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Comparative study of cerebral blood flow between postural tachycardia and neurocardiogenic syncope, during head-up tilt test

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We assessed the cerebral blood flow velocity response to head-up tilt test in patients with typical neurocardiogenic syncope compared with patients showing postural tachycardia. Fifty patients (21 men) with history of orthostatic intolerance, younger than 50 years (mean 27 ± 10), participated in the study. Transcranial Doppler sonography of the middle cerebral artery, heart rate and brachial blood pressure were recorded during a head-up tilt test. According to the outcome of the test, patients were categorized in two groups: neurocardiogenic syncope (29 patients) and postural tachycardia (21 patients). The clinical history of the two groups was similar. During baseline in the supine position, no differences in haemodynamic parameters were observed. From the first min of tilt, the heart rate was higher in patients with postural tachycardia than in patients with neurocardiogenic syncope. Although, during tilt, the absolute values of the cerebral blood flow parameters were similar in the two groups, throughout tilt, continuous observation of the Doppler recording in patients with postural tachycardia showed intermittent fluctuation of the blood flow velocity, with an oscillatory pattern, which were not observed in the recordings in patients with neurocardiogenic syncope. Comparison of patients with neurocardiogenic syncope, and those with postural tachycardia also showed larger variations of the pulsatility index ($P<0{\cdot}05$) in the postural tachycardia group. These findings support the possibility that abnormalities within the central nervous system play a pivotal role in the pathogenesis of postural tachycardia.

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Key Words: Neurocardiogenic syncope, postural tachycardia, head-up tilt, orthostatic intolerance, cerebral blood flow

Introduction

The aetiology of orthostatic intolerance is diverse, it is seen in syndromes such as postural hypotension, neurocardiogenic syncope and postural orthostatic tachycardia syndrome. An episode of neurocardiogenic syncope is diagnosed when there is loss of consciousness occurring suddenly while in the upright position, occasionally related to unpleasant or painful events, and consciousness returns within seconds in the supine position. Mild orthostatic tachycardia can occur in normal subjects related to anxiety, hyperventilation, hypovolemia[1] or prolonged bed rest[2,3]. However, the combination of severe orthostatic tachycardia accompanied by symptoms of orthostatic intolerance are related to autonomic dysregulation[4–6]. The postural orthostatic tachycardia syndrome is characterized by tachycardia accompanied by symptoms of cerebral hypoperfusion and sympathetic activation, which become manifest with assumption of upright posture and are relieved by sitting or lying down. The main symptoms are lightheadedness, blurred vision, palpitations, breathing difficulties, nausea and fatigue during standing; which are relieved by recumbency[7,8]. About 40% of patients have a history of loss of consciousness after prolonged standing, but they usually learn to avoid syncope by sitting or lying down as symptoms build in intensity[6].

Head-up tilt testing (HUT) is widely accepted as a tool to assess unexplained syncope[9]. It is known that, during HUT, postural orthostatic tachycardia can be differentiated from neurocardiogenic syncope because

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patients with postural tachycardia show heart rate increments of greater than 30 beats . min (bpm), accompanied by symptoms of cerebral hypoperfusion on standing[10]. Although there are systematic studies of cerebral blood flow on patients with neurocardiogenic syncope[8,11,12] and in patients with postural tachycardia[7,13,14], to our knowledge there are no comparative studies. This study was aimed to evaluate cerebral blood flow velocity response to HUT in patients suffering from typical neurocardiogenic syncope compared with patients showing postural tachycardia.

Methods

Subjects

Fifty patients with orthostatic intolerance, accepted to participate in the study, mean age 27 ± 10 years (21 men and 29 women). All the subjects gave their informed consent, and the Ethics Committee of the Instituto Nacional de Cardiología 'Ignacio Chávez' approved the study protocol. Subjects were selected because they were younger than 50 years and for having a history of at least two episodes of malaise while standing up. The episodes of malaise were characterized by: weakness, sweating, pallor, palpitations, warmth, nausea, and blurred vision. Twenty-eight (44%) of them also had a history of recurrent loss of consciousness. To assess specific causes of the orthostatic intolerance, a clinical evaluation was performed in all patients. Patients with structural heart disease, sick sinus syndrome, intraventricular conduction disturbance, orthostatic hypotension, chronic and paroxysmal atrial fibrillation, and permanent pacemakers were excluded from the study.

Head-up tilt test

HUT was performed between 9:00 am and 11:00 am, in a quiet room and after overnight fasting. Subjects were tilted to 70 degrees head-up, using a motorized tilt-table with a foot-board support. During the test, electrocardiogram leads I, II and III were continuously monitored and blood flow velocity in the middle cerebral artery was assessed by continuous transcranial Doppler sonography (DTC Multigon 500 Neurovision, Multigon Industries Inc., NY, U.S.A.). A 2-MHz Doppler probe was placed over a temporal window and fixed at a constant angle and position with an adjustable headband according to standard technique[15]. Doppler signals were recorded at least at 5 min intervals or more often if symptoms developed, to evaluate systolic peak velocity, end diastolic velocity and Gosling's pulsatility index ([(systolic velocity) − (diastolic velocity)]/mean velocity). The latter is an index of vascular resistance which reflects changes in cerebral small-vessel resistance[16]. Brachial blood pressure was recorded using a standard cuff sphygmomanometer at intervals of 5 min, whenever symptoms of malaise developed and immediately after each transcranial Doppler recording.

The HUT was considered to be positive when malaise symptoms appeared accompanied by systemic hypotension (systolic BP<90 mmHg or ≥30% reduction from baseline) and/or bradycardia (heart rate less than 50 bpm or ≥20% reduction in heart rate from baseline)[17]. According to the heart rate response to HUT, patients were categorized in two groups, neurocardiogenic syncope and postural tachycardia. Postural tachycardia was diagnosed when during the first 10 min of HUT patients showed an increase in heart rate of more than 30 bpm[4]. For ethical reasons, all patients were rapidly returned to the supine position once systemic hypotension was evident[18].

Statistical analysis

Results are described using mean values, standard deviation and 95% confidence intervals. Comparison between groups was performed using ANOVA and *t* test for independent samples. Differences were considered significant when the *P* value was less than 0·05.

Results

The clinical history of the patients showing postural tachycardia during HUT was similar to the history of the patients with typical neurocardiogenic syncope:

- Twenty-one patients showed postural tachycardia, four men and 17 women (mean age 26·2 years, SD 10·4). They had a history of orthostatic intolerance of 20·8 years (SD 10·3) and 13 (38%) of them also reported a history of loss of consciousness.
- Twenty-nine patients were positive for typical neurocardiogenic syncope, 17 men and 12 women (mean age 27·6 years, SD 10·1). They had a history of orthostatic intolerance of 21·6 years (SD 11·4) and 15 (49%) of them also reported a history of loss of consciousness.

As summarized in Table 1, during baseline in the supine position, no differences in haemodynamic parameters were observed between the two groups. During tilt, just heart rate was different between the two groups ($P<0·05$), while blood pressure and absolute values of cerebral blood flow parameters were similar. The difference in the heart rate response was patent throughout the HUT test, from the first min of tilt up to the occurrence of hypotension ($P<0·01$) (Table 2).

During HUT, the time to develop hypotension was similar for the two groups, mean time for patients with postural tachycardia 10·28 ± 5·01 min and for patients with neurocardiogenic syncope 14·58 ± 6·75 min. In most patients, the symptoms related to hypotension

Table I Baseline recordings of blood pressure and blood flow parameters in 50 patients with orthostatic intolerance, on supine position

Variable	Neurocardiogenic syncope (n=29)		Postural tachycardia (n=21)	
	Mean, SD	95% CI	Mean, SD	95% CI
Heart rate (bpm*)	73·9, 12·9	69·1–78·9	78·2, 13·2	72·1–84·2
Systolic blood pressure (mmHg)	116, 6	114–119	112, 8	109–116
Diastolic blood pressure (mmHg)	74, 5	72–76	72, 5	70–74
Cerebral blood flow parameters				
Systolic peak velocity (cm/sec)	92·4, 27·5	82·3–102·4	93·6, 19·3	85·2–102
End diastolic (cm/sec)	40·4, 12·8	35·7–45	41·9, 9·9	37·7–46·1
Pulsatility index	0·92, 0·14	0·86–0·97	0·89, 0·15	0·82–0·95

bpm = beats . min^{-1}.

Table II Heart rate during head up tilt (HUT) on 50 patients with orthostatic intolerance

Time of recording	Neurocardiogenic syncope (n=29)		Postural tachycardia (n=21)	
	Mean, SD (bpm*)	95% CI (bpm)	Mean, SD (bpm)	95% CI (bpm)
Baseline	73·9, 12·9	69·1–78·9	78·2, 13·2	72·1–84·2
HUT, min 1	84·9, 15·4	79·0–90·8	97·5, 17·2	89·7–105·4
HUT, min 5	86·4, 12·7	81·4–91·4	109·0, 18·2	99·9–118·1
HUT, min 10	90·5, 12·1	85·1–95·9	113·0, 22·5	99·9–126·0
End of the test	65·0, 19·8	57·5–72·5	90·0, 27·2	77·6–102·4
Highest recording	95·6, 14·4	90·1–101·1	117·6, 20·0	108·5–126·8

bpm = beats . min^{-1}.

Table III Heart rate, blood pressure and blood flow parameters when HUT was considered positive in 50 patients with orthostatic intolerance

Variable	Neurocardiogenic syncope (n=29)		Postural tachycardia (n=21)	
	Mean, SD	95% CI	Mean, SD	95% CI
Heart rate (bpm*)	65, 19	58·1–71·9	75, 26	73·8–86·1
Systolic blood pressure (mmHg)	63, 16	57·2–68·8	71, 24	60·7–81·3
Diastolic blood pressure (mmHg)	28, 11	23·9–32	34, 20	25·4–42·5
Cerebral blood flow parameters				
Systolic peak velocity (cm/sec)	79·6, 32·3	73·6–85·6	86·4, 35·6	71·1–101·6
End diastolic (cm/sec)	19·3, 6·9	16·8–21·8	18·5, 6·5	15·7–21·3
Pulsatility index	1·5, 0·3	1·39–1·61	1·6, 0·3	1·47–1·73

were lightheadedness and blurred vision, followed by nausea. In the two groups, hypotension was associated with an increase of the pulsatility index (Table 3), which was mainly related to a decrease in the end diastolic blood flow velocity.

During tilt, continuous observation of the Doppler recording showed that patients with postural tachycardia had intermittent fluctuations of the end diastolic blood flow velocity, with an oscillatory pattern. In these patients, a decrease of the end diastolic blood flow velocity (>20%) was evident earlier than in patients with typical neurocardiogenic syncope, mean time $3{\cdot}9 \pm 3{\cdot}8$ min and $9{\cdot}3 \pm 6{\cdot}2$ min respectively ($P<0{\cdot}001$). Before hypotension developed, only in patients with postural tachycardia, the decrease of the end diastolic blood flow velocity was just evident during brief periods and it was associated with heart rate increase (Fig. 1). The oscillations of the blood flow velocity produced

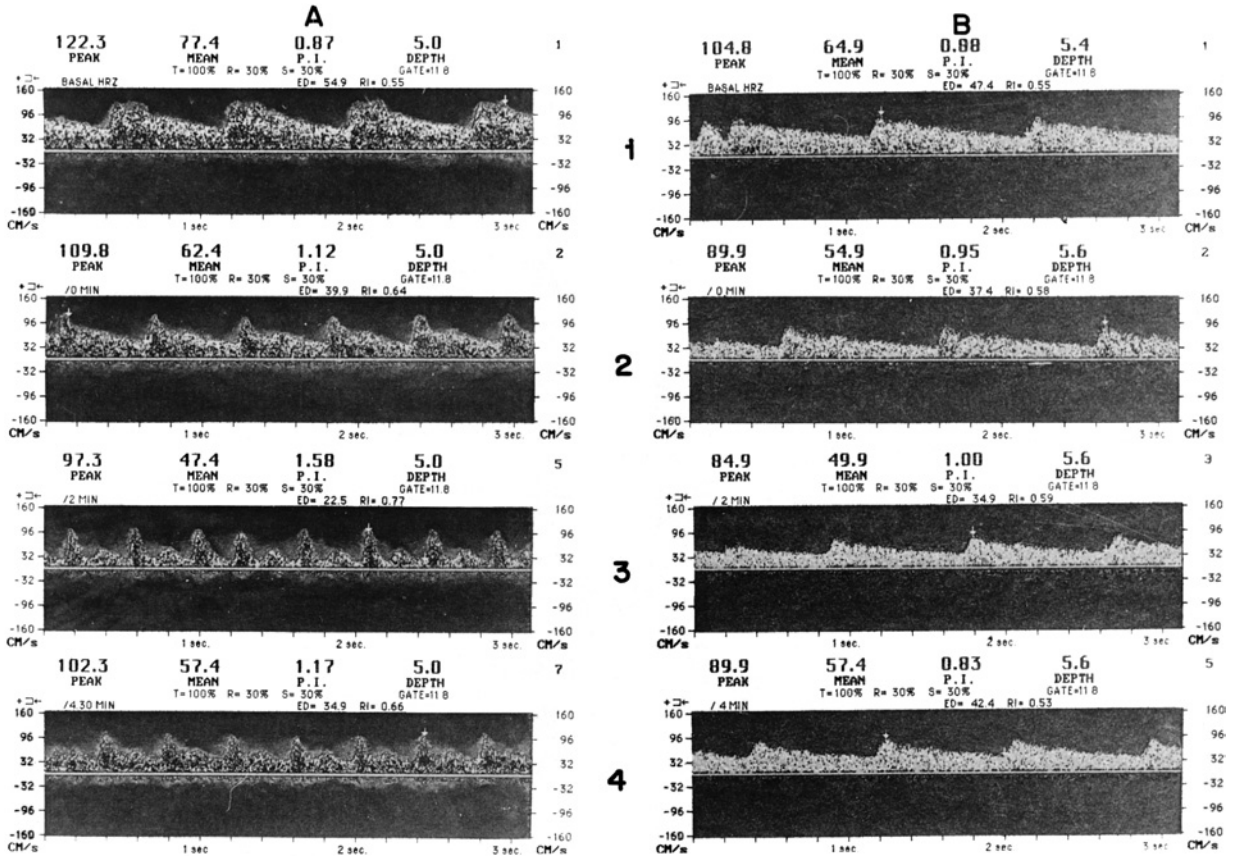

Figure 1 **Transcranial Doppler waveform of right middle cerebral artery flow recorded in a patient with postural tachycardia (panel A) and in a patient with neurocardiogenic syncope (panel B) during HUT test: (1) basal supine rest, (2) 1 min of tilt, (3) 2 min of tilt, and (4) 4 min of tilt. Notice waveform fluctuations from min to min in the recording from the patient with postural tachycardia due to the variation in the pulsatility index (PI) related to changes in diastolic velocity (ED). These oscillations were not observed in any patient with typical neurocardiogenic syncope.**

variation of the pulsatility index throughout the HUT. The difference between the smallest and the largest pulsatility index, recorded in each patient during HUT before hypotension developed, was significantly greater for patients with postural tachycardia (mean 0·46 ± 0·24) than for patients with neurocardiogenic syncope (mean 0·32 ± 0·18; $P<0·05$).

Discussion

Orthostatic intolerance is a common medical problem occurring in patients with primary or secondary autonomic dysfunction. Loss of consciousness during orthostatic stress is due to reduction in cerebral blood flow. Normally, cerebral blood flow remains constant over a wide range of variations in systemic blood pressure[19]. However, in patients with syncope, systemic blood pressure decrease is related to decrease in cerebral blood flow velocity[20,21] while in patients with postural tachycardia, a substantial decrease in blood flow velocity can occur despite a well sustained blood pressure[7,11]. In this study we also observed that, during HUT, cerebral blood flow velocity of patients with postural tachycardia fluctuates in spite of there being no systemic hypotension.

The main finding of the study is that, continuous observation of cerebral blood flow velocity during HUT in patients with postural tachycardia can show brief periods of intermittent decrease in blood flow velocity, accompanied by heart rate increase without hypotension [Figs 1, 2(A) and 2(B)]. Pulsatility and resistance indexes, as described by Grubb[11] increase with arteriolar vasoconstriction and decrease with arteriolar vasodilation. Analysis of the pulsatility has a reported specificity of 98–100% in the diagnosis of cerebral vasospasm[22].

The results suggest that patients with postural tachycardia, on standing up, could have a inefficient regulation of cerebral blood vessels. Narkiewicz *et al.*[23] suggested that the symptoms of postural tachycardia may somehow be elicited by central responses to the inappropriate tachycardia, even in absence of any actual reduction in perfusion. However, during HUT, we observed that patients with postural tachycardia can have oscillatory fluctuations of cerebral blood flow velocity and pulsatility index related to the heart rate increase. Then, the latter may occur as a response to increased

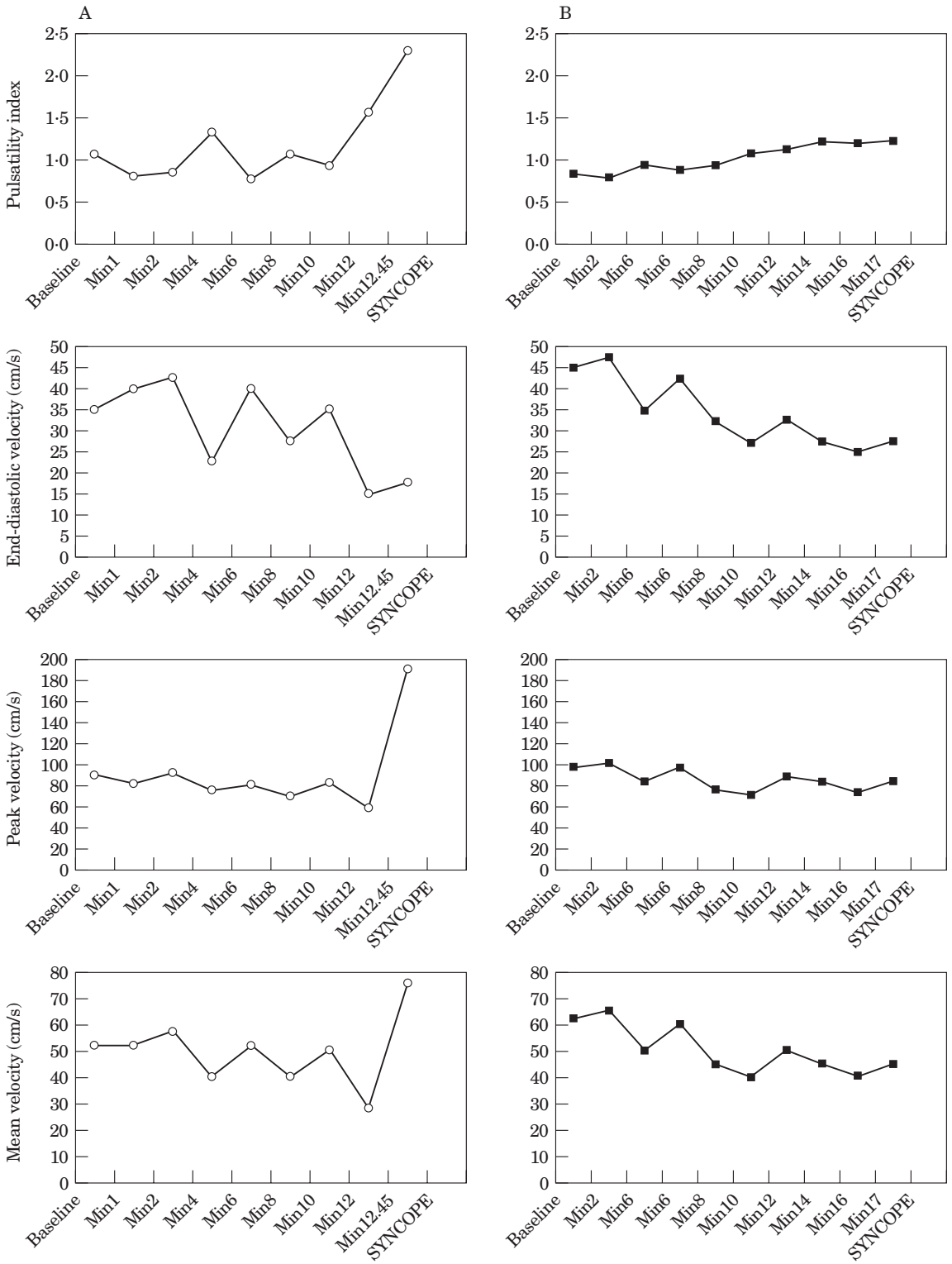

Figure 2 **(A) Profile of cerebrovascular responses to HUT in a patient with postural tachycardia. Notice the oscillations in the pulsatility index, similar to those observed in end-diastolic velocity. (B) Profile of cerebrovascular responses to HUT in a patient with neurocardiogenic syncope. Compared with Fig. 2(A) there are minimal fluctuations in the pulsatility index.**

sympathetic activation, and even contribute to prevent hypotension, but clinical symptoms are related to an abnormal cerebral blood flow.

When hypotension developed, the two groups of patients showed a rise in the pulsatility index, which was mainly related to decrease in diastolic cerebral blood flow velocity. This is in agreement with the findings of Schondorf *et al*.[21] who demonstrated that cerebral autoregulation functions significantly limit the cerebral reduction in cerebral blood flow during syncope.

The findings of this study support the possibility that abnormalities within the central nervous system may play a pivotal role in the pathogenesis of postural tachycardia. Then, treatment strategies could be developed to target the cerebral circulation to attenuate the vascular resistance elicited by orthostatic stress.

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