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Model-free causality analysis of cardiovascular variability detects the amelioration of autonomic control in Parkinson's disease patients undergoing mechanical stimulation

Tito Bassani[1], Vlasta Bari[2], Andrea Marchi[3], Stefano Tassin[4], Laura Dalla Vecchia[5], Margherita Canesi[6], Franca Barbic[1,7], Raffaello Furlan[1,7] and Alberto Porta[8,9]

[1] Department of Internal Medicine, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[2] Department of Cardiothoracic-Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, Milan, Italy
[3] Department of Anesthesia and Intensive Care Unit, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[4] Department of Research and Development, Ecker Technologies Sagl, Lugano, Switzerland
[5] IRCCS Fondazione Salvatore Maugeri, Istituto Scientifico di Milano, Milan, Italy
[6] Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy
[7] Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy
[8] Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[9] IRCCS Galeazzi Orthopedic Institute, Milan, Italy

E-mail: alberto.porta@unimi.it

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Abstract

We tested the hypothesis that causality analysis, applied to the spontaneous beat-to-beat variability of heart period (HP) and systolic arterial pressure (SAP), can identify the improvement of autonomic control linked to plantar mechanical stimulation in patients with Parkinson's disease (PD). A causality index, measuring the strength of the association from SAP to HP variability, and derived according to the Granger paradigm (i.e. SAP causes HP if the inclusion of SAP into the set of signals utilized to describe cardiovascular interactions improves the prediction of HP series), was calculated using both linear model-based (MB) and nonlinear model-free (MF) approaches. Univariate HP and SAP variability indices in time and frequency domains, and

bivariate descriptors of the HP–SAP variability interactions were computed as well. We studied ten PD patients (age range: 57–78 years; Hoehn-Yahr scale: 2–3; six males, four females) without orthostatic hypotension or symptoms of orthostatic intolerance and 'on-time' according to their habitual pharmacological treatment. PD patients underwent recordings at rest in a supine position and during a head-up tilt before, and 24 h after, mechanical stimulation was applied to the plantar surface of both feet. The MF causality analysis indicated a greater involvement of baroreflex in regulating HP–SAP variability interactions after mechanical stimulation. Remarkably, MB causality and more traditional univariate or bivariate techniques could not detect changes in cardiovascular regulation after mechanical stimulation, thus stressing the importance of accounting for nonlinear dynamics in PD patients. Due to the higher statistical power of MF causality we suggest its exploitation to monitor the baroreflex control improvement in PD patients, and we encourage the clinical application of the Granger causality approach to evaluate the modification of the autonomic control in relation to the application of a pharmacological treatment, a rehabilitation procedure or external intervention.

Keywords: Granger causality, heart rate variability, baroreflex sensitivity, head-up tilt, Parkinson disease, autonomic nervous system, cardiovascular control

Introduction

Although Parkinson's disease (PD) patients are characterized primarily by motor impairment, alterations of autonomic control are detectable in 10%–40% of cases (Linden *et al* 1997, Ziemssen and Reichmann 2010). It was observed that plantar mechanical or electrical stimulation improves gait (Jenkins *et al* 2009, Novak and Novak 2006, De Nunzio *et al* 2010, Barbic *et al* 2014) and autonomic control (Barbic *et al* 2014). These results stress the role played by peripheral sensory-motor afferents in promoting disability in PD patients (Pratorius *et al* 2003).

In PD patients, autonomic impairment can be quantified through the computation of non-invasive indices derived from spontaneous variability of the heart period (HP) and systolic arterial pressure (SAP) (Kallio *et al* 2000, Haapaniemi *et al* 2001, Barbic *et al* 2007). Among all possible markers, the most frequently exploited ones are the HP power in the high frequency (HF) band, (from 0.15 to 0.5 Hz) (Akselrod *et al* 1981, Task Force 1996), the SAP power in the low frequency (LF) band, (from 0.03 to 0.15 Hz) (Pagani *et al* 1986) and the baroreflex sensitivity assessed as the square root of the ratio of the HP to SAP variability in LF and HF bands (Pagani *et al* 1988, Laude *et al* 2004). Recently, it was suggested that causality indices, quantifying the strength of the relation from SAP to HP variability as a measure of the degree of involvement of baroreflex in regulating HP, can be used fruitfully to describe the autonomic response to experimental maneuvers (Porta *et al* 2011) and pharmacological challenges (Porta *et al* 2013). We hypothesize that causality analysis may provide information complementary to that derived from traditional cardiovascular variability indices in PD patients, and may be exploited to monitor changes of the autonomic regulation linked to plantar mechanical stimulation.

The aim of the present study is to test the capability of causality analysis applied to HP and SAP variabilities to detect changes of autonomic control in PD patients after plantar mechanical stimulation. A linear model-based (MB) approach and a nonlinear model-free (MF) method for the assessment of Granger causality were applied. While the MB approach

is widely used in several fields of science (e.g. neuroscience and finance), and is based upon a traditional multivariate linear regression model (Granger 1969), more recently MF techniques have been devised to deal with the possible presence of nonlinear dynamics, and to prevent the dependence of the results upon the adopted model structure (Chen *et al* 2004, Faes *et al* 2011, Vicente *et al* 2011, Porta *et al* 2014). The performance of Granger causality approaches to detect the modification of the autonomic regulation induced by mechanical stimulation was compared to the capability of more standard, widely utilized, methods in time and frequency domains (Task Force 1996, Laude *et al* 2004). A gravitational stimulus was exploited to solicit baroreflex control before and after plantar mechanical stimulation.

Methods

Study population

The data belong to a recently built database, designed to assess the effects of plantar mechanical stimulation on cardiovascular control in PD patients (Barbic *et al* 2014).

We considered ten PD patients (mean age: 66 $\pm$ 6 years; range: 57–78 years; six males, four females). They were enrolled at the PD Center of Istituti Clinici di Perfezionamento, Milan, Italy. All patients were free from orthostatic hypotension or symptoms of orthostatic intolerance, and they were characterized by a moderate to severe motor impairment (Hoehn-Yahr scale 2–3). The mean duration of the disease was 13 $\pm$ 4 years and the Unified PD rating scale was 25 $\pm$ 14. Subjects had a similar disorder duration, and were free from any other diseases based on their clinical history, symptoms, physical examination and routine tests. Patients were studied 'on-time' according to their habitual pharmacological treatment.

Experiment protocol

All patients gave their written informed consent. The protocol adhered to the principles of the Declaration of Helsinki and it was approved by the Bolognini Hospital Institutional Review Board (no. R-156). Electrocardiogram (lead II), non-invasive arterial blood pressure (Finapress 2300, Ohmeda, Englewood, CO, USA) and respiratory activity via a thoracic belt (Marrazza, Monza, Italy) were recorded. Arterial pressure was measured from the middle finger of the left hand, which was maintained at the level of the heart by fixing the subject's arm to the thorax while in the upright position. All the signals were sampled by an analogical-to-digital board (AT-MIO-16-E2, National Instruments, Austin, TX, USA). The sampling frequency was 300 Hz. Recordings were carried out at rest in a supine position (REST) and during a head-up tilt with a tilt table inclination of 75° (TILT). Each experimental session lasted 20 min. REST was preceded by a period of stabilization in a supine position and TILT always followed REST. The arterial pressure signal was cross-calibrated in each session with the use of a measure provided by a sphygmomanometer at the onset of REST. During the entire protocol the subjects breathed spontaneously, but they were not allowed to talk. Patients were recorded before (PRE) and 24 h after (POST) mechanical stimulation. The mechanical stimulation consisted of the application of pressure at two specific skin points over the plantar surface of both feet. The sites of the stimulation corresponded to the tip of the hallux and the first metatarsal joint of the big toe's lower plantar surface. Pressure was applied using a steel stick with a smooth 2 mm diameter tip, for 6 s at each of the two sites on both feet. The imposed pressure was 0.58 $\pm$ 0.04 Kg mm^{-2} and was continuously monitored via a dynamometer connected to the steel stick. The procedure was repeated four times for every

subject, so the overall stimulation time was less than 2 min. More details on the stimulation procedure and experimental protocol can be found in (Barbic *et al* 2014).

Extraction of the beat-to-beat variability series

The *R*-wave apex was located over the electrocardiogram using parabolic interpolation. The HP was approximated as the time distance between two consecutive *R*-wave peaks. The ith SAP, SAP(i), was assessed as the maximum arterial blood pressure inside the ith HP, HP(i). The respiratory series (RESP) was obtained by sampling the respiratory activity signal in correspondence with the *R*-wave peak. The ith RESP, RESP(i), was taken at the first *R*-peak delimiting HP(i). All signals were manually edited to avoid artifacts. HP $= \{\text{HP(i)}, i = 1, \ldots, N\}$, SAP $= \{\text{SAP(i)}, i = 1, \ldots, N\}$ and RESP $= \{\text{RESP(i)}, i = 1, \ldots, N\}$ were extracted on a beat-to-beat basis, where N is the series length. N was set to 250, thus analyzing recordings of a few minutes and focusing short-term cardiovascular control (Task Force 1996). The sequences were randomly selected from the entire series during REST and TILT. The stationarity of the selected sequence was tested according to (Magagnin *et al* 2012) over the original series after linear detrending. If the test for the steadiness of mean and variance was not fulfilled, a new random selection was carried out until the fulfillment of the prerequisites for restricted weak stationarity (Magagnin *et al* 2012). Synchronous stationary sequences of HP, SAP and RESP values were always found. The mean and 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.

Traditional variability indices

We calculated the absolute power of the HP variability in the HF band (HF_{HP}), expressed in ms^2, as an index of vagal modulation directed to the sinus node (Akselrod *et al* 1981, Task Force 1996) and the absolute power of the SAP variability in the LF band (LF_{SAP}), expressed in mmHg^2, as an index of sympathetic modulation directed to vessels (Pagani *et al* 1986). Power spectral density was estimated via a parametric approach. After modeling HP and SAP series as an autoregressive process, the power spectrum was calculated directly from the coefficients of the autoregressive process that best fitted the series. The parameters of the autoregressive process were estimated via the Levinson–Durbin recursion (Kay and Marple 1981). The model order ranged between 12 and 18 and was optimized according to the Akaike figure of merit (Akaike 1974). The whiteness of the residual was verified in correspondence of the selected model order (Soderstrom and Stoica 1988). The power spectrum was decomposed into components, the sum of which gave the whole power spectrum (Baselli *et al* 1997). The LF and HF powers were obtained as the sum of the powers of all the components, the central frequency of which dropped in the LF and HF bands respectively.

We computed the square root of the ratio of the power of HP on that of SAP in the LF and HF bands as indices of baroreflex sensitivity (α_{LF} and α_{HF}, respectively). α_{LF} and α_{HF} were expressed in ms mmHg^{-1} (Pagani *et al* 1988). The reliability of α_{LF} and α_{HF} was tested by checking, at the frequency of interest, whether HP and SAP series were significantly associated, and whether the phase suggested that HP changes lagged behind SAP variations. These prerequisites were tested according to the calculation of the squared coherence function ($K^2_{HP,SAP}$) and the phase spectrum ($Ph_{HP\text{-}SAP}$). $K^2_{HP,SAP}$ was computed as the ratio of the square HP–SAP cross-spectrum modulus divided by the product of the power spectra of the HP and SAP series. $K^2_{HP,\,SAP}$ ranged between 0 and 1, indicating null and perfect association between HP and SAP series, respectively. As suggested in (De Boer *et al* 1985), $K^2_{HP,\,SAP} > 0.5$ was taken as an indication of the presence of a significant HP–SAP correlation. $Ph_{HP–SAP}$ was the

phase of the HP–SAP cross-spectrum. It was expressed in radians, and ranged between $+\pi$ and $-\pi$ indicating phase opposition. With the convention adopted for the computation of the HP–SAP cross-spectrum, $Ph_{HP-SAP} < 0.0$ suggested that HP changes lagged behind SAP variations. The HP–SAP cross-spectrum was estimated according to a bivariate parametric approach (Baselli *et al* 1997). A fixed model order approach was exploited (Porta *et al* 2000), and here the model order was set to 12. Whiteness of the HP and SAP residuals and their uncorrelation were verified in correspondence of the assigned model order (Soderstrom and Stoica 1988). $K^2_{HP,\,SAP}$ and Ph_{HP-SAP} were sampled in correspondence of the weighted average of the central frequencies detected on the SAP series in the LF and HF bands, where the weights were the powers of the components. These values were labeled as $K^2_{HP,\,SAP}(LF)$, $Ph_{HP-SAP}(LF)$, $K^2_{HP,\,SAP}(HF)$ and $Ph_{HP-SAP}(HF)$.

Granger-causality indices

The Granger causality approach was exploited to quantify the strength of the causal link from SAP to HP, as an indication of the degree of involvement of the baroreflex in governing HP–SAP variability interactions. We defined $\Omega = \{HP, SAP, RESP\}$ as the universe of the knowledge about the system under study. All of the series were first normalized to have a zero mean and unit variance. The strength of a causal relation from SAP to HP (SAP→HP), while accounting for the confounding influences of RESP (Porta *et al* 2012a), was assessed by MB and MF techniques. Both approaches exploited the definition of Granger causality (Granger 1980).

The MB approach describes the HP series by a linear time invariant multivariate regression model, accounting for past values of HP and for current and past values of SAP and RESP (Soderstrom and Stoica 1988, Lutkepohl 2005). The optimal model order was chosen according to the extension of the Akaike figure of merit for the multivariate process (Baselli *et al* 1997). The whiteness of the HP residual and its lack of correlation to SAP and RESP were verified in the correspondence of the selected model order (Soderstrom and Stoica 1988). As a measure of the ability of the estimated model in predicting HP series in Ω, we chose the mean squared prediction error in Ω, indicated as $\lambda^2_{HP|\Omega}$ in the following. Since all of the series were normalized to have a unit variance, $\lambda^2_{HP|\Omega}$ ranged between 0 and 1, where 0 and 1 indicated respectively full predictability and complete unpredictability of HP. The presence of a causal relation from the SAP to HP variability series was assessed by evaluating the fractional improvement in predicting HP series when SAP was included in the $\Omega\backslash SAP = \{HP, RESP\}$ using the causality ratio (CR) (Lutkepohl 2005):

$$CR_{SAP\rightarrow HP}{}^{MB} = \frac{\lambda^2_{HP}\big|_{\Omega} - \lambda^2_{HP}\big|_{\Omega\backslash SAP}}{\lambda^2_{HP}\big|_{\Omega\backslash SAP}} \tag{1}$$

where $\lambda^2_{HP|\Omega\backslash SAP}$ represents the mean squared prediction error assessed in $\Omega\backslash SAP$, and was bounded from 0 to 1 like $\lambda^2_{HP|\Omega}$. Since $\lambda^2_{HP|\Omega}$ and $\lambda^2_{HP|\Omega\backslash SAP}$ were assessed by accounting for RESP, $CR_{SAP\rightarrow HP}{}^{MB}$ was made independent of the direct RESP influences on HP. The same model order chosen in Ω was adopted in $\Omega\backslash SAP$ but the coefficients of the multivariate regression were estimated again. A $CR_{SAP\rightarrow HP}{}^{MB}$ smaller than 0 indicated that the SAP series carried unique information about the future evolution of HP series that could not be derived from any signal in $\Omega\backslash SAP$, and according to the concept of Granger causality (Granger 1980), we stated that the SAP changes Granger-caused HP modifications in Ω.

The MF approach was proposed in (Porta *et al* 2014). This strategy is based on the concept of local predictability (Abarbanel *et al* 1994). Briefly, it relies on the construction of a multivariate embedding space and on the assessment of the degree of unpredictability of the

Table 1. Traditional HP and SAP variability indexes.

	PRE		POST	
	REST	TILT	REST	TILT
μ_{HP} (ms)	887.6 ± 89.0	743.9 ± 96.5*	867.9 ± 128.7	735.5 ± 105.4*
σ^2_{HP} (ms^2)	607.1 ± 687.8	271.2 ± 198.8*	536.6 ± 369.1	308.5 ± 262.1*
HF_{HP} (ms^2)	117.6 ± 191.1	17.2 ± 20.9	124.3 ± 164.2	34.6 ± 55.7
μ_{SAP} (mmHg)	124.8 ± 13.3	119.8 ± 20.6	123.9 ± 12.2	113.4 ± 23.6
σ^2_{SAP} (mmHg^2)	18.7 ± 7.7	28.4 ± 15.6*	24.7 ± 16.4	40.9 ± 32.9*
LF_{SAP} (mmHg^2)	2.4 ± 1.6	7.1 ± 5.3*	3.5 ± 5.2	6.9 ± 7.6*
α_{LF} (ms mmHg^{-1})	10.3 ± 5.7	2.7 ± 0.7	12.7 ± 9.5	4.7 ± 6.8

μ_{HP} = HP mean; σ^2_{HP} = HP variance; HF_{HP} = HF power of the HP series expressed in absolute units; μ_{SAP} = SAP mean; σ^2_{SAP} = SAP variance; LF_{SAP} = LF power of the SAP series expressed in absolute units; α_{LF} = baroreflex sensitivity assessed in LF band; PRE = before mechanical stimulation; POST = 24 h after mechanical stimulation; REST = at rest in supine position; TILT = 75° head-up tilt. The symbol * indicates $p < 0.05$ versus REST within the same treatment (i.e. PRE or POST). Data are reported as the mean ± standard deviation.

HP series in Ω via the k-nearest-neighbor approach. Unlike the MB method, this approach did not make any specific assumptions about the dynamical relationship among the series in Ω (Abarbanel *et al* 1994). The multivariate embedding space was built incrementally by selecting at each step of the procedure the component in Ω that minimized the uncorrelation between the original and predicted series. The global minimum of uncorrelation between the original and predicted series allowed the identification of the optimal multivariate embedding dimension. We utilized equation (1) to assess the presence of a causal relation from SAP to HP where $\lambda_{HP}{}^2|_{\Omega}$ and $\lambda_{HP}{}^2|_{\Omega\backslash SAP}$ were substituted with the uncorrelation between the original and predicted series in Ω and Ω\SAP respectively (Porta *et al* 2014). Like in $\lambda_{HP}{}^2|_{\Omega}$ and $\lambda_{HP}{}^2|_{\Omega\backslash SAP}$, the uncorrelation between the original and predicted series was bounded between 0 and 1, where 0 and 1 indicated respectively full predictability and complete unpredictability of HP. The CR based on MF approach was termed as $CR_{SAP\rightarrow HP}{}^{MF}$. Like in the case of $CR_{SAP\rightarrow HP}{}^{MB}$, $CR_{SAP\rightarrow HP}{}^{MF}$ was made independent of the direct RESP influences on HP. The best multivariate embedding space in Ω\SAP was obtained from the best multivariate embedding space in Ω by discarding components relevant to SAP. A $CR_{SAP\rightarrow HP}{}^{MF}$ smaller than 0 indicated that the SAP series carried a unique information about the future evolution of HP variability that could not be derived from any signal in Ω\SAP, and according to the concept of Granger causality (Granger 1980), we stated that the SAP changes Granger-caused HP modifications in Ω.

Statistical analysis

A two-way repeated measures analysis of variance (one factor repetition, Holm–Sidak test for multiple comparisons) was performed to assess the significance of changes of the calculated parameters within the same experimental condition (i.e. REST or TILT) as a function of the treatment and within the same treatment (i.e. PRE or POST) as a function of the experimental condition. Statistical analysis was carried out using a commercial statistical program (Sigmastat, SPSS, version 3.0.1). All data were expressed as mean ± standard deviation. A $p < 0.05$ was always considered as significant.

Results

Table 1 reports traditional HP and SAP variability indices assessed at REST and during TILT as a function of the treatment (i.e. PRE and POST). The HP mean, μ_{HP}, and the HP variance,

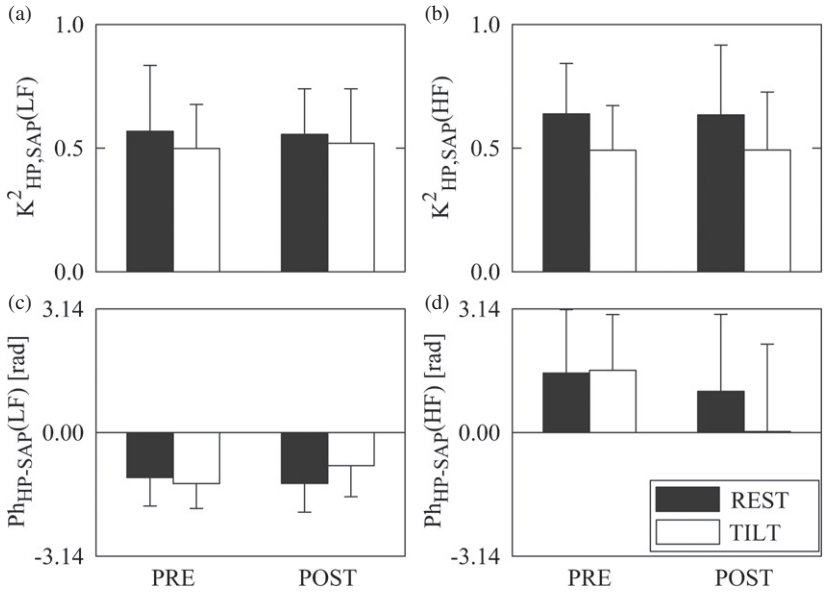

Figure 1. Bar graphs show the squared coherence between HP and SAP series in the LF band, $K^2_{HP,SAP}(LF)$, and in the HF band, $K^2_{HP,SAP}(HF)$, as a function of the treatment (i.e. PRE and POST) in (a) and (b) respectively. Bar graphs of the phase between HP and SAP series in the LF band, $Ph_{HP-SAP}(LF)$, and in the HF band, $Ph_{HP-SAP}(HF)$, as a function of the treatment are reported in (c) and (d) respectively. Values are reported as mean + standard deviation in (a), (b) and (d) and as mean − standard deviation in (c). Mean and standard deviation was computed for all PD patients. Dark bars are relevant to REST, white bars are relevant to TILT.

σ^2_{HP}, were reduced during TILT compared to REST in both PRE and POST. Conversely, the SAP variance, σ^2_{SAP}, and the LF power of the SAP series, LF_{SAP}, increased during TILT compared to REST in both PRE and POST. The SAP mean, μ_{SAP}, and the HF power of the HP series, HF_{HP}, were unaffected by TILT in both PRE and POST. The percentage of the subjects fulfilling the prerequisites for a reliable assessment of baroreflex sensitivity was adequate in the LF band, while it was insufficient in the HF band. Indeed, while the percentage of subjects with both $K^2_{HP,SAP}(LF)>0.5$ and $Ph_{HP-SAP}(LF)<0.0$ was larger than 50% in either experimental condition (i.e. REST and TILT) and either treatment (i.e. PRE and POST), the percentage of subjects featuring both $K^2_{HP,SAP}(HF)>0.5$ and $Ph_{HP-SAP}(HF)<0.0$ was below 30% in either experimental condition and either treatment. Remarkably, the percentage of subjects with both $K^2_{HP,SAP}(HF)>0.5$ and $Ph_{HP-SAP}(HF)<0.0$ was 0% during TILT in PRE. This finding was mainly due to the effect of the large presence of positive Ph_{HP-SAP} especially in the HF band. As a consequence only α_{LF} was reported in table 1. α_{LF} was unaffected by TILT in both PRE and POST. None of the indices reported in table 1 could distinguish PRE from POST, neither at REST nor during TILT.

Figure 1 shows the bar graphs relevant to $K^2_{HP,SAP}(LF)$ (figure 1(a)), $K^2_{HP,SAP}(HF)$ (figure 1(b)), $Ph_{HP-SAP}(LF)$ (figure 1(c)), and $Ph_{HP-SAP}(HF)$ (figure 1(d)). Values were calculated for all PD patients. None of these bivariate indices could differentiate either the experimental condition within the same treatment or the treatment within the same experimental condition.

Figure 2 depicts the bar graphs relevant to CR from SAP to HP, CR_{HP-SAP}, as computed from the MB approach (figure 2(a)) and from the MF method (figure 2(b)). Values were

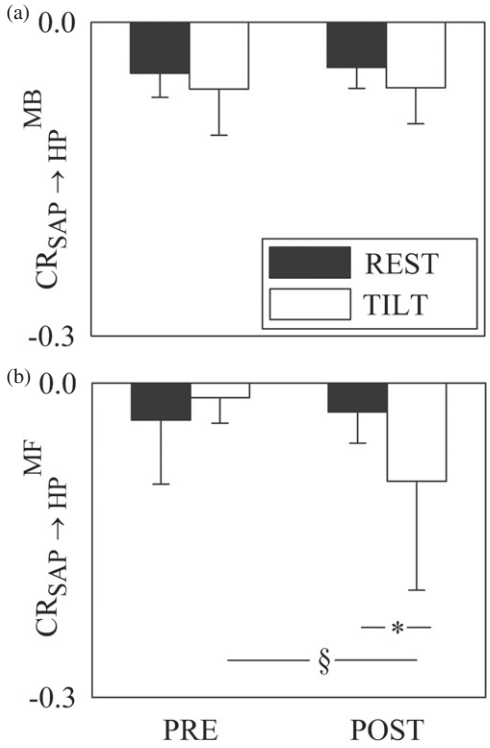

Figure 2. Bar graphs show the CR from SAP to HP calculated according to the linear MB approach ($CR_{SAP \rightarrow HP}^{MB}$) and to the nonlinear MF approach ($CR_{SAP \rightarrow HP}^{MF}$) as a function of the treatment (i.e. PRE and POST) in (a) and (b) respectively. Dark bars are relevant to REST, white bars are relevant to TILT. The symbols § and * indicate a significance difference with $p < 0.05$ when comparing POST to PRE within TILT, and REST to TILT within POST respectively. Values are shown as mean − standard deviation.

calculated for all PD patients. The MB approach could not detect any variation of the degree of association in the temporal direction from SAP to HP (figure 2(a)). Conversely, the $CR_{HP–SAP}$ computed according to the MF approach was significantly more negative in POST than in PRE during TILT (figure 2(b)). In POST the effect of TILT was also detectable by the MF approach (figure 2(b)). Indeed, after mechanical stimulation the $CR_{HP–SAP}$ computed by the MF technique was significantly more negative during TILT than at REST.

Discussion

The main finding of this study is that causality analysis applied to the HP, SAP and RESP series enabled us to detect changes of cardiovascular control after plantar mechanical stimulation in PD patients. Neither univariate nor bivariate traditional analyses could achieve the same result. As an ancillary finding, only the MF causality approach detected modifications of the cardiovascular regulation in PD patients, while the MB causality approach could not.

Traditional variability markers and the effect of plantar mechanical stimulation

Spectral indices of HP and SAP variability were found useful to monitor the modifications of the cardiovascular regulation associated with plantar mechanical stimulation (Barbic *et al*

2014). In the present study, none of the traditional variability indices computed from HP and SAP series were influenced by plantar mechanical stimulation. Indeed, given the experimental condition (i.e. REST or TILT) all indices were similar in PRE and POST. The low statistical power of the spectral indices might be the direct consequence of the small population. Also the modality of the selection of the SAP and HP sequences might have played a role in limiting the statistical power of traditional variability indices. Indeed, here the analysis was based on a random selection of the HP and SAP sequences. This strategy usually increases inter-subject variability and, consequently, reduces the statistical power of the traditional HP and SAP variability indices. However, we adopted this policy because it is fully automatic and repeatable, thus paving the way for a user-independent application of variability tools. Remarkably, a tendency toward an increased amplitude of the SAP and HP changes about their mean values was observed after mechanical stimulation as well as toward an enhanced baroreflex sensitivity. These trends are in keeping with (Barbic *et al* 2014), thus suggesting the potential improvement of cardiovascular control after mechanical stimulation.

Traditional HP and SAP variability parameters could identify the effect of TILT. Indeed, we observed a significant increase of the LF power of the SAP series during TILT. This response to orthostatic stimulus was expected in a PD group without signs of orthostatic intolerance and hypotension (Barbic *et al* 2007) as a likely consequence of the preserved ability to increase sympathetic modulation and/or activity to the vessels during TILT (Cooke *et al* 1999, Furlan *et al* 2000). This study confirmed previously reported results in PD patients undergoing TILT. Indeed, in agreement with (Barbic *et al* 2007) we confirmed that the HF power of the HP series and cardiac baroreflex sensitivity was unmodified by TILT. An impairment of the vagal control to the sinus node with consequent abnormal HP responses to SAP changes might explain these findings.

MF causality and the effect of plantar mechanical stimulation

The increase of the strength of the casual relation from the SAP to HP series observed after plantar mechanical stimulation using the MF causality approach can be considered a sign of improvement of cardiovascular control. Indeed, the larger correlation in the temporal direction from SAP to HP after mechanical stimulation indicates a more relevant role of baroreflex in governing HP–SAP variability interactions compared to PRE. The possible mechanism underlying this positive effect on cardiovascular regulation might be related to the solicitation of the somatosensory afferent pathway imposed by the plantar mechanical stimulation (Barbic *et al* 2014). Since this afferent circuit projects onto the brain stem structures involved in cardiovascular homeostasis (Terui and Koizumi 1984, Toney and Mifflin 2000), the activation of a somatosensory afferent pathway might influence the activity of the cardiovascular regulatory centers. However, it is unclear why this stimulation improves cardiovascular control in PD patients. Notably, this amelioration was observed only during TILT because this condition evokes a major involvement of the causal pathway from SAP to HP to counteract the effect of the gravitational stimulus (Porta *et al* 2011, 2012b), thus unveiling the improvement of this regulatory mechanism.

MB causality, phase analysis and the effect of plantar mechanical stimulation

Differing from the MF approach, the MB approach could not identify any improvement of cardiovascular control after mechanical stimulation. Indeed, the strength of the causal relation from the SAP to HP series was similar in PRE and POST, regardless of the experimental condition. We hypothesize that in PD patients, without episodes of orthostatic intolerance

or hypotension, the relation from SAP to HP variability was characterized by relevant nonlinearities. The inability of the MB approach to deal with nonlinear dynamics might explain such a lack in interpreting HP–SAP causality. As a confirmation of this observation, the CR from SAP to HP, assessed according to the MB approach during TILT in POST, was significantly less negative than that computed according to the MF method, thus indicating that the MB approach is less powerful in predicting HP due to the introduction of SAP variability than in the MF approach.

We confirm the inability of phase analysis to assess causality (Porta *et al* 2011). In addition to the well-known limitation in converting phases into delays or advancements due to phase multiples, phase values had a large variability, probably in relation to phase wrapping phenomenon. This variability is responsible for the low statistical power of phases in LF and HF bands.

Conclusions

MF causality analysis applied to HP and SAP variabilities can detect improvements of autonomic control after plantar mechanical stimulation in PD patients without a history of episodes of orthostatic intolerance and hypotension. This result was achieved with a statistical power greater than that of more traditional cardiovascular variability tools and multivariate linear MB techniques. We recommend the application of the MF causality approach in clinical settings for the assessment of the effect of a treatment, intervention or rehabilitation strategy on autonomic control. The exploitation of MF causality might be more fruitful if treatment, intervention or rehabilitation strategy enhances nonlinear dynamics.

Conflict of interest disclosure

ST is one of the founders and owners of Ecker Technologies Sagl, Lugano, Switzerland (i.e. the company that developed and patented the method of plantar mechanical stimulation we exploited in this study). ST and RF were the inventors of a patent currently owned by Ecker Technologies Sagl, Lugano, Switzerland on plantar mechanical stimulation. People who analyzed data (i.e. TB, VB, AM and AP) were blinded to experimental conditions and treatments.

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