Differences in the dynamic cerebrovascular response between stepwise up tilt and down tilt in humans

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Sato, Jiro, Masatoshi Tachibana, Tsutomu Numata, Takashi Nishino, and Akiyoshi Konno. Differences in the dynamic cerebrovascular response between stepwise up tilt and down tilt in humans. Am J Physiol Heart Circ Physiol 281: H774–H783, 2001.—We studied dynamic cerebrovascular responses in eight healthy humans during repetitive stepwise upward tilt (SUT) and stepwise downward tilt (SDT) maneuvers between supine and 70° standing at intervals of 60 s. Mean cerebral blood flow velocity (FVMCA) was measured at the middle cerebral artery (MCA) with transtemporal Doppler ultrasound. Mean arterial blood pressure (ABP) was measured via the radial artery and adjusted cranial Doppler ultrasonography. Mean arterial blood pressure (MABP) at the level of the MCA (ABPMCA) was measured at the MCA with transcranial Doppler sonography (TCD) provides a continuous measurement of cerebral blood flow velocity (FVMCA) at the middle cerebral artery (MCA) (1, 2, 4, 27, 28, 37, 38). Dynamic CVA has been studied using FVMCA signals obtained during sudden decreases in arterial pressure induced by rapid thigh cuff deflations (1, 2, 27, 28, 37, 38) or rapid head-up tilting (3–6).

Aaslid et al. (1, 2, 37) proposed a second-order linear system describing the dynamic CVA (referred to hereafter as the Aaslid model). When a step decrease in cerebral arterial blood pressure (arterial blood pressure (ABP) at the level of the MCA (ABP_MCA)] is applied to the system, FVMCA exhibits an initial sudden decrease immediately followed by a damped oscillatory recovery. Several studies (28, 38) employing frequency domain (transfer function) analysis also suggested essentially similar mathematical models.

We studied the dynamic CVA in healthy volunteers as a matched control for patients with impaired CVA. Our study employs repetitive stepwise upward tilt (SUT) and stepwise downward tilt (SDT) maneuvers between supine and 70° standing posture, producing repetitive stepwise decreases and increases in ABP_MCA. A remarkable finding that we discovered is asymmetries in the FVMCA responses between SUT and SDT (Fig. 2). It may suggest that a rapid increase in cerebral perfusion pressure (CPP) induced by SDT produces a different pattern of the dynamic CVA from a rapid CPP decrease induced by SUT.

In this study, therefore, we aimed 1) to examine whether the Aaslid model represents the dynamic CVA response to a CPP increase induced by SDT as well as that to a CPP decrease invoked by SUT, and 2) if not, to construct a mathematical model that better describes the dynamic CVA for changes in CPP produced by the stepwise tilting in both directions.

We studied healthy relatively young volunteers because model construction for the dynamic CVA was the main purpose of this study. Model application to patients with impaired CVA will be the next scope of our investigation.

METHODS

Subjects

Eight healthy volunteers (5 men and 3 women, age 16–31 yr) took part in the study. Requirements were fully explained to all participants in writing and verbally, and each gave informed consent before participating in the study. The research was approved by the institutional ethics committee. Participants were not taking any medication, and none had a history of cardiovascular, cerebrovascular, autonomic, or respiratory disease.

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Measurements

A 2-MHz pulsed Doppler ultrasound system (PCDop 842, SciMed; Bristol, UK) was used to measure back-scattered Doppler signals from the right or left MCA. The Doppler signals were transformed to the maximum and weighted mean blood flow velocities. The mean velocity (FV MCA) was stored on a computer for off-line analysis. FV MCA was identified by an insonation pathway through the right or left temporal window using a standard search technique. Small movements of the probe can cause some FV MCA changes, which could be erroneously interpreted. To avoid this problem, extreme care was taken to identify the center of MCA where the signal was maximized and to attach the probe securely by a plastic headband. The average insonation depth (the distance from the probe to the start of the Doppler sample volume for detecting signals from the MCA) was 5.3 ± 0.5 cm (means ± SD).

Continuous measurements of ABP were performed invasively via a catheter punctured into the left or right radial artery (Hewlett-Packard M1090A). The wrist where the ABP catheter was inserted was supported together with a pressure transducer at the level of the FV MCA probe to adjust the ABP reading to the MCA blood pressure (ABP MCA).

The FV MCA and ABP MCA signals were sampled, digitized at 200 Hz, and stored on a computer for off-line analysis.

Expired gas was drawn continuously via a catheter placed just inside the naris to an infrared gas monitor (Normocap 200 oxy, Datex; Helsinki, Finland) to measure the end-tidal CO₂ tension (P ETCO₂). Subjects were instructed to breathe through their noses whenever possible throughout the measurement; however, breathing was not controlled by the investigators.

Experimental Procedures

Subjects were requested not to take foods or caffeine-containing beverages within 4 h before their testing sessions. The experiment was performed in a quiet room with ambient temperature maintained at 25°C.

Subjects were requested to keep their eyes open to maintain stable conscious levels throughout the measurement. Subjects lay in the supine position on a tilt table for 10 min; however, breathing was not controlled by the investigators.

Data Analysis

Data were analyzed off-line using the mathematical package Splus 2000 (MathSoft; Cambridge, MA).

The cerebral critical closing pressure (P CC) at which cerebral arteries would collapse was estimated beat by beat, employing a systolic-diastolic relationship between FV MCA and ABP MCA (10, 26). Mean values of FV MCA and ABP MCA for every single heartbeat and P CC were resampled at 2 Hz by a linear interpolation to create a uniform time base. The difference between the mean ABP MCA and P CC was considered as CPP driving cerebral blood flow. FV MCA and CPP were scaled by dividing by the averages of the first 60-s segments (the initial supine interval before the start of the tilt procedure) to align between-individual variances. The scaled signals are denoted hereafter simply as FV MCA and CPP, respectively.

A relative measure of cerebrovascular resistance (CVRr) was obtained by dividing CPP by FV MCA. Examples of the processed signals are presented in Fig. 2. The repetition of SUT and SDT produced stepwise variations in both CPP and FV MCA, which are hereafter referred to as SUT responses and SDT responses, respectively.

Mathematical Modeling

The Aaslid model is characterized by three parameters: a time constant, a damping factor, and an autoregulatory gain (37). It was originally constructed from the FV MCA response to a stepwise decrease in CPP (ABP minus a constant P CC) induced by sudden deflation of thigh cuffs. In this study, we adopted a time-varying P CC instead of assuming a constant P CC because the level of P CC was indicated as a factor regulating the cerebral circulation (10, 26).

First, the model was fit to the CPP-FV MCA relationship for the data segment between 50 and 420 s containing whole three SDT and three SUT responses. Model fitting with parameter estimation was performed by employing a nonlinear least square regression (Gauss-Newton method) with a nonnegativity criterion so that parameter values were constrained to be nonnegative.

Thereafter, the model was fit to the CCP-FV MCA relationship of each SDT and each SUT response separately. Each response contained the signals between 5 s before and 60 s after a step was undertaken.

Next, to resolve the systematic discrepancy observed between the data and Aaslid model in the SDT responses (Figs. 3 and 4), we constructed a model composed of a fast and a slow components, described in detail in the appendix. The two-component model (Two-C model) was fit to each SUT response and each SDT response separately.

The best-fit models obtained were presented in the form of a step response in the time domain, i.e., a temporal FV MCA behavior in response to a unit step increase in CPP. We chose a graphical expression of the step response instead of either using arbitrary parameters expressing certain features of transient changes (1, 2, 37) or frequency-domain (transfer function) analysis (5, 28, 38) because the step response seemed more visually intuitive.

Statistics

Fitting performances of the two models were compared using the multiple partial F-test with significance at P < 0.05 (20). In the F-test, the number of degrees of freedom was corrected for longitudinal correlation of the signal in each tilt response (32).

RESULTS

Figure 1 shows temporal variations in ABP MCA and P CC during tilt maneuvers in four subjects. SUT and SDT produced sudden decreases and increases in ABP MCA of >20 mmHg in all step responses in any subject. P CC exhibited small oscillations roughly in synchrony with changes in ABP MCA.

Figure 2 shows temporal changes in CPP, FV MCA, CVRr, and P ETCO₂ during tilt maneuvers in the same four subjects whose variations in ABP MCA and P CC were presented in Fig. 1. It indicates that the dynamic autoregulatory response induced by the maneuvers
varied widely even among healthy humans. Subject 1, in general, exhibited CVRr oscillations around baseline but did not change in synchrony with the trend in CPP. It suggests that this subject did not exhibit effective autoregulatory responses, so that FV_{MCA} behaved roughly dependent on the time course of CPP. In contrast, subject 4 presented almost perfect autoregulation, indicated by constant FV_{MCA} despite repetitive stepwise CPP changes. This is also reflected by the temporal pattern of CVRr, almost identical to that of CPP. Subjects 2 and 3 presented moderate autoregulatory responses somewhere between those produced in subjects 1 and 4.

PETCO2 exhibited temporal variations that did not exceed the range of the control value \( \pm 3 \) mmHg throughout the experiment in any subject (Fig. 2). The variations tended to be clearer at the instances of posture change. However, the effects of posture on PETCO2 (i.e., lower PETCO2 at upright than at supine posture) seemed evident in only two subjects (e.g., subject 3 in Fig. 2).

What we speculated from the results in subjects 2 and 3 is that the CPP-FV_{MCA} relationship might differ between the SUT and SDT responses. FV_{MCA} seemed to follow temporal variations of CPP in the SUT re-

Fig. 1. Temporal changes in arterial blood pressure (ABP) in the middle cerebral artery (ABP_{MCA}) and critical closing pressure (P_{CC}) during repetitive tilt maneuvers in 4 subjects. Shaded and open areas indicate the stepwise upward tilt (SUT; 70° standing) and stepwise downward tilt (SDT; supine) intervals, respectively. Roughly, P_{CC} seemed to vary depending on the changes in ABP_{MCA}.

Fig. 2. Temporal changes in cerebral perfusion pressure (CPP), cerebral blood flow velocity in the middle cerebral artery (FV_{MCA}), the relative measure of cerebrovascular resistance (CVRr), and end-tidal CO2 tension (PETCO2) during tilt maneuvers in 4 subjects. A–D: results from subjects 1–4. Shaded and open areas indicate the SUT (70° standing) and SDT (supine) intervals, respectively.
sponse. In the SDT response, however, $FV_{MCA}$ presented a somewhat different pattern from the CPP contour. After an initial sudden increase, CPP gradually decayed down, whereas $FV_{MCA}$ presented a slow increase after an initial spiky overshoot.

Figure 3 shows the results of the fitting with the Aaslid model to the data segment between 50 and 420 s including whole three SUT and three SDT responses in subjects 2 and 3. The model seemed to fit to the SUT responses well, whereas systematic discrepancies between the data and model were observed in the SDT responses.

Figure 4 shows the model fitting performances of the Two-C model and Aaslid model. The model fitting was performed separately for the SUT and SDT responses. In the SUT responses, both models fit to the data well, with no discernible difference observed between the two models. It implies that the SUT response can be characterized adequately by the Aaslid model with no need of a more complicated model structure. On the other hand, the SDT responses revealed clear discrepancies with the Aaslid model. The Two-C model fit well to the SDT responses, indicating a biphasic behavior of the SDT response with two distinct time constants.

Figure 5 compares the step responses estimated from both models fit separately to the SUT and SDT responses. The responses presented are the averages of the three individual responses. In general, both models seemed to create similar step response curves for the SUT responses. In the SDT responses, in contrast, greater differences were observed between the step response curves estimated from the two models than in the SUT responses.

Table 1 shows the model performances of the two models. For the SUT responses, the Two-C model presented significantly better fitting in 11 of 24 responses and significantly worse fitting in 2 responses. No significant difference between the two models were obtained in 11 responses. For the SDT responses, in contrast, the Two-C model produced significantly better fitting ($P < 0.05$, $P < 0.01$, or $P < 0.001$) than the Aaslid model in 21 responses. The remaining three responses showed no significant difference between the two models.

Table 2 shows the parameter values of the best fit models in the SDT responses (the averages of three SDT responses) in the individual subjects. The time parameters ($b$ and $t_0$) for the second phase response were similar among all subjects except subject 3, although the magnitude (the parameter $K$) of the second phase varied among subjects.

**DISCUSSION**

**Methodological Considerations**

Before discussing the results of this study, the limitations of the methods employed should be considered:

![Fig. 3](image-url)
1) neither the true MCA blood flow nor true ABP_MCA was measured, and 2) the arterial carbon dioxide tension (approximated by PETCO2) was not included in the models.

This study assumed that the tilt maneuvers induced only minimal changes in the MCA diameter compared with changes in FV_MCA. Otherwise, variations in FV_MCA would be produced by changes in the MCA diameter even if the true MCA blood flow remains constant, i.e., increases and decreases in FV_MCA by vasoconstriction and vasodilation of MCA, respectively. Previous invasive studies (1, 14, 22, 27) have indicated relative constancy of the MCA diameter during sudden changes in ABP_MCA of 20–30 mmHg induced by thigh cuff deflations or vasoactive agents. To our knowledge, there have been no studies concerning whether the tilt maneuver itself induces significant variations in the MCA diameter. It has been, however, demonstrated that an application of lower body negative pressure (LBNP), which would produce blood redistribution similar to the head-up tilt, induced a significant decrease in FV_MCA with no change in the MCA diameter (33). Furthermore, the head-up tilt has been reported to increase sympathetic activity (25), implying that if anything happened to MCA during the head-up tilt, it would be vasoconstriction but not vasodilation. This may suggest at least that decreases in FV_MCA during SUT in this study were not produced by the MCA diameter increases with no change in MCA blood flow, and the same holds for increases in FV_MCA during SDT. Therefore, we could expect that the assumption of the constancy in the MCA diameter during the tilting is a reasonable one in this study.

To estimate the true ABP_MCA, we employed a hydrostatic compensation of the radial arterial pressure, because we did not have any noninvasive method to determine the true ABP_MCA directly and the compensation has been of the common techniques to estimate ABP_MCA in this kind of study (4–6, 15). Although the initial transient of the compensated pressure reading at the instances of the tilting might differ from that of true ABP_MCA, the FV_MCA-CPP relationships during SUT observed in this study were similar to those in previous studies (1, 37). Furthermore, the second phase in the SDT response commenced relatively slowly, at ~20 s after a step was undertaken. Therefore, the hydrostatic compensation would have adequate resolution to estimate ABP_MCA in this study.

Arterial carbon dioxide tension is among the major determinants of the cerebrovascular regulation. It has been shown that the head-up tilt produces a small but significant decrease in PETCO2 several minutes after tilt was undertaken (5, 8). We observed small variations of PETCO2 throughout the measurement (Fig. 2). Although the variations tended to be clearer at the instances of tilt maneuvers, no systematic postural effect on PETCO2 consistent in all subjects seemed evident. The discrepancy between previous studies and this study may be due to the durations of the tilting (i.e., at least several minutes in the previous studies vs. at most 1 min in this study). Therefore, we did not include the contribution of PETCO2 to the models. Moreover, we were afraid of increasing the chances of overdetermined parameter problems in the model fitting by increasing the number of the model parameters. However, this may remain to be clarified because the enrollment of arterial carbon dioxide tension was suggested in the dynamic CVA response (1, 29, 30).

We estimated PCC beat by beat instead of assuming a constant PCC. We wondered whether PCC behaved...
differently between SUT and SDT, leading in part to the difference in the \( F_{\text{MCA}} \) behavior between the SUT and SDT responses. The values of \( P_{\text{CC}} \) estimated during supine posture (SDT) in this study were similar to those shown in previous studies (10, 26). Moreover, \( P_{\text{CC}} \) presented temporal patterns roughly dependent on \( ABP_{\text{MCA}} \) (Fig. 1), which were also similar to the results obtained in previous studies (10, 26).

**Interpretation of the results of this study.** A new finding in this study is that SDT produced biphasic \( F_{\text{MCA}} \) responses. A first phase, delineated by the Aaslid model, was followed by a second phase, a gradual \( F_{\text{MCA}} \) increase. It differed from the \( F_{\text{MCA}} \) response induced by SUT, which could be described solely with the Aaslid model.

The discrepancy between the SUT and SDT responses is reflected by the model fitting performances of the two models. As shown in Table 1, the Two-C model, despite its structural complexity, did not necessarily produce better fitting results than the Aaslid model for the SUT responses. It indicates that the Aaslid model was adequate enough for a precise description of the SUT response. On the other hand, the Two-C model obviously presented better fitting performances than the Aaslid model for the SDT responses. It indicates an enrollment of some different mechanisms for the dynamic cerebrovascular response to SDT, which would emerge at \( 20 \) s after a stepwise tilt down maneuver is undertaken, as indicated in the values of the model parameter \( t_0 \) (Table 2).

We employed repetitive SUT and SDT maneuvers to induce stepwise changes in \( ABP_{\text{MCA}} \) because we aimed to investigate the dynamic CVA, i.e., cerebrovascular responses to rapid changes in CPP. However, the tilting would induce also a variety of cardiovascular changes in an interrelated manner such as blood volume redistribution, baroreflex, and autonomic reflexes, which, in turn, likely affect the cerebrovascular dynamics.

For example, Levine et al. (21) suggested that sympathetic activation induced by LBNP (analogous to orthostatic stress) increased both the cerebrovascular (CVR) and systemic vascular resistances (SVR), although the CVR increase were much smaller than the SVR increase. They also hypothesized that the LBNP-induced sympathetic activation shifted the autoregula-

![Fig. 5. Step responses estimated from the best-fit Two-C model and Aaslid model in individual subjects. A–H: subjects 1–8, respectively. Each response presented is the average of three responses in each subject. Thin solid lines indicate unit step changes in CPP. Thick solid and thick dashed lines represent the \( F_{\text{MCA}} \) responses constructed from the Two-C model and Aaslid model, respectively. The second phase of the Two-C model is described as a slow incremental slope after the first phase, an initial downward damped oscillation.](http://ajpheart.physiology.org/)

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tory cerebral blood flow-CPP curve to the right. Cen-
cetti et al. (9) presented significant correlation between
the sympathetic component of the cerebrovascular
(FVMCA) oscillations and that of cardiovascular (ABP)
oscillations both at supine rest and during head-up tilt.
These observations, although made in rather quasi-
static conditions, indicate that the autonomic modula-
tion induced by tilt maneuvers might affect the tempo-
ral behaviors of the SDT and SUT responses observed
in the study. Furthermore, it has been demonstrated
that the electrical stimulation of sympathetic nerves
attenuated the initial rise in cerebral blood flow at the

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<th>Table 1. Fitting performances of the two models</th>
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SUT and SDT, stepwise upward tilt and stepwise downward tilt, respectively; Two-C model, two-component model; R², coefficient of determination for the regression with the two models; DF, number of degrees of freedom corrected for longitudinal correlation of the signal. Partial F values were obtained by the multiple partial F-test. *P < 0.05, **P < 0.01, and ***P < 0.001, Two-C model is significantly better than the Aaslid model. #P < 0.05, Aaslid model is significantly better than the Two-C model. No significant differences were found between the two models.

Table 2. Values of the model parameters for the Aaslid and Two-C models in the SDT response

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<tr>
<th>Subject</th>
<th>Aaslid Model</th>
<th>Two-C Model</th>
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<tr>
<td>τ</td>
<td>D</td>
<td>G</td>
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<tr>
<td>1</td>
<td>2.3</td>
<td>0.46</td>
</tr>
<tr>
<td>2</td>
<td>2.7</td>
<td>0.22</td>
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<tr>
<td>3</td>
<td>2.0</td>
<td>0.71</td>
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<tr>
<td>4</td>
<td>3.0</td>
<td>0.41</td>
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<tr>
<td>5</td>
<td>2.2</td>
<td>0.56</td>
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<tr>
<td>6</td>
<td>2.8</td>
<td>0.77</td>
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<tr>
<td>7</td>
<td>2.7</td>
<td>0.58</td>
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<tr>
<td>8</td>
<td>2.7</td>
<td>0.68</td>
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Values are the averages of 3 SDT responses. τ, D, and G indicate the time constant, damping factor, and autoregulatory gain for the Aaslid model and for the first phase response of the Two-C model, respectively. K, b, and t₀ indicate the magnitude, rise time, and delay time from the start of the step of the second phase in the Two-C model.
onset of sudden hypertension produced by the occlusion of the descending aorta in cats (7).

Therefore, the results of this study should be interpreted with combined respects both to cardiovascular (systemic) responses to tilting and to CVA (regional).

**Effects of cardiovascular responses to tilting.** Several studies (23, 34, 35) have indicated asymmetries between the cardiovascular reflexes induced by SUT and those induced by SDT. For example, variations in heart rate were smaller and more sluggish at SUT than at SDT, with similar blood pressure variations. The baroreflex sensitivity was greater for SDT than for SUT. Furthermore, fast-responding vagal and slow-responding sympathetic pathways of the autonomic outflows (34) would also work in different manners for either SUT or SDT. These different dynamic cardiovascular responses between SUT and SDT would contribute in part to the different temporal patterns between the cerebrovascular SUT and SDT responses observed in this study.

**Dynamic autoregulation in the cerebral vessels.** CVA is a response that attempts to maintain relatively constant levels of cerebral blood flow whether the CPP increases or decreases. CVA is, however, carried by completely opposing behaviors of cerebral vessels in response to either an increase or a decrease in perfusion pressure; i.e., vasodilation in hypotension or vasoconstriction in hypertension. Therefore, different mechanisms for CVA might be involved between acute increases and decreases in cerebral blood pressure.

The mechanisms responsible for CVA include myogenic responses, metabolic factors, neural mechanisms, and activation of potassium channels (12, 16–19). The myogenic response is primarily a contraction of vascular smooth muscle elicited by forces distending vascular walls mostly at hypertension. In contrast, the myogenic response to a decrease in blood pressure is relaxation of the smooth muscle, i.e., a relief from the contraction (17). Therefore, temporal patterns of the myogenic process may differ between increases and decreases in cerebral blood pressure.

Decreases in blood flow associated with hypotension induce retention of vasodilating metabolites in the surrounding tissue, responsible for vasodilatory autoregulation at cerebral hypotension. This metabolic response emerges as fast as in a few seconds after a rapid decreases in blood pressure. In contrast, hypertension causes increases in blood flow that, in turn, decrease the concentration of vasoactive metabolites (16). This difference in metabolic responses may also partly explain the different behaviors between the SUT and SDT responses observed in this study.

Symon et al. (36) also found a biphasic cerebrovascular response to an acute increase in CPP in anesthetized baboons, although the biphasic responses observed by them were slightly faster than those in this study. The second phase presented between-individual variability in this study (Fig. 5).

Some subjects (subjects 3 and 7) exhibited $FV_{MCA}$ increases even beyond the control levels in response to CPP increases. This would imply that CVA was impaired in as many as two of eight healthy subjects. Paterno et al. (31) presented a bimodal nature of the cerebroarteriolar response to acute hypertension in rats. Acute hypertension induced cerebral arteriolar constriction as long as blood pressure increases remained small to moderate. However, once the extent of hypertension exceeded the point of “breakthrough,” cerebral vessels dilated as an active process via calcium-dependent potassium channels. Although no subjects in this study produced hypertension, the rapidness of the CPP increase might induce the active vasodilation after the initial vasoconstriction in the SDT responses. This may be a possible mechanism for the wide between-individual variability in the second phase response.

Busija et al. (7) found that sudden increases in arterial pressure, even within physiological ranges, pro-

![Fig. 6. A plausible step response that may explain the biphasic SDT response observed in the study. A: $FV_{MCA}$ response to a step increase in CPP is composed of a fast and a slow component. B: the assumptions for the Two-C model are that the fast component is characterized by the Aaslid model and that the slow component may be the initial fraction of a slowly adapting process. The total response is the weighted sum of the fast autoregulation and the slowly adapting process. The relationship between the two components shown in $B$ is formulated in Eq. 1A.](http://www.ajpheart.org/)

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duced transient increases in cerebral blood flow, which were then attenuated by sympathetic stimulation. This mechanism may also contribute to the second phase observed in the present study. However, we believe this vasodilation to be only transitional. Otherwise, the dynamic CVA for increases in blood pressure would be impaired, with an unexpectedly high incidence even in healthy humans. This would have to be addressed by employing repeated stepwise blood pressure changes at longer time intervals.

Previous studies (4–6, 15) have investigated mainly the dynamic CVA only for decreases in blood pressure, presumably with direct relevance to cerebral symptoms induced by hypotension, such as dizziness, light-headedness, falls, or syncope. However, the present study indicates a more complicated behavior of cerebral vessels in response to SUT. Similar to our results, several studies (7, 11, 13, 36) have indicated transient increases in cerebral blood flow induced by a rapid recovery from hypotension or at an onset of acute mild hypertension. Therefore, it may be vital to be aware of the possible occurrence of this "reactive cerebral hyper-tension. Therefore, it may be vital to be aware of the following approximation. The slow component with a large time constant does not vary much and may be approximated to be constant within 60 s after a step CPP change. Therefore, the whole response \( Y(t) \) may be reduced to

\[
Y(t) = [1 - W(t)] \times F(t) + K \times W(t) \tag{A2}
\]

where \( K \) is a constant indicating the magnitude of the slowly adapting process. We chose a logistic function for \( W(t) \)

\[
W(t) = 1 - 1/[1 + (t/t_0)^b] \tag{A3}
\]

where \( b \) and \( t_0 \) are constants. As indicated by Tiecks et al. (37), the fast component reaches a stable plateau in several seconds after a step change in CPP. It would be reasonable to assume that the slow component would commence more than several seconds after a step in CPP. Equation A2 could then be further simplified as follows

\[
Y(t) = F(t) + K \times W(t) \tag{A4}
\]

This model has six parameters to be determined. Besides the parameters \( K, b, \) and \( t_0 \) for \( W(t) \) for the slow component, the fast component parameters are a time constant \((\tau)\), a damping factor \((D)\), and an autoregulatory gain \((G)\). The fast component \( F(t) \) is formulated (37) as follows

\[
dP = (\text{ABP}_{\text{MCA}} - \text{cABP}_{\text{MCA}})/(\text{cABP}_{\text{MCA}} - \text{P}_{\text{CC}}) \tag{A5}
\]

\[
x_2 = x_2 + (x_1 - 2D \times x_2)/(f \times \tau) \tag{A6}
\]

\[
x_1 = x_1 + (dP - x_2)/(f \times \tau) \tag{A7}
\]

\[
F(t) = c\text{FV}_{\text{MCA}} \times (1 + dP - G \times x_2) \tag{A8}
\]

where \( x_1 \) and \( x_2 \) are state variables that are assumed to be equal to 0 before a step change in the arterial blood pressure \((\text{ABP})\) in the middle cerebral artery \((\text{ABP}_{\text{MCA}})\), \( f \) is a sampling frequency, \( P \) is pressure, \( \text{P}_{\text{CC}} \) is the critical closing pressure at which cerebral arteries would effectively collapse, and \( \text{cABP}_{\text{MCA}} \) and \( \text{cFV}_{\text{MCA}} \) are the respective control values before a step change.

Our choice of the logistic function for the weighting function that further describes the slow component is simply arbitrary, and other functions can also be plausible, such as an exponential function with a pure time delay.

The present study indicates a more complicated behavior of cerebral vessels in response to SUT. Similar to our results, several studies (7, 11, 13, 36) have indicated transient increases in cerebral blood flow induced by a rapid recovery from hypotension or at an onset of acute mild hypertension. Therefore, it may be vital to be aware of the possible occurrence of this "reactive cerebral hypertension." At sudden increases whether within or beyond physiological ranges.

In summary, we studied dynamic cerebrovascular responses to SUT and SDT by measuring FV\text{MCA} and CPP (ABP\text{MCA} minus \text{P}_{\text{CC}}). Cerebrovascular dynamics during SUT was well characterized by a linear second-order system. However, SDT produced a biphasic cerebrovascular response: an initial rapid response described by the second-order model followed by a gradual vasodilation. This difference between the SUT and SDT responses may be produced concomitantly by both the different responsibilities of cardiovascular system to SUT and SDT and different CVA behaviors to increases and decreases in CCP.

**APPENDIX**

Figures 3 and 4 exhibit greater discrepancies between the measured cerebral blood flow velocity in the middle cerebral artery (FV\text{MCA}) and the best-fit Aaslid model in the stepwise downward tilt (SDT) responses than in the stepwise upward tilt (SUT) responses. In the SDT response, after an initial rapid increase, cerebral perfusion pressure (CPP) decayed down, whereas FV\text{MCA} presented an initial overshoot followed by a gradual increase. This biphasic response could not be fit with the Aaslid model even by separate regressions to the SDT responses (Fig. 4). This implies that the second phase in the SDT response had a distinctly greater time constant than the first phase so that the two phases could not be resolved into a single damped oscillatory behavior. Instead, the SDT response could be better described by a composition of two components with two distinct response time constants.

Figure 6 shows a possible two-component model describing the SDT response of FV\text{MCA}. The FV\text{MCA} response is composed of two phases: an initial spiky response followed by a gradual increase. We considered the whole shape of the SDT response as the weighted sum of a fast autoregulation and a slow component. The fast component is characterized by the Aaslid model \( [F(t)] \). On the other hand, the slow component may be a fraction of the slowly adapting process \( [G(t)] \), which takes place gradually. The SDT response \( [Y(t)] \) is expressed as follows

\[
Y(t) = [1 - W(t)] \times F(t) + W(t) \times G(t) \tag{A1}
\]

where \( t \) is time, and \( W(t) \) indicates a weighting function taking values between 0 and 1. The relationship formulated in Eq. A1 is schematically shown in Fig. 6B.

To restrict the model as simply as possible, we made the following approximation. The slow component with a large time constant does not vary much and may be approximated to be constant within 60 s after a step CPP change. Therefore, the whole response \( Y(t) \) may be reduced to

\[
Y(t) = [1 - W(t)] \times F(t) + K \times W(t) \tag{A2}
\]

where \( K \) is a constant indicating the magnitude of the slowly adapting process. We chose a logistic function for \( W(t) \)

\[
W(t) = 1 - 1/[1 + (t/t_0)^b] \tag{A3}
\]

where \( b \) and \( t_0 \) are constants. As indicated by Tiecks et al. (37), the fast component reaches a stable plateau in several seconds after a step change in CPP. It would be reasonable to assume that the slow component would commence more than several seconds after a step in CPP. Equation A2 could then be further simplified as follows

\[
Y(t) = F(t) + K \times W(t) \tag{A4}
\]

This model has six parameters to be determined. Besides the parameters \( K, b, \) and \( t_0 \) for \( W(t) \) for the slow component, the fast component parameters are a time constant \((\tau)\), a damping factor \((D)\), and an autoregulatory gain \((G)\). The fast component \( F(t) \) is formulated (37) as follows

\[
dP = (\text{ABP}_{\text{MCA}} - \text{cABP}_{\text{MCA}})/(\text{cABP}_{\text{MCA}} - \text{P}_{\text{CC}}) \tag{A5}
\]

\[
x_2 = x_2 + (x_1 - 2D \times x_2)/(f \times \tau) \tag{A6}
\]

\[
x_1 = x_1 + (dP - x_2)/(f \times \tau) \tag{A7}
\]

\[
F(t) = c\text{FV}_{\text{MCA}} \times (1 + dP - G \times x_2) \tag{A8}
\]

where \( x_1 \) and \( x_2 \) are state variables that are assumed to be equal to 0 before a step change in the arterial blood pressure \((\text{ABP})\) in the middle cerebral artery \((\text{ABP}_{\text{MCA}})\), \( f \) is a sampling frequency, \( P \) is pressure, \( \text{P}_{\text{CC}} \) is the critical closing pressure at which cerebral arteries would effectively collapse, and \( \text{cABP}_{\text{MCA}} \) and \( \text{cFV}_{\text{MCA}} \) are the respective control values before a step change.

Our choice of the logistic function for the weighting function that further describes the slow component is simply arbitrary, and other functions can also be plausible, such as an exponential function with a pure time delay.

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