Cerebral Blood Flow Velocity Declines Before Arterial Pressure in Patients With Orthostatic Vasovagal Presyncope

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OBJECTIVES
We studied hemodynamic changes leading to orthostatic vasovagal presyncope to determine whether changes of cerebral artery blood flow velocity precede or follow reductions of arterial pressure.

BACKGROUND
Some evidence suggests that disordered cerebral autoregulation contributes to the occurrence of orthostatic vasovagal syncope. We studied cerebral hemodynamics with transcranial Doppler recordings, and we closely examined the temporal sequence of changes of cerebral artery blood flow velocity and systemic arterial pressure in 15 patients who did or did not faint during passive 70° head-up tilt.

METHODS
We recorded photoplethysmographic arterial pressure, RR intervals (electrocardiogram) and middle cerebral artery blood flow velocities (mean, total, mean/RR interval; Gosling’s pulsatility index; and cerebrovascular resistance [mean cerebral velocity/mean arterial pressure, MAP]).

RESULTS
Eight men developed presyncope, and six men and one woman did not. Presyncope symptoms occurred light-headedness, diaphoresis, or a sensation of fatigue 155 s (range: 25 to 414 s) before any cerebral or systemic hemodynamic change. Average cerebral blood flow velocity (CBFV) changes (defined by an iterative linear regression algorithm) began 67 s (range: 9 to 198 s) before reductions of MAP. Cerebral and systemic hemodynamic measurements remained constant in nonsyncope patients.

CONCLUSIONS
Presyncope symptoms and CBFV changes precede arterial pressure reductions in patients with orthostatic vasovagal syncope. Therefore, changes of cerebrovascular regulation may contribute to the occurrence of vasovagal reactions. (J Am Coll Cardiol 2002;39:1039–45) © 2002 by the American College of Cardiology Foundation

Syncope, sudden transient loss of consciousness, accounts for 3% of all U.S. emergency department visits each year, and 6% of all hospital admissions (1,2). In patients with orthostatic vasovagal syncope, systemic arterial hypotension occurs in association with reductions of efferent muscle sympathetic nerve activity (3,4), and syncope results from cerebral hypoperfusion (5) and hypoxia (6). It is clear that changes of cerebral arterial blood flow velocity precede vasovagal syncope (7). What is unclear, however, is whether these changes contribute to syncope or reflect simply a normal cerebral autoregulatory response to systemic arterial hypotension. We measured transcranial middle cerebral artery Doppler blood flow velocities during passive upright tilt in patients who did or did not faint, and we attempted to answer the critical question: which comes first, changes of cerebral artery blood flow velocity (7) or arterial hypotension (8)?

METHODS
Study patients and protocol. We performed tilt-table testing on 18 patients (17 men, 1 woman, average age [± SEM] 57 ± 4 years) with histories of recurrent syncope or near-syncope. No patient had diabetes, and none were being treated with alpha-adrenergic blocking, antiarrhythmic or antidepressant drugs. All patients gave their written, informed consent for this study, which was approved by the human research committees of the Medical College of Virginia and the Hunter Holmes McGuire Department of Veterans Affairs Medical Center, Richmond, Virginia.

Tilt-table tests were performed in the morning in a quiet room, with subjects postabsorbitive. After 15 min in the supine position, patients were tilted to 70°, where they remained for 20 min. If presyncope did not occur, patients were returned to the supine position and given low intravenous-dose isoproterenol, sufficient to increase their heart rates by 20%. Patients were then re-tilted for 15 min, or until symptoms developed.

We measured RR intervals from the electrocardiogram and estimated arterial pressures with a finger photoplethysmograph (Finapres, Ohmeda, Englewood, Colorado), maintained at heart level. We recorded left and right middle cerebral artery flow velocities with a transcranial Doppler device (MultiDop T, DWL Electronics, Sipplingen, Germany) with bitemporal 2-MHz probes. Doppler recordings were analyzed with a software-implemented outliner that translates the velocity spectrum outline into an analog voltage.

We recorded data on digital tape and analyzed results with commercial hardware and software (Windaq, Dataq...
Instruments, Akron, Ohio). Maximum and minimum middle cerebral artery blood flow velocities were derived with an automatic peak and valley detection algorithm. The area under the Doppler signal was integrated as total cerebral blood flow velocity (CBFV). Because this area is proportional to RR intervals, we normalized the signal by dividing each integral of CBFV by its RR interval. We calculated mean CBFV as

\[
\text{mean CBFV} = \left( \frac{\text{maximum CBFV} + 2 \times \text{minimum CBFV}}{3} \right)
\]

d and cerebral vascular resistance as

\[
\text{cerebral vascular resistance} = \frac{\text{mean arterial pressure [MAP] } - 15 \text{ mm Hg}}{\text{mean CBFV}}
\]

(The latter formula was corrected for the reduction of arterial pressure at the level of the middle cerebral arteries during tilt [8,9]). Figure 1 illustrates the measurements and calculations we made.

The beginning of hemodynamic and neural changes leading to presyncope may be very difficult to time precisely (3). Therefore, we defined the onset of changes objectively with a mathematical break-point analysis developed earlier (10), with software provided by Jones and Molitoris (11). This method iteratively calculates least squares linear regressions to the left and right of all points on continuous time series, and adds and plots the sum-squared errors of each regression, at each point. The point in the relation for which the sum-squared errors is least is taken as the bending point. We also used an F test of residual sum-squared errors to determine whether each relation was described better by one than two regressions (10,11). (If the sum-squared error was smaller for one regression calculated for the entire series, the relation was considered not to have bent at all.)

Data are given as mean ± SEM. Statistical analyses were performed with SigmaStat (SPSS Inc., Chicago, Illinois). Comparisons within groups were made with a one-way repeated measures analysis of variance (ANOVA) for data

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**Figure 1.** Recording from one patient indicating the measurements made. Sbp, map, dbp = systolic, mean arterial and diastolic pressures. **Bottom panel** shows middle cerebral artery velocity (V) and calculations of indexes of cerebral blood flow velocity (CBFV). CBFV_c = cerebral blood flow velocity corrected for RR interval (RRI); PI = pulsatility index.
that were distributed normally, and Friedman’s repeated measures ANOVA on Ranks for data that were not distributed normally. The time of the break-point of CBFV indexes was subtracted from the time of the break-point of MAP and compared to ‘0’ (no difference) with the Student t test. Differences were tested with the Tukey honestly significant difference test. Differences between presyncopal and nonsyncopal groups were evaluated with a one-way ANOVA with the Student t test or the Wilcoxon rank-sum test.

We also compared average data from presyncopal and nonsyncopal groups during the last 5 min of tilt, with a mixed model with repeated measures (12). These analyses were based on the assumption that, although the data were distributed independently among different subjects, they correlated serially in each subject. We modeled the variance by assuming the data were extracted from an autoregressive process (13). We considered a p value of <0.05 to be significant.

RESULTS

We excluded 3 of the 18 patients from the final analysis; 2 presyncopal patients had frequent premature ventricular beats, and 1 nonsyncopal patient had a poor acoustic window and uninterpretable Doppler recordings. Of the

Table 1. Measurements Made During the Final 5 Min of Tilt

<table>
<thead>
<tr>
<th></th>
<th>Syncopal Group (n = 8)</th>
<th>p Value (Presyncopal vs. Nonsyncopal)</th>
<th>Nonsyncopal Group (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (s)</td>
<td>0.890 ± 0.023</td>
<td>0.001</td>
<td>0.700 ± 0.023</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>67.7 ± 2.1</td>
<td>0.001</td>
<td>109.8 ± 2.1</td>
</tr>
<tr>
<td>Mean velocity (cm/s)</td>
<td>50.0 ± 1.9</td>
<td>0.31</td>
<td>46.8 ± 1.9</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>1.30 ± 0.05</td>
<td>0.001</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>Total velocity (cm²/beat)</td>
<td>49.5 ± 2.3</td>
<td>0.001</td>
<td>33.1 ± 2.3</td>
</tr>
<tr>
<td>Total velocity/RR interval (cm²/s)</td>
<td>54.5 ± 2.5</td>
<td>0.056</td>
<td>47.8 ± 2.5</td>
</tr>
<tr>
<td>Resistance (mm Hg/cm/s)</td>
<td>1.19 ± 0.07</td>
<td>0.001</td>
<td>2.11 ± 0.07</td>
</tr>
</tbody>
</table>

Hemodynamic and cerebrovascular Doppler data are presented as mean ± SEM.
remaining 15 patients, 8 experienced symptoms of impending syncope ("presyncope") and 7 did not ("nonsyncope"). Arterial pressures, RR intervals and CBFVs before and during the first 3 min of tilt were similar in the two groups. Systolic, mean and diastolic pressures rose during tilting in both groups.

Eight men (58 ± 4 years) experienced presyncope, 958 ± 630 s (16 ± 11 min) after the beginning of tilt. Three had been given low dose (1 μg/min) intravenous isoproterenol before syncope occurred. Of the eight, six had near syncope (reductions of systolic pressure <70 mm Hg, or heart rates <50 beats/min), and two had postural orthostatic tachycardia (symptoms of presyncope with heart rate increases >30 beats/min). Six men and one woman (55 ± 4 years) had negative tilt-table tests (no symptoms or cerebral or systemic hemodynamic changes). All of the nonsyncopal patients were given intravenous isoproterenol. Figure 2 shows total CBFV and MAP (left), and the results of bending-point analyses (right), for one presyncopal subject, whose bending points were obvious to visual inspec-

Figure 3. Average of all systemic hemodynamic and cerebrovascular indices of last 300 s of tilt in syncopal and nonsyncopal patients. Time “0” (vertical dashed line) represents the time of syncope for the syncopal patients, and 2 min before the end of tilt for nonsyncopal patients.
tion. In this subject, total CBFV began to decline 28 s before MAP.

Table 1 lists and Figure 3 depicts the average values for presyncopal and nonsyncopal patients during the final 5 min of tilt. (Data from presyncopal patients were aligned at the nadir of arterial pressure and back-averaged; data from nonsyncopal patients were aligned at 2 min before the end of tilt and back-averaged.) Compared with nonsyncopal patients, presyncopal patients had significantly higher average RR intervals and pulsatility indexes, and significantly lower MAPs and calculated cerebrovascular resistances. All measurements were constant in the nonsyncopal patients during the final 5 min of tilt. Table 2 gives pretilt and late-tilt measurements for presyncopal patients. There were significant trends of RR intervals (increasing), and MAP and cerebrovascular resistance (both decreasing) in presyncopal patients during tilt.

In presyncopal patients, symptoms (dizziness, light-headedness, sweating, fatigue or nausea) occurred 155 s (range: 25 to 414 s) before MAP began to fall. Figure 4 shows individual and average break-points from which the MAP break-point was subtracted. (Average measurements to the left of the vertical dashed line in Fig. 4 indicate that the change occurred before MAP began to fall.) Three measures of CBFV began to drop at times significantly earlier than MAP: CBFV normalized for RR intervals (range: −67 s [−198 to −9 s], p = 0.025); total CBFV (range: −48 s [−119 to 57 s], p < 0.05); and mean CBFV velocity (range: −34 s [−96 to 4 s], p < 0.05).

**DISCUSSION**

The ultimate cause of orthostatic vasovagal syncope is cerebral hypoperfusion (5) and hypoxia (6). Although it is clear that cerebral circulatory changes occur before the onset of presyncope, it is unclear whether these changes contribute to presyncope (7) or merely reflect appropriate autoregulatory responses to arterial hypotension (8). We measured

<table>
<thead>
<tr>
<th></th>
<th>MAP</th>
<th>CBFV\textsubscript{mean}</th>
<th>CBFV</th>
<th>CBFV/RRI</th>
<th>PI</th>
<th>CVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>88 ± 16</td>
<td>53 ± 12</td>
<td>50 ± 11</td>
<td>54 ± 14</td>
<td>1.08 ± 0.1</td>
<td>1.41 ± 0.21</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>52 ± 5</td>
<td>44 ± 15</td>
<td>43 ± 9</td>
<td>30 ± 9</td>
<td>1.7 ± 0.14</td>
<td>0.96 ± 0.16</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.07</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM.

CBFV\textsubscript{mean} = mean cerebral blood flow velocity; CBFV/RRI = cerebral blood flow velocity/RR interval; CVR = calculated cerebrovascular resistance; MAP = mean arterial pressure; PI = pulsatility index (see Methods).

Figure 4. Average differences among break-points of onset of symptoms, cerebrovascular indexes, and mean arterial pressure. Open circles are individual values for the tilt-positive subjects, and the closed circles are means ± SEM. Negative values signify break-points occurring before the mean arterial pressure break-point. RRI = RR interval.
middle cerebral artery blood flow velocity and performed iterative regression analyses to define mathematically the precise times at which hemodynamic changes occurred. The significant new finding from this analysis is that, in presyncopal patients, several indexes of CBFV begin to change before MAP begins to fall. These results suggest that altered cerebrovascular autoregulation contributes to physiologic changes leading to orthostatic vasovagal syncope.

Hemodynamic and neural changes leading to presyncope.
Before 1997, individual case reports had documented reductions and ultimate disappearance of muscle sympathetic nerve activity during human vasovagal reactions (14). In 1997, Morillo et al. (3) and Mosqueda-Garcia et al. (4) published the first series of patients studied with sympathetic microneurography during orthostatic vasovagal reactions. These groups reported that muscle sympathetic nerve activity disappears or begins to disappear as arterial pressure falls. Although abrupt reductions of arterial pressure are sufficient to explain cerebral hypoperfusion, they do not exclude the possibility that changes of cerebral autoregulation contribute to vasovagal physiology.

This possibility was suggested first by Grubb et al. (7), who also reported reductions of diastolic and mean CBFVs, and increases of pulsatility indexes and cerebrovascular resistance prior to presyncope, and they concluded that “paradoxical cerebral vasoconstriction” may contribute to orthostatic vasovagal reactions. The recordings on which this conclusion were based were discontinuous, however; therefore, the results of Grubb et al. (7) did not indicate whether changes of CBFV preceded or followed systemic arterial pressure reductions.

Schondorf et al. (8) documented similar changes of CBFV before orthostatic vasovagal syncope, based on continuous rather than discontinuous measurements. They concluded that changes of CBFV reflect normal cerebral autoregulatory responses to systemic arterial pressure reductions, rather than changes of cerebral autoregulation. Our study extends that of Schondorf et al. (8). Although these investigators made their recordings continuously, they did not analyze their time series mathematically to determine precisely when the changes they observed began. Such changes may begin imperceptibly, and their precise timing may be difficult or impossible to determine by visual inspection. For these reasons, we analyzed our data with a mathematical method, iterative least squares linear regression (10), which yielded objective determinations of the timing of the changes that occurred. Our analysis supports the conclusion of Grubb et al. (7)—changes of several indexes of cerebral blood flow velocity precede reductions of arterial pressure during vasovagal presyncope (Fig. 4) and, therefore, cannot be caused by changes of arterial pressure.

Noninvasive measures of cerebral hemodynamics.
Transcranial Doppler recordings represent the only noninvasive technology capable of defining changes of cerebral hemodynamics on a heart-beat-by-heart-beat basis. Others have expertly discussed the strengths and limitations of transcranial Doppler recordings (15,16). A key reference in the published reports is that of Lindegaard et al. (17), who documented a striking ($r = 0.95$) linear relation between middle cerebral artery blood flow velocity and carotid arterial blood flow, measured invasively during surgery with carotid artery flowmeters. We emphasize, however, that the validity of our conclusions does not hinge on assumptions regarding correspondence between cerebral arterial blood flow velocity and cerebral blood flow—were we concerned about the timing of changes; we report that CBFV changes occur before reductions of arterial pressure (Figs. 2 to 4).

Our study was not designed to determine what initiates changes leading to vasovagal presyncope. We were intrigued by the fact that our patients reported symptoms before any measurable hemodynamic change occurred. We suggest that the timing of patients' symptoms and the changes of transcranial Doppler signals indicate strongly that the earliest changes in the cascade of events culminating in vasovagal syncope result from a central nervous system trigger, whatever that trigger may be (18).

Study limitations. The principal limitation of our study is the small number of subjects (eight) who became presyncopal. This may not be an important shortcoming, because the changes of transcranial Doppler blood flow velocity we documented in our eight patients are nearly identical to those reported by Grubb et al. (7) and Schondorf et al. (8), who studied larger numbers of subjects. We did not record end-tidal carbon dioxide concentrations; therefore, we cannot exclude the possibility that our subjects became hypocapnic during upright tilt (19). This may not be a major problem, however, because Levine et al. (16) showed that hypocapnia secondary to hyperventilation does not cause presyncope, even though it increases CBFV more than lower body suction, which does cause presyncope.

Conclusions. In summary, our study shows that CBFV changes begin before arterial pressure reductions during orthostatic presyncope. Therefore, changes of cerebrovascular autoregulation may contribute to the physiology of vasovagal reactions.

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REFERENCES