Dynamic cerebral autoregulation is preserved in neurally mediated syncope

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Cerebral autoregulation is defined as the intrinsic capacity of cerebral vasculature to maintain cerebral blood flow constant over a wide range of cerebral perfusion pressures (2, 19, 23, 34). The overall efficiency of cerebral autoregulation is usually inferred from observed changes in average cerebral blood flow during maintained changes in cerebral perfusion pressure (9, 23, 34, 43). Quantification of cerebral autoregulation in this fashion, as a static process, obscures the fact that most of the challenges to cerebral perfusion originate from rapid shifts in cerebral perfusion pressure that occur over seconds during normal activities of daily living (1, 31, 32). The presence of dynamic cerebral autoregulation has been demonstrated by observing the quick recovery of cerebral perfusion after transient changes in blood pressure (BP) induced by rapid deflation of large cuffs previously placed around the upper thigh (2), by performance of the Valsalva maneuver (42), or after transient carotid artery compression (40).

One of the most frequent forms of syncope encountered in clinical practice is vasovagal or neurally mediated syncope (NMS) (36). Despite its frequency of occurrence, the pathophysiology of NMS remains unclear, but all consider that loss of consciousness during NMS is due to cerebral hypoperfusion that accompanies the cardiovascular collapse at syncope (28, 45). Have patients with NMS lost the ability to defend against sudden hypotension because of an intrinsic impairment of cerebral autoregulation? Insights pertaining to this question have been obtained from continuous transcranial Doppler (TCD) sonographic measurements of middle cerebral artery (MCA) blood velocity (CBV) in patients with NMS and in normal control subjects in whom syncope was induced by lower body negative pressure (LBNP). Static autoregulation is not impaired during head-up tilt (HUT) in patients with NMS (37), although this may not be the case in some normal subjects during high levels of orthostatic stress simulated by LBNP (7, 51).

Loss of dynamic autoregulation may be a more sensitive index of a threatened cerebral circulation than the standard static measures of cerebral autoregulation (12). Therefore, even if static autoregulation is not impaired, subjects with NMS may have a selective defect in dynamic cerebral autoregulation. Several laboratories have observed a decline in diastolic CBV with preservation of systolic CBV during the profound collapse in BP at syncope (13, 16, 37). Two discrepant conclusions have been drawn from this observation. Some have considered the increased CBV pulsatility at syncope to be indicative of a paradoxical vasoconstriction that would obscure dynamic cerebral autoregulation (16). In contrast, we have argued that the limited decrease in mean CBV in the face of large decreases in mean BP at syncope constitutes clear evidence of relatively preserved dynamic cerebral autoregulation.
MATERIALS AND METHODS

We evaluated 37 patients (4 men, 33 women) referred for recurrent syncope without warning or for evaluation of symptomatic orthostatic intolerance that included multiple episodes of near syncope or syncope. Many had symptoms of presyncope that were exacerbated by exposure to heat or prolonged standing. In all patients, physical examination, routine clinical chemistry, complete blood count, Holter monitor, electroencephalogram (EEG), electrocardiogram, and echocardiographic evaluation did not reveal the cause of syncope. No patient took medication of any kind. Fifteen healthy subjects (6 men, 9 women) with no history of syncope or orthostatic intolerance served as the control group. Both groups were similar (controls vs. NMS) in age (30.7 ± 1.7 vs. 32.7 ± 1.2 yr), height (167.7 ± 1.8 vs. 165.5 ± 1.2 cm), and weight (63.1 ± 2.2 vs. 62.4 ± 2.4 kg).

The HUT test protocols were approved by the hospital internal review board, and informed consent was obtained from all subjects. All patients were supine for 30–45 min before recordings. The HUT protocol consisted of a 10-min resting period in the supine position, a maximum of 40 min of 80° HUT with footrest support, and a second 5-min period with the subject supine. HUT was ended if a subjective sensation of impending syncope was associated with a clear precipitous drop in BP or heart rate (HR). Episodes of syncope during HUT were preceded by or associated with lightheadedness, nausea, blurred vision, and sweating.

BP was continuously recorded from the third finger of the left hand with a volume-clamp photoplethysmograph (Finapres model 2300, Ohmeda Monitoring Systems, Madison, WI) and was also intermittently measured from the brachial artery with a sphygmomanometer. During the recording period, the subject’s hand was warmed with a heated pad to prevent finger vasoconstriction (37). The arm was maintained at the level of the heart. Respiratory movements were measured with a nasal thermistor. The right MCA was insonated through the temporal window at depths ranging from 45 to 55 mm with a 2-MHz Doppler probe (model TC-64, Eden Medical Equipment) that was firmly strapped in place with an adjustable headband to ensure a fixed angle of insonation. Analog electrocardiogram, BP, spectral envelope of CBV, and respiratory signals were fed to a PC equipped with an eight-channel analog/digital acquisition card and software (Dataq, Akron, OH) and were sampled at 200 Hz.

Beat-to-beat HR, systolic and diastolic BP, and CBV were derived off-line with an automatic peak and trough detection algorithm. In all cases, placement of the cursors was verified by visual inspection of the waveforms. Data were then resampled at 2 Hz with a linear interpolation algorithm and averaged every 2 s. Data obtained at baseline and during early (minutes 1–3), mid- (minutes 17–21), and late (minutes 34–38) HUT were directly compared with uncover trends in the hemodynamic profile of control subjects during HUT. Direct comparisons were also made between the hemodynamic response of control and syncopal subjects from data obtained while supine and during early HUT. The hemodynamic profile of minutes 2–4 preceding syncope (before onset of syncope) was compared with end HUT of control subjects. Because the average latency to the onset of syncope in our patients was 14.5 ± 1.7 min (range = 3.5–39.5 min), we also compared the minutes preceding syncope to mid-HUT of control subjects. Cerebrovascular resistance (CVR) was calculated by dividing mean BP by mean CBV after correcting for the difference in hydrostatic pressure between the site of BP recording and MCA insonation. Changes in CVR during HUT served as an index of static autoregulation.

To assess dynamic cerebral autoregulation, 20-Hz continuous waveforms of BP, CBV, and respiration were band-pass filtered between 0.02 and 0.8 Hz. Filtered data segments of 4,096 (204.8 s), 8,192 (409.6 s), or 16,384 (819.2 s) points were subsampled at 2.5 Hz. Power spectra were constructed from Hann-windowed segments of 256 points overlapped by 50%. The powers of the low- and high-frequency BP and CBV bands were integrated by using the commonly accepted definitions of 0.04–0.15 Hz and 0.15–0.40 Hz, respectively (8, 11). Transfer functions were constructed from Hann-windowed segments of 128 points overlapped by 69%. For each segment, squared coherence, phase, and transfer gain were calculated. Phase is defined as positive when CBV leads BP. Transfer gain expresses the degree to which input (BP) oscillations are transmitted to output (CBV). The gain was normalized by dividing admittance magnitude by mean conductance of the analyzed data segment (35, 46). Gain > 1 indicates perfect transmission of the BP fluctuations to CBV, gain > 1 indicates amplification, and gain < 1 indicates attenuation of the transmitted BP fluctuations (i.e., presence of dynamic autoregulation). Minimal gain was calculated as the square of points between 0.02 and 0.04 Hz, the frequency range at which the best attenuation of transmitted BP fluctuations was observed. To compare curves of gain and phase between syncopal and control subjects, points between 0.02 and 0.12 Hz where the gain was <1 were averaged.

Nonparametric statistical tests (Mann-Whitney U test) were used to assess the statistical significance of simple paired or unpaired data. Multiple comparisons of the hemodynamic data sampled at baseline, early, mid, and late HUT were effected by using a two-way repeated-measures ANOVA correcting for multiple comparisons using Tukey’s protected t-test. Data are expressed as means ± SE. Statistical significance was defined as P < 0.05.

RESULTS

Cardiovascular and cerebrovascular profiles at rest and during HUT. Raw BP and TCD signals from a single patient with NMS are shown in Fig. 1. Figure 2 shows the temporal profiles of the hemodynamic data from control subjects during baseline, early, and late HUT compared with that obtained from patients with
syncope during baseline, early HUT, and the last minutes of HUT preceding syncope. Baseline values were not different between the two groups.

In controls and in subjects with NMS, early HUT caused an increase in HR and in diastolic BP and a decrease in systolic and diastolic CBV and in CVR ($P < 0.0001$) and CVR ($P < 0.02$) increased over the course of HUT, systolic BP ($P < 0.0005$) and systolic ($P = 0.04$) and diastolic ($P < 0.0001$) CBV decreased, and diastolic BP did not change ($P = 0.97$).

Expressing data at end HUT as a change from baseline values shows a decline in systolic BP in NMS but not in controls ($-10.1 \pm 1.7$ vs. $3.4 \pm 4.1$ mmHg, $P = 0.002$), and the increase in diastolic BP was less in NMS than in controls ($7.3 \pm 1.6$ vs. $14.1 \pm 1.7$ mmHg, $P = 0.01$). In contrast, changes in systolic ($-15.9 \pm 1.7$ vs. $-20.0 \pm 3.4$ cm/s, $P = 0.37$) and diastolic ($-7.9 \pm 0.9$ vs. $-8.8 \pm 2.0$ cm/s, $P = 0.88$) CBV were not different between NMS and controls. Consequently, CVR is less in NMS than in controls ($0.86 \pm 0.03$ vs. $1.03 \pm 0.06$ mmHg cm$^{-1}$ s$^{-1}$, $P = 0.01$). Similar conclusions were obtained when values from control mid-HUT were substituted for end HUT.

Figure 2 shows that at syncope there was a sudden decrease in HR, systolic and diastolic BP, and diastolic CBV, whereas systolic CBV did not change (also see

Fig. 1. Raw blood pressure (BP) and transcranial Doppler signals from a single patient with neurally mediated syncope (NMS). A: the entire period of head-up tilt (HUT) is shown. B: expanded time course of the BP and cerebral blood velocity (CBV) immediately before syncope. Note the selective decline in diastolic CBV at syncope. C: expanded time course of spontaneous oscillations in BP and CBV. Note that the fluctuations in CBV precede and appear to be related to those in BP.

In controls, HR, diastolic BP, and CVR increased ($P < 0.0001$) over the course of HUT (early vs. mid vs. late), systolic and diastolic CBV decreased ($P = 0.0001$ and $P = .0006$, respectively), and systolic BP did not change ($P = 0.202$). In patients with NMS, HR ($P < 0.0001$) and CVR ($P < 0.02$) increased over the course of HUT, systolic BP ($P < 0.0005$) and systolic ($P = 0.04$) and diastolic ($P < 0.0001$) CBV decreased, and diastolic BP did not change ($P = 0.97$).

Expressing data at end HUT as a change from baseline values shows a decline in systolic BP in NMS but not in controls ($-10.1 \pm 1.7$ vs. $3.4 \pm 4.1$ mmHg, $P = 0.002$), and the increase in diastolic BP was less in NMS than in controls ($7.3 \pm 1.6$ vs. $14.1 \pm 1.7$ mmHg, $P = 0.01$). In contrast, changes in systolic ($-15.9 \pm 1.7$ vs. $-20.0 \pm 3.4$ cm/s, $P = 0.37$) and diastolic ($-7.9 \pm 0.9$ vs. $-8.8 \pm 2.0$ cm/s, $P = 0.88$) CBV were not different between NMS and controls. Consequently, CVR is less in NMS than in controls ($0.86 \pm 0.03$ vs. $1.03 \pm 0.06$ mmHg cm$^{-1}$ s$^{-1}$, $P = 0.01$). Similar conclusions were obtained when values from control mid-HUT were substituted for end HUT.

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Fig. 2. Temporal profiles of hemodynamic parameters in control ($n = 15$) and NMS subjects ($n = 37$) during a 2-min supine period before HUT (baseline), minutes 1–3 of HUT (early HUT), and the last 4 min of HUT (late HUT). For statistical analysis, data points during the baseline period were pooled, as were those during the early HUT and the first 2 min of late HUT. These data were subjected to a multivariate analysis, and significant changes within or between groups are described in the text.
prominently during HUT. From the data trace shown in Fig. 1, A and B), To quantify this response, we compared 12 s of data measured 4 min before the end of HUT with the last 12 s of HUT. HR decreased from 99.2 ± 0.2 to 84.9 ± 0.9 beats/min, systolic BP from 99.1 ± 0.6 to 77.0 ± 2.2 mmHg, diastolic BP from 63.9 ± 0.4 to 47.8 ± 1.2 mmHg, and diastolic CBV from 31.0 ± 0.3 to 22.1 ± 0.4 cm/s (P < 0.0001 for all values). CVR decreased significantly from 1.19 ± 0.01 to 0.88 ± 0.04 mmHg·cm·s⁻¹ (P = 0.0002). This response was observed in all subjects with NMS. In no case was any change in CBV observed before the rapid decline in BP.

Transfer function analysis of dynamic cerebral autoregulation. Both normal controls and subjects with NMS exhibited spontaneous low-frequency (<0.1 Hz) oscillations in BP and CBV while supine and more prominently during HUT. From the data trace shown in Fig. 1C, it can be seen that the two oscillations are similar in frequency, that they are coherent, and that the peak of the CBV oscillations precedes that of the BP. Figure 3 (data from another subject) shows how application of linear-transfer analysis allows the definition of the relationship between CBV and BP. The two signals have a coherence >0.5 at frequencies above 0.05 Hz. The phase is positive, indicating that the CBV fluctuations precede those in BP. This is also apparent from the data segment shown in Fig. 3A. Amplitudes of the CBV oscillations at frequencies below 0.14 Hz are attenuated relative to BP (gain < 1). This constellation of findings is the signature of an autoregulatory system, which effectively isolates flow from BP fluctuations slower than 0.14 Hz (3, 20, 21).

Dynamic cerebral autoregulation in normal control subjects during HUT. Initially, studies were done in normal subjects to determine the parameters to use in the transfer function analyses of patients with NMS. Because the latency to onset of syncope was variable, it was necessary to ascertain that transfer function estimates of dynamic cerebral autoregulation were independent of the duration of HUT and to verify that 3.4-min data segments provide accurate estimates of dynamic autoregulation. We therefore compared estimates obtained from intermediate length (6.8 min) data segments during early HUT with those obtained during mid or late HUT. As shown in Fig. 4, A–C, dynamic cerebral autoregulation estimates are independent of HUT duration. We then compared estimates derived from data segments of 6.8 or 13.6 min with those derived from short data segments. As shown in Fig. 4, D–F, estimates obtained from 3.4 min of data accurately reflect those obtained from longer data segments. Shorter estimates (<1.7 min) were not evaluated because the lowest frequency that could be estimated would be 0.04 Hz and too few data points would be available in the autoregulatory frequency band of interest (<0.14 Hz).

Dynamic cerebral autoregulation in subjects with NMS during HUT. Transfer function estimates and periodograms obtained from short data segments back-sampled from just before the onset of syncope (usually 45–60 s before the point of maximal hypotension) (n = 38 tilts) were compared with those obtained from normal controls near the end of HUT (n = 15). As shown in Fig. 5, D–E, both groups displayed similar fluctuations in BP and CBV with a peak at ~0.02–0.03 Hz, a low-frequency band at 0.07–0.11 Hz, and a higher-frequency band at 0.20–0.27 Hz. The range of respiratory frequencies (0.2–0.35 Hz) was more tightly defined for control subjects (Fig. 5F). As shown in Table 1, amplitudes of BP and CBV fluctuations in the low-frequency range in which autoregulation occurs were similar, whereas high-frequency BP fluctuations were greater in subjects with NMS. Transfer functions of controls and NMS subjects were very similar (Fig. 5, A–C). In both groups, coherence remained >0.5 between 0.06 and 0.36 Hz (average coherence 0.71 ± 0.04 for controls vs. 0.72 ± 0.02 for NMS, P = 0.78). Gain was <1 at frequencies <0.14 Hz. Values for minimal gain, average gain, and phase presented in Table 1 show no difference between control and NMS subjects. We also verified in NMS patients that dynamic cerebral autoregulation remains stable over the duration of HUT. Figure 6 represents data taken from 22 subjects with NMS who had HUT of sufficient duration to allow separate transfer functions from the beginning and end of HUT. As shown in Fig. 6, A–C, curves from these
Fig. 4. Dynamic cerebral autoregulation estimates are independent of the duration of HUT, and transfer function estimates obtained from short data segments (3.4 min) during HUT accurately reflect those obtained from longer data segments. A–C: averaged transfer functions from intermediate-length (6.8 min) data segments obtained from 15 control subjects during the beginning, middle, or end of a 40-min HUT. D–F: averaged transfer functions taken from data segments of different length (3.4–13.6 min) during HUT. Gain (A and D), phase (B and E), and coherence (C and F) are shown. For clarity, SE bars have been omitted.

Fig. 5. Group-averaged transfer function gain (A), phase (B), coherence (C), and spectral analysis of the fluctuations in BP (D), CBV (E), and respiration (Resp; F) in control (n = 15 subjects) and syncopal subjects (n = 37 patients and 38 tilts). Data were acquired during the last 204 s of HUT immediately preceding the onset of syncope. Transfer functions of both groups are very similar (A–C). Both groups displayed similar fluctuations in BP and CBV (D and E). Range of respiratory frequencies was more tightly defined for control subjects (F). AU, arbitrary units.
two time periods are essentially superimposable. This was confirmed by showing no statistical difference between the paired data of minimal and average gain as well as phase taken from these 22 subjects. As shown in Fig. 6, D–F, the properties of dynamic cerebral autoregulation were also not affected by subjects’ orthostatic tolerances. Transfer-function profiles of 16 subjects who fainted within 400 s (average HUT duration = 533 ± 32 s) were similar to those of 17 subjects who fainted after more than 800 s (average HUT duration = 1,456 ± 129 s). Minimal (0.54 ± 0.08 and 0.48 ± 0.07, \( P = 0.61 \)) and average (0.67 ± 0.05 and 0.7 ± 0.06, \( P = 0.73 \)) gains and the average phase (0.49 ± 0.1 vs. 0.7 ± 0.09 rads, \( P = 0.13 \)) were not different between these two groups of patients.

### Table 1. Comparison of power spectra and transfer function analysis

<table>
<thead>
<tr>
<th></th>
<th>Control HUT</th>
<th>NMS HUT</th>
<th>Control Supine</th>
<th>NMS Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-frequency BP power, mmHg^2/Hz</td>
<td>1,786 ± 259</td>
<td>2,279 ± 290</td>
<td>839 ± 185^†</td>
<td>989 ± 115§</td>
</tr>
<tr>
<td>High-frequency BP power, mmHg^2/Hz</td>
<td>304 ± 72</td>
<td>484 ± 48*</td>
<td>142 ± 31</td>
<td>215 ± 25§</td>
</tr>
<tr>
<td>Low-frequency CBV power, (cm/s)^2/Hz</td>
<td>1,064 ± 156</td>
<td>1,528 ± 249</td>
<td>715 ± 155</td>
<td>895 ± 114‡</td>
</tr>
<tr>
<td>High-frequency CBV power, (cm/s)^2/Hz</td>
<td>353 ± 58</td>
<td>636 ± 100^*</td>
<td>232 ± 44</td>
<td>320 ± 40§</td>
</tr>
<tr>
<td>Minimal gain</td>
<td>0.46 ± 0.05</td>
<td>0.53 ± 0.05</td>
<td>0.85 ± 0.13§</td>
<td>0.72 ± 0.08^†</td>
</tr>
<tr>
<td>Average gain</td>
<td>0.68 ± 0.03</td>
<td>0.71 ± 0.04</td>
<td>0.86 ± 0.08‡</td>
<td>0.85 ± 0.04‡</td>
</tr>
<tr>
<td>Average phase, radians</td>
<td>0.66 ± 0.08</td>
<td>0.59 ± 0.07</td>
<td>0.62 ± 0.10</td>
<td>0.71 ± 0.07</td>
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Values are means ± SE. BP, blood pressure; CBV, cerebral blood velocity; HUT, head-up tilt; NMS, neurally mediated syncope. Low-frequency band = 0.04–0.15 Hz; high-frequency band = 0.15–0.40 Hz; minimal gain bandwidth = 0.02–0.04 Hz; average gain and average phase bandwidth = 0.02–0.12 Hz.*NMS significantly different from control (\( P \leq 0.05 \)). Significantly different from HUT for controls or NMS: ^†\( P \leq 0.05 \), ‡\( P \leq 0.01 \), §\( P \leq 0.001 \).

Dynamic cerebral autoregulation in controls and in subjects with NMS while supine. Dynamic cerebral autoregulation of both groups was also assessed in the absence of orthostatic stress from short data segments derived from the supine pre-HUT period. As shown in Fig. 7 and in Table 1, once again there was no difference in the magnitude of BP or CBV fluctuations or in transfer signatures of supine controls compared with those of supine subjects with NMS. In the absence of orthostatic stress, the amplitude of BP fluctuations, as expected, was less in both groups. This reduction was also apparent in the amplitude of CBV fluctuations of NMS subjects but not in that of control subjects. Calculated gains were elevated in both supine groups compared with HUT, but there was no difference in the

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**Fig. 6.** Dynamic cerebral autoregulation remains stable over the duration of HUT in NMS and is not affected by subjects’ orthostatic intolerances. A–C: data taken from 22 subjects with NMS who had HUTs of a sufficient duration to allow construction of separate transfer functions at the beginning and end of HUT. D–F: data taken from subjects with low (HUT < 400 s) and high (HUT > 800 s) orthostatic tolerance. Group-averaged transfer function gain (A and D), phase (B and E), and coherence function (C and F) are obtained from 3.4-min data segments. For clarity, SE bars have been omitted.
average phase relationship of BP and CBV fluctuations. As was seen during HUT, the coherence of BP and CBV fluctuations while supine were 0.5 at frequencies between 0.06 and 0.36 Hz (average coherence 0.55 ± 0.02 for controls and 0.62 ± 0.02 for NMS, P = 0.11).

DISCUSSION

The results of this study provide several new insights concerning cerebral autoregulation in NMS. First, we have confirmed that static autoregulation as assessed from the CVR response to early HUT was similar in NMS and normal control subjects. In no case was a paradoxical increase in CVR noted. Second, we have extended our observations (37) concerning the cardiovascular and cerebrovascular profile at syncope and have demonstrated in each case a further decline in CVR during the cardiovascular collapse at syncope. Both of these observations suggest that autoregulation is intact in NMS. Third, we have used standard techniques of linear transfer function analysis to more precisely define characteristics of dynamic cerebral autoregulation in NMS and have made the following important observations: 1) in the 3 min preceding syncope, dynamic cerebral autoregulation of subjects with NMS does not differ from that of controls; 2) dynamic cerebral autoregulation does not change over the course of HUT in patients with NMS or in control subjects; and 3) dynamic cerebral autoregulation is unaffected by the degree of orthostatic intolerance as inferred from latency to onset of syncope.

In this study, we used TCD as an index of cerebral blood flow. TCD is the only technology currently available that permits noninvasive prolonged monitoring of rapid changes in cerebral perfusion. CBV, the actual parameter measured, is considered to be an index of cerebral blood flow because changes in cerebral artery lumen area of the insonated vessel are minimal (39, 41) and because carotid blood flow is closely correlated with CBV (25, 29). Moreover, estimates of cerebral perfusion using TCD correlate well with symptoms of orthostatic intolerance (30) and with estimates of cerebral oxygenation measured with near-infrared spectroscopy (NIRS) over a wide range of BP in patients with autonomic failure (18). There are conditions, however, in which MCA diameter does not remain constant. For example, increases in MCA diameter may occur during severe hypercapnia (44), and MCA vasoconstriction may occur after nitric oxide synthase inhibition (48). Under these and other similar conditions, CBV may not provide adequate estimates of cerebral blood flow.

Loss of consciousness at syncope is undoubtedly due to severe cerebral hypoperfusion. Only rarely has cerebral hypoperfusion without hypotension been reported in patients with unexplained recurrent syncope (15, 17). Zero diastolic velocity or even diastolic flow reversal has been observed in some patients at syncope (22), during severe orthostatic hypotension (49), and during cough syncope (27). None of our patients actually lost consciousness because for ethical reasons they were rapidly returned to the supine position once the typical hemodynamic profile of syncope was evident. We have previously suggested that the selective decrease of diastolic CBV during impending syncope is due to a collapse of downstream vessels as diastolic BP de-
creases below critical closing pressure of cerebral vessels (37).

Severe hemorrhagic hypotension sufficient to decrease diastolic CBV to zero is associated with EEG burst suppression (47). EEG abnormalities (diffuse high-amplitude slow waves or disappearance of EEG activity) during HUT-induced syncope are recorded only at clinically evident syncope and at a time when BP is no longer measurable by auscultation (4). Multifocal myoclonus, visual or auditory hallucinations, may often be associated with such profound cerebral hypoperfusion at syncope (24). However, the EEG record is normal before syncope, indicating that, before actual syncope, cerebral perfusion is still well preserved (4). Simultaneous measurements of cerebral perfusion (TCD) and oxygenation (NIRS) in normal volunteers during HUT without footrest support have also confirmed decreased cerebral oxygenation only at syncope when BP and CBV have significantly decreased (26). Thus, before syncope, cerebral autoregulation is preserved.

From the array of methodologies currently available, we chose analysis techniques that model dynamic cerebral pressure autoregulation as a frequency-dependent phenomenon approximating a high-pass filter (3, 6, 20, 31, 50). The signature of a dynamic autoregulating system is easily recognizable. At frequencies at which autoregulation is operant (<0.14 Hz in our case), fluctuations in blood flow lead those in BP and normalized gain is <1, indicating the presence of an active mechanism that limits the transfer of BP fluctuations into flow. At higher frequencies, at which autoregulation is no longer operant, normalized gain is >1 because vascular compliance amplifies BP fluctuations into flow. Limitations of linear transfer analysis techniques have been addressed extensively (33, 50, 52). We feel that, despite limitations, linear-transfer analysis techniques do provide a reliable measure of dynamic cerebral autoregulation for the following reasons. First, and most importantly, the phase and gain curves that we obtained accurately approximate visual inspection of our data (Figs. 1 and 3). Second, fluctuations in MCA CBV also precede mechanically generated BP fluctuations, but only when cerebral autoregulation is intact (5, 14). Third, estimates of cerebral autoregulation obtained by using linear transfer methods accord well with those obtained by using the thigh cuff deflation technique (50). Fourth, linear models of cerebral autoregulation appear to be more robust than nonlinear models (33).

In our study, we limited our analysis to relatively short (3.4 min) data segments so as to selectively capture any impairment in autoregulation evident in the time period immediately preceding syncope. These short data segments yielded transfer estimates that were comparable to those obtained from substantially longer data sets. It should be noted that any conclusions regarding dynamic cerebral autoregulation in control subjects and subjects with NMS are restricted to the frequency band of fluctuations analyzed (0.02–0.8 Hz). Transfer estimates of dynamic cerebral autoregulation are also limited by the magnitude of spontaneous BP fluctuations. This is evidenced by the fact that transfer estimates obtained from subjects during HUT were clearly more robust than those obtained from supine subjects. The magnitude of the BP fluctuations during HUT was similar in normal control subjects and in subjects with NMS, and, therefore, comparison of dynamic autoregulation between the two populations is appropriate.

One possible limitation of our study would be that end-tidal CO₂ was not measured. Although end-tidal CO₂ does decline when subjects assume an upright posture and does affect mean CBV (10), it is unlikely that there were substantial differences in end-tidal CO₂ between patients with NMS and control subjects. As shown in Fig. 2, there were no differences between controls and patients in the profiles of CBV at baseline and during HUT until just before the onset of syncope. We interpret this to suggest an equivalent reduction of end-tidal CO₂ in the two groups because hyperventilation in patients would be associated with larger decreases in mean CBV (30). Moreover, preliminary data obtained in our laboratory suggest that the decline in end-tidal CO₂ at syncope does not contribute substantially to the decline in CBV (38).

In normal subjects, high levels of orthostatic stress simulated by LBNP provoke a selective decline in CBV and an increased transfer gain without a corresponding decline in BP (7, 51). These observations, which suggest that both dynamic and static cerebral autoregulation are impaired in normal subjects during LBNP, contrast with our data obtained in patients during prolonged HUT. To our knowledge, direct measurements that compare dynamic cerebral autoregulation during LBNP and HUT have not been made. The level of orthostatic stress induced by LBNP in normal subjects may have been greater than the stress induced by HUT. Higher degrees of orthostatic stress may increase sympathetic outflow to the cerebral vasculature and the resulting increased cerebral vasoconstriction may obscure the presence of dynamic cerebral autoregulation. It is unlikely that our patients with NMS would have been able to attain or tolerate such high levels of orthostatic stress.

In conclusion, our data, obtained from a large group of subjects, provide further evidence that both static and dynamic cerebral autoregulation remains intact during HUT-induced NMS in subjects with recurrent syncope. Impaired cerebral autoregulation is therefore not a cause of syncope in NMS. Whether cerebral autoregulation is impaired during very high levels of orthostatic stress awaits further study.

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