Short-term complexity indexes of heart period and systolic arterial pressure variabilities provide complementary information

A. Porta, P. Castiglioni, M. Di Rienzo, V. Bari, T. Bassani, A. Marchi, A. C. M. Takahashi, E. Tobaldini, N. Montano, A. M. Catai, F. Barbic, R. Furlan, A. Cividjian and L. Quintin

J Appl Physiol 113:1810-1820, 2012. First published 25 October 2012;
doi: 10.1152/japplphysiol.00755.2012

J Appl Physiol 113: 1810–1820, 2012.
First published October 18, 2012; doi:10.1152/japplphysiol.00755.2012.

Short-term complexity indexes of heart period and systolic arterial pressure variabilities provide complementary information

A. Porta,[1] P. Castiglioni,[2] M. Di Rienzo,[2] V. Bari,[3,4] T. Bassani,[1] A. Marchi,[5] A. C. M. Takahashi,[6] E. Tobaldini,[7] N. Montano,[7] A. M. Catai,[6] F. Barbic,[8] R. Furlan,[9] A. Cividjian,[10] and L. Quintin[10]

[1]*Department of Biomedical Sciences for Health, Galeazzi Orthopedic Institute, University of Milan, Milan, Italy;* [2]*Don C. Gnocchi Foundation, Milan, Italy;* [3]*Gruppo Ospedaliero San Donato Foundation, Milan, Italy;* [4]*Department of Bioengineering, Politecnico di Milano, Milan, Italy;* [5]*Department of Emergency, L. Sacco Hospital, Milan, Italy;* [6]*Department of Physiotherapy, Federal University of São Carlos, São Carlos, Brazil;* [7]*Department of Biomedical and Clinical Sciences, Internal Medicine II, L. Sacco Hospital, University of Milan, Milan, Italy;* [8]*Medical Clinics, Istituto Clinico Humanitas, Rozzano, Milan, Italy;* [9]*Department of Medical Biotechnologies and Translation Medicine, Medical Clinics, Istituto Clinico Humanitas, University of Milan, Rozzano, Milan, Italy; and* [10]*Physiology (EA 4612: Neurocardiology), University of Lyon, Lyon, France*

Submitted 18 June 2012; accepted in final form 18 October 2012

Porta A, Castiglioni P, Di Rienzo M, Bari V, Bassani T, Marchi A, Takahashi AC, Tobaldini E, Montano N, Catai AM, Barbic F, Furlan R, Cividjian A, Quintin L. Short-term complexity indexes of heart period and systolic arterial pressure variabilities provide complementary information. *J Appl Physiol* 113: 1810–1820, 2012. First published October 18, 2012; doi:10.1152/japplphysiol.00755.2012.—It is unclear whether the complexity of the variability of the systolic arterial pressure (SAP) provides complementary information to that of the heart period (HP). The complexity of HP and SAP variabilities was assessed from short beat-to-beat recordings (i.e., 256 cardiac beats). The evaluation was made during a pharmacological protocol that induced vagal blockade with atropine or a sympathetic blockade (beta-adrenergic blockade with propranolol or central sympathetic blockade with clonidine) alone or in combination, during a graded head-up tilt, and in patients with Parkinson's disease (PD) without orthostatic hypotension undergoing orthostatic challenge. Complexity was quantified according to the mean square prediction error (MSPE) derived from univariate autoregressive (AR) and multivariate AR (MAR) models. We found that: *1*) $MSPE_{MAR}$ did not provide additional information to that of $MSPE_{AR}$; *2*) SAP variability was less complex than that of HP; *3*) because HP complexity was reduced by either vagal blockade or vagal withdrawal induced by head-up tilt and was unaffected by beta-adrenergic blockade, HP was under vagal control; *4*) because SAP complexity was increased by central sympathetic blockade and was unmodified by either vagal blockade or vagal withdrawal induced by head-up tilt, SAP was under sympathetic control; *5*) SAP complexity was increased in patients with PD; and *6*) during orthostatic challenge, the complexity of both HP and SAP variabilities in patients with PD remained high, thus indicating both vagal and sympathetic impairments. Complexity indexes derived from short HP and SAP beat-to-beat series provide complementary information and are helpful in detecting early autonomic dysfunction in patients with PD well before circulatory symptoms become noticeable.

heart rate variability; head-up tilt; pharmacological blockade; Parkinson's disease; autonomic nervous system

SHORT-TERM CARDIOVASCULAR control is performed by multiple, simultaneously active, regulatory mechanisms (28). These mechanisms prevent cardiovascular variables from assuming values that are incompatible with life while assuring that the organism can function under most conditions. The measurable effect of the action of cardiovascular control is the beat-to-beat fluctuations in cardiovascular variables such as heart period (HP) and systolic arterial pressure (SAP), even in the absence of any external stimulus (10). Because these short-term mechanisms are weakly coupled and operate over different time scales spanning from 0.04 to 0.5 Hz in humans (56), the time course of cardiovascular variables is characterized by patterns with different dominant frequencies and shapes. This variety of features is usually referred to as dynamical complexity (43). Indexes that quantify cardiovascular complexity have been shown to contain physiological and clinical information (17). Indeed, the complexity of the beat-to-beat HP series has been found to decrease with age (26, 37, 53, 64), it is altered in pathological conditions (7, 15, 24, 51, 62, 65), and it is modulated by the autonomic nervous system (9, 40, 45, 46, 55, 58, 60, 61, 69).

The dynamical complexity of cardiovascular control is usually quantified over the time course of a single variable using univariate approaches essentially based on the evaluation of entropy, predictability, recurrence of symbols, or scaling behavior (9, 23, 26, 39, 45, 46, 49, 58, 66, 67). The variable most used to infer complexity of cardiovascular control is HP, due to its informative value about the state of the autonomic nervous system and its accessibility. Two main issues remain unresolved: *1*) it is unclear whether the complexity of SAP variability can provide additional information over the complexity of HP variability; and *2*) it is unknown whether the exploitation of a multivariate approach that observes several cardiovascular variables at the same time might provide additional insight over a univariate approach alone. We hypothesize that complexity indexes relevant to SAP variability are informative with respect to those relevant to HP variability, especially under physiological and pathological conditions that primarily affect vascular control. In addition, we conjecture that complexity indexes derived from a multivariate approach (i.e., jointly analyzing the HP and SAP variability series and accounting for respiration, R), can provide information that is different from that obtained from a univariate approach. Indeed, the explicit consideration of additional variables more directly linked to

Address for reprint requests and other correspondence: Alberto Porta, Università degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Istituto Ortopedico Galeazzi, Laboratorio di Modellistica di Sistemi Complessi, Via R. Galeazzi 4, 20161 Milan, Italy (e-mail: alberto.porta@unimi.it).

specific systems such as the respiratory system for R and the vascular system for SAP, might allow a more precise description of cardiovascular control. Moreover, the shortness of the data sets traditionally used to derive information about short-term cardiovascular regulation (i.e., ~5 min or ~300 cardiac beats) might limit the reliability of reconstructing the dynamical behavior of cardiovascular control when derived from a unique variable, while the exploitation of multivariate recordings might allow a more complete reconstruction.

Thus the aim of this study is to compare complexity indexes derived from HP variability with those derived from SAP variability and to contrast a multivariate approach with a univariate approach. Complexity indexes derived from a multivariate autoregressive (MAR) model that jointly considers the HP, SAP, and R series will be compared with those derived from a univariate autoregressive (AR) model. Complexity will be estimated according to a predictability approach that estimates the best MAR and AR models directly from short-term recordings of HP and SAP variabilities. The portion of total variance that cannot be explained by the model will be taken as an index of the complexity of the HP and SAP series. Three experimental protocols will be considered: *1*) selective pharmacological blockade of the sympathetic and parasympathetic branches of the autonomic nervous system alone or in combination to elucidate the physiological mechanisms that underlie the complexity of cardiovascular control (35); *2*) a graded, head-up tilt test to induce a progressive sympathetic activation and vagal withdrawal in healthy subjects to clarify the ability of complexity indexes to track gradual modifications of cardiovascular regulation (11, 31, 47); and *3*) a head-up tilt in patients with Parkinson's disease (PD) without clinical evidence of orthostatic intolerance and hypotension to highlight the ability of complexity indexes to detect an early impairment of cardiovascular control (2).

MATERIALS AND METHODS

Autonomic blockade protocol. This protocol was originally designed to study the effects of pharmacological blockades of the parasympathetic and sympathetic branches of the autonomic nervous system on cardiac baroreflex sensitivity (see Ref. 35 for a detailed description). Briefly, we studied nine healthy male physicians (age range 25–46 years) who were familiar with the study setting. None of the subjects presented an abnormal medical history, physical examination, or electrocardiography, nor did they take any medication. All subjects had normal resting brachial arterial pressure as measured by sphygmomanometer. They were instructed to avoid tobacco, alcohol, and caffeine for 12 h and strenuous exercise for 24 h before each experiment. Electrocardiographic (ECG) and noninvasive finger blood pressure (Finapress 2300, Ohmeda, Englewood, CO) data were recorded during the experiments. Subject's hands were maintained at heart level. Signals were sampled at 500 Hz. Experimental sessions were performed over 3 days at approximately 2-wk intervals. One volunteer took part only in the first-day experiments. Subjects remained at rest in the supine position in a quiet, darkened room during all recordings. Each experiment started in the morning between 8:00 and 9:00 AM and consisted of 15–20 min of baseline (B) recording followed by 15–20 min of recording after drug administration. Recordings were obtained: *1*) on day 1 after parasympathetic blockade with 40 μg/kg iv atropine sulfate (atropine, AT) to block muscarinic receptors; *2*) on day 2 after β-adrenergic blockade with 200 μg/kg iv propranolol (PR) to block β_1 cardiac and β_2 vascular peripheral adrenergic receptors; *3*) on day 1 when PR was administered at the end of the AT session (the dose of AT was reinforced by 10 μg/kg) to combine the effect of AT and PR (AT+PR) and to obtain a cardiac parasympathetic and sympathetic blockade; *4*) on day 3, 120 min after oral administration of 6 μg/kg clonidine hydrochloride (clonidine, CL) to centrally block the sympathetic outflow to the heart and vasculature and to centrally increase the cardiac parasympathetic activity (57). All subjects gave their written, informed consent; the protocol adhered to the principles of the Declaration of Helsinki; and the human research and ethical review board of the Hospices Civils de Lyon approved the protocol.

Graded, head-up tilt protocol. This protocol was originally designed to monitor the progressive involvement of baroreflex in controlling HP-SAP variability interactions as a function of the tilt-table inclination (i.e., the magnitude of the orthostatic challenge) (see Ref. 42 for a detailed description). Briefly, we studied 19 nonsmoking healthy men and women (age range 21–48 years, median = 30 years; 8 men). Subjects had no history or clinical evidence of any disease nor did they take any medication. They refrained from consuming any caffeine or alcohol-containing beverages for 24 h before the recordings. All experiments were performed in the morning. The subjects were supported on the tilt table by two belts at the thigh and waist, respectively, and with both feet touching the footrest of the tilt table. ECG (lead II), continuous plethysmographic AP (Finometer MIDI, Finapres Medical Systems, the Netherlands), and respiratory movements via thoracic belt (Marazza, Monza, Italy) were recorded. Signals were sampled at 300 Hz. The arterial pressure was measured from the middle finger of the left hand being maintained at the level of heart by fixing the subject's arm to his or her thorax during the upright position. All experimental sessions of the protocol included three periods in the same order: *1*) 7 min of B at rest in the supine position; *2*) 10 min during passive head-up tilt (T); and *3*) 8 min of recovery. The inclination of the tilt table, expressed in degrees, was randomly chosen within the set (15°, 30°, 45°, 60°, 75°, 90°). Sessions were labelled as T15, T30, T45, T60, T75, and T90 according to the tilt table inclination. Each subject underwent all six tilt-table inclination experimental sessions. Each subject completed the sequence of tilt-table angles without experiencing any sign of presyncope. The arterial pressure signal was cross-calibrated in each session using a measure provided by a sphygmomanometer at the onset of B. The autocalibration procedure of the arterial pressure device was switched off after the first automatic calibration at the onset of the session. Analyses were performed after about 2 min from the start of each period. During the entire protocol the subjects breathed spontaneously but they were not allowed to talk. Informed consent was obtained from all subjects; the protocol adhered to the principles of the Declaration of Helsinki; and the human research and ethical review boards of the L. Sacco Hospital and Department of Biomedical and Clinical Sciences, University of Milan, approved the protocol.

PD protocol. This protocol was originally designed to monitor the early impairment of cardiovascular control in patients with PD via spectral analysis of spontaneous HP and SAP variabilities (see Ref. 2 for a detailed description). Briefly, we studied 12 patients with PD without orthostatic hypotension or symptoms of orthostatic intolerance (age range 55–79 years, median = 65 years; 8 men) and 12 healthy control (HC) subjects matched by age and gender with those in the PD group (age range 58–72 years, median = 67 years; 7 men). Patients with PD (i.e., stages 2–4 using the Hoehn and Yhar scale) were at the best of their habitual pharmacological treatment. ECG (lead II), noninvasive arterial pressure (Finapress 2300, Ohmeda, Englewood, CO) and respiratory movements via thoracic belt (Marazza, Monza, Italy) were recorded. Sample frequency was 300 Hz. Signals were recorded with the subject lying on the tilt table, gently fastened by two belts, and with both the feet touching the footrest of the tilt table. Recordings of 10 min were obtained at B and at T75. During the protocol, the subjects breathed spontaneously but were not allowed to talk. All subjects gave their written informed consent; the study adhered with the principles of the Declaration of Helsinki for medical research involving human subjects; and the

human research and ethical review boards of the Bolognini Hospital of Seriate, Bergamo, Italy, approved the protocol.

Extraction of the beat-to-beat variability series. After detecting the QRS complex on ECG readings and locating the R-apex using parabolic interpolation, the temporal distance between two consecutive R parabolic apexes was computed and used as an approximation of HP. The maximum arterial pressure inside the HP was defined as SAP, and the nth SAP [i.e., SAP(n)] was taken inside the nth HP [i.e., HP(n)]. For the autonomic blockade protocol, R was inferred from ECG readings; that is, the area of the first QRS complex delimiting HP(n), assessed with respect to the isoelectric baseline, was taken as the nth R measure [i.e., R(n)] (32). Conversely, in the graded, head-up tilt and PD protocols R(n) was obtained by sampling the R signal in correspondence with the first QRS delimiting HP(n). The occurrences of QRS and SAP peaks were carefully checked to avoid erroneous detections or missed beats. If isolated ectopic beats affected HP and SAP values, these measures were linearly interpolated using the closest values that were unaffected by ectopic beats. HP, SAP, and R were extracted on a beat-to-beat basis. The series were linearly detrended. Sequences of 256 consecutive measurements were randomly selected inside each experimental condition. If evident nonstationarities (such as very slow drifting of the mean or sudden changes in the variance) were present despite the linear detrending, the random selection was carried out again. The mean and the variance of HP and SAP were indicated as μ_{HP}, μ_{SAP}, σ^2_{HP}, and σ^2_{SAP} and expressed in ms, mmHg, ms^2, and $mmHg^2$, respectively.

Model-based complexity analysis. The complexity of the HP and SAP series was assessed according to an MAR model (see Appendix for further details). Briefly, this approach described the HP series as a linear combination of its own past values, of present and past values of SAP, and R series, plus a random, unpredictable, noise. Reversing the role between HP and SAP allowed a description of SAP dynamics. The coefficients of the linear combination were estimated directly from the HP, SAP, and R series via least-squares identification (52). The number of coefficients was optimized via the Akaike criterion for multivariate processes (1). After identifying the coefficients of the MAR model, the variance of the random, unpredictable part calculated as the mean square prediction error (MSPE) between the original and MAR-predicted series, provided a complexity index. It was labeled as $MSPE_{MAR}$. Given that the HP, SAP, and R series were normalized to have zero mean and unit variance before identifying the model coefficients, $MSPE_{MAR}$ was bound between 0 and 1, where 0 indicates null complexity (full predictability) and 1 indicates maximum complexity (full unpredictability).

The complexity of the HP and SAP series was assessed according to an AR model as well (see Appendix for further details). In this case, the HP (or SAP) series was described exclusively on the basis of a linear combination of its own past values without accounting for any additional exogenous influence. The coefficients of the linear combination were again estimated directly from the HP (or SAP) series via Levinson-Durbin recursion (27) and the number of the coefficients was optimized via the Akaike criterion for univariate processes (1). The ability of the AR model to describe the HP (or SAP) dynamics was quantified again as the MSPE between the original and AR-predicted series. The complexity index was labeled as $MSPE_{AR}$. As a result of the normalization of HP and SAP series, $MSPE_{AR}$, like $MSPE_{MAR}$, ranged from 0 (full predictability) to 1 (full unpredictability).

Statistical analysis. We performed a paired *t*-test to check the significance of the difference between $MSPE_{MAR}$ and $MSPE_{AR}$ regardless of the series and experimental condition in each experimental protocol. If the normality test (Kolmogorov-Smirnov test) was not fulfilled, a Wilcoxon signed-rank test was used. The same test was used to check the significance of the difference between $MSPE_{AR}$ (or $MSPE_{MAR}$) assessed over the HP and SAP series regardless of the experimental condition. One-way repeated measures analysis of variance (i.e., Dunnett's test), or a Friedman repeated measures analysis of variance on ranks when appropriate, was applied to check whether experimental conditions affected the time domain and MSPE indexes compared with B in both the autonomic blockade and graded, head-up tilt protocols. In the graded, head-up tilt protocol, linear regression analysis of the time domain and MSPE indexes on tilt-table inclination was carried out. Global linear regression analysis was carried out by pooling together all data. The Pearson product moment correlation, *r*, was calculated. If *r* was significantly different from 0, then a significant linear relationship of the parameter on tilt-table angles was detected. In the protocol of patients with PD, two-way repeated measures analysis of variance (one factor repetition, Holm-Sidak test for multiple comparisons) was performed to assess the significance of changes in the time domain and MSPE parameters induced by head-up tilt within the same population (HC or PD group) and differences between groups within the same experimental condition were determined (B or T75). Statistical analysis was carried out using a commercial statistical program (Sigmastat, SPSS, ver.3.0.1). A value of $P < 0.05$ was always considered as significant.

RESULTS

Time domain characterization of the experimental protocols. Table 1 shows the medians (25th–75th percentiles) of μ_{HP}, σ^2_{HP}, μ_{SAP}, and σ^2_{SAP} during the autonomic blockade protocol. Although μ_{HP} was significantly modified by all the pharmacological interventions (i.e., μ_{HP} decreased after AT and AT+PR, and increased after PR and CL), σ^2_{HP} was significantly modified only after AT and AT+PR (i.e., σ^2_{HP} was dramatically reduced after AT and AT+PR); μ_{SAP} was significantly modified after AT and CL (i.e., μ_{SAP} increased after AT and decreased after CL); and σ^2_{SAP} was not affected by the pharmacological protocol except after CL (i.e., σ^2_{SAP} was significantly decreased after CL).

Table 2 shows the medians (25th–75th percentiles) of μ_{HP}, σ^2_{HP}, μ_{SAP}, and σ^2_{SAP} during the graded, head-up tilt protocol. During all head-up tilt sessions μ_{HP} was significantly lower than at B, whereas σ^2_{HP} was significantly reduced when the tilt-table inclination was $\geq 75°$. Head-up tilt did not affect μ_{SAP} except at T90, when μ_{SAP} was significantly increased. Tilt-table inclination $\geq 60°$ induced a significant increase in σ^2_{SAP}. All these variables were significantly, linearly related to tilt-table angles: the correlation coefficient, *r*, was -0.59 ($P = 1.91 \cdot 10^{-13}$) for μ_{HP}, -0.31 ($P = 2.72 \cdot 10^{-4}$) for σ^2_{HP}, $+0.26$

Table 1. *HP and SAP mean and variance during autonomic blockade protocol*

	B	AT	PR	AT+PR	CL
μ_{HP} [ms]	1043 (955–1107)	629* (613–649)	1228* (1181–1353)	726* (697–756)	1352* (1304–1401)
σ^2_{HP} [ms^2]	2419 (1516–5653)	58* (20–89)	3121 (2654–8873)	26* (13–51)	3782 (3058–6452)
μ_{SAP} [mmHg]	115.4 (107.9–118.8)	130.7* (126.2–145.0)	118.3 (114.9–120.2)	122.6 (117.1–138.4)	92.7* (87.7–102.5)
σ^2_{SAP} [$mmHg^2$]	30.2 (20.3–42.0)	37.0 (23.5–45.6)	31.6 (23.8–53.4)	31.1 (17.2–37.2)	7.7* (3.4–11.5)

Values are expressed as median (first quartile − third quartile). μ_{HP}, HP mean; σ^2_{HP}, HP variance; μ_{SAP}, SAP mean; σ^2_{SAP}, SAP variance; B, baseline; AT, atropine; PR, propranolol; AT+PR, atropine plus propranolol; CL, clonidine. *Significant difference from baseline ($P < 0.05$).

Table 2. *HP and SAP mean and variance during graded, head-up tilt protocol*

	B	T15	T30	T45	T60	T75	T90
μ_{HP} [ms]	1005 (918-1052)	917* (859–1018)	871* (819–968)	804* (761–882)	784* (680–854)	732* (659–806)	736* (654–786)
σ^2_{HP} [ms^2]	3402 (2561–5794)	3294 (1502–5862)	3531 (2318–4443)	2904 (1895–3581)	2610 (1980–3995)	2168* (1628–2871)	1850* (1349–3419)
μ_{SAP} [mmHg]	121.2 (118.5–121.7)	119.7 (115.7–123.0)	121.7 (115.9–126.3)	125.9 (118.3–131.4)	128.6 (117.5–132.6)	124.6 (116.9–135.6)	131.2* (125.0-138.8)
σ^2_{SAP} [mmHg^2]	18.3 (12.6–24.1)	15.1 (8.1–26.4)	20.1 (12.0–30.2)	24.4 (14.1–37.4)	31.6* (18.3–49.5)	35.7* (20.4–52.6)	26.7* (18.0–35.9)

Values are expressed as median (first quartile − third quartile). μ_{HP}, HP mean; σ^2_{HP}, HP variance; μ_{SAP}, SAP mean; σ^2_{SAP}, SAP variance; B, baseline; T15, T30, T45, T60, T75, and T90 represent, respectively, 15°, 30°, 45°, 60°, 75°, and 90° head-up tilt. *Significant difference from baseline ($P < 0.05$).

($P = 2.32 \cdot 10^{-3}$) for μ_{SAP}, and +0.27 ($P = 1.46 \cdot 10^{-3}$) for σ^2_{SAP}.

Table 3 shows the medians (25th–75th percentiles) of μ_{HP}, σ^2_{HP}, μ_{SAP}, and σ^2_{SAP} in the PD protocol. While μ_{HP} decreased significantly at T75 in both HC and PD groups, σ^2_{HP} and μ_{SAP} were insignificantly affected by T75. The vascular response to head-up tilt in the population of patients with PD was blunted; indeed, although σ^2_{SAP} in the HC group increased at T75 compared with B, no significant changes were observed in the PD group. As a consequence, at T75, σ^2_{SAP} in patients with PD was significantly smaller than in HC subjects.

Short-term complexity of HP and SAP series during the autonomic blockade protocol. Figure 1 summarizes the results of short-term complexity analysis during autonomic blockade protocol. Figure 1, *A* and *B,* shows $MSPE_{AR}$ and $MSPE_{MAR}$ pooled together regardless of the pharmacological challenge as a function of the predicted series (i.e., HP and SAP). The $MSPE_{AR}$ of the HP group was significantly larger than the $MSPE_{AR}$ of the SAP group (Fig. 1*A*; $P < 0.001$). The same finding was observed for $MSPE_{MAR}$ (Fig. 1*B*; $P < 0.001$). When MSPE values were pooled together independently of their assessment over HP and SAP and independently of the experimental condition, $MSPE_{AR}$ was found to be significantly higher than $MSPE_{MAR}$ ($P < 0.001$). $MSPE_{AR}$ and $MSPE_{MAR}$ of HP and SAP as a function of the pharmacological challenge are shown in Fig. 1, *C–F*. $MSPE_{AR}$ of HP significantly decreased from B during AT and AT+PR administration (Fig. 1*C*; $P < 0.05$), while $MSPE_{AR}$ of SAP significantly increased during CL administration (Fig. 1*D*; $P < 0.05$). The same results were obtained for $MSPE_{MAR}$ (Fig. 1, *E* and *F*).

Short-term complexity of HP and SAP series during graded, head-up tilt protocol. Figure 2 shows the results of short-term complexity analysis during the graded, head-up tilt protocol. Figure 2, *A* and *B,* shows $MSPE_{AR}$ and $MSPE_{MAR}$ pooled together regardless of the tilt-table inclination as a function of the predicted series (i.e., HP or SAP). The $MSPE_{AR}$ of HP was significantly larger than the $MSPE_{AR}$ of SAP (Fig. 2*A*; $P < 0.001$). The same result held for $MSPE_{MAR}$ (Fig. 2*B*; $P < 0.001$). When MSPE values were pooled together regardless of their evaluation from the HP and SAP series and regardless of the tilt-table inclination, $MSPE_{AR}$ was found to be significantly higher than $MSPE_{MAR}$ ($P < 0.001$). Individual values for $MSPE_{AR}$ assessed over the HP and SAP series are depicted as open circles as a function of the experimental condition in Fig. 2, *C* and *D*. Similar representation is given for the $MSPE_{MAR}$ of HP and SAP (Fig. 2, *E* and *F*). For HP, both $MSPE_{AR}$ and $MSPE_{MAR}$ were significantly decreased from B when the tilt-table angle was ≥30° (Fig. 2, *C* and *E*; $P < 0.05$). Both $MSPE_{AR}$ and $MSPE_{MAR}$ of HP were significantly linearly related to tilt-table angles ($r = -0.56$, $P = 2.23 \cdot 10^{-12}$ and $r = -0.57$, $P = 1.21 \cdot 10^{-12}$, respectively). For the SAP series, $MSPE_{AR}$ and $MSPE_{MAR}$ were not affected by head-up tilt (Fig. 2, *D* and *F*).

Short-term complexity of the HP and SAP series during the PD protocol. Figure 3 summarizes the results of short-term complexity analysis in the PD protocol. Figure 3, *A* and *B*, shows $MSPE_{AR}$ and $MSPE_{MAR}$ pooled together regardless of the experimental condition, as a function of the predicted series (i.e., HP or SAP) in both HC and PD groups. $MSPE_{AR}$ of HP was similar to $MSPE_{AR}$ of SAP in both HC and PD groups (Fig. 3*A*). On the contrary, the MAR approach was able to

Table 3. *HP and SAP mean and variance during PD protocol*

	HC		PD	
	B	T75	B	T75
μ_{HP} [ms]	855 (782–983)	758* (695–827)	912 (824–942)	710* (691–829)
σ^2_{HP} [ms^2]	1075 (446–1906)	604 (326–1625)	504 (374–1106)	215 (85–342)
μ_{SAP} [mmHg]	120.9 (115.6–132.2)	134.8 (121.6–161.4)	124.5 (118.1–127.8)	127.2 (113.8–135.0)
σ^2_{SAP} [mmHg^2]	37.9 (25.1–47.7)	72.4* (53.6–116.6)	16.8 (11.4–27.4)	21.5# (12.1–30.4)

Values are expressed as median (first quartile − third quartile). μ_{HP}, HP mean; σ^2_{HP}, HP variance; μ_{SAP}, SAP mean; σ^2_{SAP}, SAP variance; B, baseline; T75, 75° head-up tilt; HC, healthy control group; PD, group with Parkinson's disease. *Significant difference within group vs. baseline ($P < 0.05$). #Significant difference within condition vs. HC ($P < 0.05$).

discern significant differences between MSPE of HP and SAP. Indeed, $MSPE_{MAR}$ of HP was larger than $MSPE_{MAR}$ of SAP in both HC and PD groups (Fig. 3*B*). Although $MSPE_{AR}$ of HP was similar in the HC and PD groups, $MSPE_{AR}$ of SAP was larger in patients with PD than in HC subjects (Fig. 3*A*). Similar findings were obtained for $MSPE_{MAR}$ (Fig. 3*B*). $MSPE_{AR}$ and $MSPE_{MAR}$ are shown as a function of the experimental condition (i.e., B and T75) in both HC and PD groups in Fig. 3, *C–F*. For HP, $MSPE_{AR}$ significantly decreased at T75 in HC subjects, it remained unchanged in the PD group and, in both experimental conditions (i.e., B or T75) it was similar in both groups (Fig. 3*C*). At difference with HP, $MSPE_{AR}$ of SAP was unmodified by T75 in both HC and PD groups and, in both experimental conditions (i.e., B or T75), it was significantly larger in patients with PD than in HC subjects (Fig. 3*D*). Similar results held for $MSPE_{MAR}$ (Fig. 3, *E* and *F*).

DISCUSSION

This study suggests that a complexity index derived from an MAR approach (i.e., $MSPE_{MAR}$) does not provide additional information from that derived from an AR approach (i.e., $MSPE_{AR}$). In addition to this methodological result, the main experimental findings can be summarized as follows: *1*) SAP variability is less complex than HP; *2*) vagal activity keeps HP complexity high; *3*) sympathetic activity keeps SAP complexity low; *4*) in patients with PD, HP and SAP complexity indexes can detect the early abnormalities of cardiac and vascular controls, respectively; and *5*) SAP complexity is increased in patients with PD without any modification in HP complexity. These findings suggest that complexity indexes assessed from HP and SAP variabilities provide complementary information and should be utilized for the detection of early abnormalities in both cardiac and vascular controls.

Univariate and multivariate approaches to the assessment of HP and SAP complexity provide similar information. When short-term variability recordings (i.e., 256 samples) are considered, the shortness of the data sequence might prevent a consistent reconstruction of the dynamical behavior of the cardiovascular regulatory system from the time course of a single variable (54) and, thus, a robust assessment of quantities

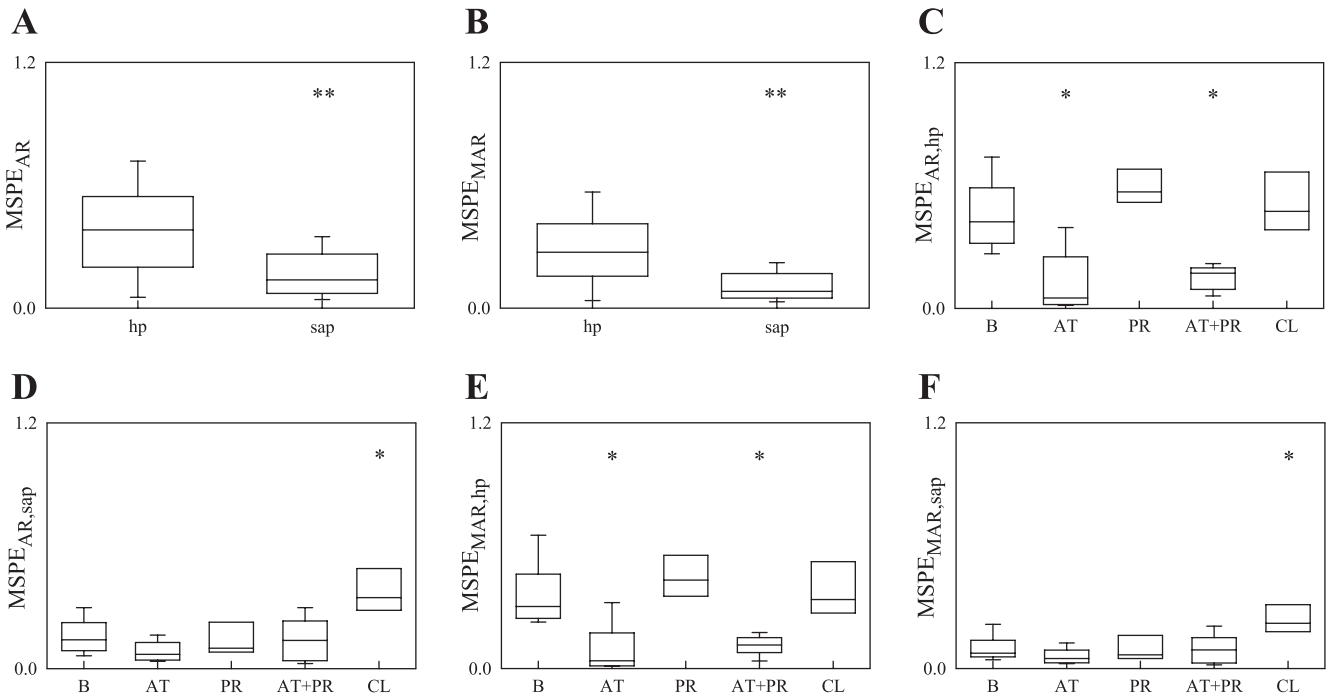

Fig. 1. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of MSPE computed from the HP and SAP series during the autonomic blockade protocol. $MSPE_{AR}$ and $MSPE_{MAR}$ are shown as a function of the series (i.e., HP and SAP) and regardless of the experimental condition in (*A*) and (*B*), respectively. $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the HP series is depicted as a function of the experimental condition in (*C*) and (*E*), respectively, while $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the SAP series is shown in (*D*) and (*F*), respectively. $^{**}P < 0.001$ vs. HP; and $^{*}P < 0.05$ vs. baseline.

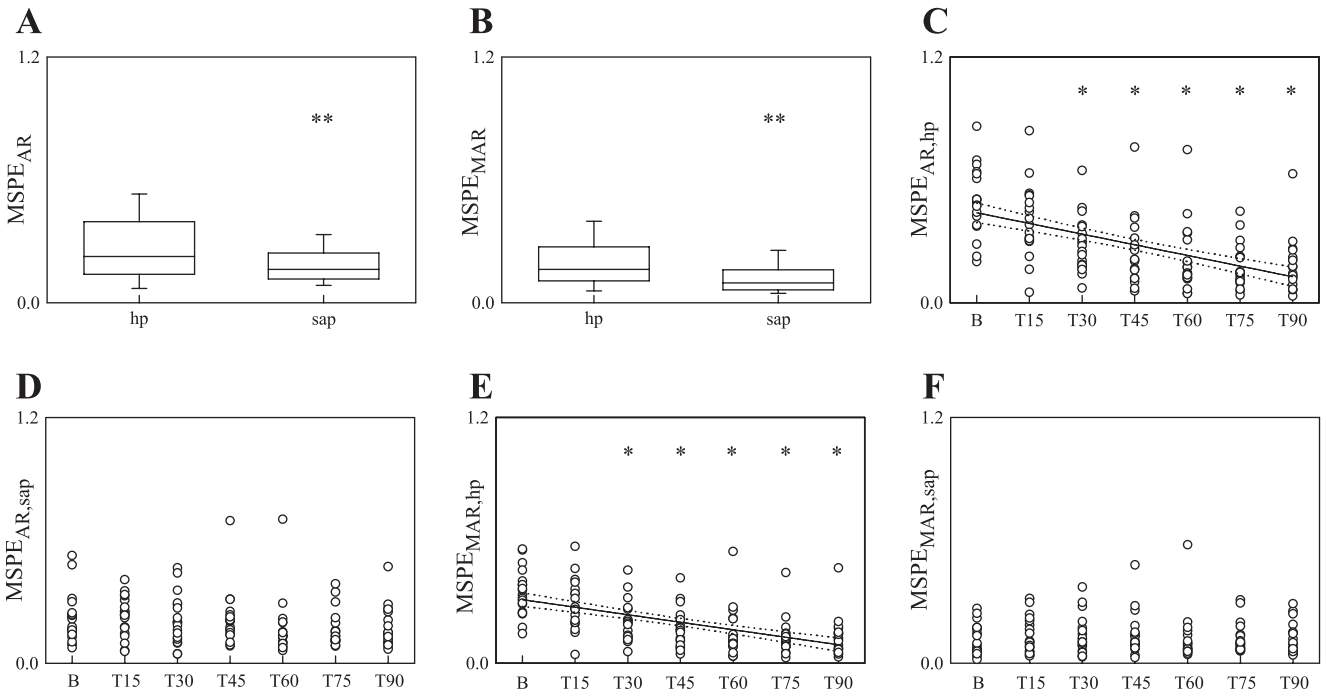

Fig. 2. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of MSPE computed from the HP and SAP series during graded head-up tilt protocol. $MSPE_{AR}$ and $MSPE_{MAR}$ are shown as a function of the series (i.e., HP and SAP) and regardless of the experimental condition in (*A*) and (*B*), respectively. Individual values (open circles) for $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the HP series are depicted as a function of the experimental condition in (*C*) and (*E*), respectively, while $MSPE_{AR}$ and $MSPE_{MAR}$ are assessed over the SAP series in (*D*) and (*F*), respectively. While $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the SAP series is similar to baseline in (*D*) and (*F*), $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the HP series decrease significantly in (*C*) and (*E*) when the tilt-table angles are ≥30° (*$P < 0.05$ vs. baseline). The linear regressions (solid line) of all the MSPE values on tilt-table inclination and their 95% confidence interval (dotted lines) are plotted when correlation coefficient is significantly different from 0 with $P < 0.01$.

describing the complexity of dynamics. Conversely, it can be hypothesized that using more than one signal (i.e., a multivariate approach) might be helpful in obtaining a more reliable reconstruction of the system dynamics given the same length of recording. In addition, multivariate recordings might allow the exploration of features of the cardiovascular regulatory system that would otherwise remain unobservable, thus making more comprehensive the description of cardiovascular control. For example, in the assessment of complexity using the HP series, the additional exploitation of SAP variability and R signal might allow a more direct and insightful description of parts of the cardiovascular control system (i.e., vascular and respiratory systems, respectively) that otherwise might be only indirectly assessed from HP dynamics. In disagreement with this hypothesis, the MAR approach to the quantification of complexity accounting for exogenous variables did not add new information to that of univariate AR. This disappointing conclusion contrasted with the better ability of the MAR approach to predict dynamics: indeed, $MSPE_{MAR}$ is significantly smaller than $MSPE_{AR}$ regardless of the experimental protocol and population. The better predictability of the MAR approach over the AR approach might be the effect of the larger number of coefficients. We conclude that the joint exploitation of past samples of HP, SAP, and R to predict the HP (or SAP) series does not produce any practical advantage in terms of estimation of complexity compared with using an adequate number of past samples drawn from the sole series to be predicted. This finding suggests that no hidden portions of the dynamical behavior of the cardiovascular control system can be discovered by considering additional variables (i.e., the full observability of the cardiac and vascular regulatory systems using a single variable). In addition, because complexity indexes derived from a single time series are not improved by adding new informative signals, we suggest that the size of the considered sequences, despite its shortness, is sufficient to reliably estimate short-term complexity indexes.

SAP variability is less complex than HP variability. This study confirms that the complexity of the SAP variability is smaller than that of the HP series (40). The high complexity of the HP variability compared with that of SAP might be the result of the concomitant action of vagal and sympathetic branches of the autonomic nervous system on the heart while the vascular bed is under sympathetic control (40). This finding suggests that vagal inputs produce HP oscillations independent of those of sympathetic circuits, thus indicating that the well-recognized reciprocal (30) or parallel (36) interactions between the two branches of the autonomic nervous system do not occur via frequency locking mechanisms that lead to a decrease in the overall complexity of HP dynamics. In addition, the low complexity of the SAP series suggests the tendency of vascular sympathetic control to synchronize the sparse vasomotor activity of peripheral districts to produce phase-locked, regular, SAP oscillations over a limited range of frequencies (i.e., the low frequency band) (4). The different levels of HP and SAP complexity were detected both in young healthy subjects undergoing pharmacological challenges or graded, head-up tilt test, and in HC subjects used to contrast results with patients with PD, thus suggesting that this feature is preserved in aging. In our pathological population, constituted by patients with PD without ortho-

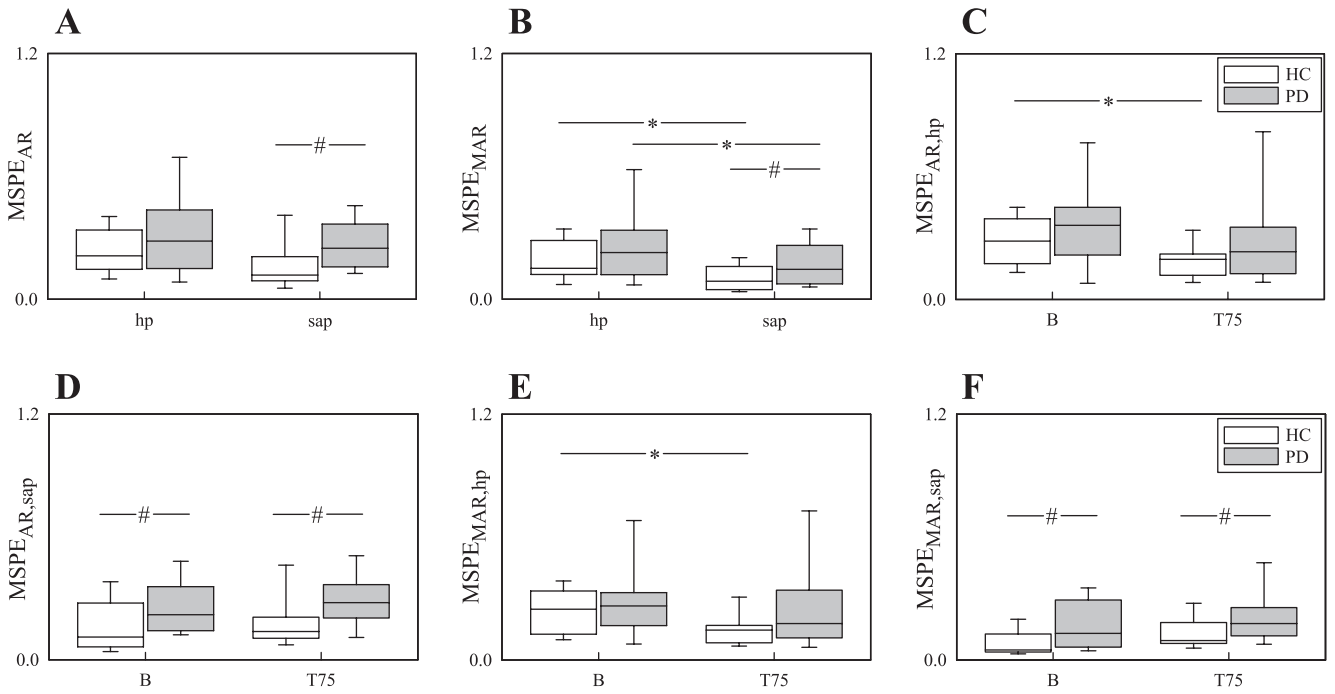

Fig. 3. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of MSPE computed from the HP and SAP series in HC subjects (white box) and in patients with PD (gray box). $MSPE_{AR}$ and $MSPE_{MAR}$ are shown as a function of the series (i.e., HP and SAP) and regardless of the experimental condition in (*A*) and (*B*), respectively. $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the HP series are depicted as a function of the experimental condition in (*C*) and (*E*) respectively, while $MSPE_{AR}$ and $MSPE_{MAR}$ assessed over the SAP series are shown in (*D*) and (*F*), respectively. $*P < 0.05$ within population while varying series or experimental condition or series. $\#P < 0.05$ within experimental condition or series while varying population.

static hypotension or symptoms of orthostatic intolerance, different levels of HP and SAP complexity were preserved, thus indicating that at this early stage of the disease vagal innervation of the heart is still able to raise the complexity of the HP series, and sympathetic innervation of the vessels is still able to keep the complexity of the SAP series low.

Vagal activity keeps the complexity of the HP variability high. It is well known that short-term complexity of the HP series assessed over short data sequences (about 300 cardiac beats) is reduced in healthy subjects in the presence of an increase in sympathetic activity and vagal withdrawal; indeed, it was lower during head-up tilt, inducing a reflex sympathetic activation in response to a reduced venous return (45), during vagal blockade carried out with AT (46), after iv infusion of nitroprusside evoking a sympathetic reflex response by lowering arterial pressure (46), and during daytime compared with nighttime (44). This study points out the following in regard to the short-term complexity of the HP series as assessed from predictability measures: *1*) it declines progressively as a function of the tilt-table inclination in healthy young subjects, and this reduction is still detectable in an older population; *2*) it is reduced by blocking the vagal activity directed to the heart with AT; *3*) it remains unmodified after β-adrenergic blockade carried out via PR administration or after central blockade of the sympathetic outflow to the heart and vasculature performed by CL; and *4*) it is decreased after double autonomic blockade performed via administration of PR after AT to a level comparable to that observed after the sole administration of AT. All these findings suggest that HP complexity is governed primarily by vagal influences in healthy humans. We suggest that in situations of sympathetic overactivity in which sympathovagal balance is working (36), such as during head-up tilt (34), the reduction in HP complexity is induced by vagal withdrawal. Vagal departure contributes to the decrease in HP complexity by limiting the effectiveness of fast circuits, thus reducing the number of temporal scales actually exploited to regulate cardiovascular variables (46) and augmenting the isolation of the heart from neural inputs (38). It can be hypothesized that an additional contribution of the regularization of HP dynamics is given by the ability of the sympathetic circuits to synchronize several control mechanisms working over temporal scales close to, but not completely coincident, in the low-frequency band (from 0.04 to 0.15 Hz) (45). These findings are in agreement with those of previous studies using methods for the assessment of fractal characteristics of HP variability. These studies found a significant change in the fractal features of HP variability toward less random dynamics (i.e., toward a Brownian motion) after AT (9, 60, 69), head-up tilt (55, 58), and combined β-adrenergic and vagal blockade (9, 55), while no modifications were observed after β-adrenergic blockade performed by PR (9, 68) or after central sympathetic blockade performed by CL (9). It is worth noting that the proposed approach to the quantification of complexity is much simpler than fractal analysis and, thus easier to implement; indeed, it is based on the estimate of a limited number of coefficients of a linear regression over past values of the series according to an AR model, and it does not require large sets of data to become consistent. In addition, it allows a direct comparison with the result of AR power spectral analysis: indeed, the estimated coefficients allow the evaluation of low- and high-frequency powers as well (34).

Sympathetic activity keeps the complexity of the SAP variability low. Few studies have assessed the complexity of SAP variability (8, 9, 26, 40, 61), thus making it difficult to understand whether SAP complexity indexes carry additional information over HP indexes. In addition, some reports did not compare complexity indexes derived from HP and SAP variabilities (26). We speculate that this is due primarily to the length of the blood pressure recordings necessary to obtain reliable complexity estimates on the basis of fractal indexes (8, 9) or multiscale entropy indexes (61). Duration of recordings makes the experimental setup involving arterial pressure recordings more complicated than that based on sole ECG acquisition. In this regard, the approach proposed here on the basis of model-based, short-term predictability might stimulate further research on the complexity of SAP variability.

This study suggests that sympathetic activity directed to the vessels keeps the complexity of the SAP series low. Indeed, CL, by inducing a central blockade of the sympathetic activity both at the cardiac and vascular levels, significantly increased SAP complexity. We suggest that sympathetic activity directed to the vessels contributes to the synchronization of peripheral vascular districts, thus producing measurable effects at the level of a systemic variable, such as SAP, and keeps the SAP series complexity low. Complete sympathetic blockade induced by CL abolishes synchronization, thus rendering sparse the contributions of the peripheral districts to SAP variability and increasing the complexity of SAP dynamics. Because blockade of β_1-adrenergic cardiac and β_2-adrenergic vascular receptors induced by PR did not produce any alteration in SAP complexity variability, we suggest that α-adrenergic receptors are more involved in governing SAP complexity. The lack of modification in the complexity of SAP variability after AT and combined vagal and β-adrenergic blockade obtained via the administration of PR after AT corroborates the observation that SAP complexity is mainly under sympathetic control.

It has been suggested that an increase in HP complexity as detected via a breakdown in fractal features toward more random dynamics, can be interpreted as an index of coactivation of sympathetic and vagal outflow (59). Here, the mechanisms exploited by CL to cause a loss of predictability and, consequently, a rise in the complexity of SAP variability, did not seem to involve parallel modifications in the activity of both branches of the autonomic nervous system. Indeed, the activity of sympathetic arm is abolished (35) and vagal activity is increased (57). The proposed mechanism on the basis of the loss of synchronization of the vasomotion of peripheral districts after sympathetic blockade (4) might be tested using specific physiological protocols involving the assessment of peripheral flows and resistances in different districts and the direct evaluation of the effect of a sympathetic activation or deactivation.

The progressive increase in sympathetic activity as a function of the tilt-table angle during graded, head-up tilt (11, 14, 31) did not modify the complexity of SAP variability, and this result held for the HC group in the PD protocol. This finding is in agreement with a lack of modification in the fractal properties during graded, lower-body negative pressure protocol inducing a sympathetic activation as a function of the reduction in central venous pressure and stroke volume (8). We speculate that the baseline level of sympathetic activity is sufficient to synchronize the vasomotor activity of peripheral districts, thus keeping the SAP variability complexity low, and extra activation did not produce further synchronization, nor in turn, additional regularization of the SAP dynamics.

HP and SAP complexity indexes detect early abnormalities in cardiovascular control in patients with PD. Patients with PD are characterized primarily by motor symptoms such as postural instability, rigidity, and bradykinesia, but also by nonmotor symptoms such as those induced by a concomitant autonomic dysfunction (21, 29, 70). The causes leading to autonomic dysfunction in patients with PD are related to the presence of Lewis bodies not only in preganglionic structures of sympathetic and vagal autonomic nervous systems, but also in postganglionic sympathetic ganglia (63). Additional conditions concurring with autonomic dysfunction include cardiac sympathetic denervation, extracardiac noradrenergic denervation, and arterial baroreflex failure (18–20). The impairment of vagal control can be detected by spectral analysis of HP variability in terms of a reduced magnitude of respiratory sinus arrhythmia (22, 25), by an altered circadian rhythm (33), and by a blunted response to an orthostatic stimulus (2). Impairment of sympathetic regulation can be assessed by spectral analysis of SAP variability in terms of a reduced low-frequency power and by the inability to raise the amplitude of the low-frequency oscillations during head-up tilt (2).

The issue of early recognition of the abnormalities of vagal and sympathetic controls in patients with PD is crucial. Indeed, early treatment of these patients might reduce arterial pressure dysregulation, thus preventing the effects of both hypotensive and hypertensive episodes on cardiovascular and central nervous systems. Patients with PD without orthostatic hypotension or symptoms of orthostatic intolerance were still able to significantly decrease HP and maintain unchanged SAP during head-up tilt. Among time domain indexes solely SAP variance suggests an abnormal vascular control: indeed, SAP variance did not increase during the head-up tilt. Complexity indexes derived from both short-term HP and SAP variabilities were able to detect the early anomaly of cardiovascular control. Indeed, the initial impairment of cardiac regulation was detected by the missed decrease in HP complexity during head-up tilt in the group of patients with PD. In this population, head-up tilt was unable to induce a vagal withdrawal, thus leaving unmodified the HP complexity as a likely result of both the damage to vagal control and the inability of the cardiovascular regulatory mechanisms to shift sympatho-vagal balance toward sympathetic predominance. Early impairment of vascular regulation was detected by the larger value of SAP complexity both at B and at T75. It appears that SAP complexity analysis was able to detect early abnormalities in vascular control just at B without the application of any external stimulus or experimental maneuver. We speculate that the early sympathetic denervation that characterizes patients with PD is already sufficient to prevent synchronization of vasomotor activities of peripheral districts even in the absence of any significant effect on SAP mean maintained at a normal level by an operating baroreflex (2). As a consequence of the lack of synchronization of vasomotion of peripheral districts, the magnitude in SAP changes (i.e., the SAP variance) remained low in patients with PD during head-up tilt, while it increased in HC subjects.

Complexity of SAP variability is increased in patients with PD without modification of HP complexity. Findings from this study agree with the view that the complexity of the dynamical

changes in cardiovascular variables reflects the action of physiological control mechanisms and complexity indexes might be helpful in assessing the state of cardiovascular control (16, 43). This study disagrees with the stereotype that disease is characterized by a loss of physiological complexity (15) when the physiological complexity is ranked according to the scale providing at its extremes a fractal process, as an example of high physiological complexity, and white noise or a strictly periodic signal, as examples of null physiological complexity. Here, the PD group was characterized by an increase in dynamical complexity, and this increase cannot be explained in terms of a breakdown in physiological complexity toward a more random behavior because the power spectrum of HP and SAP variabilities in the PD group is different from that of a white random noise (i.e., evident spectral peaks are still detectable).

HP and SAP complexity indexes provide complementary information. All the findings reported in this study suggest that complexity indexes derived from short-term HP and SAP variabilities provide complementary information. Even the observation that HP complexity is more related to vagal activity and SAP complexity is more related to sympathetic activity supports this conclusion. However, the most straightforward evidences are as follows: *1*) the increase in SAP complexity in the absence of any variation in HP complexity after CL; *2*) the decrease in HP complexity after AT without a significant change in SAP complexity; and *3*) the lack of changes in SAP complexity during sympathetic activation induced by the graded, head-up tilt protocol in the presence of a progressive decrease in HP complexity. Therefore, this study strongly recommends the joint assessment and comparison of complexity indexes derived from both short-term HP and SAP variabilities to derive a deeper view about cardiovascular control.

Perspective and significance. This study provides a simple index (i.e., $MSPE_{AR}$) to assess the complexity of short HP and SAP variabilities based on the AR model, and demonstrates that $MSPE_{AR}$ is equivalent to a more advanced approach based on the MAR model. The proposed index might be a valid alternative to more sophisticated methods for the evaluation of complexity on the basis of fractal analysis. Indeed, the index is more reliable in the presence of short series, thus triggering applications over arterial pressure variability recordings and enlarging the field of application of complexity analysis. In addition, the study proves that complexity analysis of the HP and SAP series provides different information about the cardiovascular control and links HP and SAP complexity indexes to different physiological control mechanisms. The study also suggests that complexity indexes might be fruitfully utilized for early detection of the impairment of the autonomic nervous system in pathological populations, thus prompting for a clinical application of complexity analysis. Future studies should be focused on the generalization of this approach by introducing nonlinear terms in the multivariate model (6, 50) or by using model-free approaches based, for example, on *k*-nearest neighbors (13), thus accounting for possible nonlinear mechanisms overlooked by the present linear approach. The proposed analysis of complexity, on the basis of an assessment of the variance of the unpredictable part, can be complemented by decomposing the variance of the predictable part of HP (or SAP) into contributions due to each source (i.e., HP, SAP, and R) (48) with the aim of clarifying the strength of the casual interactions and relations. Because stationarity is a prerequisite for this analysis, future studies should clarify the contribution of nonstationarities to the variance of the unpredictable part and, consequently, to the estimation of complexity indexes.

APPENDIX

MAR and AR model-based assessment of complexity. Given the series HP = {HP(n), $n = 1, \ldots, N$}, SAP = {SAP(n), $n = 1, \ldots, N$}, and R = {R(n), $n = 1, \ldots, N$} where n is the progressive cardiac beat counter and N is the series length, the series was first normalized, thus obtaining an hp, sap, and r series with zero mean and unit variance. Interactions among the series were described according to the MAR model (52), $y(n) = A(z) \cdot y(n) + w(n)$, where $y = |hp\ sap\ r|^T$ is the column vector of the signals (the symbol ^{T} indicates the transpose operator), $w = |w_{hp}\ w_{sap}\ w_r|^T$ is the column vector of uncorrelated white noises, and A(z) is the 3×3 matrix of the finite impulse response filters describing the relations among signals, and z is the forward shift operator [i.e., $y(n + 1) = z \cdot y(n)$] (52). The elements of A(z) on the main diagonal describe the dependence of hp, sap, and r on their own q_{MAR} past values, and the elements outside the main diagonal of A(z) describe the dependence of a series on present and q_{MAR} past values of a different one. The immediate action of r on sap, r on hp, and sap on hp was allowed, thus accounting for a potential fast vagal reflex (12, 41). One beat delay was introduced from hp to r (3), from sap to r, and from hp to sap, thus preventing the presence of loops without delay and making it possible to identify the model parameters (5). The coefficients of the finite impulse response filters of A(z) were estimated directly from the hp, sap, and r series using the Cholesky decomposition method (27). The model order, q_{MAR}, was optimized in the range of 4 to 16 according to the Akaike figure of merit for multivariate processes (1). After model coefficients were identified and the best model order was selected, A(z) was completely determined as $\hat{A}(z)$, thus allowing the prediction of y, $\hat{y}$, by filtering y(n) with $\hat{A}(z)$ as $\hat{y}(n) = \hat{A}(z) \cdot y(n)$. Defining the prediction error as the difference between y(n) and $\hat{y}(n)$ allowed the $MSPE_{MAR}$ of hp, sap, and r to be computed. Because the series were normalized to have unit variance, $MSPE_{MAR}$ ranged from 0 to 1. The larger the $MSPE_{MAR}$, the larger the unpredictability and the dynamical complexity of the series, and the smaller its predictability and regularity. $MSPE_{MAR}$ was compared with that derived from a univariate AR model (i.e., $MSPE_{AR}$). The AR model was again described as $y(n) = A(z) \cdot y(n) + w(n)$ (52), but where y represents hp (or sap) and A(z) represents the finite impulse response filter, and it exclusively describes the autodependence of y(n) on its own q_{AR} past values (cross-dependences were prevented). The coefficients of A(z) were estimated using the Levinson-Durbin recursion (27) procedure and the best model order, q_{AR}, was selected in the range of 4 to 16 according to the Akaike figure of merit for univariate processes (1). After the estimation of the model coefficients, the best prediction can be again computed as $\hat{y}(n) = \hat{A}(z) \cdot y(n)$, thus allowing the evaluation of $MSPE_{AR}$.

GRANTS

Support for this study was provided by Telethon Grant GGP09247 to A. Porta. A. M. Catai was financially supported by Pos-Doutorado No Exterior Grant 200717/2008-1 from the National Council for Scientific and Technological Development (CNPq) of Brazil, and A. C. M. Takahashi was supported by Grant PDEE/1228/08-0 from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior and by Grant 06/52860-0 from Fundação de Amparo a Pesquisa do Estado de São Paolo.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: A.P. conception and design of research; A.P., P.C., V.B., T.B., A.M., and A.C. analyzed data; A.P., P.C., M.D.R., V.B., T.B.,

A.M., and L.Q. interpreted results of experiments; A.P. and V.B. prepared figures; A.P. drafted manuscript; A.P., P.C., M.D.R., V.B., T.B., A.M., A.C.T., E.T., N.M., A.M.C., F.B., R.F., A.C., and L.Q. edited and revised manuscript; A.P., P.C., M.D.R., V.B., T.B., A.M., A.C.T., E.T., N.M., A.M.C., F.B., R.F., A.C., and L.Q. approved final version of manuscript; A.C.T., E.T., N.M., A.M.C., F.B., R.F., A.C., and L.Q. performed experiments.

REFERENCES

1. **Akaike H.** A new look at the statistical novel identification. *IEEE Trans Automat Contr* 19: 716–723, 1974.
2. **Barbic F, Perego F, Canesi M, Gianni M, Biagiotti S, Costantino G, Pezzoli G, Porta A, Malliani A, Furlan R.** Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. *Hypertension* 49: 120–126, 2007.
3. **Baselli G, Cerutti S, Badilini F, Biancardi L, Porta A, Pagani M, Lombardi F, Rimoldi O, Furlan R, Malliani A.** Model for the assessment of heart period and arterial pressure variability interactions and respiratory influences. *Med Biol Eng Comput* 32: 143–152, 1994.
4. **Baselli G, Porta A, Pagani M.** Coupling arterial windkessel with peripheral vasomotion: modeling the effects on low-frequency oscillations. *IEEE Trans Biomed Eng* 53: 53–64, 2006.
5. **Baselli G, Porta A, Rimoldi O, Pagani M, Cerutti S.** Spectral decomposition in multichannel recordings based on multivariate parametric identification. *IEEE Trans Biomed Eng* 44: 1092–1101, 1997.
6. **Batzel J, Baselli G, Mukkamala R, Chon KH.** Modelling and disentangling physiological mechanisms: linear and nonlinear identification techniques for analysis of cardiovascular regulation. *Philos Transact A Math Phys Eng Sci* 367: 1377–1391, 2009.
7. **Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bar KJ.** Altered diurnal autonomic variation and reduced vagal information flow in acute schizophrenia. *Clin Neurophysiol* 117: 2715–2722, 2006.
8. **Butler GC, Yamamoto Y, Hughson RL.** Fractal nature of short-term systolic BP and HR variability during lower body negative pressure. *Am J Physiol Regul Integr Comp Physiol* 267: R26–R33, 1994.
9. **Castiglioni P, Parati G, di Rienzo M, Carabalona R, Cividjian A, Quintin L.** Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. *J Physiol* 589: 355–369, 2011.
10. **Cohen MA, Taylor JA.** Short-term cardiovascular oscillations in man: measuring and modelling the physiologies. *J Physiol* 542: 669–683, 2002.
11. **Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KUO, Eckberg DL.** Human responses to upright tilt: a window on central autonomic integration. *J Physiol* 517: 617–628, 1999.
12. **Eckberg DL.** Temporal response patterns of the human sinus node to brief carotid baroreceptor stimuli. *J Physiol* 258: 769–782, 1976.
13. **Faes L, Porta A, Nollo G.** Mutual nonlinear prediction as a tool to evaluate coupling strength and directionality in bivariate time series: comparison among different strategies based on k nearest neighbors. *Phys Rev E Stat Nonlin Soft Matter Phys 78 (2 Pt 2)*: 026201, 2008.
14. **Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, Robertson D, Malliani A, Moscheda-Garcia R.** Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. *Circulation* 101: 886–892, 2000.
15. **Goldberger AL.** Fractal variability versus pathologic periodicity: complexity loss and stereotypy in disease. *Perspect Biol Med* 40: 543–561, 1997.
16. **Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PCh Peng CK, Stanley HE.** Fractal dynamics in physiology: alterations with disease and age. *Proc Natl Acad Sci U S A* 99, Suppl 1: 2466–2472, 2002.
17. **Goldberger AL, Peng CK, Lipsitz LA.** What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging* 23: 23–26, 2002.
18. **Goldstein DS.** Dysautonomia in Parkinson's disease: neurocardiological abnormalities. *Lancet Neurol* 2: 669–676, 2003.
19. **Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST.** Orthostatic hypotension from sympathetic denervation in Parkinson's disease. *Neurology* 58: 1247–1255, 2002.
20. **Goldstein DS, Holmes CS, Li ST, Bruce SR, Metman LV, Cannon RO.** Cardiac sympathetic denervation in Parkinson disease. *Ann Intern Med* 133: 338–347, 2000.
21. **Gross M, Bannister R, Godwin-Austen R.** Orthostatic hypotension in Parkinson's disease. *Lancet* 1: 174–176, 1972.
22. **Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV.** Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 70: 305–310, 2001.
23. **Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA.** Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am J Physiol Regul Integr Comp Physiol* 271: R1078–R1084, 1996.
24. **Javorka M, Trunkvalterova Z, Tonhajzerova I, Javorkova J, Javorka K, Baumert M.** Short-term heart rate complexity is reduced in patients with type 1 diabetes mellitus. *Clin Neurophysiol* 119: 1071–1081, 2008.
25. **Kallio M, Haapaniemi TH, Turkka J, Suominen K, Tolonen U, Sotaniemi KA, Heikkila VP, Myllyla VV.** Heart rate variability in patients with untreated Parkinson disease. *Eur J Neurol* 7: 667–672, 2000.
26. **Kaplan DT, Furman MI, Pincus SM, Ryan SM, Lipsitz LA, Goldberger AL.** Aging and the complexity of cardiovascular dyanmics. *Biophys J* 59: 945–949, 1991.
27. **Kay SM.** *Modern spectral analysis: theory and application*. Englewood Cliffs, NJ: Prentice-Hall, 1989.
28. **Koepchen HP.** Physiology of rhythms and control systems: an integrative approach. In: *Rhythms in physiological systems,* edited by Haken H and Koepchen HP. Berlin: Springer-Verlag, 1991, p. 3–20.
29. **Linden D, Diehl RR, Berlit P.** Sympathetic cardiovascular dysfunction in long-standing idiopathic Parkinson's disease. *Clin Auton Res* 7: 311–314, 1997.
30. **Malliani A, Pagani M, Lombardi F, Cerutti S.** Cardiovascular neural regulation explored in the frequency domain. *Circulation* 84: 482–492, 1991.
31. **Montano N, Gnecchi-Ruscone T, Porta A, Lombardi F, Pagani M, Malliani A.** Power spectrum analysis of heart rate variability to assess changes in sympatho-vagal balance during graded orthostatic tilt. *Circulation* 90: 1826–1831, 1994.
32. **Moody G, Mark R, Bump M, Weinstein J, Berman A, Mietus J, Goldberger AL.** Clinical validation of the ECG-derived respiration (EDR) technique. *Comput Cardiol* 13: 507–510, 1986.
33. **Niwa F, Kuriyama N, Nakagawa M, Imanishi J.** Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. *Auton Neurosci* 165: 195–200, 2011.
34. **Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A.** Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 59: 178–193, 1986.
35. **Parlow J, Viale JP, Annat G, Hughson RL, Quintin L.** Spontaneous cardiac baroreflex in humans: comparison with drug-induced responses. *Hypertension* 25: 1058–1068, 1995.
36. **Paton JFR, Boscan P, Pickering AE, Nalivaiko E.** The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. *Brain Res Rev* 49: 555–565, 2005.
37. **Pikkujämsä SM, Mäkikallio TH, Sourander LB, Räihä IJ, Puukka P, Skyttä J, Peng CK, Goldberger AL, Huikuri HV.** Cardiac interbeat interval dynamics from childhood to senescence. Comparison of conventional and new measures based on fractals and chaos theory. *Circulation* 100: 393–399, 1999.
38. **Pincus SM.** Greater signal regularity may indicate increased system isolation. *Math Biosci* 122: 161–181, 1994.
39. **Pincus SM, Cummins TR, Haddad GG.** Heart rate control in normal and aborted-SIDS infants. *Am J Physiol* 33: R638–R646, 1993.
40. **Porta A, Baselli G, Guzzetti S, Pagani M, Malliani A, Cerutti S.** Prediction of short cardiovascular variability signals based on conditional distribution. *IEEE Trans Biomed Eng* 47: 1555–1564, 2000.
41. **Porta A, Baselli G, Rimoldi O, Malliani A, Pagani M.** Assessing baroreflex gain from spontaneous variability in conscious dogs: role of causality and respiration. *Am J Physiol Heart Circ Physiol* 279: H2558–H2567, 2000.
42. **Porta A, Catai AM, Takahashi ACM, Magagnin V, Bassani T, Tobaldini E, van de Borne P, Montano N.** Causal relationships between heart period and systolic arterial pressure during graded head-up tilt. *Am J Physiol Regul Integr Comp Physiol* 300: R378–R386, 2011.
43. **Porta A, di Rienzo M, Wessel N, Kurths J.** Addressing the complexity of cardiovascular regulation. *Philos Transact A Math Phys Eng Sci* 367: 1215–1218, 2009.
44. **Porta A, Faes L, Masé M, D'Addio G, Pinna GD, Maestri R, Montano N, Furlan R, Guzzetti S, Nollo G, Malliani A.** An integrated approach based on uniform quantization for the evaluation of complexity of short-

term heart period variability: application to 24 h Holter recordings in healthy and heart failure humans. *Chaos* 17: 015117, 2007.
45. **Porta A, Gnecchi-Ruscone T, Tobaldini E, Guzzetti S, Furlan R, Montano N.** Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt. *J Appl Physiol* 103: 1143–1149, 2007.
46. **Porta A, Guzzetti S, Furlan R, Gnecchi-Ruscone T, Montano N, Malliani A.** Complexity and non linearity in short-term heart period variability: comparison of methods based on local non linear prediction. *IEEE Trans Biomed Eng* 54: 94–106, 2007.
47. **Porta A, Tobaldini E, Guzzetti S, Furlan R, Montano N, Gnecchi-Ruscone T.** Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. *Am J Physiol Heart Circ Physiol* 293: H702–H708, 2007.
48. **Porta A, Tobaldini E, Gnecchi-Ruscone T, Montano N.** RT variability unrelated to heart period and respiration progressively increases during graded head-up tilt. *Am J Physiol Heart Circ Physiol* 298: H1406–H1414, 2010.
49. **Richman JS, Moorman JR.** Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 278: H2039–H2049, 2000.
50. **Riedl M, Suhrbier A, Malberg H, Penzel T, Bretthauer G, Kurths J, Wessel N.** Modeling the cardiovascular system using a nonlinear additive autoregressive model with exogenous input. *Phys Rev E Stat Nonlin Soft Matter Phys* 78 (1 *Pt* 1), 011919, 2008.
51. **Schulz S, Koschke M, Bar KJ, Voss A.** The altered complexity of cardiovascular regulation in depressed patients. *Physiol Meas* 31: 303–321, 2010.
52. **Soderstrom T, Stoica P.** *System Identification.* Englewood Cliffs, NJ: Prentice Hall, 1988.
53. **Takahashi ACM, Porta A, Melo RC, Quiterio RJ, da Silva E, Borghi-Silva A, Tobaldini E, Montano N, Catai AM.** Aging reduces complexity of heart rate variability assessed by conditional entropy and symbolic analysis. *Intern Emer Med* 7:229–235: 2012.
54. **Takens F.** Detecting strange attractors in fluid turbulence. In: *Lecture notes in mathematics,* edited by Rand D and Young LS. Berlin: Springer, 1981, p. 366–381.
55. **Tan CO, Cohen MA, Eckberg DL, Taylor JA.** Fractal properties of human heart period variability: physiological and methodological implications. *J Physiol* 587: 3929–3941, 2009.
56. **Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.** Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 93: 1043–1065, 1996.
57. **Toader E, Cividjian A, Rentero N, McAllen RM, Quintin L.** Cardioinhibitory actions of clonidine assessed by cardiac vagal motoneuron recordings. *J Hypertens* 26: 1169–1180, 2008.
58. **Tulppo MP, Hughson RL, Mäkikallio TH, Juhani Airaksinen KE, Seppänen T, Huikuri HV.** Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. *Am J Physiol Heart Circ Physiol* 280: H1081–H1087, 2001.
59. **Tulppo MP, Kiviniemi AM, Hautala AJ, Kallio M, Seppänen T, Mäkikallio TH, Huikuri HV.** Physiological background of the loss of fractal heart rate dynamics. *Circulation* 112: 314–319, 2005.
60. **Tulppo MP, Mäkikallio TH, Seppänen T, Shoemaker K, Tutungi E, Hughson RL, Huikuri HV.** Effects of pharmacological adrenergic and vagal modulation on fractal heart rate dyanmics. *Clin Physiol* 21: 515–523, 2001.
61. **Turianikova Z, Javorka K, Baumert M, Calkovska A, Javorka M.** The effect of orthostatic stress on multiscale entropy of heart rate and blood pressure. *Physiol Meas* 32: 1425–1437, 2011.
62. **Valencia JF, Porta A, Vallverdù M, Clarià F, Baranowski R, Orlowska-Baranowska E, Caminal P.** Refined multiscale entropy: application to 24-h Holter recordings of heart period variability in healthy and aortic stenosis subjects. *IEEE Trans Biomed Eng* 56: 2202–2213, 2009.
63. **van Dijk JG, Haan J, Zwinderman K, Kremer B, van Hilten BJ, Roos RA.** Autonomic nervous system dysfunction in Parkinson's disease: relation with age, medication, duration, and severity. *J Neurol Neurosurg Psychiatry* 56: 1090–1095, 1993.
64. **Viola AU, Tobaldini E, Chellappa SL, Casali KR, Porta A, Montano N.** Short-term complexity of cardiac autonomic control during sleep: REM as a potential risk factor for cardiovascualr system in aging. *PLos One* 6: e19002, 2011.
65. **Voss A, Baier V, Schulz S, Bar KJ.** Linear and nonlinear methods for analyses of cardiovascualr variability in bipolar disorders. *Bipolar Disord* 8: 441–452, 2006.
66. **Voss A, Kurths J, Kleiner HJ, Witt A, Wessel N, Saparin P, Osterziel KJ, Schurath R, Dietz R.** The application of methods of nonlinear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovasc Res* 31: 419–433, 1996.
67. **Wessel N, Ziehmann C, Kurths J, Meyerfeldt U, Schirdewan A, Voss A.** Short-term forecasting of life-threatening cardiac arrhythmias based on symbolic dynamics and finite-time growth rates. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics* 61: 733–739, 2000.
68. **Yamamoto Y, Hughson RL.** On the fractal nature of heart rate variability in humans: effects of data length and beta-adrenergic blockade. *Am J Physiol Regul Integr Comp Physiol* 266: R40–R49, 1994.
69. **Yamamoto Y, Nakamura Y, Sato H, Yamamoto M, Kato K, Hughson RL.** On the fractal nature of heart rate variability in humans: effects of vagal blockade. *Am J Physiol Regul Integr Comp Physiol* 269: R830–R837, 1995.
70. **Ziemssen T, Reichmann H.** Cardiovascular autonomic dysfunction in Parkinson's disease. *J Neurol Sci* 289: 74–80, 2010.