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Time- and frequency-domain analysis of beat to beat P-wave duration, PR interval and RR interval can predict asystole as form of syncope during head-up tilt

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Abstract

To seek possible differences in short-period temporal RR interval, P-wave and PR interval dispersion and spectral coherence in patients with a head-up tilt test positive for vasovagal syncope with or without prolonged asystole, severe symptoms and at high risk of trauma.

We retrospectively reviewed 5 min ECG and blood pressure recordings obtained at baseline, at rest and during head-up tilt in 40 patients diagnosed as having recurrent vasovagal syncope confirmed at a head-up tilt test. We analysed autoregressive spectral power for all the ECG-derived variables, focusing on temporal P-wave and PR interval dispersion indexes as well as their spectral coherence calculated on the same 5 min recordings at rest and during tilt.

ECG recordings obtained during tilt before syncope showed significantly lower P → PR spectral coherence and higher RR standard deviations in patients with tilt-induced asystole than in those without (0.567 ± 0.097 versus 0.670 ± 0.127, p: 0.010 and 84 ± 36 versus $46 \pm 22\,\text{ms}^2$, $p < 0.0001$). Differences in the RR standard deviations persisted also on the last hundred

beats ($_{-100}$) (113 ± 54 versus 34 ± 17 ms^2, $p < 0.0001$). Multiple regression analysis identified a significantly negative association between the maximum RR intervals and P → PR coherence at rest (β: −0.3, $p < 0.05$) and positive association with RR_{-100} standard deviation during tilt-induced syncope (β: 0.621, $p < 0.001$).

P → PR spectral coherence could be used to assess the risk of prolonged asystole in patients with tilt-induced vasovagal syncope as well as as a possible surrogate for tilt-testing during these patients' follow-up.

Keywords: sinus arrest, vasovagal syncope, power spectral analysis, P wave, PR segment

(Some figures may appear in colour only in the online journal)

Introduction

Fortunately, most vasovagal spells are benign and patients manifest only temporary hypotension and bradycardia, preceded by typical neurovegetative symptoms. When the subjects are able to recognize the prodromal symptoms they have generally enough time to avoid dangerous positions (stairways, window or cliffs). For these reasons patients with vasovagal syncope therefore usually need no specific pharmacological treatment or permanent cardiac pacing, even though some occasionally experience prolonged asystole accompanied by loss of consciousness, tonic–clonic movements (Sheldon *et al* 2002, Passman *et al* 2003, Donfrancesco *et al* 2005, Rangel *et al* 2014), falls and high risk of traumatic consequences (Aydin *et al* 2012, Palmisano *et al* 2012, JBhat *et al* 2014) and these events are particularly dangerous if the subjects do not perceive the prodromes. These kinds of events recur especially in older subjects and in this case it is necessary to evaluate the possibility to implant a pacemaker. Another problem is that, if the subjects have reported cranial trauma, usually they are not able to remember useful information for diagnosis and if no reliable eyewitness is available it is very difficult to discriminate vasovagal syncope from accidental fall. It could be important to have a noninvasive markers predictive for asystole during vasovagal syncope, especially if it is impossible or difficult to undergo the head-up tilt test or to follow-up the patient. No studies yet show whether tilt-induced sympathetic stress brings about changes from baseline in temporal P-wave and PR interval dispersion in patients experiencing asystole. Nor do we know whether and how these two ECG signals oscillate synchronously in time, i.e. spectral P → PR coherence. Having this information could help in developing possible non-invasive markers to predict these patients' asystole thus reducing possible traumas, facilitate the differential diagnosis between syncope and seizures, and improve the indications for implanting permanent pacing.

In this study we sought possible differences in short-term heart rate and blood pressure variability and temporal P-wave and PR interval pattern in patients with a tilt-test positive for vasovagal syncope with or without prolonged asystole. In order to obtain this result, we developed a non-invasive technique for evaluating atrial electrical remodelling in patients with atrial overload (Piccirillo *et al* 2015), assessing short-period temporal P-wave and PR-interval variability, expressed as standard deviation (SD) of the mean for P-wave and PR-interval, and their spectral coherence. We measured these variables at two time-points: at baseline during rest, and during tilt before vasovagal symptoms developed.

Methods

Study subjects and protocol

From a series of 748 consecutive outpatients referred to our Neuroautonomic Study Unit, Policlinico Umberto I, Rome, Italy, between 15 December 2010 and 28 August 2012 (20 months), 444 of whom had a diagnosis of recurrent syncope, we selected 40 recordings (fewer than 10%) obtained during rest and head-up tilt test, from outpatients with a diagnosis of recurrent vasovagal syncope (three or more spells in the preceding three month period) and with positive responses to head-up tilt testing without pharmacological stimulation. Head-up tilt test responses were considered positive if this manoeuvre elicited symptomatic hypotension with or without bradycardia. We chose these subjects to avoid possible pharmacological interference on PR interval analysis. We assigned patients to two groups according to whether head-up tilt testing induced prolonged asystole_defined as RR intervals lasting at least 3 s (figures 1(A) and (B)) or prevalently hypotension without asystole (figures 1(C) and (D)). In all subjects, arterial blood pressure and ECG variables were recorded continuously before and during the head-up tilt test according to the study protocols. After patients rested for 15 min supine, we obtained a first 5 min recording during controlled breathing (15 breaths per minute, 0.25 Hz) at rest. We then recorded the same variables during the head-up tilt test (70° for 20 min) immediately before syncope developed accompanied by an abrupt fall in blood pressure, bradycardia or sinus arrest (tilt) (Piccirillo *et al* 2004, 2006, 2014c). For ECG and systolic blood pressure (SBP) analysis we selected the same number of beats in the 5 min recording at rest, obtaining two comparable recordings at rest and during tilt. To calculate spectral power and temporal dispersion we then analysed ECG and SBP data again, studying P-wave duration and PR intervals at rest and during head-up tilt. We also analysed P-wave duration and PR interval temporal dispersion in a very short epoch. Specifically, we analysed temporal dispersion for these two variables in 100-beat ECG segments recorded at rest during controlled breathing (P_{100} and PR_{100}) and in 100-beat epochs beats during the head-up tilt test beginning from the syncope (asystole or abrupt blood pressure fall). We then selected 10 epochs lasting 100 beats during tilt (for example, $_{-100}$: 100 beats before the syncope; $_{-200}$: 100 beats from 200 to 100 before the syncope) and one during rest (P_{100} and PR_{100}).

The research was conducted according to the principles stated in the Declaration of Helsinki.

Offline data analysis

ECG and beat-to-beat blood pressure (Finometer™,FMS, Arnhem, Netherlands) signals were acquired and digitalized with a custom-designed card (National Instruments USB-6008, Austin, Texas, USA) at a sampling frequency of 500 Hz. Tags used for the ECG segment analysis were detected automatically by a classic adaptive first derivative/threshold algorithm. Software for data acquisition, storage and analysis were designed and produced by our research group with the LabView program (National Instruments, Austin, Texas, USA). An expert cardiologist (GP) checked the different ECG wave and interval tags, automatically marked by the software, and, when needed, manually corrected the mistakes.

The following ECG intervals were obtained: RR, P (from start to end of P wave) duration, PR (from the start of P-wave to the QRS onset), and P_{peak} (between the start and the peak of P wave) (figure 2) in addition to SBP. We therefore measured mean, variance and standard deviation values for each of these intervals and analysed spectral power.

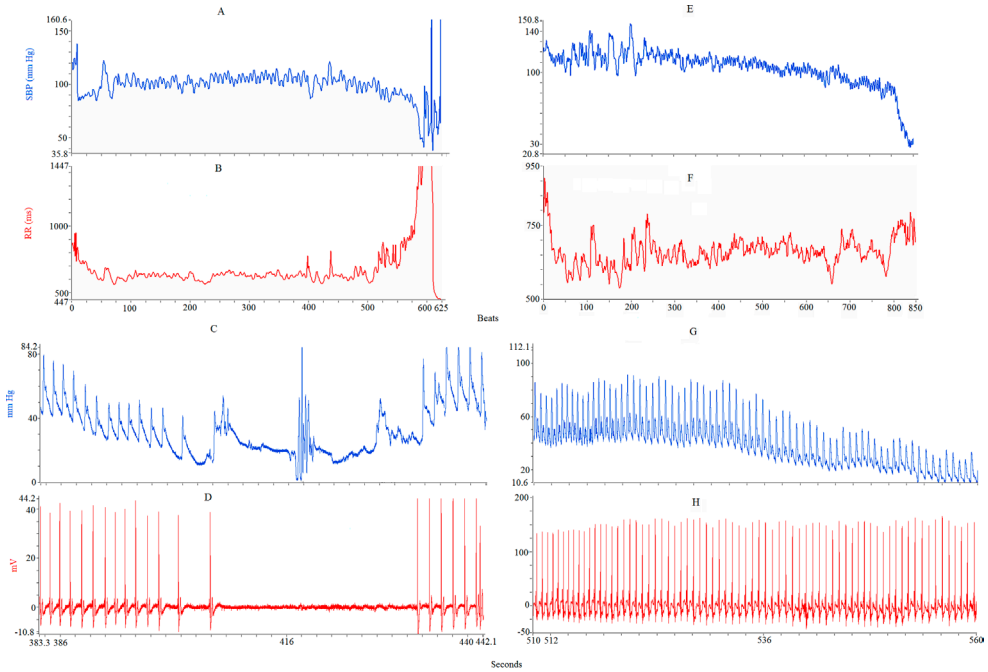

Figure 1. Representative ECG (red) and systolic blood pressure (SBP) (blue) recordings during head-up tilt test in two patients with vasovagal syncope with ((A)–(D)) and without ((E)–(H)) prolonged asystole. Panel (A) shows the recording when asystole begins at about the 575th beat: RR interval increases ((B) and (D)) and SBP decreases ((A) and (C)). Around the 500th beat RR variability increases (B). Panel (D) shows the recording when asystole continues from the 408th to 433th second. Panel (C) shows SBP signal artefacts around the 418th second when the tilt-table returned to the clinostatic position shortly after the syncope developed. Panels (E) and (G) showed hypotension without RR modifications ((F) and (H)).

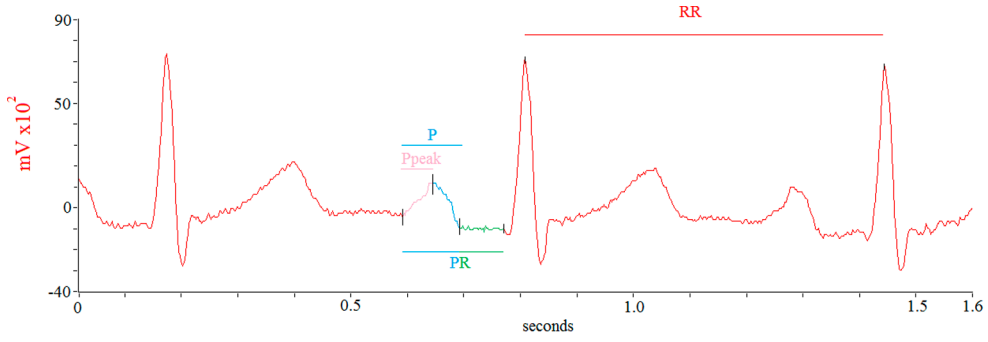

Figure 2. ECG segments analysed in this study.

An autoregressive algorithm was used to analyse the stationary segments from ECG. Stationarity was defined as the quality of process in which the statistical parameters (mean and standard deviation) of the process did not change with time. In other words, a series of RR intervals without premature beats (figure 3). For each of these variables, we then determined the total power (TP) that was their total spectral density. For RR we calculated the

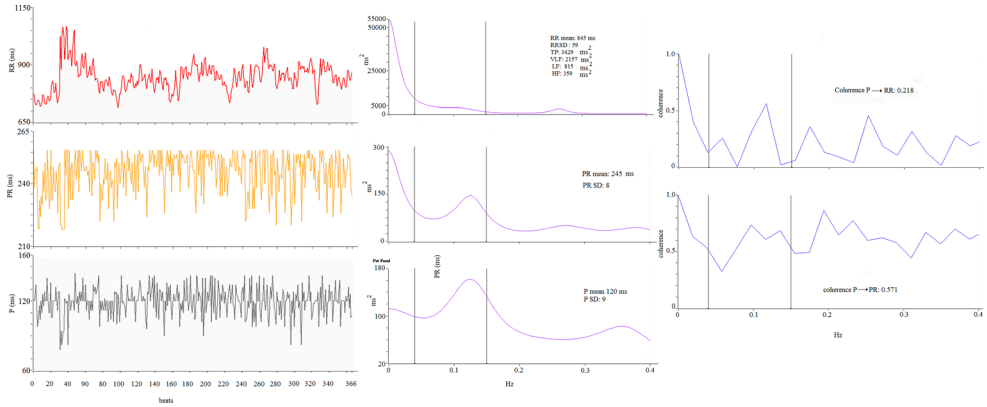

Figure 3. The right panels depict the RR (red), PR interval (yellow) and P-wave (grey) recordings durations at rest for 5 min during controlled breathing. The middle panels show the relative autoregressive power spectral analysis, and the left panels the spectral coherences.

following spectral components: a high-frequency (HF) component (from 0.15 to 0.4 Hz Eq), a low-frequency (LF) component (from 0.04 to 0.15 Hz Eq) and a very-low-frequency (VLF) component (below 0.04 Hz Eq). The relative value of each spectral power component of RR intervals was also measured and expressed in normalized units (NU). NU were calculated as follows (Piccirillo *et al* 2009b, 2013, 2014b, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996):

$$\mathrm{LF_{RRnu}} = \frac{\text{LF power}}{(\text{TP} - \text{VLF power})} \times 100.$$

$$\mathrm{HF_{RRnu}} = \frac{\text{HF power}}{(\text{TP} - \text{VLF power})} \times 100.$$

We then estimated the coherence function for the various spectral components. Coherence expresses the power fraction at a given frequency in either time series and is explained as a linear transformation of the other thus measuring the linear association between the two signals. The coherence function $\gamma(f)$ was then computed according to the formula

$$\gamma\,[f] = \frac{|Pxy[f]\,|^2}{Pxx[f]Pyy[f]}$$

where f is frequency, $Pxx[\,f]$ is the RR or PR interval spectra, $Pyy[\,f]$ are the P-wave interval spectrum (P → RR and P → PR coherences), and $Pxy[\,f]$ is the cross spectrum. The coherence function measures the linear interaction between two interval oscillations as a function of their frequency. The coherence function value ranges between zero and one (Ropella *et al* 1989, 1990, Piccirillo *et al* 2009a, 2014a, 2015). Mean coherences were measured by averaging $\gamma[f]$ over the frequency bands: from 0 to 0.40 Hz.

Statistical analysis

Unless otherwise indicated all data are expressed as means ± SD. Data with skewed distribution are given as median and interquartile range (75th percentile–25th percentile).

P values of less than or equal to 0.05 were considered statistically significant. We compared at rest and during the tilt data between the two groups with or without asystole. Categorical variables were analysed with the χ^2 test. One-way analysis of variance (ANOVA) was used to compare data for the normally distributed variables. Mann–Whitney test was used to compare non-normally distributed variables (as evaluated by Kolmogorov–Smirnov test). Paired *t*-test was used to compare data for the normally distributed variables whereas Wilcoxon test was used to compare non-normally distributed variables at rest and during tilt. A repeated-measures analysis of variance (ANOVA) was run to compare the same variables at baseline and during the 10 tilt epochs. Pearson's correlation was used to assess relations between variables with linear distribution. Stepwise multiple regression analysis was used to determine possible relationships between the studied variables. Receiver operating characteristic (ROC) curves were used to compare the predicative efficiencies of study parameters. To confirm the possibility to use our study data to individuate subjects with asystole at rest or precociously during head-up tilt test, we tested the possible predicative parameters in some consecutive subjects with the same clinical characteristics. Particularly we considered the pathologic threshold for the second study the 75th percentile of the studied parameter obtained in the first study.

All data were evaluated with the database SPSS-PC + (SPSS-PC + Inc, Chicago, Illinois).

Results

Of the 40 ECG recordings selected for study, 15 (38%) came from patients who had positive head-up tilt test responses with asystole and 25 (62%) without. Thirteen subjects with asystole had sinus arrest and two a third-degree atrioventricular block.

No difference was found in the general characteristics between the two study groups (table 1).

Time-domain and frequency-domain analysis of 5 min epochs at rest and during tilt

The data recorded during tilt came from 14 patients with asystole and 23 without. Three patients were excluded because they experienced syncope immediately after being tilted and we had too little time to record a sufficient number of beats. During rest, all data for P wave duration, PR and RR interval (tables 2 and 3) were similar in the two study groups except for P → PR spectral coherence ($p < 0.05$) (table 2). Conversely, during tilt immediately before the syncopal event developed, ECG recordings showed significantly higher RR SD ($p < 0.001$) in patients with asystole than those without (table 2). Under the same experimental conditions, the power spectral components—expressed in absolute power—were significantly higher in subjects with asystole than in those without (TP_{RR}, $p < 0.001$; VLF_{RR}, $p < 0.001$; LF_{RR}, $p < 0.001$; HF_{RR}, $p < 0.001$; (table 3). Data for relative power, calculated in normalized units, failed to confirm differences between the two groups.

In both groups the following ECG variables decreased significantly from rest to tilt: RR mean ($p < 0.05$); PR mean ($p < 0.05$), HF_{RRnu} ($p < 0.05$), (tables 2 and 3). Conversely, under the same experimental conditions and in both groups the following variables increased: VLF_{RR} ($p < 0.05$), LF_{RRNU} ($p < 0.001$), LF/HF ($p < 0.05$, $p < 0.001$) and SBP SD ($p < 0.05$, $p < 0.001$) (table 3), only in patients with asystole during tilt RR SD, PR SD ($p < 0.05$), P → PR ($p < 0.05$), TP_{RR} ($p < 0.05$) and LF_{RR} (<0.05) increased significantly ($p < 0.05$) (tables 2 and 3).

Table 1. Characteristics of the patients diagnosed with vasovagal syncope with and without prolonged asystole at head-up tilt-testing.

	With asystole *n*. 15	Without asystole *n*. 25	*P* values
Men/Women	10/5	8/17	Ns
Age, years	34 ± 17	33 ± 18	Ns
Body mass index, kg m^{-2}	24 ± 4	24 ± 6	Ns
Heart rate, beats min^{-1}	68 ± 8	69 ± 8	Ns
Systolic blood pressure, mmHg	115 ± 17	102 ± 17	Ns
Diastolic blood pressure, mmHg	71 ± 11	63 ± 14	Ns

Data are expressed as means ± standard deviation (SD).

Table 2. RR, P and PR interval data recorded in patients diagnosed with vasovagal syncope with and without prolonged asystole at head-up tilt-testing.

	With asystole *n*. 15	Without asystole *n*. 25	
	Rest		*P* values
RR mean, ms	877 ± 138	856 ± 119	Ns
RR SD, ms^2	48 ± 17	47 ± 22	Ns
P_{peak} mean, ms	58 ± 17	56 ± 14	Ns
P_{peak} SD, ms^2	8 ± 2	8 ± 3	Ns
P mean, ms	107 ± 18	105 ± 19	Ns
P SD, ms^2	8 ± 3	9 ± 3	Ns
PR mean, ms	208 ± 24	206 ± 29	Ns
PR SD, ms^2	6 ± 3	7 ± 2	Ns
P → RR, coherence	0.261 ± 0.144	0.206 ± 0.035	Ns
P → PR, coherence	0.567 ± 0.097	0.670 ± 0.127	0.010
	Tilt		
Patients, *n*	14	23	
RR mean, ms	728 ± 130[b]	672 ± 128[b]	Ns
RR SD, ms^2	84 ± 36[a]	46 ± 22	0.0001
P_{peak} mean, ms	57 ± 18	56 ± 13	Ns
P_{peak} SD, ms^2	8 ± 4	8 ± 2	Ns
P mean, ms	107 ± 15	103 ± 15	Ns
P SD, ms^2	9 ± 4	8 ± 2	Ns
PR mean, ms	198 ± 20[a]	190 ± 25[a]	Ns
PR SD, ms^2	8 ± 2[a]	7 ± 2	Ns
P → RR, coherence	0.259 ± 0.088	0.208 ± 0.041	Ns
P → PR, coherence	0.710 ± 0.119[a]	0.747 ± 0.103	Ns

[a] $p < 0.05$ rest versus tilt.
[b] $p < 0.001$ rest versus tilt.
Values are expressed as mean ± standard deviation (SD) or median (interquartile range 75th percentile–25th percentile).
P values by Student's *t*-test or Mann–Whitney.

Table 3. Power spectral analysis of RR and PP variability in patients diagnosed with vasovagal syncope with and without prolonged asystole at head-up tilt-testing.

	With asystole *n*. 15	Without asystole *n*. 25	
	Rest		*P* values
TP_{RR}, ms^2	2689 (2893)	1789 (2631)	Ns
VLF_{RR}, ms^2	909 (1226)	608 (740)	Ns
LF_{RR}, ms^2	404 (708)	355 (548)	Ns
HF_{RR}, ms^2	445 (1192)	400 (1355)	Ns
LF_{RR}, nu	45 ± 17	39 ± 21	Ns
HF_{RR}, nu	44 ± 20	54 ± 24	Ns
LF/HF_{RR}	1.18 (1.90)	0.75 (1.39)	Ns
SBP mean, mmHg	114 ± 36	108 ± 14	Ns
SBP SD, $mmHg^2$	6 ± 2	5 ± 2	Ns
	Tilt		
Patients, *n*	14	23	
TP_{RR}, ms^2	6965 (4727)[a]	1839 (2108)	0.0001
VLF_{RR}, ms^2	3830 (5767)[a]	1065 (1609)[a]	0.001
LF_{RR}, ms^2	1533 (1434)[a]	499 (680)	0.0001
HF_{RR}, ms^2	489 (533)[a]	97 (138)[b]	0.001
LF_{RR}, nu	66 ± 11[b]	71 ± 15[b]	Ns
HF_{RR}, nu	20 ± 9[b]	18 ± 10[b]	Ns
LF/HF_{RR}	3.52 (2.97)[a]	3.71 (4.93)[b]	Ns
SBP mean, mmHg	107 ± 23	99 ± 15[a]	Ns
SBP SD, $mmHg^2$	10 ± 4[a]	8 ± 2[b]	Ns

[a] $p < 0.05$ rest versus tilt.
[b] $p < 0.001$ rest versus tilt.
Values are expressed as mean ± standard deviation (SD) or median (interquartile range 75th percentile–25th percentile).
P values by Student's *t*-test or Mann–Whitney.

P-wave duration and PR, and RR intervals analysis on 100-beat epochs

No differences were found between the two groups for P-wave duration, PR and RR intervals variables recorded at rest (figures 4–6). Conversely, RR_{-100} mean ($p < 0.05$), RR_{-100} SD ($p < 0.001$) (table 4, figure 4) and P_{-100} SD ($p < 0.05$) (table 4, figure 6) were significantly higher in patients with asystole than in those without. In both groups, RR intervals decreased significantly ($p < 0.05$) (figure 4) and so did PR mean ($p < 0.05$) (figure 5) in the different analysed epochs, obtained during tilt. RR_{-100} SD increased from baseline only in the asystole group, whereas in patients without syncope this variable decreased significantly in the preceding period (RR_{-200} SD) ($p < 0.05$) (table 4, figure 4). P_{-100} SD increased from baseline only in the asystole group ($p < 0.05$) (table 4, figure 6).

Multiple regression analysis identified a significantly positive association between the maximum RR intervals during tilt-induced syncope and RR_{-100} SD whereas the maximum RR intervals correlated significantly and inversely with the P → PR at rest calculated on longer recordings (figure 7).

Finally, the ROC curve analysis showed that the increase of P → PR had better sensitivity and specificity for predicating positive head-up tilt test response without asystole (area under the curve: 0.752; asymptotic 95% confidence interval: 0.598–0.906, asymptotic significance:

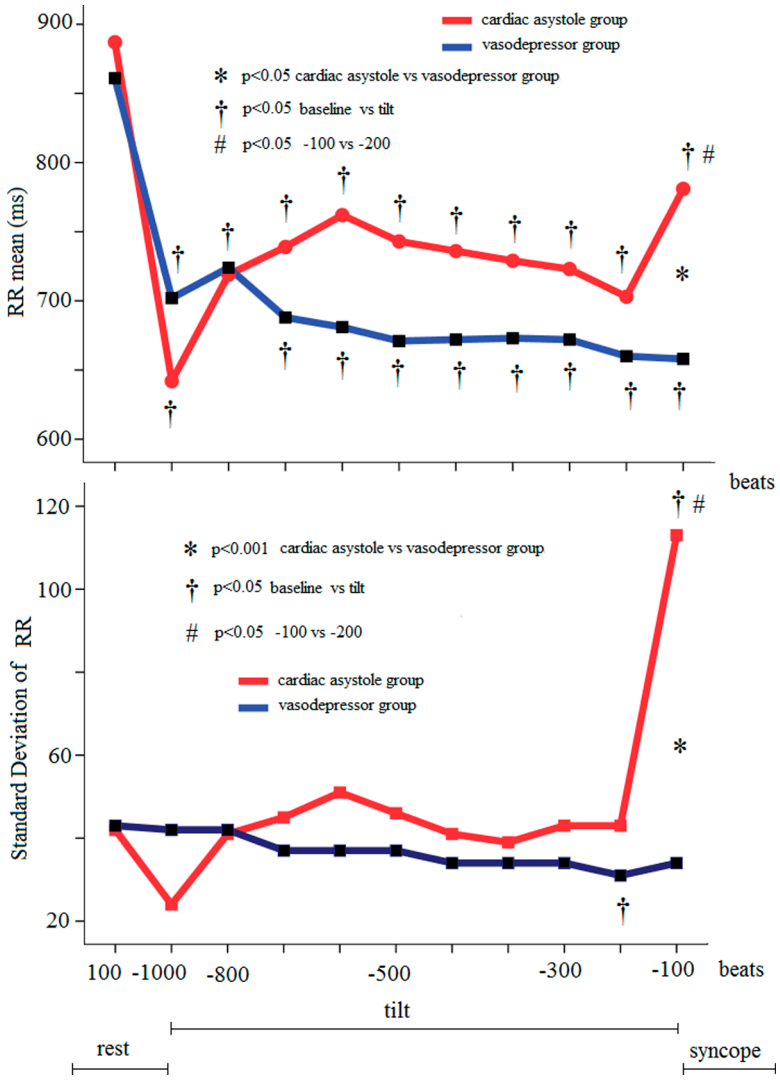

Figure 4. Mean and standard deviation of RR intervals calculated on each 100-beat epoch at rest and during head-up tilt test.

0.0001) (figure 8). The increase of RR_{-100} SD showed the higher sensitivity and specificity for predicating positive head-up tilt test response with asystole (area under the curve: 0.925; asymptotic 95% confidence interval: 0.821–1.029, asymptotic significance: 0.0001) (figure 8).

To assess the predicative value of P → PR and RR_{-100} SD we studied these two parameters in 15 consecutive subjects (age: 46 ± 19) with the same characteristics as in the previous study. Particularly, twelve and three subjects showed a positive head-up tilt test without and with asystole respectively. The threshold of P → PR coherence obtained by the previous study was less or equal to 0.512 and higher or equal to 48 for RR_{-100} SD. The three subjects with asystole showed significantly lower P → PR spectral coherence than in those without (0.466 ± 0.028 versus 0.556 ± 0.041, *p*: 0.013); conversely, the same subjects had the higher RR_{-100} SD in comparison with the other subjects (64 ± 8 versus 32 ± 17 ms^2, *p*: 0.019). As

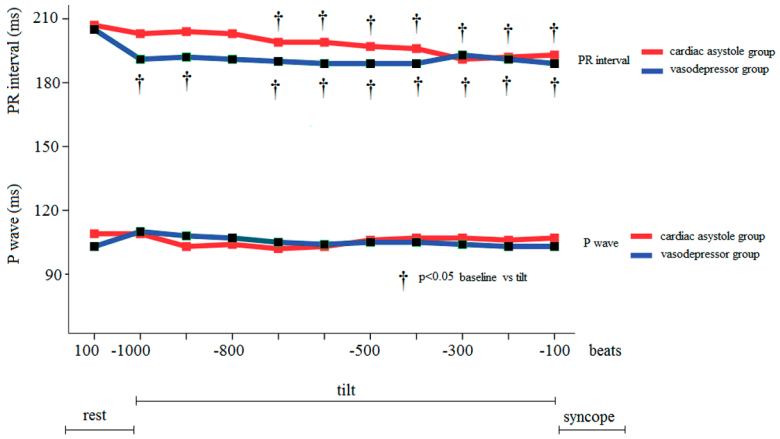

Figure 5. PR interval and P-wave durations calculated on each 100 beats at rest and during head-up tilt test.

far as the P → PR and RR_{100} SD we did not obtained subjects with false negative results, but both the parameters showed two subjects had false positive results. On other words we confirmed the trend of these two parameters in a little prospective study.

Discussion

The major finding in this study is that at baseline during rest spectral coherence between P-wave and PR interval duration was lower in patients with a history of vasovagal syncope and tilt-test induced prolonged asystole than in the group without. Particularly the receiver operating characteristic curve analysis indicated that a high level of P → PR spectral coherence could, with quite high sensitivity and specificity, exclude a prolonged asystole during head-up tilt or vasovagal syncope. In theory this non-invasive marker could be used to assess the possible presence or absence of asystole during head-up tilt without executing this test. This could be handy in subjects unable to undergo the head-up tilt test due to cranial trauma or femur fracture—in these cases it could be possible to obtain an earlier diagnosis or otherwise improve decision-making in patient management.

The mechanism underlying the reduction of P → PR spectral coherence at rest remains a matter of conjecture. Because spectral coherence is an index that measures how two ECG variables oscillate synchronously in time, P → PR spectral coherence at rest obtained under controlled breathing—an experimental condition inducing slight vagal stimulation (Pagani *et al* 1986)—might reflect synchrony in sinus node modulation, atrioventricular node refractoriness and activity in atrioventricular conduction pathways. Hence, sinus node respiratory oscillations, not directly observable on the ECG because they take place before the atrial depolarizations, should propagate immediately within the atrium, thereby generating P-waves and causing them to oscillate. In patients with normal atrial function, such as those with vasovagal syncope we studied, no electrical substrate-obstacles should prevent sinus node respiratory oscillation propagation and hence the P-wave oscillations presumably depend directly on changes in sinus node activity. Insofar as the P-wave oscillations are common to the two ECG signals P and PR and their coherence is less than 1, P → PR spectral coherence derives mainly from the differences in the oscillations between P and the ECG recording epoch going from the end of the P-wave to QRS. Accordingly, oscillations in this ECG signals presumably

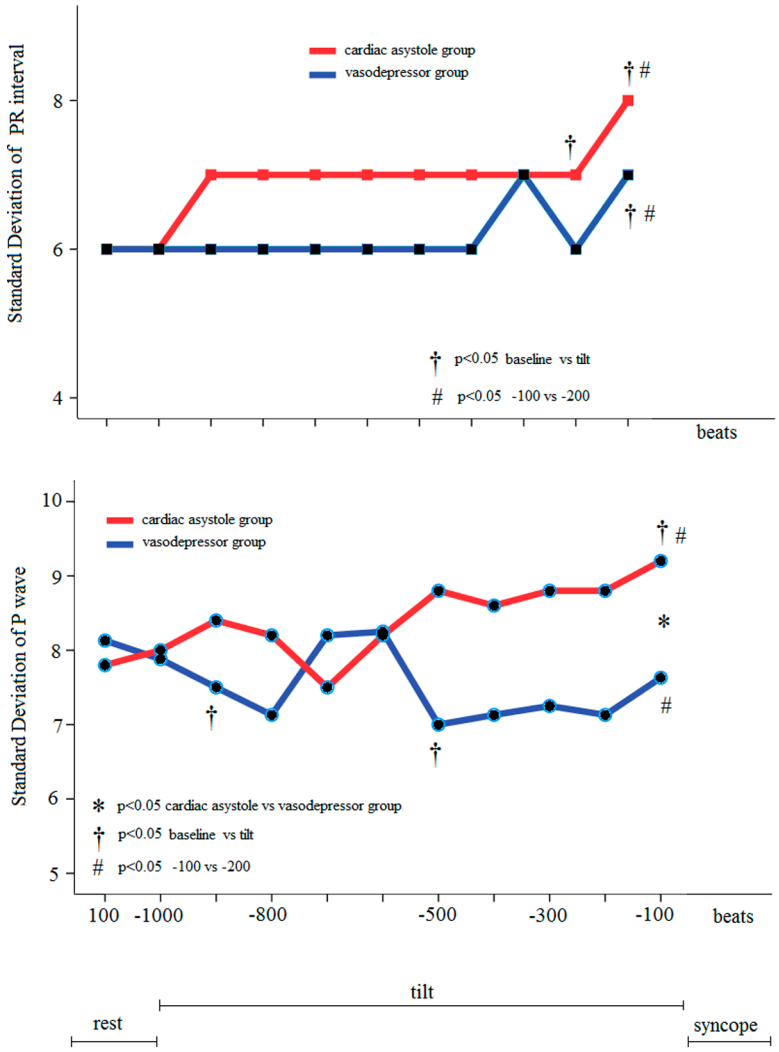

Figure 6. Standard deviation of PR intervals and P-wave durations calculated on each 100 beats at rest and during head-up tilt test.

originate in the atrioventricular node and atrioventricular conduction pathways. Patients with prolonged sinus arrest or third-degree atrioventricular block during tilt could have reduced synchrony between oscillatory activity in the sinus and atrioventricular nodes owing to different degrees of vagal activity or to differences in nodal cellular sensitivity to vagal stimulation. Spectral coherence could therefore serve as a functional marker for vagal activity in the two nodes. In our ECG recordings we found that of the fifteen patients who had prolonged asystole, thirteen had sinus arrest and two a third-degree atrioventricular block. Differences in synchrony expressed by P → PR spectral coherence in patients with prolonged asystole would become especially noticeable during mild vagal stimulation and therefore at rest during controlled breathing. This ECG pattern is opposite to what happens during sympathetic stimulation, when tilt-testing begins and during extreme vagal stimulation, namely during syncope when combined sympathetic and vagal stimulation becomes so high as to abolish synchrony

Table 4. PR and P analysis on 100 RR intervals at baseline, 100 or 200 beats before syncope in patients diagnosed with vasovagal syncope with and without prolonged asystole at head-up tilt-testing.

	With asystole *n*. 15	Without asystole *n*. 25	
	Rest		*P* values
RR_{100} mean, ms	887 ± 136	861 ± 120	Ns
RR_{100} SD, ms^2	42 ± 17	43 ± 23	Ns
P_{100} mean, ms	109 ± 19	103 ± 19	Ns
P_{100} SD, ms^2	8 ± 2	8 ± 2	Ns
PR_{100} mean, ms	207 ± 24	205 ± 29	Ns
PR_{100} SD, ms^2	6 ± 2	6 ± 2	Ns
	100 beats before syncope		
RR_{-100} mean, ms	781 ± 167[a,c]	658 ± 137[b]	**0.017**
RR_{-100} SD, ms^2	113 ± 54[b,c]	34 ± 17	**< 0.0001**
P_{-100} mean, ms	107 ± 16	103 ± 15	Ns
P_{-100} SD, ms^2	10 ± 3[a,c]	8 ± 2[c]	**0.040**
PR_{-100} mean, ms	193 ± 20[a]	189 ± 23[a]	Ns
PR_{-100} SD, ms^2	8 ± 2[a,c]	7 ± 2[a]	Ns
	200 beats before syncope		
RR_{-200} mllean, ms	703 ± 135[b,c]	660 ± 127[b]	Ns
RR_{-200} SD, ms^2	43 ± 25[c]	31 ± 12	Ns
P_{-200} mean, ms	106 ± 16	103 ± 16	Ns
P_{-200} SD, ms^2	9 ± 2[c]	7 ± 2[c]	Ns
PR_{-200} mean, ms	192 ± 20[a]	191 ± 23[a]	Ns
PR_{-200} SD, ms^2	7 ± 2[a,c]	6 ± 2	Ns

[a] $p < 0.05$ $_{100}$ versus $_{-100}$ or $_{-200}$.
[b] $p < 0.001$ $_{100}$ versus $_{-100}$ or $_{-200}$.
[c] $p < 0.05$ $_{-100}$ versus $_{-200}$.
Values are expressed as mean ± standard deviation (SD); the subscript number ($_{100}$, $_{-100}$, $_{-200}$) indicates the recording epoch ($_{100}$ at rest; $_{-100}$: 100 beats before the syncope; $_{-200}$: 100 beats from 200 to 100 before the syncope).
P values by Student's *t*-test. Data before syncope in groups with and without asystole were obtained on 14 and 23 subjects respectively.

differences between the signals. Hence differences in P → PR spectral coherence between the two groups would tend to disappear.

A second, although expected, clinical finding was that in patients with vasovagal syncope and prolonged asystole, during tilt about 100–200 beats before the asystole event, RR_{100} SD mean increased to an extraordinary extent. Accordingly, we found two possible predictive markers for tilt-induced asystole, the first being recordable at rest and the second immediately before the syncopal episode. The first marker, P → PR spectral coherence obtained at rest, could be clinically more useful than the second for the following reasons. First, it could facilitate the differential diagnosis between syncope and seizure (Sheldon *et al* 2002, Passman *et al* 2003, Donfrancesco *et al* 2005, Rangel *et al* 2014), second, it might make it easier to evaluate the indications to permanent cardiac pacing and third, it could be used to monitor patients during follow-up and evaluate the various therapeutic strategies, thus avoiding further head-up tilt

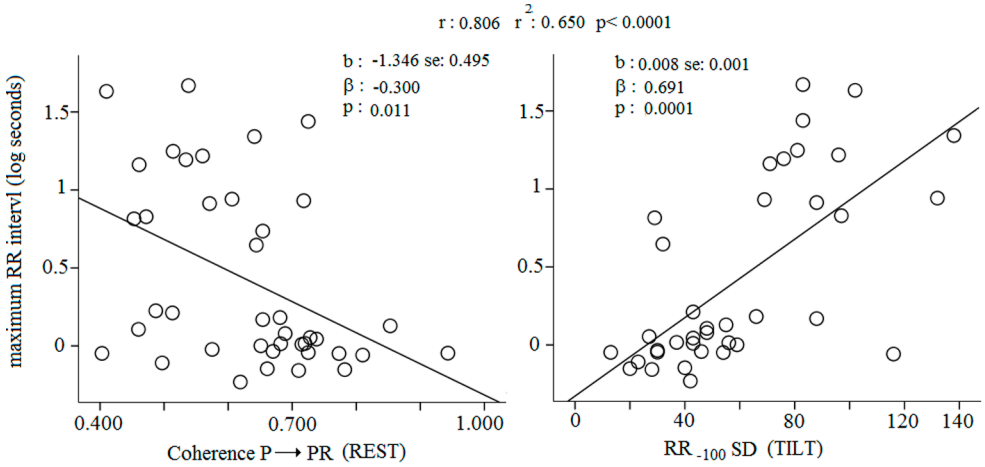

Figure 7. Multiple regression analysis between the maximum RR interval during the tilt-induced syncope and P → PR coherence at rest (left panel) and RR_{-100} SD during tilt-testing (right panel).

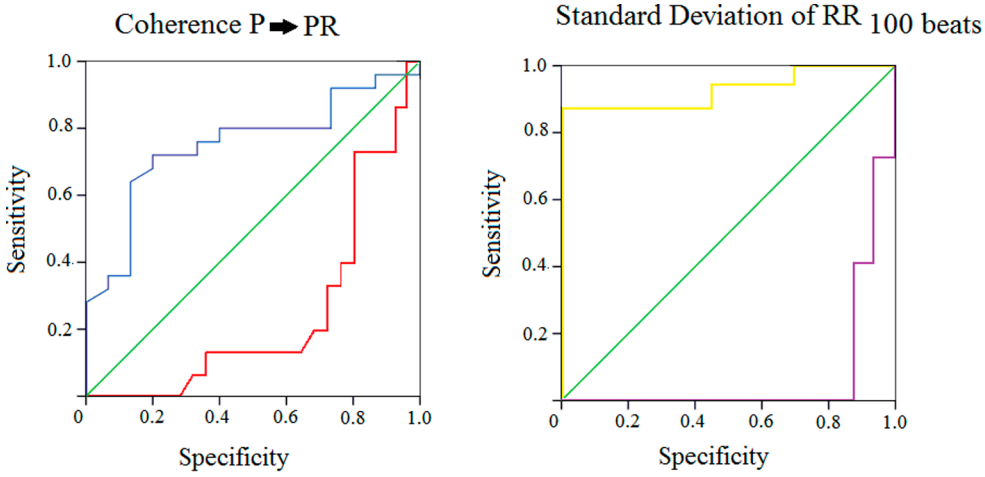

Figure 8. Receiver operating characteristic curve (ROC). On the left this analysis showed that P → PR coherence decrease at rest was a positive predictor for syncope without asystole during head-up tilt test (area under the blue curve: 0.752; asymptotic 95% confidence interval: 0.598–0.906, asymptotic significance: 0.0001). Conversely, the increase of P → PR coherence showed less sensitivity and specificity for a positive test with asystole (area under the red curve: 0.248; asymptotic 95% confidence interval 0.094–0.402, asymptotic significance: 0.0001). On the right the ROC curve of RR standard deviation calculated on 100 beats (RR_{-100} SD) before the syncope during head-up tilt test. The increase of this parameter showed the higher sensitivity and specificity for asystole during head-up tilt test (area under the yellow curve: 0.925; asymptotic 95% confidence interval: 0.821–1.029, asymptotic significance: 0.0001). Conversely, the reduction of RR_{-100} SD showed low sensitivity and specificity for positive head-up tilt without asystole (area under the purple curve: 0.925; asymptotic 95% confidence interval: 0.821–1.029, asymptotic significance: 0.0001).

tests. Hence this new marker could be used as a non-invasive surrogate for head-up tilt-test in patients with vasovagal syncope and prolonged asystole.

Whether we might apply P → PR spectral coherence in studying other paroxysmal supraventricular arrhythmias is a stimulating idea for future research. And equally advantageous, given that the ECG yields a simple and transmissible signal, this simple approach could be developed as a remote medical technology thereby saving time and economic resources.

Although the pathophysiological mechanisms underlying vasovagal syncope remain unclear, available data suggest that the SD of RR mean and all power spectral components increase enormously before the syncopal event but do so only in patients with asystole. This heart rate variability pattern reflects a strong increase in vagal activity and reduction in sinus node sympathetic control (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996, Piccirillo *et al* 2000, 2002). Our new findings now show that during the head-up tilt test sinus sympathetic activities increase and, only a few seconds before asystole develops, vagal sinus activation increases to an enormous extent, but does so only in patients with syncope but without asystole. Precisely why sympathetic stimulation increases vagus nerve sinus activity more in some patients and less in others is unclear, but we conjecture that they could have greater vagal sinus node activity.

In conclusion, our findings suggest that P → PR spectral coherence might help in assessing the risk of prolonged asystole in patients with tilt-induced vasovagal syncope, thus reducing the need for tilt-table tests and loop recording implants during follow-up. Finally, future research should aim to find out whether this non-invasive ECG marker might provide useful information in patients with other supraventricular cardiac arrhythmias.

Disclosures

None of the authors have personal conflict of interests about this paper or the data it contains.

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