International Journal of Cardiology 120 (2007) 102–107

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Modulations of autonomic activity leading to tilt-mediated syncope

Antonio Franco Folino [a,*], Giulia Russo [a], Alberto Porta [b], Gianfranco Buja [a], Sergio Cerutti [c], Sabino Iliceto [a]

[a] *Department of Cardiology, Via Giustiniani, 2, 35128 Padova, Italy*
[b] *Department of Preclinical Sciences, LITA di Vialba, University of Milan, Italy*
[c] *Department of Bioengineering, Polytechnic of Milan, Italy*

Received 4 August 2005; received in revised form 20 March 2006; accepted 25 March 2006
Available online 4 December 2006

Abstract

Background: Vasovagal syncope (VVS) results from a complex interaction among afferent vagal and sympathetic signals, cortical modulation and bulbar integration. The aim of our study was to evaluate the modifications of autonomic activity during Upright Tilt Test (UTT) in patients with unexplained syncope, and to correlate these changes with the specific cardiovascular reactions induced.
Methods and results: We studied 90 patients with a mean age of 44±17 yrs. Frequency domain analysis of heart rate variability (HRV) (normalized units) was performed on 2 periods of 300 beats: at baseline and after 5 min of 60° tilt. UTT was positive in 56 patients (62%). The responses were cardioinhibitory in 8, vasodepressive in 15, mixed in 33. Baseline LF and HF components did not show significant difference between subjects with positive or negative test (HF: 39±21 versus 41±22; LF: 50±22 versus 49±23). HRV during UTT showed similar changes in patients with positive or negative test. However, subjects with mixed or cardioinhibitory reactions were characterized by a relevant increase of LF during UTT (from 47±23 to 66±21), whereas the others by a non-significant decrease of the same component (from 57±19 to 51±31).
Conclusions: Patients developing a reflex cardioinhibitory reaction during UTT were characterized by an increase of sympathetic activity during the test, that might represent an essential factor to induce a stronger vagal reaction on the sinus node. On the contrary, in subjects with vasodepressive reactions an inadequate enhancement of the sympathetic drive, probably causing a failure of peripheral vasoconstriction, was evidenced.

Keywords: Syncope; Autonomic nervous system; Heart rate variability; Tilt Test; Spectral analysis

1. Introduction

Vasovagal syncope (VVS) represents the most frequent cause of loss of consciousness in general population. Notwithstanding the good prognosis of patients with VVS, this condition is sometimes characterized by frequent recurrences, often interfering with a normal life.

The diagnosis, based mainly on history, is usually easy, and can be confirmed by Upright Tilt Test (UTT) [1–4]. On the contrary, the pathophysiological mechanisms involved are debated and not univocally defined [5,6].

The reasons for these divergences are probably different. First of all, the autonomic nervous system, responsible for such episodes of neurally-mediated syncope, is characterized by a high instability. Therefore, it is very difficult to evaluate sudden and contrasting modifications of its activity just before onset of symptoms by conventional non-invasive methods. Moreover, it is probable that VVS could be induced by different mechanisms, even in the same subject. Therefore, the study of autonomic activity can detect different modifications of sympathetic and parasympathetic drive that lead to the same effect: the loss of consciousness.

The possibility that various mechanisms could be implicated in the genesis of VVS can also account for the difficulties in its treatment [7].

* Corresponding author. Tel.: +39 049 8211844; fax: +39 049 8761764.
E-mail address: franco.folino@unipd.it (A.F. Folino).

0167-5273/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2006.03.093

Table 1
Patients' characteristics

Patients, *n*	90
Age, yrs	44.28±17
Gender, M/F	47/43
Number of episodes of syncope, *n*	8.10±32
UTT time before symptoms, min	23.13±4
Characteristics of spontaneous syncope	
Syncope during orthostatism, pts	88
Syncope while seated, pts	36
Syncope during physical exercise, pts	5
Syncope after physical exercise, pts	6
Micturition syncope, pts	10
Injury following syncope, pts	37
Pharmacological treatments	
Diuretics, pts	1
ACE-inhibitors, pts	16
Angiotensin II receptors antagonists, pts	3
Lipid lowering drugs, pts	4

Upright Tilt Test is a powerful diagnostic tool to identify subjects with neurally-mediated syncope. However, it also offers an opportunity to study pathophysiological mechanisms leading to reflex syncope. The only doubt about UTT outcome is whether the mechanism induced by the test is the same as that operating during spontaneous episodes [8].

Several studies were addressed to evaluate the mechanisms of VVS by the use of UTT: one of the more important postulated theories suggests that neurally-mediated syncope results from the discharge of intramyocardial mechanoreceptors, induced by vigorous ventricular contraction secondary to the underfilled left ventricular cavity. [5,9–13]. In this case, an increase of the sympathetic drive before syncope occurrence is a mandatory condition to induce a vagal reaction.

In our study we analyzed the modifications of autonomic activity induced by UTT, to better understand the pathophysiological mechanisms leading to VVS. Moreover, in results analysis we correlated these changes with the different forms of vasovagal reactions induced by the test.

2. Patients and methods

2.1. Patients

We selected 95 consecutive patients, on the basis of the following inclusion criteria: two or more episode of unexplained syncope; age between 10 and 75 yrs; presence of sinus rhythm. The exclusion criteria were: documented cardiological or neurological diseases; presence of premature supraventricular or ventricular arrhythmias (>10/h); chronic treatment with drugs potentially interfering with autonomic activity.

Four patients were excluded for the occurrence of a relevant number of supraventricular or ventricular premature complexes. One patient was excluded for the presence of a wandering pacemaker and frequent premature atrial complexes. Therefore we studied a population of 90 patients, with a mean age of 44±17 yrs. The male/female ratio was 1.1 (Table 1). The study was approved by our institutional ethic review board.

2.2. Tilt Test protocol

The UTT protocol comprised a ten-minute supine first phase, a second phase at 60° for 20 min and, if the second phase was negative, a third phase maintaining 60° for 15 min, after sublingual spray nitrate administration (0.300 mg). During the test patients underwent continuous electrocardiographic monitoring, and blood pressure was recorded non-invasively, by an automatic cuff sphygmomanometer, at intervals of about 30 s. The test was considered positive if syncope occurred or if there was presyncope associated with relevant bradycardia (heart rate <40 bpm) or hypotension (defined as systolic blood pressure <70 mmHg or diastolic blood pressure <40 mmHg). Positive responses were classified, according to the Task Force on syncope of the European Society of Cardiology [14], in 4 categories: Mixed, cardioinhibitory, with or without asystole, and vasodepressive.

2.3. HRV analysis

The acquisition of the ECG signal to perform frequency domain analysis of HRV was performed in the morning, in a quite room, using an acquisition module with a sampling frequency of 500 Hz. A simultaneous recording of the respiratory rate was obtained by mean of a thoracic belt with impedance measurement.

Two periods of 300 beats each were recorded and considered for analysis: in supine position, after 5 min of rest, and after 5 min of upright tilt position at 60°. The selection of these two periods was based on the decision to obtain

Table 2
Changes of spectral component induced by Upright Tilt Test in patients with negative test and in patients with different forms of positive test

	Pts (*n*)	LF			HF		
		Baseline	TILT	*p*	Baseline	TILT	*p*
Negative UTT	34	49.3±23	61.9±24	<0.02	41.4±22	29.0±21	=0.005
Positive UTT	56	49.9±22	61.9±25	<0.005	39.0±21	27.9±21	<0.002
Vasodepressive	15	57.2±19	51.0±31	0.491	30.5±16	35.6±30	0.612
Mixed	33	46.4±24	68.6±19	<0.0001	41.8±22	23.5±16	<0.0001
Cardioinhibitory	8	43.9±18	50.7±33	0.454	46.4±25	31.2±17	0.251