Europace (1998) **1,** 000–000
Article No. eupc.1999·0050

Impaired arterial baroreceptor sensitivity before tilt-induced syncope

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Autonomic dysfunction seems to play a central role in the pathophysiology of neurocardiogenic syncope (NCS) but conflicting data has recently become available. We evaluated autonomic nervous system (ANS) function (heart rate variability (HRV), systolic blood pressure variability (SBPV) and baroreceptor gain (BRG)) and non-invasive haemodynamics (cardiac output and total peripheral resistance) in patients with neurocardiogenic syncope.

Retrospectively, we evaluated 12 NCS patients (positive head-up tilt without pharmacological provocation) in the basal state and at initial tilt, 12 non-NCS patients with tilt-negative syncope and 12 aged-matched normal controls. Prospectively, we evaluated 16 NCS patients to analyse the haemodynamics and ANS activity throughout the tilt test (beginning of test and before syncope occurs). HRV and SBPV were accessed by Fast Fourier Transforms (FFT) and spontaneous BRG by temporal sequences, slope and α index. Modelflow was used to quantify the non-invasive haemodynamics.

None of the autonomic and haemodynamic parameters at baseline or in the first 10 min of tilt was different among the retrospective NCS, non-NCS syncope and normal controls groups, except for SBP, which was higher at baseline in controls. Throughout the tilt test in the prospective NCS group, the heart rate increased (88–95 beats.min^{-1}, $P<0·05$), systolic blood pressure decreased (123–109 mmHg, $P<0·01$), and arterial baroreceptor gain was reduced (7·6 to 5·5 msmmHg^{-1}, $P<0·01$) and the absolute high frequency component of HRV (HF HRV) decreased (150–80 ms^{-2}, $P<0·05$), before syncope occurred. There was no change in the low frequency component of HRV (LF HRV), SBPV, cardiac output (CO) or total peripheral resistance (TPR).

Tilt-induced syncope could not be predicted by non-invasive haemodynamics or autonomic parameters at rest or in the initial minutes of tilt. The decrease in arterial baroreceptor gain could be a precocious expression of the transient autonomic dysfunction that characterises the occurrence of neurocardiogenic syncope.
(Europace 1999; 1: 000–000)

Key Words: Neurocardiogenic syncope, baroreflex gain, non-invasive haemodynamics, autonomic activity, tilt test.

Neurocardiogenic syncope is a common problem that seems to be due to sudden impairment of autonomic function and haemodynamics in apparently healthy subjects as a response to prolonged orthostatic stress. The pathophysiology of this type of syncope remains unclear and recently studies have revealed conflicting data about the role of the autonomic nervous system in the induction of syncope[1–8]. Reproducing syncope by tilt table testing permits a detailed study of the electrocardiographic, autonomic and haemodynamic changes throughout the test. The present study used spectral analysis of heart rate variability and systolic blood pressure variability, spontaneous assessment of baroreceptor gain and non-invasive evaluation of haemodynamics to find out if any of these data could predict the result of a provocative tilt test.

Manuscript submitted 11 January 1999, and accepted 22 July 1999.

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Population and methods

Population

The study protocol was performed in 12 consecutive neurocardiogenic syncopal (NCS) patients, aged 27 ± 07 years with a positive tilt test without pharmacological intervention — Group C, in 12 aged-matched unexplained syncope patients with a negative tilt test (with or without isoprenaline) — Group B, and in 12 aged-

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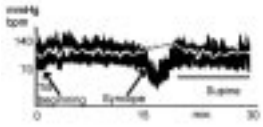

Figure 1. **Vasodepressor neurocardiogenic syncope at 13 min of tilt test. There was a sudden abrupt fall in blood pressure and a slight rise in heart rate with rapid normalization after the table was reset to the supine position.**

matched normal controls who submitted voluntarily to the tilt test — Group A. Individuals with heart disease, diabetes or any disease that could influence the results were excluded. All of them were non-smokers and were not taking any medication, except for contraceptives. Abstention from coffee was demanded and all subjects had to fast for 8 h the day before the tests.

Physical examination, electrocardiogram, Holter monitoring and 24 h ambulatory blood pressure, performed in all the individuals, were considered normal. A prospective study was performed in 16 other NCS patients, with positive tilt tests without isoprenaline provocation, aged 36 ± 22 years, also with no disease or any medication — (Group D).

Study protocol

The investigations were performed at an Autonomic Laboratory, with the approval of the hospital ethics committee. The protocol, after detailed information to the patients and volunteers, was performed in a room with temperature around 22°C, always beginning at 10:00 h.

After 30 min bed rest, the data were recorded for 10 min. Then, the subjects were tilted to 70° head-up, with footboard support, for a maximum of 45 min. If the unexplained syncope patients or control subjects did not experience syncope, the tilt test was repeated for 10 min with infusions of 1 and 3 $\mu g.min^{-1}$ isoprenaline, with an interval of 15 min of interval. During tilt, continuous recording of all parameters beat-to-beat was registered. In the first study comparisons were made of autonomic and haemodynamic parameters at baseline and at the initial tilt among the three groups, A, B and C. We analysed the results of the tilt in the 10 min supine position, and the initial 10 min of the tilt test. In the second study, we analysed the comparisons in the other NCS group, Group D, of the first 5 min of the tilt test and the 5 last min before syncope occurred (Figure 1).

Non-invasive arterial pressure and ecg signal monitoring

The digital arterial pressure was obtained non-invasively with a commercial Finapres® device (Ohmeda, model 2300, Englewood, CO, U.S.A), using a pseudo-plethysmographic technique. With this technique, a plethysmographic fingercuff is placed around the middle phalanx of the third finger. The pressure in this fingercuff is modulated in such a way that the transmural pressure stays effectively at zero. Thus, the variations in the pressure of the cuff are simultaneous with the variations in the arterial pressure of the finger. In this way continuous pressure waves are generated which have excellent correlation with the values of the intra-arterial pressure[9].

The automatic calibrations performed by the device 'servo-reset' were turned off during the recordings, to allow the acquisition of continuous beat-to-beat data, and calibrations were retaken in the intervals between the manoeuvres. The pressure curve, starting from the analogue output of the Finapres® device and the electrocardiogram were transmitted in real time and digitized, with a sampling rate of 300 Hz per channel, using a commercial A/D converter (Dataq® model DI-420), and stored in a computer for subsequent processing and analysis.

The calculation of RR intervals and systolic arterial pressure were performed with software that uses an algorithm (Dataq® calculation package, version 3·14) that allows detection of the peaks of the R wave of the ECG and the amplitude of the peaks of the Finapres arterial wave. The recordings were edited for manual correction of errors due to artefacts, ectopic beats (excluding those interpolated) and other recognition errors such as peaks of T waves. The ECG signal was obtained, after careful preparation and cleaning of the skin, so that the impedance was always <5 kW. A lead was chosen as a derivation of the 'CM5' type to allow a QRS complex of great amplitude in order to decrease recognition errors in the peaks of the R wave. This methodology leads to the discovery of extremely rare artefacts or errors of ECG and arterial waveform [10].

Heart rate variability and systolic pressure variability analysis

The spectral analysis of heart rate (RR interval) variability and systolic pressure variability were performed with software developed by Matlab® (MathWorks, Inc., South Natick, MA, U.S.A.) in a Pentium® computer system [11], specially developed to provide flexible analysis system. Spectral analysis was performed using the non-parametric Welch method [12]. The 256 RR intervals and systolic pressure values were divided into seven blocks of 64 points with 50% overlap. For each block, the data were de-trended (the mean value and the linear trend were estimated and removed), and a Hanning data window was applied. The spectrum was analysed after normalization of the frequency axis by the average mean heart rate or systolic pressure over the 256 series in three bands: 1 — the high frequency component, between 0·15 and 0·40 Hzeq, 2 — the low frequency component, between 0·04 and 0·15 Hzeq, 3 — the very low frequency component (VLF), between 0·01 and 0·04 Hzeq (Figure 2).

In HRV analysis, we also used the normalized units of LF and HF components, calculated by dividing the LF or HF power by the total power above 0·04 Hzeq and multiplying by 100, in an attempt to quantify the so-called sympathovagal balance.

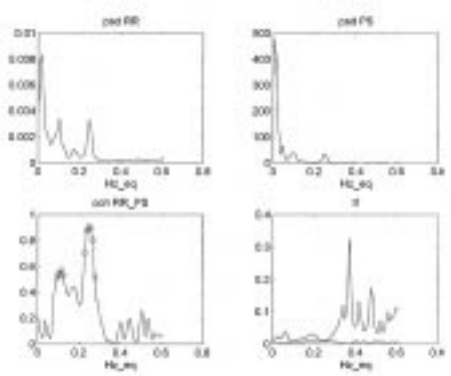

Figure 2. **Spectral analysis of heart rate variability (psd RR) and systolic blood pressure variability (psd PS). Spectral coherence of both spectra to achieve baroreceptor gain (coh RR_PS).**

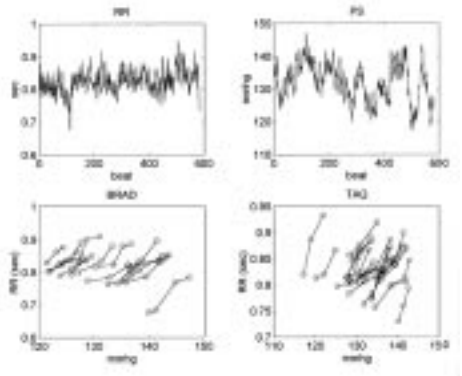

Figure 3. **RR interval tachogram and systogram. In the lower sequence we can see the linear regression between the RR interval and systolic blood pressure values for each sequence (brady and tachy sequences).**

Calculation of the spontaneous gain of arterial baroreceptor

We used two methods to calculate the spontaneous arterial baroreceptor gain:

(1) The temporal sequences method is based on the analysis of the occurrence of sequences in successive variations of the values of the systolic arterial pressure correlated inversely with the duration of the RR intervals, in a way that shows progressive increases or decreases in at least three successive beats. The software automatically chose the sequences where there are variations >3·3 ms per unit of pressure (mmHg). The linear regression relating the RR intervals and the values of systolic blood pressure are placed in graphics, for each sequence, and the 'slope' of the regression line that relates all these sequences represents the sensitivity or gain the arterial baroreceptor. By averaging all sequences, we obtained the overall measure of the gain of the baroreceptor (Figure 3) [13]. The baroreflex gain expresses the variation of the heart beat interval (in ms) for each variation of systolic arterial pressure (in mmHg). For example, a hypothetical sequence of systolic pressure of 122, 124, 127 and 129 mmHg, accompanied by changes in the RR interval of 700, 742, 775 and 806 ms will generate a slow sequence (decrease in heart rate) with a coefficient of correlation of 0·992 and a sensitivity or gain of the baroreceptor of 14·5 ms.m-mHg^{-1}. It is accepted that in this type of analysis, only sequences with a coefficient of correlation over 0·80 are used13.

(2) The method uses spectral coherence and is based on the supposition that oscillations of arterial pressure in the band centred 0·10 Hz, obtained by spectral analysis of systolic blood pressure variability, represents rhythmic fluctuations of vasomotor activity mediated by the arterial baroreflex, also known as Mayer waves. This same band, in the spectrum of HRV, seems to correspond to sympathetic and vagal adjustments mediated by the baroreflex[14]. From spectral analysis of HRV and SBPV, the crossed analysis is calculated. The baroreflex gain is estimated by the gain of the transfer function in the spectral bands when good coherence exists (over 50%), among the spectra of the systolic pressure and RR interval. The sensitivity is calculated from the module of the cross-spectra of RR interval and SBP between 0·04 and 0·15 Hz (Figure 2). There is good correlation among the spontaneous gain methodologies (temporal or spectral) in relation to pharmacological methods[15] without the inconvenience of introducing an external stimulus such as drugs with direct vascular effects.

Calculation of non-invasive haemodynamics

We chose the method developed by Wesseling *et al.*[16] because of its simplicity, low cost and non-invasive nature. We chose, to calculate cardiac output and total peripheral resistance. This method uses the analysis of the wave of digital arterial pressure obtained by Finapres®, Portapres®, or intra-arterial recordings for calculation of several haemodynamic parameters after applying the BMI®: beat-to-beat modelflow interpretation. Several studies demonstrated the application of this tri-elementary model in arterial impedance to describe the relationship between aortic pressure and flow[17]. Once model parameters are detected, flow can be computed from measured pressure by activating the model[17]. This flow calculation provides a continuous measure of cardiac output and integrated over one heartbeat provides stroke volume. The non-linear tri-elementary model, representing the three main characteristics of aortic impedance, allows precise calculation of stroke volume and cardiac output. Wesseling et al.[16] refer to the very good correlation among values obtained by these and thermo-dilution invasive techniques (with errors < ± 2%).

Statistical analysis

All results are given as means ± standard deviation. In statistical analysis we used non-parametric methods. For comparisons of means between groups we used the Kruskall–Wallis test, for comparison of changes in

Table 1 Comparison of autonomic and haemodynamic variables among groups at baseline (supine) and in the first 10 min of tilt. Results: mean (SD)

	Basal			Tilt		
	Control (A)	Tilt negative(B)	Tilt positive(C)	Control(A)	Tilt negative(B)	Tilt positive(C)
CO	4·89 (1·00)	4·96 (1·19)	4·58 (1·55)	3·80 (0·46)*	4·37 (0·73)**	3·76 (1·27)*
TPR	1546 (437)	1359 (373)	1600 (721)	2083 (272)*	1763 (557)*	2187 (990)*
HR	76·7 (8·5)	73·9 (14·5)	71·5 (8·2)	88·7 (9·2)*	90·2 (18·0)*	91·9 (12·4)*
SBP	125·9 (11·9)	112·2 (12·1)*	116·3 (12·0)*	131·7 (9·0)	125·2 (19·0)*	121·3 (18·4)
BRG-α	12·3 (3·3)	14·6 (7·3)	16·0 (6·2)	7·0 (1·3)*	7·7 (3·7)*	8·4 (3·4)*
BRG-t	12·3 (4·0)	14·3 (6·6)	13·7 (4·7)	6·8 (1·1)*	7·6 (4·3)*	7·8 (3·5)*
LF (RR)	731 (380)	899 (819)	856 (942)	704 (296)	625 (532)	832 (984)
LF (nu)	54·3 (14·8)	51·3 (14·3)	43·4 (18·0)	76·2 (7·2)*	70·4 (14·8)*	67·8 (17·9)*
HF (RR)	559 (320)	1056 (1213)	1234 (1590)	201 (110)*	349 (565)**	352 (328)**
HF (nu)	40·5 (14·1)	42·5 (13·7)	46·7 (16·0)	21·1 (6·9)*	24·9 (14·6)*	26·3 (16·3)*
LF (SBP)	6·2 (3·9)	4·1 (2·1)	5·6 (4·6)	15·9 (8·9)*	12·6 (10·9)*	12·7 (14·5)*
HF (SBP)	1·46 (0·82)	1·48 (1·23)	1·88 (1·61)	4·64 (2·82)*	3·42 (2·81)**	4·51 (2·64)*

CO=cardiac output in $l.min^{-1}$; TPR=total peripheral resistance in $dyn.s.cm^{-5}$; HR=heart rate in $beats.min^{-1}$; heart rate variability in nu; SBP=systolic blood pressure variability in $mmHg^2$; BRG=baroreceptor gain (as α index or temporal sequences) in $ms.mmHg^{-1}$; LF, HF=low/high frequency.
*$P<0·01$ for changes among basal and tilt in each group
**$P<0·05$ for changes among basal and tilt in each group
***$P<0·05$ for comparison among the three groups (no other significant differences were found in the comparison of the three groups, or in comparisons between tilt negative and tilt positive groups in basal or in tilt)

paired samples we used the Wilcoxon signed test. A P value <0·05 was considered for statistical significance.

Results

None of the haemodynamic or autonomic parameters were different among the groups, either in the basal condition or tilt position, except for systolic blood pressure which was higher in the control group in the supine position (Table 1). The normalization of the HRV data was performed; the absolute values were skewed. Nevertheless, the so-called sympathetic/parasympathetic balance was not different among the groups.

All the parameters changed between the basal condition and tilt upright in each group, except for systolic blood pressure and low frequency RR interval absolute power. As expected, cardiac output decreased with tilt in all groups, total peripheral resistance increased, heart rate increased, baroreceptor gain decreased, the normalized low frequency of HRV increased, vagal parameters of HRV (normalized or absolute) decreased and the systolic blood pressure variability increased in all bands.

We compared the differences (delta values) in the several autonomic parameters and haemodynamic variables between supine and tilt for all groups (Table 2) and no differences were observed among the groups. There was no significant change throughout the tilt test (beginning of tilt test and end of tilt test before occurrence of syncope) in cardiac output, total peripheral resistance, low frequency heart rate variability components (absolute or normalized), the high frequency component of HRV (normalized units) or any spectral oscillation of systolic blood pressure variability (Table 3). There was a rise in heart rate and a decrease in baroreceptor gain, systolic blood pressure and a decrease in the high frequency component in absolute units.

Discussion

Conflicting data about autonomic and haemodynamic roles in neurocardiogenic syncope were published recently (Table 4). It seems, however, there is agreement in all studies, that neurocardiogenic syncope patients and controls are not different when studied in the basal (supine) condition. Our results are very similar to those of Jardine *et al.*[19], except for the absence of performing muscle sympathetic nerve activity MSNA in our patients and the absence of performing non-invasive determination of cardiac output or peripheral resistance in their group.

Our data suggest that, except for lower levels of systolic blood pressure among the two syncope groups and controls in the supine position, neurocardiogenic syncope patients are not different from normal controls or from, patients with other types of syncope as regards autonomic and haemodynamic data. The reason for this is not obvious and it seems in related to sympathetic drive, cardiac output or peripheral total resistance. These data should be confirmed with a larger number of patients.

The orthostatic stress induced by head-up tilt provoked a similar change in all variables, autonomic or haemodynamic, in all groups. As expected, there was a significant fall in cardiac output, in spite of a rise in heart rate. Total peripheral resistance rose, as did sympathetic indexes (Lf_{nu} and LF_SBP). There was no change in LF_RR absolute power with head-up tilt,

Table 2 Differences in autonomic and haemodynamic variables in the first 10 min of tilt in comparison with basal (∇ Tilt/Basal), between groups. Results: mean (SD)

	Control (A)	Tilt negative (B)	Tilt positive (C)
CO	− 1·05 (0·71)	− 0·56 (1·07)	− 0·78 (0·61)
TPR	537 (314)	403 (369)	587 (382)
HR	12·0 (6·3)	16·3 (9·7)	20·4 (12·9)
SBP	5·8 (12·4)	13·0 (10·5)	5·1 (10·9)
BRG-α	− 5·3 (2·6)	− 6·7 (5·0)	− 7·5 (6·6)
BRG-t	− 5·5 (4·0)	− 6·5 (4·2)	− 5·8 (4·1)
LF (RR)	− 27·1 (382)	− 107 (470)	203 (923)
LF (nu)	22·0 (12·6)	19·2 (11·9)	24·5 (20·0)
HF (RR)	− 357 (322)	− 226 (276)	− 187 (305)
HF (nu)	− 19·3 (11·6)	− 17·6 (11·1)	− 20·4 (16·2)
LF (SBP)	9·7 (7·5)	8·5 (10·4)	7·1 (11·3)
HF (SBP)	3·2 (2·1)	1·9 (2·9)	2·6 (2·5)

CO=cardiac output in $l.min^{-1}$; TPR=total peripheral resistance in $dyn.s.cm^{-5}$; HR=heart rate in $beats.min^{-1}$; heart rate variability in ms^2 and nu; SBP=systolic blood pressure variability in $mmHg^2$; BRG=baroreceptor gain (as α index or temporal sequences) in $ms.mmHg^{-1}$.
No significant differences were found in the comparison of the three groups or in comparisons between tilt-negative and tilt- positive groups.

which agrees with previous published data.[11, 23] which, in turn, confirms that it is not related to the sympathetic nervous system. Unlike the high frequency component of heart rate variability, the HF component of systolic blood pressure variability does not seem to be autonomically (vagal) related since it rises with orthostatic stress. It is probably related to the mechanical effect on haemodynamics provoked by respiration.[24] The baroreceptor gain fell significantly at the beginning of head-up tilt, probably due to the abrupt inhibition of vagal reflexes.

Table 3 Comparison of autonomic and haemodynamic variables obtained in the first 5 min of tilt and 5 min before syncope occurrence in patients with a positive tilt — Group D

	First 5 min or tilt	5 min before sycope
CO	3·2 (1·5)	2·9 (1·4)
TPR	2686 (1410)	2781 (1232)
HR	87·6 (19·3)	94·9 (23·1)*
SBP	122·6 (18·7)	109·4 (16·7)*
BRG-α	7·6 (3·5)	5·5 (3·1)**
BRG-t	6·9 (3·0)	5·1 (2·2)*
LF (RR)	390 (352)	290 (294)
LF (nu)	59 (25)	63 (24)
HF (RR)	150 (148)	80 (81)**
HF (nu)	30 (16)	22 (10)
LF (SBP)	9·5 (7·7)	10·9 (8·2)
HF (SBP)	2·0 (1·1)	3·1 (2·7)

CO=cardiac output in $l.min^{-1}$; TPR=total peripheral resistance in $dyn.s.cm^{-5}$; HR=-heart rate in $beats.min^{-1}$; heart rate variability in nu; SBP=systolic blood pressure variability in $mmHg^2$; BRG=baroreceptor gain (as α index or temporal sequences) in $ms.mmHg^{-1}$.
*$P<0·01$ for changes between the first 5 min of tilt and the 5 min before syncope
**$P<0·05$ for changes between the first 5 min of tilt and the 5 min before syncope

The absolute power of HRV (tonic vagal effect) falls significantly with head-up tilt in spite of the skewed nature of the data.

Although not significant, there was a tendency for the induced neurocardiogenic syncope group to [??009] a more pronounced tachycardia response to tilt than the other groups (20 $beats.min^{-1}$ compared with 12 $beats.min^{-1}$ in controls and 16 in the non-neurocardiogenic syncope group).

In the other subset study, only in neurocardiogenic syncope patients, with an average tilt time of 24 ± 9 min did we observe several differences between the initial 5 min of head-up tilt and the 5 min before syncope. Similar to the findings of others, we observed an increase in heart rate before syncope occurred[5,7,19] and a fall in systolic blood pressure[5,7,19,20]. Surprisingly, there was no change in cardiac output or total peripheral resistance, probably because in these patients the pre-syncoper disturbance is not haemodynamically mediated but baroreceptor/autonomic related. There was a fall in baroreceptor gain before syncope, as well as a fall in the index of vagal heart rate modulation. The sympathetic HRV and SBPV indexes did not change before the occurrence of syncope. In spite of the fact that we did not performe MSNA, it seems that the occurrence of neurocardiogenic syncope is preceded by inhibition of vagal activity (reflex and tonic) with no alteration in the sympathetic drive to the sinus node or arterial wall. In the future it would be wise to study the effect of drugs that enhance baroreceptor gain and vagal activity in the treatment of neurocardiogenic syncope patients.

Recently, Furlan *et al.*[25] showed that vasovagal responses in healthy subjects have different patterns, that may reflect different or even opposing changes in the cardiac autonomic profile of fainting subjects. One pattern shows a progressive increase in cardiac sympathetic modulation, up to the sudden onset of

Table 4 Comparison of autonomic and haemodynamic variables in several recent studies

Study	HRV	HR	BP	SBPV	BRG	MSNA
Kochiadakis[5]	↑ LF/HF only before syncope	↑ before syncope	↓ before syncope	?	?	?
Morillo[7]	No change	↑ before syncope	↓ before syncope	?	↓ basal No change in tilt	↓ only before syncope
Thomson[18]	?	?	?	?	↓ only cardiopulmonar not carotid BR	?
Jardine[19]	?	↑ before syncope	↓ before syncope	?	↓ before syncope	↓ only before syncope
Lagi[20]	↓ LF and LF/HF before syncope, ↑ HF	↓ before syncope	↓ before syncope	↓ LF	?	?
Mosqueda-Garcia[21]	?	?	?	?	↓ before syncope	↓ in all phases of tilt, particularly before syncope
Prinz-Zaiss[22]	↓ LF only before syncope, ↓ HF, no change in LF/HF	No change	?	?	?	?

HRV=heart rate variability; HR=heart rate; BP=blood pressure; SBPV=systolic blood pressure variability; BRG=baroreceptor gain; MSNA=muscle sympathetic nerve activity

bradycardia, and the second displays a gradual inhibition of sympathetic and concomitant enhancement of cardiac vagal modulation. These findings show that there are different pathophysiological mechanisms underlying neurocardiogenic syncope which could explain why beta-blockers are not effective in all cases of this type of syncope.

Conclusions

Our group of patients with neurocardiogenic syncope and a positive tilt response had preserved autonomic function and haemodynamics and are not different from normal controls or tilt-negative syncope patients in the supine position or in the initial minutes of head-up tilt. These patients are prone to syncope with prolonged head-up tilt, probably because of a spontaneous fall in baroreceptor gain (vagal reflex) and in parasympathetic tonic activity. Our data suggest that the sympathetic drive to the sinus node and vasomotor activity do not change, at least until syncope develops.

We gratefully acknowledge the assistance of the laboratory personnel, research assistant Rosa Santos and of registered nurse Emilia Teixeira.

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