Cerebral Autoregulatory Responses to Head-Up Tilt in Normal Subjects and Patients With Recurrent Vasovagal Syncope

Brian J. Carey, MRCPI; Bradley N. Manktelow, MSc; Ronney B. Panerai, PhD; John F. Potter, DM

Background—The effect of orthostatic stress on dynamic cerebral autoregulation (CA) in normal subjects and patients with recurrent vasovagal syncope (VVS) is unclear. This study assessed the dynamic CA responses of both groups to head-up tilt.

Methods and Results—Seventeen patients with recurrent VVS and 17 pair-matched control subjects underwent 70° head-up tilt for up to 30 minutes. Bilateral middle cerebral artery blood flow velocities (CBFV) were measured with transcranial Doppler ultrasound along with noninvasive beat-to-beat blood pressure (BP), heart rate, and transcutaneous and end-tidal CO2 concentrations. Indices of dynamic CA were derived for periods before, during, and after tilt. Eight normal subjects who developed VVS in an identical protocol but who had no previous clinical history of syncope were also studied. CBFV and transcutaneous and end-tidal CO2 levels declined significantly during head-up tilt in all groups (P<0.0001). Dynamic CA indices were unchanged throughout tilt in nonsyncopal control subjects and were initially unchanged in patients but deteriorated significantly in patients and syncopal control subjects in the minutes before (P=0.027 and P=0.012, respectively) and after (P=0.002 and P=0.007, respectively) syncope.

Conclusions—Dynamic CA is preserved in patients and control subjects initially after head-up tilt. Autoregulatory function remains intact in nonsyncopal control subjects during prolonged orthostasis but deteriorates in patients and syncopal control subjects immediately before and after VVS. 

Key Words: syncope ■ cerebrovascular circulation ■ ultrasonics
The middle cerebral artery (MCA) was insonated bilaterally as face mask and an infrared capnograph (Capnogard, Novametrix). End-tidal CO\(_2\) was measured via a close-fitting (TINA, Radiometer), with the probe placed at heart level in the anterior axillary line. From 9 AM to 11 AM the temperature of the controlled (21°C to 24°C) laboratory was measured. Subjects who were otherwise similar to the control subjects but had developed VVS during head-up tilt in a protocol identical to that of the patients were selected. Subjects who were otherwise similar to the control subjects but had remained asymptomatic during a standard autonomic function tests, had no previous history of syncope or presyncope, and had remained asymptomatic during a previous 30-minute 70° head-up tilt test. In addition, we studied 8 subjects who were otherwise similar to the control subjects but developed VVS during head-up tilt in a protocol identical to that outlined below (syncopal control group). None of the patients or control subjects were taking any medication known to affect the cardiovascular system.

Subjects avoided caffeine-containing products, nicotine, and alcohol for >12 hours before the study and attended a temperature-controlled (21°C to 24°C) laboratory between 9 AM and 11 AM ≥2 hours after a light breakfast. Subjects lay supine on a padded table that could be tilted manually, with their heads supported by 2 pillows. After 10 minutes of supine rest, 3 semiautomated BP readings were taken 1 minute apart (Omron 711). The mean of the last 2 readings, provided that values differed by <10 mm Hg, was taken as the baseline casual BP measurement. A surface 3-lead ECG and noninvasive beat-to-beat arterial BP measurements (Finapres 2300, Ohmeda) were recorded, with the BP cuff kept at the right atrial level while supine and during tilt by use of a custom-made, adjustable arm rest. Transcutaneous CO\(_2\) partial pressure was measured with a previously validated transcutaneous gas monitor (TINA, Radiometer), with the probe placed at heart level in the anterior axillary line. End-tidal CO\(_2\) was measured via a close-fitting face mask and an infrared capnograph (Capnogard, Novametrix). The middle cerebral artery (MCA) was insonated bilaterally as described by Aaslid et al.\(^2\) with 2-MHz pulse transcranial Doppler ultrasound (SciMed QVL 842X). The Doppler frequency shift and the other parameters were recorded on a digital-audio tape. The vertical height in centimeters from the point of insonation of the right MCA to the second intercostal space (height) was recorded for each subject. After the subjects had rested supine for a minimum of 30 minutes to obtain stable values (<10% variation over 5 minutes), a 5-minute baseline recording was made. The subjects were then tilted head-up to an angle of 70° for 30 minutes or until syncope was imminent. To minimize discomfort and improve compliance with the study protocol, end-tidal CO\(_2\) measurements were discontinued 5 minutes after tilt in all subjects. The imminence of syncope was recognized by the occurrence of a subjective sensation of impending syncope in association with the typical hemodynamic profile.\(^2\) For ethical reasons, all presyncopal subjects were returned to the supine position before loss of consciousness, the point at which this was done being taken as the point of syncope. The point of syncope was synchronized for all subjects by use of a mark generated by an electrical device each time the tilt table passed through 45°. Recording continued for a further 5 minutes after return to the supine position.

All files were inspected individually, and data analysis was performed by previously well-described methods.\(^2\) with estimates of mean arterial pressure, pulse interval, mean CBFV, and transcutaneous and end-tidal CO\(_2\) calculated for each cardiac cycle. Calculated MCA mean pressure (MCA,MP) during head-up tilt was estimated from mean arterial pressure by subtraction of the hydrostatic pressure (height ×0.735× sin 70°). By methods described previously,\(^2\) dynamic autoregulatory index (ARI) values ranging from 0 (absent) to 9 (most efficient) were calculated for the 1-minute period before tilt, the first and third minutes after tilt, the third-last and last minutes before return to the supine position, and the first and third minutes after return to supine for each subject. In short, the model proposed by Tiecks et al.\(^2\) was fitted to each of the 1-minute data segments by selection of the value of ARI leading to the minimum quadratic error between measured CBFV and the model-predicted CBFV.\(^2\) In addition, the model allowed the calculation of correlation coefficients, assessing how closely the measured CBFV fit the model-predicted velocity for each subject during each time period.

### Statistical Analysis

Demographic details and baseline characteristics of the 3 groups were compared by 2-sample Student’s \(t\) tests. The between-group and within-subject changes in the patient and nonsyncopal control groups were modeled for each outcome measure by use of a mixed model for repeated-measures data. Model selection was by changes in the log likelihood, and denominator degrees of freedom were calculated by Satterthwaite’s method. Different covariance patterns were investigated by use of Akaike’s information criterion. ARI values immediately before and after syncope were compared between the syncopal control group and other groups by Student’s 2-sample \(t\) tests. Data were analyzed with the SAS version 6.12 and Minitab 12 software packages. Statistical significance was set at the \(p<0.05\) level.

The study was approved by the Leicestershire Health Authority Research Ethics Committee, and fully informed written consent was obtained from each subject.

### Results

No significant differences were demonstrated between the 3 groups in demographic details or baseline characteristics (Table 1). All 17 patients developed syncope within 30 minutes of head-up tilt (mean time to syncope 757±539...
All 17 nonsyncopal control subjects remained asymptomatic during the 30 minutes of tilt. Actual data records for a nonsyncopal control subject before and after tilting and a patient before and after syncope are displayed in Figures 1A and 1B, respectively.

Changes in parameters from baseline for the patient and nonsyncopal control groups are contained in Table 2. Mean CBFV and MCA cMP changes for the 1-minute period before tilt and first 3-minute period after tilt for both patient and nonsyncopal control groups are displayed in Figure 2.

Mean CBFV was significantly lower in patients than nonsyncopal control subjects 3 minutes before syncope (difference 8.9 cm/s; 95% CI 0 to 18 cm/s; \( P = 0.044 \)) and at syncope (difference 24.6 cm/s; 95% CI 16 to 33 cm/s; \( P < 0.0001 \)) but was similar at all other times (see Table 2). MCA cMP was lower in patients than nonsyncopal control subjects at syncope (difference 52.5 mm Hg; 95% CI 45 to 60 mm Hg; \( P < 0.0001 \)) but was similar at all other times. End-tidal and transcutaneous CO₂ levels declined significantly during tilt (Table 2), but no differences were demonstrated between patients and nonsyncopal control subjects in transcutaneous CO₂ levels declined significantly during tilt (Table 2), but no differences were demonstrated between patients and nonsyncopal control subjects in transcutaneous CO₂ levels declined significantly during tilt (Table 2), but no differences were demonstrated between patients and nonsyncopal control subjects in transcutaneous (\( P = 0.31 \)) or end-tidal (\( P = 0.10 \)) CO₂ values at any stage.

Mean dynamic ARI values of the patient and nonsyncopal control groups for the 7 chosen time points are contained in Table 3. ARI values were similar to pretilt values during and after tilt in nonsyncopal control subjects (Table 3). Patient dynamic ARI values were similar to nonsyncopal control values at baseline and initially after tilt but were significantly lower during the last minute before syncope and the first minute after syncope (Table 3).

ARI values of the 8 control subjects who developed VVS were similar to patient values during the last minute before (3.1 ± 2.2 versus 3.6 ± 3.0; difference −0.5; 95% CI −1.3 to 0.3; \( P = 0.25 \)) and first minute after (2.1 ± 1.7 versus 2.3 ± 1.8; difference −0.2; 95% CI −1.0 to 0.6; \( P = 0.60 \)) syncope and significantly lower than nonsyncopal control values during the same periods (\( P = 0.012 \) and \( P = 0.007 \), respectively).

Correlation coefficients reflecting model accuracy did not differ between groups and were similar to baseline coefficients before and after syncope (Table 3).

**Discussion**

We have not demonstrated any deterioration in dynamic CA during orthostatic stress in nonsyncopal control subjects and have shown that dynamic CA is initially preserved after head-up tilt in patients susceptible to VVS. We have also shown, however, that dynamic CA deteriorates in patients and control subjects during presyncope and remains impaired during the immediate postsyncope period. Our baseline ARI values are comparable to values previously derived by similar methods⁡ and suggest that baseline dynamic CA is normal in all groups studied. In addition to these new findings, we have confirmed that CBFV and CO₂ levels decline significantly in normal subjects after passive head-up tilt⁢ and reveal that similar changes occur initially after tilt in patients with recurrent VVS.

Zhang et al⁠ used frequency-domain analysis and lower-body negative pressure to demonstrate that dynamic CA may deteriorate in normal subjects during high levels of orthostatic stress. An increased low-frequency CBFV/arterial BP transfer function gain was shown during presyncope, suggesting a closer relationship between CBFV and ABP and therefore, impairment of dynamic CA. There may be important differences, however, between head-up tilt and lower-body negative pressure in cardiovascular and cerebrovascular responses, and the significance of changes in transfer function gain are the subject of some debate.⁢ More recently, Leftheriotis et al⁠ used rapid thigh-cuff deflation to demonstrate preserved dynamic CA in normal subjects 5 minutes after 40° head-up tilt. In many ways, this study forms a link between the studies of Zhang et al⁠ and Leftheriotis et al⁠ and shows that the findings of all 3 studies are compatible with each other. The finding of Zhang et al⁠ that dynamic CA deteriorates in normal subjects during presyncope is supported by our demonstration of decreased ARI values during presyncope in the syncopal control group. In addition, we have demonstrated that similar changes occur in patients with recurrent VVS. The conclusion of Leftheriotis et al⁠ that dynamic CA is preserved in normal subjects at low levels of orthostatic stress is similarly supported by our initial data after...
head-up tilt, which also demonstrate similar preservation of dynamic CA in patients with recurrent VVS. 

Because loss of consciousness during syncope is probably caused by cerebral hyperperfusion, the hypothesis that impaired CA is the underlying problem in patients with recurrent VVS is an attractive one. Our findings of preserved ARI values in patients initially after head-up tilt and similarly impaired ARI values in normal subjects immediately before and after syncope tend to refute this hypothesis. The reason for impairment of dynamic CA values during the perisyncope period is unclear, but we think it is most likely to result from MCA,MP falling outside the proposed autoregulatory range of 60 to 150 mm Hg during this period (Table 2). Another potential reason for impairment of dynamic CA before and after syncope is a build-up of cerebral metabolites (including CO2) during a period of relative hypoxia, but our methods did not allow us to explore this hypothesis.

The model proposed by Tiecks et al was initially developed by use of hypotension induced by rapid thigh-cuff deflation, but our group has previously applied this model to spontaneous BP changes at rest and shown it to be valid. Correlation coefficients between measured and model-predicted

### Table 2. Mean MCA, MP, MAP, Mean CBFV, Pulse Interval, and Transcutaneous and End-Tidal CO2 of the Patient and Nonsyncopal Control Groups Before, During, and After Head-Up Tilt

<table>
<thead>
<tr>
<th>Time</th>
<th>A (±SD)</th>
<th>B (±SD)</th>
<th>C (±SD)</th>
<th>D (±SD)</th>
<th>E (±SD)</th>
<th>F (±SD)</th>
<th>G (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.4±2.7</td>
<td>...</td>
<td>0.69±0.16</td>
<td>4.2±2.7</td>
<td>...</td>
<td>0.63±0.16</td>
<td>-0.3(1.9, 1.4)</td>
</tr>
<tr>
<td>B</td>
<td>5.5±2.6</td>
<td>1.1(-0.5, 2.6)</td>
<td>0.62±0.21</td>
<td>4.9±2.9</td>
<td>0.7(-0.8, 2.2)</td>
<td>0.36</td>
<td>0.62±0.19</td>
</tr>
<tr>
<td>C</td>
<td>6.2±1.4</td>
<td>1.7(0.2, 3.2)</td>
<td>0.73±0.16</td>
<td>5.4±2.6</td>
<td>1.2(-0.3, 2.7)</td>
<td>0.12</td>
<td>0.74±0.19</td>
</tr>
<tr>
<td>D</td>
<td>5.4±2.5</td>
<td>0.9(-0.6, 2.5)</td>
<td>0.68±0.16</td>
<td>5.5±2.3</td>
<td>1.3(-0.2, 2.8)</td>
<td>0.096</td>
<td>0.68±0.13</td>
</tr>
<tr>
<td>E</td>
<td>3.8±3.0</td>
<td>0.9(-0.6, 2.4)</td>
<td>0.69±0.18</td>
<td>5.4±2.0</td>
<td>1.2(-0.3, 2.7)</td>
<td>0.12</td>
<td>0.69±0.14</td>
</tr>
<tr>
<td>F</td>
<td>2.3±1.8</td>
<td>-2.1(-0.6, -3.6)</td>
<td>0.0066</td>
<td>4.9±2.3</td>
<td>0.8(-0.8, 1.8)</td>
<td>0.33</td>
<td>0.62±0.21</td>
</tr>
<tr>
<td>G</td>
<td>5.3±2.6</td>
<td>0.9(-0.7, 2.4)</td>
<td>0.26</td>
<td>5.4±1.8</td>
<td>-1.2(-0.3, 2.7)</td>
<td>0.12</td>
<td>0.66±0.12</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of Dynamic ARI Values Between Different Time Periods for Both Patient and Nonsyncopal Control Subjects

<table>
<thead>
<tr>
<th>Time</th>
<th>ARI Difference from A (95% CI)</th>
<th>P</th>
<th>Correlation Coefficient</th>
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<th>P</th>
<th>Correlation Coefficient</th>
<th>Controls vs Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.4±2.7</td>
<td>0.69±0.16</td>
<td>4.2±2.7</td>
<td>0.63±0.16</td>
<td>-0.3(-1.9, 1.4)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5.5±2.6</td>
<td>1.1(-0.5, 2.6)</td>
<td>0.62±0.21</td>
<td>4.9±2.9</td>
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<td>0.12</td>
<td>0.66±0.12</td>
</tr>
</tbody>
</table>

Correlation coefficients are given for how closely measured CBFV fitted the model-predicted CBFV for each time period. Values are given as mean±SD.

* A indicates last minute before tilt (baseline); B, first minute after tilt; C, third minute after tilt; D, third last minute of tilt before return to supine position; E, last minute of tilt before return to supine; F, first minute after return to supine; G, third minute after return to supine.
CBFV were similar to previously reported coefficients and did not differ immediately before or after syncope, suggesting that the model used for assessing dynamic CA is accurate and valid at low extremes of CBFV and MCA MP.

The major limiting factor of our work remains the indirect measurement of MCA MP. Although arterial pressure waveforms change with head-up tilt, noninvasive plethysmography correlates very well with intra-arterial pressure recordings during head-up tilt. A direct measurement of MCA pressure is impossible without very invasive procedures that would, in themselves, affect the interpretation of our work. Because original work with the model used MCA pressure derived by use of Finapres monitoring as the input parameter and assumed that fluctuations in perfusion pressure were reflected, in the main, by MCA pressure fluctuations, we believe that it is important that we use MCA pressure when calculating ARI values. Intracranial pressure changes after head-up tilt are likely to be relatively small and similar in syncopal and nonsyncopal subjects alike, and changes in venous pressure will occur to a degree equal and proportionate to those in arterial pressure. In the absence of better, noninvasive alternatives, therefore, we believe that our calculations with noninvasive plethysmography provide acceptable estimates of MCA pressure.

Our calculations also assume that MCA diameter remains constant during head-up tilt and presyncope. MCA caliber does not change during simulated orthostatic stress, and changes in CO₂ concentrations to the degree we have demonstrated would not be expected to affect MCA diameter significantly. Profound hypotension during presyncope, however, could potentially influence MCA caliber through myogenic vasodilation or passive elastic vasoconstriction, but our methods did not allow us to assess this possibility. Because we did not measure MCA diameter during this study, our results must be interpreted with caution.

Transcutaneous CO₂ measurements correlate highly with arterial CO₂ levels but rely on gas diffusion and therefore have poor dynamic response characteristics. In addition, doubts exist about the accuracy of end-tidal and transcutaneous CO₂ measurements during changes in cardiac output. Our CO₂ findings, however, are consistent with the findings of others and are, we believe, a reasonable reflection of arterial CO₂ levels in our subjects.

In conclusion, we have demonstrated preservation of indices of dynamic CA in nonsyncopal control subjects throughout orthostasis and initially after head-up tilt in patients with recurrent VVS. We have also shown, however, that indices of dynamic CA decline in late presyncope and the early postsyncope period in both patients and syncopal control subjects.

References
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