy subjects with intact autonomic cardiovascular regulation. Results have been analyzed by means of an analysis of variance (ANOVA) for repeated measures. When the factor

TABLE III
SIGNIFICANCE OF THE MANEUVER FOR TRADITIONAL AND COMPLEXITY BASED ESTIMATORS OF HRV

| TYPE | ESTIMATOR | SIGNIFICANCE *P* |
|---|---|---|
| Traditional | LF/HF | **$5 \times 10^{-10}$** |
| | HF | **$4 \times 10^{-7}$** |
| | RMSSD | **$6 \times 10^{-8}$** |
| | pNN50 | **$3 \times 10^{-8}$** |
| Entropy | SampEn | **$4 \times 10^{-5}$** |
| | ApEn | **$8 \times 10^{-4}$** |
| | $SampEn_{500}$ | **$1.5 \times 10^{-4}$** |
| | $ApEn_{500}$ | **$4 \times 10^{-4}$** |
| Fractal Dimension | FD | **$7 \times 10^{-4}$** |
| Self-Similarity | $H_{AV}$ | **$5 \times 10^{-3}$** |
| | $H_{DFA}$ | NS (=0.07) |
| Lyapunov Exponents | $\lambda_{LLE}$ | NS (=0.12) |

was significant ($p < 0.05$) we further checked the significance of the differences between consecutive conditions (supine vs. sitting rest and sitting rest vs. exercise) by the Fisher's LSD post-hoc test (Statistica 6.0, StatSoft, Tulsa, OK).

In the second part, we evaluated the statistical significance of the factor "lesion level" (no lesion; $C_6 - T_4$; and $T_5 - L_6$), the factor "maneuver" and the interaction between the two factors, by means of repeated measures ANOVA. Differences among the three groups of subjects were tested by Fisher's LSD post-hoc test.

## III. RESULTS

*HRV changes in subjects with intact autonomic cardiovascular regulation.* The statistical significance of the differences among conditions is shown in Table III for the group of healthy subjects. Traditional HRV indexes were very sensitive in identifying the effect of postural change and exercise, with p values lower than $10^{-6}$. The HF power quantified the expected progressive reduction in cardiac vagal modulation from supine rest to sitting rest and exercise (see also the post-hoc analysis in Fig. 2, left). Changes in RMSSD and pNN50 were consistent with those of the HF powers. RMSSD decreased from supine (48.1 ± 4.4 ms) to sitting rest (34.6 ± 2.7 ms, $p < 0.01$) and from sitting rest to exercise (26.4 ± 1.9 ms, $p < 0.01$; $M \pm$ SEM). Similarly, pNN50 decreased significantly ($p < 0.01$) from supine (0.26 ± 0.04) to sitting rest (0.13 ± 0.02) and exercise (0.07 ± 0.01). This progressive reduction in parasympathetic indices was coupled with progressive increase of LF/HF ratio, suggesting a progressive shift of the sympathovagal balance toward a sympathetic predominance (Fig. 2, right).

The entropy estimators (Table III) also showed highly significant changes. However, post-hoc analysis demonstrated that SampEn and ApEn changed significantly in the transition between supine and sitting rest only, while they did not show any change during the transition from sitting rest to exercise (Fig. 3). It is worth noting that the values of SampEn are always higher than those of ApEn in all conditions, possibly because of the known bias affecting ApEn. We also estimated SampEn and ApEn by using a fixed number of beats ($N = 500$) instead of a fixed time duration ($T = 10$ min). This approach did not substantially modify the entropy estimates, and we observed the same order of magnitude for the statistical significance of differences between conditions.

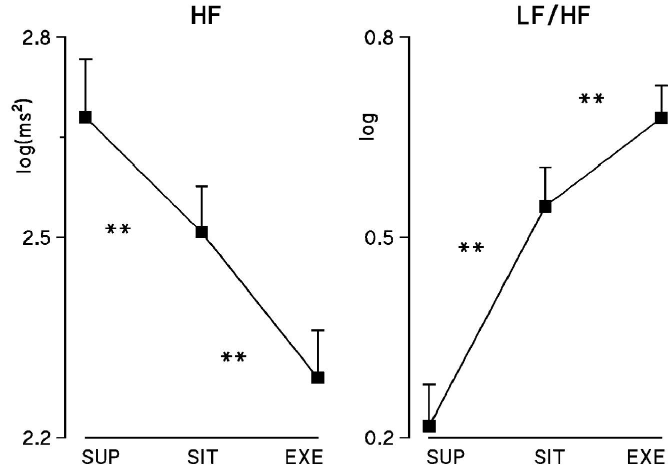


Fig. 2. Traditional frequency-domain indexes in healthy subjects while resting supine (SUP), sitting at rest (SIT) and during a light exercise in sitting position (EXE); left: HF power; right: LF/HF powers ratio. Data are shown as means and standard errors estimated over the whole group of subjects. The "**" symbol indicates a significant difference between consecutive conditions at the $p < 0.01$ level.

The analysis of the fractal dimension gave results comparable to the entropy analysis. In fact, the significance of ANOVA (Table III) and the trend among the conditions (Fig. 3) were very similar to those observed for the entropy estimates.

Also self-similarity coefficients, like entropy, were only partially sensitive to the maneuver. However, while entropy changed significantly because of the postural modifications, the Hurst exponent $H_{AV}$ remained unchanged from the supine to the sitting rest condition, and showed a significant reduction only during exercise. The self-similarity coefficient from detrended fluctuation analysis, $H_{DFA}$, did not show any significant difference among all the conditions (Fig. 3), and this was the case also for the largest Lyapunov exponent (Table III and Fig. 3).

*HRV and the level of spinal cord lesion.* Table IV shows the results of ANOVA comparing the effects of the experimental conditions ("maneuver"), the lesion level ("lesion"), and the interaction between the two. Interestingly, the lesion level was not a significant factor for any traditional index. For example, Fig. 4 (right) shows that both SCI groups are characterized by a trend of LF/HF toward an increase in its value, statistically similar to that of healthy controls. The interaction was also not significant for all the indexes except HF power. Indeed, Fig. 4 (left) shows that SCI subjects seem to produce a more pronounced inhibition of HF power during exercise, independently on the lesion level.

By contrast, all the entropy estimators showed a significant influence not only of the maneuver, but also of the lesion level (Table IV).

Considering the overall effect of the lesion factor on SampEn (Fig. 5, left), entropy was significantly lower in subjects with SCI below $T_4$ than in healthy subjects.

As to the maneuver, entropy clearly showed discrepancy between the control group and the whole group of SCI subjects with respect to exercise. While exercise did not induce any change of entropy in controls ($p = 94\%$), it further decreased

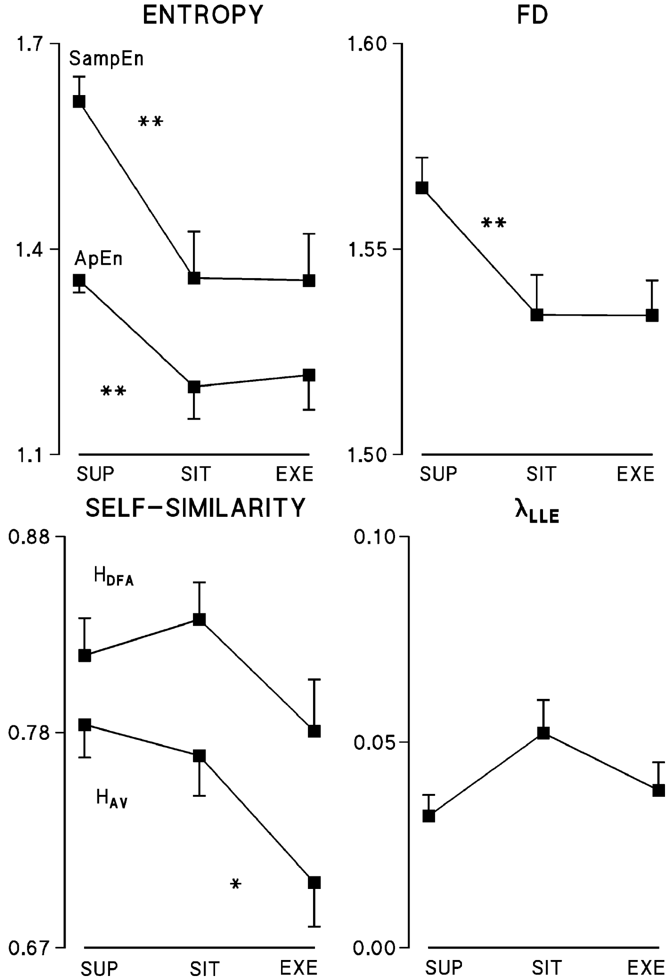


Fig. 3. Complexity-based indexes in healthy subjects during three experimental conditions (see Fig. 2); SampEn = Sampling Entropy; ApEn = approximate entropy; FD = Fractal Dimension; $H_{DFA}$ = detrended fluctuation analysis coefficient; $H_{AV}$ = Hurst exponent; $\lambda_{LLE}$ = largest Lyapunov exponent. Data are shown as means and standard errors estimated over the whole group of subjects. The "*" and "**" symbols indicate significant differences between consecutive conditions at the $p < 5\%$ and $p < 1\%$ levels.

TABLE IV
FACTORS (MANEUVER, LESION, AND THEIR INTERACTION) SIGNIFICANCE FOR ALL THE CONSIDERED HRV ESTIMATORS

| TYPE | ESTIMATOR | SIGNIFICANCE *P* | | |
|---|---|---|---|---|
| | | MANEUVER | LESION | INTERACTION |
| Traditional | LF/HF | **$4 \times 10^{-11}$** | NS(=0.85) | NS(=0.15) |
| | HF | **$4 \times 10^{-12}$** | NS(=0.07) | **$7 \times 10^{-3}$** |
| | RMSSD | **$2 \times 10^{-8}$** | NS(=0.35) | NS(=0.38) |
| | pNN50 | **$1 \times 10^{-8}$** | NS(=0.73) | NS(=0.89) |
| Entropy | SampEn | **$3 \times 10^{-6}$** | **$2 \times 10^{-2}$** | NS(=0.44) |
| | ApEn | **$4 \times 10^{-5}$** | **$2 \times 10^{-2}$** | NS(=0.25) |
| | $SampEn_{500}$ | **$7 \times 10^{-5}$** | **$3 \times 10^{-2}$** | NS(=0.75) |
| | $ApEn_{500}$ | **$2 \times 10^{-4}$** | **$3 \times 10^{-2}$** | NS(=0.50) |
| Fractal Dimension | FD | **$6 \times 10^{-6}$** | NS(=0.31) | NS(=0.47) |
| Self-Similarity | $H_{AV}$ | NS(=0.69) | **$1 \times 10^{-2}$** | **$3 \times 10^{-3}$** |
| | $H_{DFA}$ | **$1 \times 10^{-3}$** | **$3 \times 10^{-4}$** | **$6 \times 10^{-4}$** |
| Lyapunov Exponents | $\lambda_{LLE}$ | **$1 \times 10^{-2}$** | NS(=0.33) | **$2 \times 10^{-2}$** |

entropy with respect to sitting rest in paraplegic subjects. This reduction was of the magnitude of the reduction observed

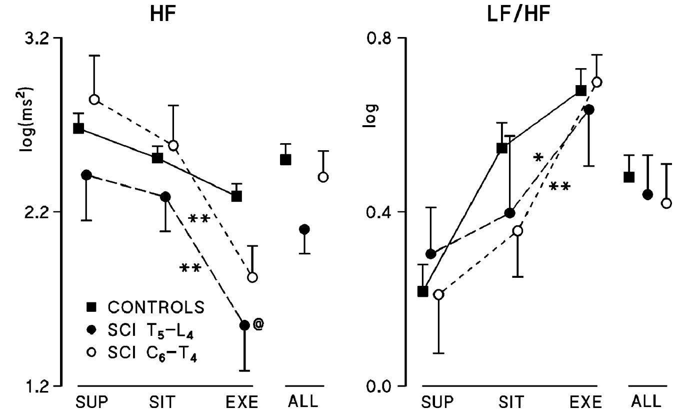


Fig. 4. Frequency-domain indexes in the three groups of subjects over the whole experiment (ALL) and separately in the three conditions. Data are shown as means and standard errors estimated over each group of subjects. Significant differences between controls and SCI $T_5 - L_4$ are shown by "@" $(p < 5\%)$ and "@@" $(p < 1\%)$ symbols; between controls and SCI $C_6 - T_4$ by "#" $(p < 5\%)$ and "##" $(p < 1\%)$; between consecutive conditions by "*"$(p < 5\%)$ and "**"$(p < 1\%)$ for the two SCI groups (for the significance of the differences between consecutive conditions in controls, see Fig. 2).

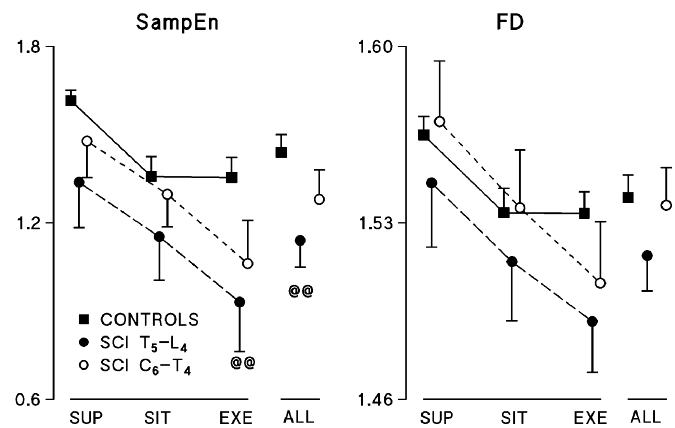


Fig. 5. SampEn and FD in the three group of subjects: data are shown as means and standard errors estimated over each group of subjects. Symbols as in Fig. 4 (for the significance of the differences between consecutive conditions in controls, see Fig. 3).

during the change of posture from supine to sitting. The entropy difference between sitting at rest and exercise was statistically significant $(p < 5\%)$ when all the SCI subjects were considered as a whole. However, when we split the SCI group into the high- and low-lesion level groups, the difference between sitting at rest and exercise was close to the significance level, reaching $p = 7\%$ in each of the two SCI groups. For this reason, the "*" between consecutive conditions could not be plotted in Fig. 5, although the factor "maneuver" and the difference between inconsecutive conditions (supine vs. exercise) was still largely significant.

The effect of maneuver was significant also for the fractal dimension. The order of magnitude of the p value (Table IV) and the pattern of changes in each group (Fig. 5, right) were similar to those observed for entropy, but, different from entropy, the lesion factor did not reach the significance level. The changes of FD within each group were similar to the changes of SampEn. However, the relative position of each group was different, and the differences among the three groups were not significant.

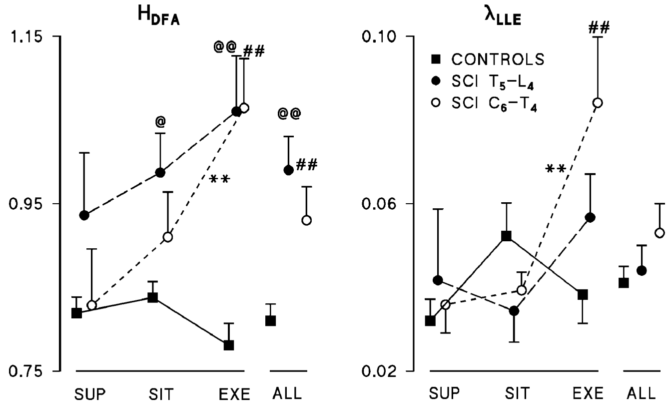


Fig. 6. DFA coefficient ($H_{\mathrm{DFA}}$) and ($\lambda_{\mathrm{LLE}}$) in the three groups of subjects: data are shown as means and standard errors estimated over the whole group of subjects. Symbols as in Fig. 4 (for the significance of the differences between consecutive conditions in controls, see Fig. 3).

Self-similarity coefficients were the only indexes of this study which were sensitive to both the lesion and the interaction between lesion and maneuver. $\mathrm{H}_{\mathrm{DFA}}$ was significantly higher in the two SCI groups than in healthy controls (Fig. 6). In particular, $\mathrm{H}_{\mathrm{DFA}}$ showed opposite trends with the maneuver in SCI subjects and in controls: while healthy subjects showed the lowest $\mathrm{H}_{\mathrm{DFA}}$ value during exercise, this self-similarity coefficient progressively increased with the maneuver in the SCI groups. Because of these opposite trends, differences between controls and both SCI groups were highly significant during exercise.

Finally, maneuver and interaction were both significant factors for the largest Lyapunov exponent, $\lambda_{\mathrm{LLE}}$. Fig. 6 shows that during exercise $\lambda_{\mathrm{LLE}}$ changed toward a more chaotic system for the SCI group with the higher lesion. In fact, $\lambda_{\mathrm{LLE}}$ increased significantly from sitting at rest to exercise in paraplegic subjects with lesion affecting the sympathetic efferents of the heart, and that during exercise $\lambda_{\mathrm{LLE}}$ was significantly higher in this group than in healthy controls.

## IV. Discussion

This study focused on methods based on complexity analysis, capable of identifying self-similarity, fractality, entropy and the largest Lyapunov exponent. We considered estimators applicable on small data sets (about 10 min) because they are appropriate for the experimental protocols routinely used by clinicians, which typically provide brief ECG recordings in various experimental conditions (e.g., pharmacological administration, exercise, postural changes, pre- and post-operative conditions). Our experimental model allowed us to study how HRV indexes changed in response to postural stimulations of autonomic control, both in an intact and in a variably impaired sympathetic control of heart and vessels due to spinal cord lesions at different levels.

*Traditional methods*. This study revealed the efficacy of traditional methods in identifying the changes in autonomic tone, both in control and in SCI subjects. The statistical power was the greatest among all the methods considered ($p$ values between $10^{-10}$ and $10^{-7}$). In addition, such methods disclose changes of the autonomic tone when they are caused by the "blood shift" subsequent to the postural changes (from supine to sitting), or when they are produced by a light muscular activation without changing the posture. Conversely, traditional methods of HRV analysis seem unable to differentiate the alterations of HRV dynamics due to the lesion level, as the factor "lesion" did never reach the statistical significance.

*Entropy*. Among the complexity-based indexes more sensitive to the maneuver effect we found the entropy estimators, ApEn and SampEn. They showed $p$ values greater than those of traditional indexes, but remained highly significant ($p$ between $10^{-5}$ and $10^{-4}$). Entropy decreased with the increase of sympathetic tone associated with the transition from supine to sitting at rest. However, it is noteworthy that unlike traditional indexes, ApEn and SampEn did not differ between rest and exercise conditions in healthy subjects. In fact, changes of entropy were only associated with postural changes with an intact sympathetic control. Are the entropy measures sensitive only to the changes of heart rate dynamics due to the "blood shift"? We can hypothesize that this phenomenon might be somehow connected to the vascular autonomic control. In fact, entropy is further reduced in both groups of SCI patients during exercise. It may be suggested that a sort of "blood shift" can occur in paraplegics also during exercise. This may be due to the possible disruption of the balance between cardiac output and total peripheral resistance. In fact the latter is governed by the interplay among the autonomic control on the heart, the releases of vasodilator substances from the working muscles, and the sympathetic mediated vasoconstriction (including active skeletal muscles), which is partially impaired in SCI subjects. In any case, entropy was significantly lower in the SCI group with lesion below $\mathrm{T}_4$, where a compensatory activation of the sympathetic activity is expected, than in healthy controls. Also this finding suggests an inverse relation between sympathetic activation and entropy.

We found that ApEn substantially underestimated SampEn. This was expected because of the known bias affecting ApEn [26]. However, we also found that such bias reduced the statistical significance only slightly. In addition a fixed time constant ($\mathrm{T} = 10$ min) or a fixed number of beats ($\mathrm{N} = 500$) did not substantially alter the results, suggesting that these two approaches are actually interchangeable in HRV analysis.

*Fractal Dimension*. The effects of the maneuver on the estimates of fractal dimension and the trends associated with the maneuver are quite similar to those observed for entropy in all three groups of subjects. This finding is remarkable because estimators of entropy and estimators of fractal dimension belong to different classes of complexity-based estimators, the former quantifying the rate of new information given by each point, the latter measuring the "space filling propensity" of a curve by geometric methods. However, as opposed to the entropy measures, FD failed to discriminate the lesion level.

In summary, from the findings obtained from the analysis of entropy and fractal dimension, we conclude that the alterations of HRV associated with spinal cord lesions are better detected by the entropy estimators than by FD. In particular, it appears that the spinal cord lesion mainly increases the "regularity" of the R-R interval dynamics (as quantified by the entropy reduction) without changing its space-filling characteristics (as quantified by the unchanged fractal dimension). This finding might

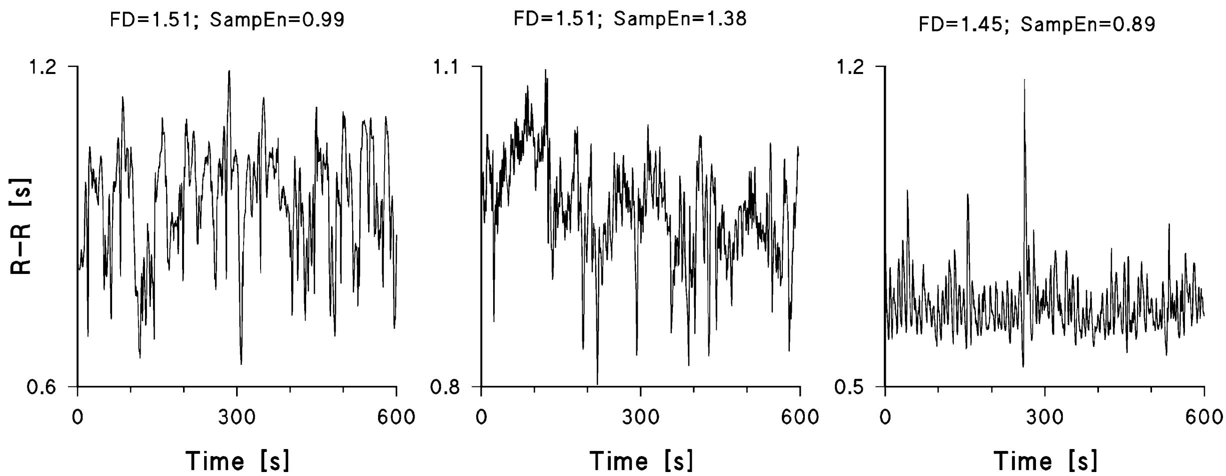


Fig. 7. Relation between fractal dimension and entropy: measures in three exemplificative R-R interval series. Left and central panels: time series with the same value of fractal dimension FD but with rather different entropy values, SampEn. These recordings were obtained during supine rest in a $\mathrm{C}_6 - \mathrm{T}_4$ paraplegic subject (left) and in a control subject (centre). Right: series obtained in sitting at rest condition for the control subject showing the lowest fractal dimension: this series is also characterized by one of the lowest values of entropy.

be explained by the reduction in the number of different neural inputs acting on the heart subsequent to the spinal lesion. Indeed, it has been previously suggested that in generic physiological systems, decoupling between variables and reduction of external inputs decrease entropy [29].

The links between the theoretic concepts of entropy and fractal dimension from one side, and the corresponding characteristics of "regularity" and "space-filling" (or "convolutedness") in real time-series profiles, are exemplified in Fig. 7. The first two panels of the figure show two R-R interval segments characterized by the same fractal dimension and different values of entropy, respectively obtained in a paraplegic and in a healthy subject during supine rest. The third panel shows a segment of R-R interval data with lower values of both fractal dimension and entropy, recorded in a control subject during sitting rest. It is apparent that the two data segments with the same fractal dimension fill the space to the same degree, at variance from the third data segment, where the lower FD value corresponds to signal dynamics mostly restricted in a limited zone of the plot. Concerning entropy, from the first two panels of the figure it is apparent that different values of this quantity actually reflect different levels of signal regularity. In particular, the greater regularity observable in the time series of the paraplegic subject seems to be due to a power concentration over a narrower frequency band, a phenomenon also known as "loss of spectral reserve" [29]. In the third panel it is possible to observe that the reduction of the space-filling degree of the heart rate curve induced by the sitting posture is associated with an even more regular signal dynamics, and this is mirrored by a lower value of entropy.

*Self-similarity*. The self-similarity indexes were not sensitive to autonomic-tone changes in control subjects. They tended to decrease with exercise, but their decrease was significant only when estimated by the method of aggregated variances. Conversely, the maneuver had a pronounced effect in paraplegic subjects: self-similarity increased with the sympathetic tone, and this was particularly evident during exercise, where $H_{\mathrm{DFA}}$ values were close to 1. This indicates a tendency toward the dynamics of Brownian motion rather than of white noise (to which, in contrast, control subjects seem to converge during exercise). The $H_{\mathrm{DFA}}$ index thus appears to adequately reflect the sympathetic tone in subjects with spinal cord lesion. It increases with the maneuver in both SCI groups, but, on average, we found it to be higher in $\mathrm{T}_5 - \mathrm{L}_4$ subjects, in which a compensatory higher sympathetic tone is expected. Since we observed $H_{\mathrm{DFA}}$ greater than 1 in some SCI subjects during exercise, it seems that detrended fluctuation analysis would be preferable for the estimation of the self-similarity coefficient, as it may be possible to observe long-term correlations in heart rate data which cannot be correctly quantified by the Hurst coefficient. Finally, it should be noted that recently it has been shown that the information provided by detrended fluctuation analysis can be approximated by a proper combination of the LF and HF powers [30]. Our study shows that even if $H_{\mathrm{DFA}}$ offers information that can partly be derived from traditional spectral analysis, it can emphasize changes in HRV associated with an impairment of autonomic control which are not revealed by HF or LF/HF indexes.

*Lyapunov exponent*. The largest Lyapunov exponent is not significantly sensitive to the maneuver effect in control subjects and in SCI subjects with intact sympathetic efferents on the heart. However, when we considered the SCI group with the higher lesion level, we observed a marked increase of $\lambda_{\mathrm{LLE}}$, which means a higher level of chaos during exercise. Therefore it seems that $\lambda_{\mathrm{LLE}}$, which measures the sensitivity of the system to small perturbations, can quantify the loss of the cardio-circulatory control due to the spinal cord lesion. However, when short segments of data are considered, like in our study, this phenomenon appears clearly only if the control system is sufficiently stressed, as during exercise.

*Study limitations*. Only scant knowledge actually exists on the strategies used by the autonomic system to maintain the control of heart rate when part of the efferent neural pathways are impaired. Thus, it was hard to accurately anticipate which complex component of variability would have been modified by the spinal lesion, and this fact precluded an a-priori selection of the best estimators. Despite this lack of experimental evidence, a pathophysiologically-motivated hypothesis helped us to select the complex characteristics of HRV included in this study. However, because of unavoidable simplifications and the incompleteness of our hypothesis, we may have failed to consider other features of complex heart rate dynamics which could have provided further contributions to a comprehensive assessment of autonomic function in health and disease.

In conclusion, while traditional indexes remain preferable for the quantification of changes in the autonomic tone, pathological alterations of autonomic cardiovascular regulation can be revealed only by some of the complex and nonlinear indexes considered here. In particular, measures of self-similarity provided by detrended fluctuation analysis seem to distinguish an altered sympathetic control of peripheral circulation; an increase of the Lyapunov exponents might reveal an altered sympathetic control on the heart and the vessels; and a decrease of entropy could reflect a compensatory incremented sympathetic tone on the heart secondary to an impaired vascular autonomic control. In the last decades, a large body of literature has been devoted to the physiological and pathological interpretation of changes in the traditional estimators of HRV. This was not the case for indexes based on measures of HRV complexity for which the role of autonomic control of circulation is still largely unknown. However, our study indicates that even if their physio-pathological interpretation is still not completely understood, specific methods of complexity analysis may help us, in addition to the traditional approaches, to get a deeper insight into the autonomic control of circulation from HRV analysis.

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**Giampiero Merati** was born in 1964. He received the degree in medicine from the University of Milan, Milan, Italy, in 1991. He specialized in biochemistry in 1995 at the University of Milan and in Sports Medicine in 1999 at the University of Brescia, Brescia, Italy.

Since 2002, he is a Researcher at the Institute of "Physical Exercise, Health and Sports" (IEFSAS), University of Milan, Italy, and a scientific consultant for the Don C. Gnocchi Foundation, Milan. His primary research interests include autonomic cardiovascular control in health and disease and exercise physiology.

Dr. Merati is an ordinary member of the Italian Society for Chaos and Complexity (SICC) and of the Italian Medical Society of Paraplegia (IMSOP).

**Marco Di Rienzo** (M '87) received the doctoral degree in electronic engineering from the Politecnico of Milano, Milan, Italy in 1980.

Since 1980, he has been a Career Researcher at the Centre of Bioengineering, Fondazione Don C. Gnocchi, Milano. He is currently head of the Centre as well as Professor in the Faculty of Medicine, University of Milan. His main research interests are in signal processing, modeling of the cardiovascular system, and development of wearable systems for monitoring biological signals.

**Gianfranco Parati** was born in 1951. He received the M.D. degree at the University of Milan, Milan, Italy, in 1977.

From 1978 to 1985, he was Resident in Cardiology and in Internal Medicine at the Milan University Hospital, receiving the Certificate of Specialist in Cardiology and Specialist in Internal Medicine. Between 1977 and 1990, he was with the laboratories of the Institute of Internal Medicine and Medical Therapeutics, University of Milan. In 1991, he was Visiting Professor at the Massachusetts Institute of Technology, Health Science and Technology, Cambridge, and at Children's Hospital, Harvard Medical School, Boston, MA. Since the end of 1991, he is Coordinator of the Laboratory for Cardiovascular Research, Istituto Auxologico Italiano, Milan. He is currently Associate Professor of Medicine, University of Milano-Bicocca, and Head of II Department of Cardiology at S. Luca Hospital, Istituto Auxologico Italiano, in Milan (Italy).

Prof. Parati is international fellow of the High Blood Pressure Council of the American Heart Association, and member of International Society of Hypertension, European Society of Hypertension, European Society of Cardiology, Italian Society of Cardiology, and Italian Society of Hypertension. Since 1998, he is member of the Scientific Committee of the Italian Society of Cardiology. He is member of the Reviewer Board of several International Journals, member of the Editorial Board of *Hypertension* and of *Blood Pressure Monitoring*, Assistant Editor of *High Blood Pressure and Cardiovascular Prevention*, the official Journal of the Italian Society of Hypertension, and Executive Editor of the *Journal of Hypertension*. Since 2001, he is member of the Editorial Board of the *American Journal of Physiology*.

**Arsenio Veicsteinas** was born in 1944. He received the M.D. degree from the University of Milan, Milan, Italy, in 1970, and specialized in cardiology in 1973 (University of Turin, Turin, Italy) and in Sports Medicine in 1980 (University of Chieti, Chieti, Italy).

From 1979 to 1981, he was a Research Assistant Professor at the Department of Physiology, State University of New York at Buffalo; from 1981 to 1986, Associate Professor of Physiology, and from 1986 to 2001 Professor of Physiology at the University of Brescia, Brescia, Italy. Since 2001, he is Director of the Institute of "Physical Exercise, Health and Sport" (IEFSAS) at the University of Milan, and Director of the Sports Medicine Center, Don C. Gnocchi Foundation, Milan. His primary areas of teaching and research are human physiology, exercise physiology and muscle function.

Prof. Veicsteinas is a member of the American Physiological Society, of the Italian Society of Physiology and of the European Society for Engineering and Medicine.

**Paolo Castiglioni** received the M.Sc. degree in electronic engineering and the Ph.D. degree in biomedical engineering from the Politecnico di Milano University, Milan, Italy, in 1987 in 1993.

Since 1989, he is a Researcher at the Centro di Bioingegneria of Fondazione Don Carlo Gnocchi, Milan. His research interests include signal analysis, modeling of cardiovascular system, and biomedical signals monitoring by wearable devices.