Dynamic cardiorespiratory interaction during head-up tilt-mediated presyncope

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Krishnamurthy, S., X. Wang, D. Bhakta, E. Bruce, J. Evans, T. Justice, and A. Patwardhan. Dynamic cardiorespiratory interaction during head-up tilt-mediated presyncope. Am J Physiol Heart Circ Physiol 287: H2510–H2517, 2004. First published August 5, 2004; doi:10.1152/ajpheart.00485.2004.—In 28 healthy adults, we compared the dynamic interaction between respiration and cerebral autoregulation in 2 groups of subjects: those who did and did not develop presyncope symptoms during 70° passive head-up tilt (HUT), i.e., nonpresyncope (23 subjects) and presyncope (5 subjects). Airflow, CO₂, cerebral blood flow velocity (CBF), ECG, and blood pressure (BP) were recorded. To determine whether influences of mean BP (MBP) and systolic BP (SBP) on CBF were altered in presyncope subjects, coherences and transfer functions between these variables and mean and peak CBF (CBFₘ and CBFₚ) were estimated. To determine the influence of end-tidal CO₂ (ETCO₂) on CBF, the relative CO₂ reactivity (% change in CBFₘ per mmHg change in ETCO₂) was calculated. We found that in presyncope subjects before symptoms during HUT, coherence between SBP and CBFₚ was higher (P = 0.02) and gains of transfer functions between BP (MBP and SBP) and CBFₘ were larger (MBP, P = 0.01; SBP, P = 0.01) in the respiratory frequency region. In the last 3 min before presyncope, presyncope had a reduced relative CO₂ reactivity (P = 0.005), likely a consequence of the larger decrease in ETCO₂. We hypothesize that the CO₂-mediated increase in resistance attenuates autoregulation such that the relationship between systemic and cerebral hemodynamics is enhanced. Our results suggest that an altered cardiorespiratory interaction involving cerebral hemodynamics may contribute in the cascade of events during tilt that culminate in unexplained syncope. Cerebral blood flow (CBF) is dynamically regulated, primarily in response to changes in perfusion pressure, metabolic activity of the brain, humoral factors, and autonomic neural activity (3). In studies exploring orthostatically mediated syncope, blood pressure (BP) is often used as a surrogate for perfusion pressure at the brain level (25, 26). A characteristic feature of cerebral circulation is the ability of CBF to remain almost constant despite oscillations in BP; this feature is termed cerebral autoregulation (CA). This autoregulation is interrupted if mean BP (MBP) values are outside the range of about 60–160 mmHg (4, 15, 22, 26). The chemoregulatory mechanism, that is, CO₂ reactivity, also plays an important role in the determination of CBF even when MBP is inside the autoregulatory range. In subjects who are orthostatically intolerant, i.e., those who often develop either syncope or presyncope (symptoms that precede syncope), during orthostasis, hypocapnia may contribute to a reduction in cerebral blood flow velocity (CBF) and thus contribute to orthostatic intolerance (9, 10). Consistent with this hypothesis, several studies indicate that CO₂ breathing might increase orthostatic tolerance (1, 12). Results of a recent study by Serrador et al. (19) suggest that just before the onset of symptoms of presyncope, there was a stronger correlation between end-tidal CO₂ (ETCO₂) and CBF. Taken together, the above results support the hypothesis that the influence of ETCO₂ on CBF may contribute to the phenomenon of orthostatically mediated syncope. However, some recent data suggest that CO₂ reactivity is less in the hypocapnic range than in the hypercapnic range (8); it remains unclear, therefore, to what extent chemoregulatory mechanisms contribute to orthostatically mediated syncope.

In the upright position, reduced mean arterial pressure and cardiac output challenge CA (22). Small, but significant, decreases in ETCO₂ and arterial PCO₂ are also observed in the upright position compared with the supine position (18, 24). Whether this link between ETCO₂ and CBF is causal and necessary or just facilitates the onset of presyncope is unclear. Our objective in the present study was to determine whether changes in BP and ETCO₂ influence CBF before the onset of presyncope.

We estimated coherencies and transfer functions between BP [both MBP and systolic BP (SBP)] and CBF and computed relative CO₂ reactivity in a group of subjects who did not develop any symptoms during 70° passive head-up tilt (HUT), referred to as the nonpresyncope group, and a group of subjects who developed presyncope symptoms during HUT, i.e., the presyncope group. Our results show that during tilt, the presyncope subjects had an increased coherence between SBP and CBF [peak CBF (CBFₚ)]. Dynamic autoregulation between MBP and mean CBF (CBFₘ) quantified as transfer function gain showed an increase in presyncope subjects compared with nonpresyncope subjects. During the 3-min period before the development of presyncope symptoms, relative CO₂ reactivity was decreased in the presyncope group; this decrease was probably a result of a larger decrease in ETCO₂ in this group. These observations suggest that there was an increased transfer of changes in MBP to CBF and that the decreased CO₂ reactivity was offset by a larger decrease in

REFLEX AUTONOMIC MECHANISMS adjust hemodynamic and respiratory parameters in response to orthostasis, i.e., in response to change in posture from supine to an upright position. Altered cerebral hemodynamics preceding the development of syncope (temporary loss of consciousness) is thought to be one of the primary contributors of syncope (15, 22, 26).

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ETCO2, which may have contributed in part to the development of presyncope. These results support the hypothesis that a cardiorespiratory interaction might contribute to the genesis of orthostatically mediated syncope.

METHODS

Twenty-nine healthy adults (age: mean 29 yr, range 21–41 yr check: 15 men and 14 women) participated in our study. The study was approved by the Institutional Review Board at the University of Kentucky. All subjects gave written informed consent.

During the study, the subjects breathed through a mouthpiece connected to a pneumotachograph (Fleisch) and a nonrebreathing valve. A rubber nose clip was used to ensure that the subjects breathed through the mouthpiece. An infrared CO2 monitor (Novametrix) was used for measuring CO2 fraction (in mmHg) in inspired and expired gas. The lead II electrocardiogram was recorded. Continuous BP waveforms were recorded using a noninvasive finger BP monitor (Finapres). A sling was used to hold the hand with the finger cuff at the level of the heart during HUT. In some subjects, a venous cannula was placed to have intravenous access. CBF was measured using a Transcranial Doppler (500M TCD, 2 MHz, Multigon). The right middle cerebral artery was insonated from the anterior temporal side. The Doppler probe was positioned to record maximal flow velocity, and a headband was used to stabilize the Doppler probe in position.

To elicit an orthostatic response, subjects were passively tilted to a 70° head-up position. The experimental protocol included four sections. In the first section, subjects were asked to lie supine on the tilt table and breathe room air for 10 min (supine control). For the next 10 min, subject breathed either room air or room air plus 5% CO2 in a pseudorandom binary sequence (supine PRBS). The PRBS was such that on an average, half of the total number of breaths were of room air and the other half were of air mixed with 5% CO2. At the end of supine PRBS, the table was tilted to a 70° head-up position. Once in the tilt position, we again switched the inspired gases between room air or room air plus 5% CO2 in a pseudorandom binary sequence (tilt PRBS). The tilt PRBS was continued for another 20 min, during which time subjects breathed room air only (tilt control). Symptoms that often precede a syncopal episode are referred to as presyncope. We used development of any of the following conditions to indicate the onset of presyncope: symptoms reported by the subjects such as feeling lightheaded, dizzy, nauseas, sudden feeling of warmth or sweating, loss of peripheral vision, or if the investigator monitoring the tilt observed a sudden drop in arterial pressure (decrease in SBP), and CBF (CBFm and CBFp) were estimated to compare dynamic CA between presyncopals and nonpresyncopals.

Among the 29 subjects, 6 subjects developed presyncopal symptoms during tilt control, and tilt control was prematurely ended in these cases. One presyncopal subject developed symptoms early in tilt control (2 min). Because we did not have an adequate length of data collected from this subject, data from this subject were not included in further analyses, and all subsequent results are presented from 28 subjects. On the basis of the development of presyncopal symptoms, the subjects were classified into two groups as presynodal (5 subjects) and nonpresynodal (23 subjects).

Analysis. All data were digitized at a rate of 500 samples/s. From the digitized airflow and CO2 trace, we calculated the following on a breath-by-breath basis: tidal volume (Vt), breath duration (Tb), minute ventilation (Ve), and ETCO2. With the use of a threshold detection algorithm, beat-by-beat RR intervals were computed from the ECG. Beat-by-beat SBP and MBP values were computed from the continuous BP signal. Between each RR interval, the peak systolic velocity waveform was recorded using a noninvasive finger BP monitor (Finapres). A sling was used to hold the hand with the finger cuff at the level of the heart during HUT. In some subjects, a venous cannula was placed to have intravenous access. CBF was measured using a Transcranial Doppler (500M TCD, 2 MHz, Multigon). The right middle cerebral artery was insonated from the anterior temporal side. The Doppler probe was positioned to record maximal flow velocity, and a headband was used to stabilize the Doppler probe in position.

Coherence and transfer function estimates between BP (MBP and SBP) and CBF (CBFm and CBFp) were estimated to compare dynamic CA between presyncopals and nonpresyncopals.
The transfer function relation $|H(f)|$ between the input signal $[x(t)]$ and the output signal $[y(t)]$ was calculated as (2)

$$H(f) = S_x(f)/S_y(f)$$

where $S_x(f)$ is the autospectrum of the input signal (BP) and $S_y(f)$ is the cross-spectrum between the input and output signals (CBF).

The coherence relation $|C(f)|$ between the two signals was calculated as (2)

$$C(f) = |S_x(f)/S_y(f)|$$

where $S_x(f)$ is the autospectrum of the signal $x(t)$.

For the transfer function estimation, we used 100-s data segments with 50% overlap. After removal of the mean from each segment, a Hamming window was used for spectral smoothing. The estimated transfer functions and coherencies were integrated within the respiratory frequency region, which we refer to as the high-frequency (HF) region to be consistent with the literature (14, 25). The HF region was defined as $[ABF - (0.2ABF)]$ Hz to 0.5 Hz, where ABF is the average breathing frequency of the individual subject during the tilt control section of the study protocol.

CBF (CBFm and CBFp), BP (MBP and SBP), and ETCO2 measurements were used to compute their variabilities. The variability was computed as autospectra using the Welch’s method of averaging spectrograms (13, 14). As for transfer functions and coherencies, data were segmented into 100-s segments with 50% overlap, and a Hamming window was used. The estimated spectra were integrated in the HF region as defined above. Our aim was to study the cardiorespiratory interaction, and hence we focused on differences between the groups in the HF region, i.e., the respiratory frequency region. However, we did integrate transfer functions and coherencies within frequencies lower than the respiratory region as well [these are the so-called very-low- and low-frequency regions (25)]. The results from transfer function and coherence estimates integrated within these lower than respiratory frequency regions were not significantly different between the groups.

All subjects who developed presyncope symptoms did so during the tilt control segment of the study. Although comparisons of coherencies, transfer functions, and spectral variabilities between presyncope and nonpresyncope were made during supine control and tilt control, differences between the groups were evident only during tilt control. Therefore, comparisons of coherencies, transfer functions, and spectral variabilities between the groups were made from these estimates computed from data collected during the tilt control segment of the study. The average duration from the onset of tilt control to when the subjects developed presyncope was 13 min (range: 8–20 min). To maintain consistent variance in these auto- and cross-spectral estimates, which can be influenced by data record length, data during the last 13 min of tilt control were used to compute these estimates from nonpresyncope subjects.

Relative CO2 reactivity was calculated during the last 3 min leading to presyncope and from the last 3 min of tilt control in nonpresyncope subjects. Similar to the approach used by Markwalder et al. (11) in their study, relative CO2 reactivity was calculated as the percent change in CBFm per millimeter of mercury change in ETCO2.

All analyses were performed using MATLAB 6.0. Differences between the groups were tested for statistical significance using a t-test with unequal variance. Within a group, differences between the protocol segments were tested for statistical significance using single-factor ANOVA. Significance was accepted at a level of $P < 0.05$.

### RESULTS

In the nonpresyncope group, mean heart rate and MBP increased during tilt PRBS and tilt control compared with supine control (Table 1). $V_E$ and $V_t$ increased significantly in tilt PRBS compared with supine control. $V_E$ and $V_t$ were higher during tilt control compared with supine control, but this was not significant. During tilt control, ETCO2 decreased compared with both supine control and tilt PRBS, and, as expected, ETCO2 increased during supine PRBS. There was no increase in ETCO2 during tilt PRBS compared with supine control, with the increase due to inspired CO2 likely being offset by a decrease in mean ETCO2 in response to a change in posture. In the presyncope group, changes in these variables were generally in the same direction as for the nonpresyncope group, although some differences were not significant (Table 2). The lack of significance in some variables was probably a consequence of the limited number of subjects in the presyncope group. Comparison between the two groups showed that during tilt control, nonpresyncope had a significantly higher MBP and SBP than presyncope, whereas presyncope had a significantly higher $V_t$ (Tables 1 and 2).

Average coherence functions estimated between MBP and CBFm are shown in Fig. 2A. Consistent with other studies (16, 25, 26), we assumed a linear relation between input (BP) and output (CBF). In the HF region, integrated coherence between MBP and CBFm was higher in the presyncope group, although the difference did not meet our threshold of significance ($P = 0.09$; Fig. 2A, inset).

Coherencies estimated between MBP and CBFp and between SBP and CBFp are shown in Fig. 3A and B. Integrated coherencies between BP (both MBP and SBP) and CBFp in the

### Table 1. Average cardiovascular and respiratory variables from 23 nonpresyncope subjects during the 4 sections of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Supine Control</th>
<th>Supine PRBS</th>
<th>Tilt PRBS</th>
<th>Tilt Control</th>
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</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>74.05 ± 2.51</td>
<td>72.01 ± 2.4</td>
<td>86.87 ± 2.35&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91.5 ± 2.42&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>91.04 ± 2.54</td>
<td>92.56 ± 2.3</td>
<td>103.3 ± 3.63&lt;sup&gt;a&lt;/sup&gt;</td>
<td>105.71 ± 4.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>123.81 ± 3.79</td>
<td>127.55 ± 3.99</td>
<td>135.36 ± 4.59&lt;sup&gt;a&lt;/sup&gt;</td>
<td>132.39 ± 4.55&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CBFm, cm/s</td>
<td>73.41 ± 3.19</td>
<td>74.17 ± 3.28</td>
<td>64.58 ± 2.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64.2 ± 2.45&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CBFp, cm/s</td>
<td>85.59 ± 3.91</td>
<td>86.69 ± 3.92</td>
<td>74.28 ± 3.51&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73.97 ± 3.16&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>$V_c$, ml</td>
<td>585.03 ± 40.7</td>
<td>634.17 ± 37.7</td>
<td>727.54 ± 48.55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>617.87 ± 33.51&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>14.26 ± 0.56</td>
<td>13.95 ± 0.59</td>
<td>13.93 ± 0.83</td>
<td>13.87 ± 0.53</td>
</tr>
<tr>
<td>$V_E$, l/min</td>
<td>7.62 ± 0.4</td>
<td>8.72 ± 0.48</td>
<td>9.94 ± 0.57&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.51 ± 0.42&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ETCO2, mmHg</td>
<td>45.37 ± 0.84</td>
<td>47.57 ± 0.76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>45.71 ± 0.83</td>
<td>41.47 ± 0.89&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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</table>

Values are means ± SE. PRBS, pseudorandom binary sequence; BP, blood pressure; CBFm and CBFp, mean and peak cerebral blood flow velocities, respectively; $V_c$, tidal volume; $V_E$, minute ventilation; ETCO<sub>2</sub>, end tidal CO2. <sup>a</sup>$P < 0.05$, significant difference between supine control and supine PRBS; <sup>b</sup>$P < 0.05$, significant difference between supine control and tilt PRBS; <sup>c</sup>$P < 0.05$, significant difference between supine control and tilt control; <sup>d</sup>$P < 0.05$, significant difference between presyncope and nonpresyncope.

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HF region were higher in the presyncopal group; the difference for SBP was significant \( (P < 0.02; \text{Fig. 3B}) \), whereas that for MBP was not \( (P > 0.05; \text{Fig. 3A, inset}) \). Figure 4A shows the coherence functions estimated between SBP and CBF\(_m\). In the HF region, presyncopals exhibited a higher integrated coherence \( (P = 0.07) \) between SBP and CBF\(_m\) than nonpresyncopals (Fig. 4A, inset).

In the HF region, the transfer function gain between MBP and CBF\(_m\) was larger in the presyncopal subjects \( (P < 0.01; \text{Fig. 2B}) \). Similarly, transfer function gain between SBP and

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</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>71.02 ± 4.0</td>
<td>69.27 ± 5.46</td>
<td>92.45 ± 5.58*</td>
<td>100.07 ± 5.32†</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>87.92 ± 2.59</td>
<td>89.59 ± 1.5</td>
<td>92.73 ± 2.13</td>
<td>91.78 ± 1.45</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.03 ± 4.54</td>
<td>125.69 ± 3.94</td>
<td>125.06 ± 4.63</td>
<td>118.93 ± 5.17</td>
</tr>
<tr>
<td>CBF(_m), cm/s</td>
<td>81.66 ± 5.95</td>
<td>82.44 ± 5.15</td>
<td>75.42 ± 5.3</td>
<td>70.29 ± 4.44</td>
</tr>
<tr>
<td>CBF(_p), cm/s</td>
<td>96.17 ± 7.22</td>
<td>96.57 ± 6.22</td>
<td>85.86 ± 6.2</td>
<td>80.88 ± 4.99</td>
</tr>
<tr>
<td>V(_m), ml</td>
<td>686.82 ± 102.5</td>
<td>717.26 ± 87.88</td>
<td>886.42 ± 95.04</td>
<td>824.3 ± 92.51‡</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>12.94 ± 1.15</td>
<td>13.44 ± 0.79</td>
<td>12.98 ± 1.06</td>
<td>10.88 ± 1.6</td>
</tr>
<tr>
<td>V(_t), l/min</td>
<td>8.36 ± 0.76</td>
<td>9.93 ± 1.07</td>
<td>11.77 ± 0.93*</td>
<td>10.37 ± 1.03</td>
</tr>
<tr>
<td>ETCO(_2), mmHg</td>
<td>45.63 ± 2.83</td>
<td>48.15 ± 2.73</td>
<td>45.34 ± 2.76</td>
<td>39.11 ± 3.08</td>
</tr>
</tbody>
</table>

Values are means ± SE. *\( P < 0.05 \), significant difference between supine control and tilt PRBS; †\( P < 0.05 \), significant difference between supine control and tilt control; ‡\( P < 0.05 \), significant difference between presyncopals and nonpresyncopals.
CBF$_m$ in the HF region was larger in the presyncopal group ($P = 0.01$) than in the nonpresyncopal group (Fig. 4B).

Relative CO$_2$ reactivity calculated for the last 3 min before the end of HUT showed a decreased reactivity in presyncopal subjects compared with nonpresyncopal subjects (1.45 ± 0.49 vs. 3.51 ± 0.51%/mmHg, $P = 0.005$). Relative CO$_2$ reactivity was calculated as the ratio of the percent change in CBF$_m$ per millimeter of mercury change in ETCO$_2$ (11). The presyncopals exhibited a larger percent decrease in CBF$_m$ (4.6%) than nonpresyncopals (3.3%) during the 3 min before presyncope compared with early tilt control, although this decrease was not significant. Both groups decreased ETCO$_2$ significantly from initial tilt control to the last 3 min of tilt. However, the decrease in presynopals was larger (from 40.4 to 37.7 mmHg, $P = 0.009$) than that in nonpresynopals (from 41.54 to 41.06 mmHg, $P = 0.05$). The larger decrease in ETCO$_2$ in presynopals than nonpresynopals was significant ($P = 0.03$).

Spectral analysis did not indicate any significant differences in variabilities between the two groups in BP, CBF, and ETCO$_2$.

**DISCUSSION**

The primary findings of our study were that before the development of presyncope symptoms during HUT, the coherence between SBP and CBF$_p$ and gains of transfer functions between BP (both MBP and SBP) and CBF$_m$ were higher in the respiratory frequency region. In the last 3 min before presyncope, there was a reduced relative CO$_2$ reactivity in the presyncope group compared with the nonpresyncope group. However, the presyncope group had a larger decrease in CBF; the decreased reactivity was a result of a much larger decrease in ETCO$_2$ in these subjects. These findings suggest a compromised CA in the respiratory frequency region; the relationship between systemic changes in BP and those in cerebral hemo-
dynamics was enhanced during the time interval before the development of HUT-induced presyncope. On the basis of these observations, we hypothesize the following chain of events: as discussed later, results from our study and those of others show that the dynamics between systemic BP and cerebral flow displays a high-pass filter type of transfer relationship. The gain of this transfer relationship at any frequency is inversely related to the characteristic frequency of the high-pass dynamics; the lower the characteristic frequency, the higher the gain. Considering a simple resistor-compliance model of circulation, the characteristic frequency in this case is inversely related to the resistance. Our results are consistent with this construct: a larger decrease in CO₂ in presyncopal subjects likely resulted in a larger increase in cerebral vascular resistance. Increased resistance would lead to decreased average flow but increased gain of the transfer function relationship between systemic BP and CBF, also observed in our study. Although hypothetical, the above mechanism suggests that the compromised CA function before presyncope may be secondary to the decrease in arterial PCO₂. The mechanisms that trigger the decrease in CO₂ in presyncope subjects, however, remain unclear.

As stated in the introduction, a characteristic feature of the cerebral circulation is CA, i.e., regulation of CBF. The myogenic hypothesis of CA suggests that the cerebral smooth muscles constrict or relax in response to an increase or decrease in BP (7). In our study, during tilt control, before presyncopal symptoms (13 min), subjects in the presyncopal group exhibited an increased coherence between BP and CBF (both CBF_m and CBF_p) in the HF region, the difference being significant for the coherence estimate between SBP and CBF_p. Assuming that a causal link between BP and CBF exists, an assumption supported by a previous study (7), the increased coherence indicates a greater degree of correlation between systemic BP and CBF. Although higher coherence does not necessarily indicate linearity, a higher value of coherence does...
reflect a higher degree of correlation. Conversely, a low value of coherence (coherence < 0.5) suggests either one or a combination of the following factors: 1) a nonlinear relation between BP and CBF, 2) no relationship between the two, or 3) a low signal-to-noise ratio. We interpret our results, therefore, as indicative of a more enhanced or engaged coupling between systemic BP and CBF in the group of subjects who developed presyncope compared with those that did not. Such enhancement of the coupling is consistent with the notion that CA was compromised or less active in this group than in the nonpresyncope group. Such interpretation is also consistent with the previous findings of others (4, 26).

The transfer function between BP (for both MBP and SBP) and \( \text{CBF}_m \) showed an increased gain in the HF region in the presyncope group. The increased gain suggests that oscillations in CBF, concurrent with those in BP within the respiratory frequency region, were of a larger magnitude in subjects who developed presyncope symptoms. The steady-state or mean systemic BP values were within the autoregulatory range, so we assume that cerebral BP values were as well. Our results suggest, therefore, that a larger portion of dynamic changes in systemic BP were transferred to CBF in the presyncope group than in the nonpresyncope group. Although we assume, based on systemic BP measurements, that cerebral BP values were within the autoregulatory range, it is possible that this assumption may not always hold, especially at nadirs of BP oscillations. As discussed later, our study shares a limitation with others of this type in that we use systemic BP as a surrogate of pressure at the level of the middle cerebral artery. The hydrostatic gradient during HUT suggests that it is possible that transiently, cerebral pressure may approach lower limits of the autoregulatory region. Such a situation would be expected to accentuate the effects of already compromised CA, secondary to changes in CO₂, and thus further contribute to the development of presyncope. It is not possible to measure pressure at the level of the middle cerebral artery. Although systemic BP can be adjusted by using an offset in baseline values (6), the addition of such an offset is unlikely to affect the dynamic estimates of transfer function relationships.

Zhang et al. (25) recently showed that the short-term regulation of CBF in response to changes in arterial pressure can be modeled as a transfer function with qualities of a high-pass filter spanning the frequency range of 0.07–0.30 Hz. This range of the high-pass filter was determined in their study as a frequency range for which the coherence estimate was >0.5. Consistent with this previous study, we also observed high-pass-like behavior in presyncope subjects within a range of about 0.07–0.3 Hz (Fig. 2).

The metabolic hypothesis of CA, a companion to the myogenic hypothesis, suggests that CBF responds to metabolites such as CO₂, which has vasoactive properties. The presyncope subjects exhibited a decreased relative CO₂ reactivity (%change in \( \text{CBF}_m \) per mmHg change in \( \text{ETCO}_2 \)) during the last 3 min leading to presyncope. Relative CO₂ reactivity was calculated as the ratio of the percent change in \( \text{CBF}_m \) per millimeter of mercury change in \( \text{ETCO}_2 \) (11). The presyncope groups exhibited a higher percent change in \( \text{CBF}_m \) than nonpresyncope during the 3 min before presyncope compared with early tilt control (\( P > 0.05 \)). Although both groups decreased \( \text{ETCO}_2 \) significantly from initial tilt control to the last 3 min of tilt, the decrease in \( \text{ETCO}_2 \) was significantly higher in the presyncope groups compared with nonpresyncope (\( P = 0.03 \)). The magnitude of the decrease in \( \text{ETCO}_2 \) in the presyncope subjects was larger than the decrease in \( \text{CBF}_m \); therefore, the ratio of the two, i.e., relative CO₂ reactivity, was lower. The decreased reactivity with more pronounced hypocapnia in the presyncope group is consistent with previous results (8) where they observed that CO₂ reactivity decreased with increasing levels of hypocapnia. The relative CO₂ reactivity values estimated by us are consistent with those reported by Markwalder et al. (11) and by Ide et al. (8). It is possible that the decrease in \( \text{ETCO}_2 \) in the presyncope subjects was large enough to partially offset the decreased reactivity such that the decrease in CBF was larger than that in the nonpresyncope.

We recognize that the Doppler measurement that we used measures blood flow velocity, which is different from CBF. However, Serrador et al. (19) have shown that the middle cerebral artery, i.e., the artery that we insonated, does not undergo an appreciable change in diameter upon orthostasis, suggesting that the blood flow velocity measures may be an acceptable surrogate for CBF. Similarly, we did not observe significant differences between the groups during tilt PRBS (10 min), indicating that dynamic CA was not different between the groups during the initial part of HUT. Our results suggest that autoregulatory function remains intact in nonpresyncope subjects during prolonged (i.e., 30 min) orthostasis but is compromised early in presyncope subjects. The compromise in CA function is supported by an increase in coherence and transfer function gain between systemic inputs (BP) and cerebral output (CBF). Consistent with this interpretation, Carey et al.’s results (4) also support the view that, although hypotension during presyncope is probably precipitated by sympathetic nervous system withdrawal, loss of consciousness during syncope may be caused by cerebral hypoperfusion. It is possible, therefore, that an impairment of CA may contribute to the development of early presyncope symptoms during HUT. Furthermore, Carey et al. (4) demonstrated that the impairment of CA was similar in patients and control subjects who developed presyncope symptoms. Therefore, although we recruited “nonpatient” subjects, the alterations in dynamic CA observed in presyncope subjects in our study may be relevant to the mechanisms of unexplained syncope in patients as well. Altered cerebral hemodynamics and brain oxygenation availability before neurogenic syncope was also observed by Rodriguez-Nunez et al. (15).

Zhang et al. (26) also demonstrated a deterioration of dynamic CA during lower body negative pressure (LBNP) and suggested that these changes may contribute to presyncope. There are important differences between HUT and LBNP in terms of engagement of proprioceptor and vestibular reflexes (5, 17, 21, 23). However, we observed a similar deterioration of dynamic CA in presyncope subjects during orthostatic stress using HUT. In contrast, Schondorf et al. (16) reported that dynamic CA was preserved in neuraly mediated syncope during the 3 min before syncpe from a subject pool that included patients and normals. It is possible, however, that the relatively shorter length of data (3–4 min) used to estimate the transfer functions by Schondorf et al. (16) contributed to a greater variability, leading to a possible masking of differences.
between the two groups. Schondorf et al. identified and discussed this issue in their study. However, their results show that the differences in the dynamic CA coherence in the 0.2- to 0.5-Hz frequency region estimated using data that were 3 to 4 min long and those that were 13 to 6 min long were comparable to the differences in integrated coherencies seen by us between the two groups (Figs. 2A, 3, and 4A, insets). On the other hand, any reduction in the ability to detect differences in their study due to an increased variance of estimate was possibly offset by the increased number of presyncopal subjects that they had in their study. Therefore, it is not entirely clear why the observations of Schondorf et al.’s study are inconsistent with those from our and Zhang et al.’s study (26); the possibility remains, however, that technical aspects of cross-spectral estimation may have contributed.

Carey et al. (4) suggested that, although the reason behind the altered dynamic response remains unclear, a possible cause may be mean pressure in the middle cerebral artery falling outside the autoregulatory range. The results in Tables 1 and 2 show that during tilt control, presyncopal subjects had significantly lower values of MBP and SBP than nonpresyncopal subjects. These results, together with the previously discussed issues regarding the difference between systemic and pressure at the level of the middle cerebral artery, provide support for the above-stated possibility proposed by Carey et al. (4). Sung et al. (20) suggested that it is possible that hyperventilation might lower the arterial CO2 levels and cause cerebral arteriolar constriction leading to syncope. We also observed a decrease in ETCO2 in presyncopal subjects. Whether the decrease in ETCO2 translated into similar level of decrease in arterial

REFERENCES


GRANTS

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