Cerebrovascular blood flow during the near syncopal phase of head-up tilt test: a comparative study in different types of neurally mediated syncope

Antonio G. Hermosillo*, José Luis Jordan, Maite Vallejo, Andrei Kostine, Manlio F Márquez, and Manuel Cardenas

Department of Electrocardiology, Instituto Nacional de Cardiología 'Ignacio Chávez', Juan Badiano #1, Sección XVI Tlalpan CP 14080, México DF

Received 2 April 2005; accepted after revision 18 November 2005; online publish-ahead-of-print 10 February 2006

Aims This study analyses the changes in cerebral blood flow (CBF) velocity occurring in the near syncopal phase of head-up tilt test (HUT) to determine whether their appearance during the premonitory symptoms permits the differentiation of the different types of haemodynamic response.

Methods and results Six hundred and nineteen patients aged 35.9 ± 16.4 with a prior history of syncope (55%) or presyncope (45%) were studied. Head-up tilt test was positive in 585 patients. The test was interrupted before syncope, once hypotension was evident and CBF changed. A vasovagal reaction (VVR) was observed in 245 patients. They had a 59% fall in diastolic CBF velocity, whereas systolic CBF velocity decreased by 12%. Postural orthostatic tachycardia syndrome (POTS) was observed in 82, systolic and diastolic CBF velocity decreased 44 and 60%, respectively. A similar response was observed in 258 patients with the orthostatic intolerance (OI) pattern. No significant changes were observed in the negative group.

Conclusion Patients with VVR had changes in CBF velocity, which are different from those presented by patients with POTS and OI pattern. Cerebral blood flow monitoring is useful to increase the yield of HUT and may allow early interruption before syncope occurs, reducing patient discomfort.

KEYWORDS
Tilt testing; Transcranial Doppler; Vasovagal syncope; Postural orthostatic tachycardia; Autonomic nervous system

Introduction

Tilt table testing is a useful tool in the evaluation of syncope, presyncope, or dizziness, presumed to be neurally mediated in origin. There are various positive response patterns seen during head-up tilt table testing (HUT), and they represent distinct pathophysiological processes that result in a decrease in cerebral perfusion: (i) the classical vasovagal (or neurocardiogenic), (ii) the postural orthostatic tachycardia syndrome (POTS), (iii) the dysautonomic responses.

Transcranial Doppler (TCD) sonography has been used to study cerebral haemodynamics during orthostatic testing, and different behaviours of cerebrovascular blood flow (CBF) velocity have been described. In patients with vasovagal syncope (VVS), TCD monitoring shows that the symptoms are associated with decrease of diastolic (CBF) velocity without significant change in the systolic velocity. In POTS, patients experience symptoms of cerebral hypoperfusion and excessive catecholamine effects when they stand up, and these symptoms are associated with excessive reductions in systolic (CBF) velocity, despite maintenance of arterial blood pressure.

Head-up tilt test is considered positive and diagnostic when the patient develops a syncope or presyncope with hypotension with or without bradycardia. As the decision to terminate the tilt influences the type of haemodynamic response (cardioinhibitory vs. vasodepressor), some authors propose interruption of the tilt at the moment of loss of consciousness with simultaneous loss of postural tone, whereas others consider a steadily falling blood pressure and accompanying symptoms sufficient to stop the test. Syncope during HUT is an unpleasant experience; early identification of the haemodynamic alterations leading to cerebral hypoperfusion may minimize the undesirable effects of a positive tilt test.

The purpose of this investigation was to study the CBF velocities during the near syncopal phase of HUT in patients with presumptive neurally mediated syncope and to...
determine whether TCD monitoring during HUT permits the early identification of a positive response and thus a shortening of the test, sparing the patients an induced uncomfortable syncpode.

**Methods**

From January 2001 to December 2004, 619 consecutive patients were studied for recurrent syncope or for evaluation of symptomatic orthostatic intolerance (OI) that included multiple episodes of near syncope. Many had symptoms exacerbated by prolonged standing and relieved by lying down. In all patients, clinical examination, routine laboratory studies, Holter monitoring, electroencephalogram, and echocardiography evaluation (when indicated) did not reveal the cause of syncope or pre-syncope.

Subjects with systemic illnesses that might have affected the autonomic nervous system, neurogenic orthostatic hypotension (defined as a persistent fall in systolic blood pressure of ≥20 mmHg after 5 min of standing) and with documented organic heart disease were excluded. All medications were discontinued at least five half-lives before testing.

The HUT was performed between 9:00 a.m. and 12:00 p.m., and the subjects had been fasting overnight. A surface three-lead electrocardiogram was displayed continuously and blood pressure was measured with a standard cuff sphygmomanometer by the same observer at intervals of 5 min and when symptoms of impending syncope developed. During the test, CBF velocity in the middle cerebral artery was assessed by continuous TCD. Isosorbide-induced, vasovagal reaction (VVR), and postural orthostatic tachycardia syndrome (POTS) were performed as follows.

### Table 1: Demographics data and clinical characteristics of study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Syncope (n = 339)</th>
<th>Presyncope (n = 280)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)(^a)</td>
<td>32 (22.45)</td>
<td>35 (26.44)</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>96/243</td>
<td>82/198</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HUT result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive, n(%)</td>
<td>55 (16)</td>
<td>29 (10)</td>
<td>&lt;0.05(^b)</td>
</tr>
<tr>
<td>Isosorbide-induced, n(%)</td>
<td>271 (80)</td>
<td>230 (82)</td>
<td></td>
</tr>
<tr>
<td>Negative, n(%)</td>
<td>13 (4)</td>
<td>21 (8)</td>
<td></td>
</tr>
<tr>
<td>Type of response during HUT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVR, n(%)</td>
<td>174 (51)</td>
<td>71 (25)</td>
<td>&lt;0.05(^b)</td>
</tr>
<tr>
<td>POTS, n(%)</td>
<td>38 (11)</td>
<td>44 (16)</td>
<td></td>
</tr>
<tr>
<td>OI response, n(%)</td>
<td>114 (34)</td>
<td>144 (51)</td>
<td></td>
</tr>
<tr>
<td>Negative, n(%)</td>
<td>13 (4)</td>
<td>21 (8)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Median (quartiles 25th, 75th). \(^b\)\(x^2\) test.

### Table 2: CBF measurements by TCD during passive HUT

<table>
<thead>
<tr>
<th>Variable</th>
<th>VVR (n = 73)</th>
<th>POTS (n = 11)</th>
<th>P-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Near syncope</td>
<td>Δ%</td>
</tr>
<tr>
<td>Peak systolic velocity (cm/s)</td>
<td>102 (83, 112)</td>
<td>90 (70, 117)</td>
<td>12</td>
</tr>
<tr>
<td>Mean velocity (cm/s)</td>
<td>62 (50, 70)</td>
<td>40 (33, 50)</td>
<td>36</td>
</tr>
<tr>
<td>End diastolic velocity (cm/s)</td>
<td>42 (35, 52)</td>
<td>18 (13, 23)</td>
<td>59</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>0.9 (0.8, 1.03)</td>
<td>1.8 (1.5, 1.9)</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^a\)Absolute differences between baseline and near syncope. Values are displayed as median (quartiles 25th and 75th). Δ%, percentage of change from baseline to near syncope.

500 Neurovision, Multigon Industries Inc., NY, USA). 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 the standard technique. Doppler signals were recorded to evaluate peak systolic velocity (\(V_s\)), mean flow velocity (\(V_{mean}\)), diastolic velocity (\(V_d\)), and pulsatility index (PI = \(V_s - V_d\)/\(V_{mean}\)). After the subjects had rested in a supine position for a minimum of 30 min to obtain stable values (<10% variation over 5 min), a 5 min baseline recording was made. The subjects were then tilted to 70° using a motorized table with footboard support located in a quiet room with a constant temperature of 21°C for 20 min or until syncope was imminent, associated with a clear precipitous fall in blood pressure or heart rate (positive HUT). The imminence of syncope was recognized by a subjective sensation of impending faint, dizziness, nausea, sweating, pallor, altered mentation, and visual changes accompanied by hypotension (systolic blood pressure <80 mmHg). Cerebral blood flow measurements were recorded at intervals of 5 min and when symptoms of impending syncope developed. If a positive response was not elicited during the passive tilt phase, the subjects were returned to the supine position and they received 5 mg of sublingual isosorbide dinitrate and were tilted at the same angle for a further ≤15 min until the test was considered positive. According to the haemodynamic response to HUT, subjects were divided into four groups:

(i) Negative HUT: sustained blood pressure and absence of symptoms.
(ii) Vasovagal reaction (VVR): sudden hypotension with or without coexistent bradycardia.
(iii) Postural tachycardia: during the first 10 min of standing there was a sustained increase in heart rate of >30 bpm, without systemic hypotension.

(iv) Orthostatic intolerance pattern, with an absence of adaptation of blood pressure to the upright position and slow but progressive fall in blood pressure without a clear vasovagal reaction.

Studies were approved by the Institutional Ethics Committee, and informed consent was obtained.

Statistical analysis

Initial exploratory analysis showed that data did not fit a normal distribution pattern (Shapiro-Wilk's test \( P < 0.05 \)); therefore, summary and dispersion estimates are shown as medians (quartiles 25th and 75th). Percentage changes between baseline and presyncope were estimated for CBF measurements. Statistical differences were analysed using non-parametric methods. When two categories were compared, a Mann–Whitney test was used, and for three or more categories, the sign rank Kruskal–Wallis test was used. All categorical variables were analysed by \( \chi^2 \) test. Statistical significance was set at alpha level \(<0.05\).

Results

Study population

Six hundred and nineteen subjects with history of syncope (\( n = 339 \)) or presyncope (\( n = 280 \)) underwent HUT. The demographic characteristics of patients presenting as unexplained syncope or presyncope were similar. (Table 1) Mean age was 35.9 \( \pm \) 16.4 years (range 5–89 years), 441 were females. The mean number of previously experienced syncope spells (lifetime) was 2 \( \pm \) 3 (range 1–10). Analysis of all 585 positive tests (84 during passive HUT and 501 with isosorbide challenge) revealed that patients with history of syncope had 51% of VVR, 11% of POTS, and 34% of OI responses. Patients with history of presyncope had 25% of VVR, 16% of POTS, and 51% of OI.

The clinical characteristics of the study groups for type of response during HUT are shown in Table 1.

Passive HUT

Passive HUT was positive in 84 subjects, 73 with a VVR and 11 with a POTS response. Transcranial Doppler was evaluated at near syncope in all patients and compared with baseline values. Peak systolic velocity decreased by 12% in VVR group, and 44% in POTS group (\( P < 0.05 \)). End-diastolic velocity diminished by 59% in VVR group and 60% in POTS group (\( P = \text{NS}\)). Pulsatility index increased by 50% in VVR group, and by 40% in POTS group (\( P < 0.05 \)) (Table 2).

**Isosorbide-challenge HUT**

Head-up tilt test was positive with isosorbide challenge in 501 subjects, 172 with a VVR, 71 with a POTS response, and 258 with an OI pattern. Transcranial Doppler was evaluated at near syncope in all patients and compared with baseline values. Peak systolic velocity decreased by 24% in VVR group, 35% in POTS group, and 45% in OI group (\( P < 0.05 \)). End-diastolic velocity diminished by 52% in VVR group, 60% in POTS group, and 57% in OI group (\( P = \text{NS}\)). Pulsatility index increased by 40% in VVR group, 36 in POTS group, and 31% in OI group (\( P < 0.05 \)). In Table 3, the CBF measurements by TCD during drug-induced HUT in patients with syncope and presyncope are shown. In both,
the orthostatic reduction in systolic CBF was smaller in patients with VVR compared with POTS or OI responses \((P < 0.05)\).

In all cases, symptoms always resolved and CBF velocities returned to baseline values immediately after placing the patients back in the supine position, overlapping with the normalization of blood pressure (data not shown).

**Morphological analysis of TCD waveforms**

Besides the change in velocities, a typical pattern in the middle cerebral artery blood flow velocity waveform preceded the fall in blood pressure and pre-syncopal symptoms in every case. This consisted of a progressive deepening of the dicrotic notch (Figure 1), transient at the beginning and permanent later.

**Discussion**

The present study was designed to evaluate the cerebrovascular behaviour during HUT of a population with recurrent syncope or pre-syncope. It was found that during orthostatic stress, the reduction in CBF velocity differs in the several types of haemodynamic responses that can occur during tilt table testing. The differential diagnosis of the different types of responses is important and may have an effect on the choice of therapy.

It is well accepted that loss of consciousness during VVS is due to cerebral hypoperfusion that accompanies the cardiovascular collapse during syncope.\(^{10}\) In this study, diastolic and mean CBF velocities decreased and pulsatility index increased significantly in patients with VVR at the moment of near syncope, whereas the fall in systolic velocity was limited, both during passive HUT and during drug challenge.

Grubb et al.,\(^ {11}\) using TCD demonstrated a paradoxical cerebral vasoconstriction occurring just before the loss of consciousness in patients who had HUT-induced VVS. This pattern was not seen in patients with a negative test or in control subjects. At the moment of syncope, during the collapse of blood pressure, diastolic CBF velocity diminished (75 ± 17%), whereas, systolic CBF velocity was maintained. Some consider the resultant increase in CBF pulsatility index to be indicative of an increase in cerebrovascular resistance prior to syncope.

Schondorf et al.\(^ {13}\) documented that the main change in patients with VVS is a decrease in diastolic CBF velocity during syncope and that the selective loss of diastolic flow and the increase in pulsatility index are probably caused by constriction of downstream vessels when the diastolic blood pressure decreases below the critical closing pressure of the cerebral vessels.

In the present study, patients with POTS had progressive and marked decreases in systolic (44%), diastolic (60%), and mean (46%) CBF velocities.

Jacob et al.\(^ {6}\) found that, in patients with POTS, the systolic, diastolic, and mean middle cerebral artery blood flow velocities...
velocities decreased in response to HUT, despite well-maintained arterial blood pressure. Subjects with POTS, however, present with a disproportionately greater effect of postural stress on heart rate and stroke volume than on mean arterial pressure. This has been attributed to an abnormal functional distribution of central sympathetic tone to the heart and vasculature with central hypovolaemia.\(^\text{14}\) The differences in vascular dynamics in response to orthostatic challenge between VVS and POTS have been published.\(^\text{15}\) When tilted upright, patients with VVS have normal systolic CBF velocity,\(^\text{1}\) whereas it is reduced in patients with POTS in response to HUT, despite well-sustained arterial blood pressure. It has been postulated that the decrease in flow velocity in these patients is likely to be due to increased cerebrovascular resistance, although a decrease in cardiac output due to decreased cardiac filling might contribute to the decrease in systolic CBF.\(^\text{6}\) Stewart \textit{et al}.\(^\text{16}\) compared POTS patients with VVS patients and reported that the former had increased calf blood flow, and pooling in the lower extremities, whereas the peripheral vascular physiology in patients with VVS was normal. The findings in the present study are supported by these observations; in patients with VVR with a preserved stroke volume before the vasovagal reaction, the systolic velocity was unchanged with an increase in pulsatility index. In contrast, in patients with POTS, there was a significant reduction in systolic and diastolic velocities with an increase in the pulsatility index during the test. The OI pattern was common in our study population. We found a marked decrease in systolic, mean, and diastolic velocities, a similar pattern to that found in subjects with POTS. Patterns similar to that of the OI pattern in this study are those previously defined as exaggerated responses to nitrate stimuli. Albina \textit{et al}.\(^\text{17}\) were able to differentiate these types of patients from those with true vasodepressor VVS using TCD monitoring. They showed a moderate fall in systolic, diastolic, and mean CBF velocities.

**Study limitations**

The fundamental limitation of the present study is that there were no arterial blood pressure measurements on a beat-to-beat basis. However, although intermittent measurement of pressure using a sphygmomanometer is less desirable, it is an accepted method of testing and is widely used in clinical practice.

Although we try to follow the new VASIS classification,\(^\text{3}\) a major limitation of this study is the definitions used which are in some way arbitrary and open to debate.

We believe that the pattern of CBF response to tilt during the time preceding the development of the vasovagal reaction may provide adjunctive diagnostic information. However, further studies simultaneously monitoring CBF and cardiac dynamics will be necessary to validate these haemodynamic observations.

A vasovagal response was aborted before loss of consciousness set in, and we, therefore, limited our analysis and our conclusions to the prodromal phase and onset of the vasovagal response. Finally, although TCD does not directly assess CBF, it has a favourable temporal resolution compared with the more traditional techniques for assessing CBF.\(^\text{15}\)

**Conclusions**

In summary, in patients with syncope or presyncope, various abnormal responses are observed during tilt testing, suggesting that different syndromes can be diagnosed by the test. Transcranial Doppler monitoring during HUT is useful to assess these alterations and may allow early interruption of HUT before syncope arises, preventing the unpleasant experience for the patients. The routine use of TCD during HUT may have practical implications. Future studies should enroll patients taking into account their CBF velocity patterns, and they should evaluate whether the different mechanisms responsible require different therapy.

**References**

5. Sung RYT, Du ZD, Yu CW; Yam MC, Folk TF. Cerebral blood flow during vasovagal syncope induced by active standing or head up tilt. \textit{Arch Dis Child} 2000;82:154–58.