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Psychophysiological evaluation of patients with transient consciousness loss of uncertain origin

Donatella Brisinda, Lara La Brocca, Anna Rita Sorbo, Gianmarco Lombardi, Francesco Fioravanti, Riccardo Fenici

Catholic University of Sacred Heart, Rome Italy – Biomagnetism and Clinical Physiology International Centre (BACPIC), Roma, Italy

Abstract

Background: Psychological profile (PsyP) of patients with transient loss of consciousness (TLoC) is evidence of high prevalence of anxiety and depression. However, the mechanistic link between abnormal PsyP and TLoC is still unclear.

Aim: This study aimed to evaluate: 1) prevalence of abnormal PsyP in TLoC patients; 2) cardiac autonomic response to head-up tilt test (HUTT) in patients with (PsyP+) or without abnormal PsyP (PsyP–), developing syncope (HUTT+) or not (HUTT–).

Methods: Forty-one patients (66% female, mean age 36 ± 15 years), with history of TLoC, underwent PsyP before HUTT. Short-term heart rate variability analysis was carried out under baseline rest condition and at peak heart rate and/or onset of syncope induced by nitroglycerine (NTG), during HUTT.

Results: HUTT+ occurred in 17/41 patients, more frequently in females, who had higher levels of anxiety ($p < 0.0001$). PsyP+ was prevalent in 70.5% of HUTT+ patients ($p < 0.05$). Among PsyP+ patients HUTT+ had dominant sympathetic modulation (DSM) at rest, which increased at the onset of syncope, whereas in HUTT patients vagal modulation was prevalent at rest. Among NTG-induced HUTT+ patients, fourfold higher increases of very low frequency (VLF) power were found in PsyP– compared with PsyP+.

Conclusions: 58% of patients with history of TLoC were PsyP+. In PsyP+ patients, DSM at rest correlates with higher probability of NTG-induced syncope, which occurs with 60% increment of low frequency and 530% increment of VLF power. Conversely, in patients with prevalent vagal modulation at rest and a decrease in VLF power after NTG, syncope did not occur. This supports interpretation of VLF power as an index of stress-induced sympathetic activity.

Key words: neurally mediated syncope, head-up tilt test, heart rate variability analysis, psychophysiology, anxiety

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INTRODUCTION

Syncope is defined as a transient loss of consciousness (TLoC), usually characterised by spontaneous, rapid, and complete recovery [1, 2]. Clinical presentation of vasovagal syncope, the most common cause of neurally mediated TLoC, varies from typical (characterised by prodromal symptoms as nausea, vomiting, abdominal pain, pallor, sweating, and the presence of precipitating factors such as emotional distress or orthostatic stress) to atypical pattern (no evident trigger and no prodromal symptoms), or unexplained fall, or syncope during sleep [1]. Although the diagnosis of vasovagal syncope can be confirmed with head-up tilt test (HUTT), alone or potentiated with nitroglycerine (NTG) [3, 4], the pathophysiology of individual TLoC is not always clearly understood [5], especially in the absence of structural cardiac and neurological abnormalities. Moreover, the psychological profile (PsyP) of patients with TLoC is evidence of higher levels of anxiety, fear [5, 6], panic, and depression (that ranges between 15% and 30% of cases) [7, 8], with impaired quality of life [5], which can be improved by psychological intervention such as cognitive and behavioural therapy [9].

Since the mechanistic role of abnormal PsyP (PsyP+) in the genesis of TLoC is still uncertain, this study aimed to evaluate whether baseline cardiovascular autonomic nervous system (CANS) modulation and/or HUTT-induced CANS response, evaluated with heart rate variability analysis (HRVa) [10–12], could be different as a function of individual PsyP and useful to predict and/or understand the mechanism of syncope at HUTT. More specifically we aimed to:

Address for correspondence:
Riccardo Fenici, MD, Professor of Cardiology, Director of BACPIC, Catholic University of Sacred Heart, Rome Italy – Biomagnetism and Clinical Physiology International Centre (BACPIC), Largo A. Gemelli, 8, 00168, Roma, Italy, e-mail: riccardo.fenici@unicatt.it

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— define the PsyP of patients undergoing HUTT for history of TLoC;
— evaluate if higher level of anxiety and/or depression was correlated with specific HRVa patterns;
— evaluate if the integration of PsyP, HRVa, and HUTT outcome could improve the understanding of pathophysiological mechanisms underlying TLoC, based on the hypothesis that PsyP+ might have a pathogenetic role in the occurrence of TLoC, through a specific pattern of CANS.

Our hypotheses were that:

— PsyP+ was prevalent in patients with history of TLoC;
— higher level of anxiety should be associated with dominant sympathetic modulation (DSM) at baseline rest and with higher incidence of HUTT-induced syncope;
— prevalent vagal modulation should be found in patients with normal PsyP (PsyP–), having a protective effect against the induction of syncope at HUTT.

METHODS

Patients

Data of 41 consecutive patients (14 males and 27 females, mean age 36 ± 15 years), with clinical history of one or more TLoC episodes and referred for HUTT between January 2014 and April 2016, were retrieved form our clinical database. Syncope was defined according to European Society of Cardiology (ESC) guidelines [3].

All patients were free from other diseases that could have an impact on the outcome of the study. In particular, patients with structural cardiac or neurological disease (including movement disorder diseases), hypoglycaemia, diabetes, drug intoxication, positional vertigo, or any other abnormality potentially affecting heart rate (HR) variability were excluded. None of the patients had been previously diagnosed with depression/anxiety.

All patients had been investigated for clinical needs, in agreement with good clinical practice rules and the declaration of Helsinki, after written, informed consent.

Psychological assessment

As a routine screening, all patients had filled out the following four questionnaires before HUTT:

— Zung Self-Rating Anxiety Scale [13]: a 20-item self-report assessment device**,** where overall assessment is done by total raw scores ranging from 20 to 80 (20–40: normal range; 45–59: mild to moderate anxiety level; 60–74: marked to severe anxiety level; 75–80: extreme anxiety levels);
— Spielberger's State Trait Anxiety Inventory (STAI) [14]:
  a) Y1, 20 items for assessing "trait anxiety", i.e. the anxiety the patient feels coming in contact with a stressor;
  b) Y2, 20 items for "state anxiety", i.e. the tendency to react with anxiety during everyday life;
— Zung Self-Rating Depression Scale [15]: short self-administered survey based on 20 items on the scale, which rates the affective, psychological, and somatic symptoms associated with depression. The scores fall into four ranges (20–44: normal; 45–59: mildly depressed; 60–69: moderately depressed; 70 and above: severely depressed);
— Beck Depression Questionnaire [16], i.e. multiple-choose self-report inventories measuring depression severity:
  a) BDI: 21 questions (10–19: minimal depression; 20–29: moderate depression; > 30: severe depression);
  b) BDI-II: 21 questions (0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression);
  c) BDI-PC: 7 questions (0–3: minimal depression; 4–6: mild depression; 7–9: moderate depression; 10–21: severe depression).

Depression and/or anxiety were diagnosed whenever one test was scored severely positive or two tests were scored moderately positive.

HUTT

HUTT was carried out following the Italian protocol [4], in the morning (range 8.30–12 a.m.), in a quiet room, with the patient fasting from 8 h, under continuous 12-lead telemetric electrocardiogram, non-invasive blood pressure (BP), and oxygen saturation monitoring. After a supine rest of 20 min, the patient was tilted to 60 degrees for 20 min; if syncope or pre-syncope were not induced, sublingual NTG spray (dosage 300 μg) was administrated. A positive HUTT response (HUTT+) was defined if syncope (or pre-syncope characterised by systolic BP decrease and/or bradycardia/asystole) occurred. Syncope was classified as type I, mixed (HR decreases during syncope but does not drop below 40 bpm, or drops below 40 bpm for < 10 s, with or without asystole < 3 s, and BP decreases before HR fall); type II, cardio-inhibitory (type IIA: HR drops below 40 bpm for more than 10 s, without asystole > 3 s, and BP decreases before HR fall; type IIB: cardioinhibition with asystole > 3 s; BP fall coincides with or occurs before the HR); and type III, vasodepressor (BP falls to a systolic value < 60 mmHg; HR during syncope does not fall by more than 10% of its peak value).

HRV analysis

Short-term HRVa was performed, following the ESC guidelines [17], at baseline (supine position, 10 min before tilting), at the onset of syncope (for HUTT+) or at maximum peak of HR after NTG administration, in patients without syncope occurrence (HUTT–).

All parameters were calculated with the Kubios HRV software, version 2.1 [18] from 2-min segments in the time-domain, frequency-domain (with the fast Fourier transform [FFT], and with the autoregressive model [AR]), and with non-linear methods (Table 1) [12, 17].

Table 1. Description of heart rate variability parameters

Parameter		Units	Description	
Time domain	RR mean	ms	Mean of RR intervals	
	SDNN	ms	Standard deviation of RR intervals	
	RMSSD	ms	Square root of the mean squared differences between successive RR intervals	
	NN50		Number of successive RR interval pairs that differ more than 50 ms	
	PNN50	%	NN50 divided by the total number of RR intervals	
	SDNN/RMSSD		Ratio between SDNN and RMSSD	
Frequency domain	VLFpowFFT			
	LFpowFFT	ms^2	Absolute power of VLF, LF, and HF bands	
	HFpowFFT			Fast Fourier transform
	LF/HF FFT		Ratio between LF and HF band powers	
	VLFpowAR			
	LFpowAR	ms^2	Absolute power of VLF, LF, and HF bands	
	HFpowAR			
	VLFpowprAR	%	Relative power of VLF, LF and HF bands	Autoregressive model
	totpowAR	ms^2		
	LF/HF AR		Ratio between LF and HF band powers	
Nonlinear	SD1/SD2		Ratio between SD1 and SD2	
	SD1	ms	Standard deviation of the Poincarè plot perpendicular to the line of identity	
	SD2	ms	Standard deviation of the Poincarè plot along the line of identity	
	RPLmean	beats	Recurrence plot mean line length	
	RPLmax	%	Recurrence plot maximum line length	
	rprec	%	Recurrence plot recurrence rate	
	rpadet		Recurrence plot determinism	
	rpshen		Recurrence plot Shannon entropy	
	DFA1		Detrended fluctuation short term fluctuation slope	
	DFA2		Detrended fluctuation long term fluctuation slope	
	apen		Approximated entropy	
	sampen		Sample entropy	
	d2		Correlation dimension	

Abbreviations — see text

Statistical analysis

Statistical calculations were performed with SPSS software, version 21.0 (SPSS Inc., Chicago, Illinois) [19]. Continuous variables are presented as mean ± standard deviation (SD). The t-test and the Mann-Whitney-Wilcoxon nonparametric test were used to determine differences between groups (or subgroups), considering $p < 0.05$ as statistically significant.

HRV parameters were compared among subgroups of patients, clustered on the basis of PsyP and HUTT results.

Linear discriminant analysis (LDA) [20] was used to evaluate which HRV parameters, alone and/or in combination, could provide a separation among the subgroups. LDA searches for linear combinations of the input features that can provide an adequate separation between two or more classes. The discriminant functions used by LDA are built up as a linear combination of the variables that seek to maximise the differences between the classes [12, 20]. The classification accuracy of the method is defined as the ability to discriminate between the investigated groups.

RESULTS

The majority (76%) of the enrolled patients had experienced only one episode of TloC at the time of the study.

Overall, 24/41 (58.5%) patients had abnormal PsyP (PsyP+), while 17/41 patients had normal psychological pattern.

No patient had spontaneous syncope during the first 20 min of HUTT. 17/41 patients (41.4%) had an NTG-induced positive response to HUTT (two cardio-inhibitor type; six mixed type; nine vasodepressor type). Out of them, only five

Table 2. Heart rate variability parameters of group 1 and group 2 patients with or without HUTT–induced syncope and/or abnormal psychological profile

	Abnormal psychological profile								Normal psychological profile							
	HUTT positive — Group 1A				HUTT negative — Group 2A				HUTT positive — Group 1B				HUTT negative — Group 2B			
	REST		SYNCOPE		REST		Max NTG-ind HR		REST		SYNCOPE		REST		Max NTG-ind HR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RR mean	953.8	114.1	765.8	171.3	946.1	76.4	736.1	158.2	1016.0	122.4	841.1	156.7	1003.0	185.4	671.2	100.1
SDNN	26.6	6.0	31.8	12.3	26.8	5.8	26.8	7.1	20.4	7.9	34.8	15.2	25.8	2.9	31.2	8.8
RMSSD	25.9	7.3	17.7	5.9	27.5	6.6	17.7	4.8	25.9	13.1	19.5	8.1	22.8	4.4	15.8	4.5
NN50	9.0	7.0	3.0	2.0	11.0	8.0	3.0	3.0	11.0	12.0	5.0	5.0	4.0	3.0	2.0	2.0
PNN50	7.6	6.6	2.3	2.0	8.6	6.4	1.8	1.9	9.7	11.2	3.7	4.0	3.7	2.9	1.0	1.5
SDNN/RMSSD	1.1	0.2	1.8	0.5	1.0	0.4	1.5	0.3	0.9	0.3	1.8	0.5	1.2	0.2	2.0	0.3
VLFpowFFT	65.6	70.9	409.6	457.8	77.0	87.9	50.8	60.5	27.4	43.4	636.0	603.2	89.5	55.2	114.7	103.8
LVpowFFT	399.0	235.2	647.8	516.4	247.9	235.5	604.0	393.5	117.3	71.8	861.1	493.9	412.2	161.0	753.5	365.7
HFpowFFT	240.9	131.6	124.4	119.6	270.4	133.4	165.5	128.6	244.7	220.6	161.3	116.0	183.8	91.4	89.9	62.6
LF/HF FFT	2.5	2.1	6.7	4.1	1.3	1.4	4.7	2.6	1.2	1.7	6.1	3.9	2.6	1.1	11.5	7.8
VLFpowAR	63.0	46.8	390.6	397.8	102.6	116.4	73.0	43.7	38.9	19.6	510.1	429.3	81.2	44.7	121.0	75.5
LFpowAR	395.5	229.7	658.2	392.3	298.6	226.0	510.9	270.6	153.5	73.4	730.6	400.4	406.1	154.1	824.5	450.7
HFpowAR	264.5	150.7	117.6	77.8	312.2	168.2	141.6	96.1	416.3	326.3	147.1	112.1	176.7	65.0	95.0	73.1
VLFpowprAR	9.2	5.9	27.7	13.6	12.0	8.4	10.2	2.9	9.8	9.6	29.6	18.4	12.5	7.6	11.6	5.3
totpowAR	723.4	310.0	1166.7	751.0	714.9	312.2	725.7	372.1	609.2	335.2	1388.0	816.5	664.4	178.7	1040.7	548.8
LF/HF AR	2.2	1.9	6.8	4.5	1.4	1.6	4.4	2.1	1.4	2.0	6.0	3.9	2.5	1.0	11.9	7.3
SD1/SD2	0.6	0.2	0.3	0.1	0.7	0.3	0.4	0.1	0.8	0.3	0.3	0.1	0.5	0.1	0.3	0.0
SD1	18.4	5.2	12.6	4.2	19.6	4.7	12.6	3.4	18.4	9.3	13.8	5.8	16.2	3.1	11.2	3.2
SD2	32.5	8.2	42.9	17.3	31.5	9.5	35.6	9.9	21.8	8.1	47.2	21.1	32.5	4.0	42.5	12.1
RPLmean	6.3	1.3	10.6	3.3	7.4	1.5	9.2	2.0	6.5	2.4	10.9	4.9	6.7	1.1	11.4	3.5
RPLmax	50.0	31.0	111.0	35.0	55.0	27.0	109.0	57.0	40.0	37.0	107.0	45.0	54.0	34.0	162.0	40.0
rprec	17.6	5.3	34.6	9.4	18.9	6.0	27.7	6.7	16.7	9.0	31.9	12.2	20.5	4.8	34.2	6.7
rpadet	93.9	2.9	98.4	1.3	95.0	2.6	97.7	1.6	92.7	4.0	98.3	1.2	95.3	2.0	98.9	0.6
rpshen	2.4	0.3	3.0	0.3	2.6	0.2	2.9	0.2	2.3	0.4	2.9	0.3	2.5	0.2	3.1	0.3
DFA1	1.0	0.2	1.4	0.3	0.9	0.3	1.3	0.2	0.7	0.3	1.5	0.1	1.1	0.2	1.6	0.1
DFA2	0.3	0.1	0.7	0.2	0.4	0.2	0.4	0.2	0.4	0.2	0.6	0.2	0.4	0.1	0.5	0.2
apen	0.7	0.1	0.8	0.1	0.6	0.1	0.8	0.1	0.6	0.1	0.8	0.1	0.7	0.1	0.8	0.1
sampen	1.8	0.3	1.2	0.3	1.8	0.5	1.5	0.4	2.2	0.4	1.3	0.3	1.6	0.3	1.2	0.3
d2	1.3	1.2	1.2	0.9	1.2	1.0	1.0	1.0	0.7	1.0	1.7	1.4	0.6	0.4	1.2	1.0

HR — heart rate; HUTT — head-up tilt test; NTG — nitroglycerine; SD — standard deviation; other abbreviations — see text

Table 3. Different patterns of cardiovascular autonomic nervous system modulation among patients group

HUTT	Psychological assessment					
	Abnormal psychological profile (n = 24)			Normal psychological profile (n = 17)		
	Baseline rest	Syncope	Peak HR	Baseline rest	Syncope	Peak HR
Positive (n = 17)	Group 1A (n = 12)			Group 1B (n = 5)		
	Dominant sympathetic modulation	Enhanced sympathetic dominance		Prevalent vagal modulation	Enhanced sympathetic dominance	
	Group 2A (n = 12)			Group 2B (n = 12)		
Negative (n = 24)	Prevalent vagal modulation		Physiological sympatho-vagal balance (with reduced VLFpower)	Physiological sympatho-vagal balance		Physiological sympatho-vagal balance

HR — heart rate; HUTT — head-up tilt test; other abbreviations — see text

(12%) patients with normal PsyP had NTG-induced syncope at HUTT. By integrating the results of PsyP and HUTT, four subgroups were identified, the HRVa parameters of which are summarised in Table 2:

- group 1A (12 patients) with PsyP+ and HUTT+;
- group 2A (12 patients) with PsyP+ and HUTT–;
- group 1B (5 patients) with PsyP– and HUTT+;
- group 2B (12 patients) with PsyP– and HUTT–.

Based on HRVa, it was found that patients with history of TLoC and abnormal PsyP may have different patterns of CANS modulation at baseline rest and/or at the peak of NTG-induced vasodilatation during HUTT, which correlate with and are predictive of the induction of syncope at HUTT (Table 3).

In fact, among PsyP+ patients, a significant dominance of sympathetic modulation was found in those with HUTT+ (group 1A) compared with those with HUTT– (group 2A), both at rest (> low frequency [LV] power) and at the peak HUTT response (> very low frequency [VLF] power, > LVpower%, > DFA2 and > rprec). In fact, in group 1A, a 60% increment of LVpower and 530% increment of VLFpower were found immediately before syncope.

Instead, in PsyP– patients (groups 1B and 2B), a prevalence of vagal modulation (< SDNN/RMSSD, < LVpower, and < LF/HF (1.2–1.4); > high frequency [HF] power, > totpower, > SD1/SD2, > sampen) in group 1B, or a physiological sympatho-vagal balance in group 2B were found at rest (Table 2). At the LDA, the combination of basal SDNN/RMSSD, totpower, SD1/SD2, and sampen in the formula: F1 = (0.26 × SDNN/RMSSD) + (0.003 × totpower) + (2.935 × SD1/SD2) + (1.85 × sampen) + (–2.934), provided 94% of discriminant accuracy (cross correlated), identifying HUTT+ response, if F1 < 0.

Furthermore, among PsyP– patients, syncope did not occur (group 2B) when, besides a balanced sympatho-vagal modulation at rest, VLFpower did not increase significantly after NTG administration. Instead, four-fold (VLFpower) to ten-fold (LFpower) increment of sympathetic activation was associated with the occurrence of NTG-induced syncope (in group 1B). At peak NTG-induced HR (HUTT–) or syncope (HUTT+), VLFpower, LFpower, DFA1 were significantly different.

These findings support the hypothesis that CANS imbalance towards an abnormal sympathetic dominance could be one of the mechanism favouring the occurrence of syncope in patients with abnormal PsyP.

Interestingly, the behaviour of VLFpower correlates significantly with the occurrence of syncope, its increment being highly correlated with HUTT+ response, independently of PsyP. In fact, as shown in Table 2, among HUTT+ patients VLFpower increased from 65.6 ms^2 (at rest) to 409.6 ms^2 (at syncope) in group 1A (+524%), and from 27.4 ms^2 (at rest) to 636.0 ms^2 (at syncope) in group 1B (+2221%). Conversely, in HUTT– patients a decrease in VLFpower (if compared to rest values) was found at the moment of max NTG-induced HR peak in group 2A (PsyP+), whereas average VLFpower remained almost unchanged, if compared to baseline values in PsyP– patients (group 2B).

In HUTT + patients, the timing of maximum VLFpeak with respect to the onset of syncope was different depending on the mechanism of syncope (Fig. 1). In fact, maximum VLFpeak occurred after the onset of syncope in the cardiodepressor type (Type 2b), followed the onset of syncope in the vasodepressor type (Type 3), while it occurred almost simultaneously in the mixed type (Type 1).

No significant differences were observed between patients with just one and patients with more than one episode of TLoC before the study session.

DISCUSSION

Although widely investigated with methods and algorithms standardised in international guidelines [3], the pathophysiol-

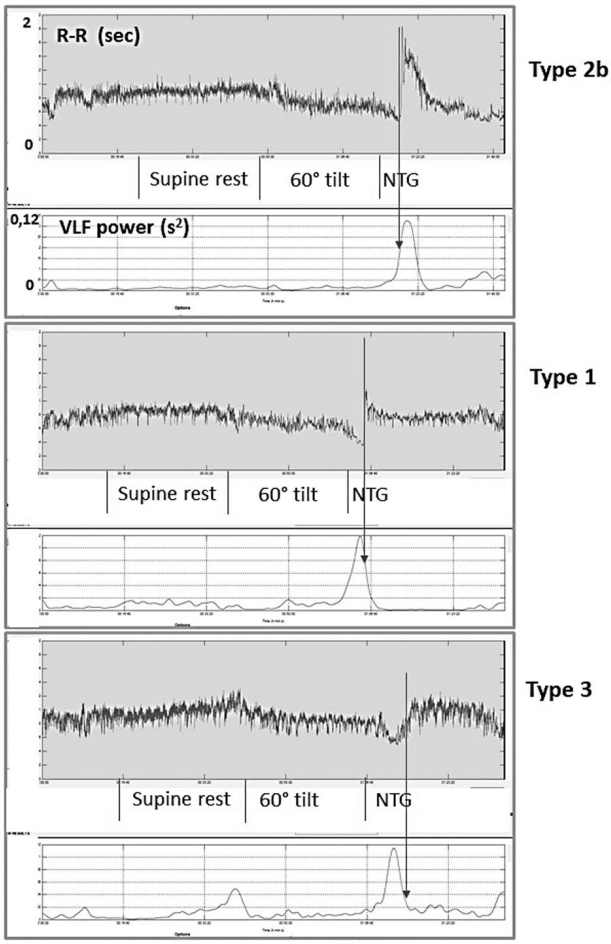

Figure 1. Time-varying changes of very low frequency (VLF) power during head-up tilt test (HUTT) in three HUTT+ patients with different kinds of neurally mediated syncope. The vertical arrows indicate the onset of syncope; Type 2b — cardiodepressor; Type 1 — mixed; Type 3 — vasodepressor; NTG — nitroglicerine

ogy of TLoC occurring in the absence of structural cardiovascular and/or neurological disorders is not yet fully elucidated and may still represent a diagnostic challenge. In particular, the mechanistic role of psychological factors in the genesis of TLoC is still undefined, although a higher prevalence of anxiety and depression in patients with TLoC compared to age-matched normal subjects has been reported [8, 9]. Such evidence was confirmed also in the present study.

Considering the possible role of psychological factors in the aetiology and in the response to treatment of neurally mediated and unexplained syncope [2, 5], we investigated the hypothesis that different CANS modulation could be found in patients with evidence of abnormal PsyP, at baseline rest and during HUTT, which would be useful in the understanding of the possible role of anxiety as an individual mechanism of TLoC.

By integrating PsyP, HRVa, and pharmacologically potentiated HUTT, we found that: among PsyP+ patients, CANS pattern of those developing syncope at HUTT (group 1A) was characterised by the prevalence of sympathetic modulation at baseline rest, which was enhanced at the onset of syncope, with 60% increment of LFpower and 530% increment of VLFpower; instead, in those with negative HUTT (group 2A) a balanced sympatho-vagal modulation was found at baseline rest, with lower (if compared to group 1A) increment of LFpower and remarkable decrease of VLFpower at the peak of NTG-induced HR increment.

Among PsyP– patients, the CANS pattern of those developing syncope at HUTT (group 1B), despite parasympathetic prevalence at rest, was reverting to marked sympathetic dominance at the onset of syncope; instead, the CANS pattern of subjects with negative HUTT response (group 2B) was characterised by physiological sympatho-vagal balance both at baseline rest and the moment of maximum HR increase, after NTG administration, with more stable HRV parameters, including non-significant changes of VLFpower (Table 3).

In patients with HUTT+ response, a considerable increase of VLFpower was found at the onset of syncope as compared to rest condition in all of them, independently of PsyP. However, the quantitative increment of sympathetic activation indices was much higher (i.e. four-fold increment of VLFpower and ten-fold increment of LFpower) in group 1B than in group 1A. Instead, in HUTT– patients, a physiological sympatho-vagal balance or prevalence of vagal modulation was found in baseline conditions, with opposite changes of LFpower and of VLFpower at the moment of max NTG-induced HR. Thus, in this study, VLFpower was a highly sensitive parameter to differentiate HUTT+ from HUTT– patients, also showing clear-cut differences in HUTT+ patients, as a function of PsyP.

The physiological explanation and mechanisms generating the VLF component of HRV have not been fully elucidated yet. However, besides autonomic nervous system activity related to thermoregulation, the renin-angiotensin system, and other hormonal factors, recent experimental findings suggest that the "VLF rhythm" is intrinsically generated by the heart itself, and that the modulation and frequency of this rhythm occurs through efferent sympathetic activity, increasing before waking, with physical activity, stress response, and other factors that enhance efferent sympathetic activation [21]. A normal VLFpower is considered and indicator of healthy function, and low VLFpower has been associated with post-traumatic stress disorders [22]. Interestingly, we found that HUTT+ response was associated with significant enhancement of VLFpower (much higher in PsyP– patients), occurring with different timing in respect of the onset of syncope depending on the kind of neurally mediated mechanism (Fig. 1). Conversely, a lack of VLFpower increment during HUTT and after NTG correlated with HUTT– response.

Limitations of the study

One obvious limitation is the relatively low number of patients included (especially in group 1B), which was mainly due to the retrospective design of the study. In fact, since the administration of psychological tests had been routinely proposed, on a voluntary basis, only to younger patients, and after clear-cut exclusion of any possible structural cardiac or neurological abnormality, a significant number of available patients with HUTT were excluded because of incomplete or missing psychological datasets. A second limitation of this retrospective study is the lack of an age-matched control group of healthy subjects without history of TLoC, investigated with the same psychological and HRVa investigational protocols. Therefore, our results must be considered as purely preliminary and as a suggestion for more structured prospective studies.

Despite such limitations, it remains true that patients with abnormal PsyP have a higher probability of developing NTG-induced syncope at HUTT if such a psychological profile is associated with enhanced sympathetic modulation. Conversely, despite signs of anxiety/depression, a physiological sympatho-vagal balance is maintained and patients are "protected" from NTG-induced syncope at HUTT. In patients with a history of TLoC undergoing HUTT, preliminary psychological profiling and HRVa might improve the understanding of individual mechanisms underlying syncope, which would be useful to identify people who may need psychological support as part of personalised treatment. Nevertheless, regarding the HRV analysis, it must be underlined that, although widely accepted to estimate the sympatho-vagal modulation in psychophysiological research [23], it remains only a surrogate for CANS assessment and the results should always be interpreted with caution, unless cross-validated with simultaneous recording of other independent markers of single autonomic components, such as the skin potential response, index of sympathetic activity [24].

CONCLUSIONS

In summary, our results show that, in patients with abnormal PsyP, baseline prevalence of sympathetic dominance in rest condition is predictive of a HUTT+ response. Conversely, despite an abnormal PsyP pattern, if baseline CANS shows physiological sympatho-vagal balance or prevalent parasympathetic modulation at rest, the probability of syncope at HUTT is lower, unless the amount of sympathetic activation induced by HUTT potentiated with NTG, is very high, as observed in the few HUTT+ cases with normal PsyP (group 1B).

It seems therefore that syncope occurrence is favoured when sympathetic dominance is prevalent or less compensated by parasympathetic modulation at rest, or when there is a fast and sudden change from vagal modulation (at rest) to sympathetic dominance after NTG. This may suggest any active intervention addressed to rebalance psychophysiological control mechanisms of BP and HR, through moderate physical activity and paced respiration, might be useful to reduce anxiety and to improve quality of life of patients with TLoC in the absence of structural cardiac or neurological abnormalities.

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