Cerebral blood flow velocity during mental activation: interpretation with different models of the passive pressure-velocity relationship

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Panerai, Ronney B., Michelle Moody, Penelope J. Eames, and John F. Potter. Cerebral blood flow velocity during mental activation: interpretation with different models of the passive pressure-velocity relationship. J Appl Physiol 99: 2352–2362, 2005. First published 11 August 2005; doi:10.1152/japplphysiol.00631.2005.—The passive relationship between arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) has been expressed by a single parameter [cerebrovascular resistance (CVR)] or, alternatively, by a two-parameter model, comprising a resistance element [resistance-area product (RAP)] and a critical closing pressure (CrCP). We tested the hypothesis that the RAP+CrCP model can provide a more consistent interpretation to CBFV responses induced by mental activation tasks than the CVR model. Continuous recordings of CBFV [bilateral, middle cerebral artery (MCA)], ABP, ECG, and end-tidal CO2 (EtCO2) were performed in 13 right-handed healthy subjects (aged 21–43 yr), in the seated position, at rest and during 10 repeated presentations of a word generation and a constructional puzzle para-digm. Subcomponent analysis can help with the interpretation of hemispheric dominance but were not sensitive to the different para-digms. CrCP also had a significant effect of P<0.046), and CVR (P = 0.002) changed significantly during activation. CrCP also had a significant effect of paradigm (P = 0.045) but not hemispheric dominance. Both RAP (P = 0.039) and CVR (P = 0.0008) had significant effects of hemispheric dominance but were not sensitive to the different para-digms. Subcomponent analysis can help with the interpretation of CBFV responses to mental activation, which were found to be dependent on the underlying model of the passive ABP-CBFV relationship.

cerebral autoregulation; neurovascular coupling; mathematical model; cerebral metabolism

The main physiological determinants of cerebral blood flow (CBF) are usually conceptualized by means of Poiseuille’s law (3), which assumes that CBF is given by the ratio between cerebral perfusion pressure and cerebrovascular resistance (CVR). Due to cerebral pressure autoregulation, which tends to maintain CBF approximately constant despite large changes in ABP (33), Poiseuille’s law can only be assumed under “pressure-passive” conditions or within a single heart beat, before the corrective effects of dynamic autoregulation are manifested through changes in CVR (2, 33). For this reason, we refer to these short-term, intrabeat relationships as “passive” to distinguish them from the classical flow-pressure curves characteristic of either “static” (33, 42) or “dynamic” autoregulation (2, 42).

In the cerebral circulation, perfusion pressure is normally approximated by the difference between arterial blood pressure (ABP) and intracranial pressure (ICP; Ref. 3). A further approximation is normally adopted in studies of healthy subjects or patients in whom intracranial hypertension is unlikely. By assuming that ICP is much smaller than ABP, the former is neglected, leading to CBF = ABP/CVR. One of the main uses of this expression is to estimate cerebrovascular resistance as CVR = ABP/CBF. In studies where CBF velocity (CBFV) is recorded with transcranial Doppler, as a surrogate to CBF, an equivalent index (CV Ri) is calculated as CV Ri = ABP/CBFV (2, 14, 21, 42, 45).

A major limitation for the above expressions for CVR or CV Ri, is the inherent assumption that flow (or velocity) only reaches zero when the perfusion pressure is also zero. Since the seminal work of Burton (7), it is well known that in many vascular beds, such as the lung (18), skin (9), liver (23), myocardium (22), and skeletal muscle (38), the instantaneous flow (or velocity) can become zero for perfusion pressures greater than zero. This value of perfusion pressure where flow becomes zero has been called the “critical closing pressure” (CrCP) by Burton (7), and the term has been widely applied. In the cerebral circulation, Sagawa and Guyton (36) and Dewey et al. (12) confirmed the existence of a cerebral critical closing pressure in dogs and monkeys, respectively. More recently, similar findings have been reported in humans (4, 6, 8). Direct measurement of CrCP in humans is not straightforward due to the ethical and practical difficulties of lowering ABP to reach the point where diastolic flow (or velocity) reaches zero. With the increasing use of Doppler ultrasound to study cerebral hemodynamics, however, the instantaneous relationship between CBFV and ABP during each heart beat shows that a linear extrapolation of the CBFV-ABP scatterplot intercepts the pressure axis at values significantly greater than zero and this method has been adopted by many investigators to obtain estimates of CrCP in human studies (3, 4, 6, 10, 21, 32, 35, 39, 44). By fitting a regression line to the scatter diagram of CBFV vs. ABP, one is implicitly assuming a linear relationship such as CBFV = a + b·ABP. From this, CrCP can be calculated as CrCP = −a/b (CBFV = 0). The inverse of the regression slope has the same units of CV Ri and has been called the “resistance-area product” (RAP) by Evans et al. (15) to take into account the corrective effects of dynamic autoregulation are manifested through changes in CVR (2, 33). For this reason, we refer to

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that velocity, instead of flow, is used in its calculation. From this it is then possible to express the linear relationship as 

$$\text{CBFV} = \frac{\text{ABP} - \text{CrCP}}{\text{RAP}}.$$

Studies of CBF regulation have often derived estimates of CVR or CVRi to shed light on situations where both CBF (or CBFV) and ABP are varying simultaneously (2, 14, 33, 41, 45). Directional changes in CVR can indicate whether vasodilatation or vasoconstriction is taking place, independently of the corresponding changes in ABP and/or CBF. Although estimates of CVR have been useful in this context, we should worry about adopting a model that does not reflect the true nature of the passive flow (or velocity)-pressure relationship. Furthermore, except for a few studies describing the influences of CO2 on cerebral hemodynamics (3, 4, 12, 18, 19, 21, 28, 32, 44), the CrCP-RAP model has not been tested in studies of CBF regulation to assess the potential advantages of using two instead of a single parameter to describe the passive relationship between pressure and flow.

We analyzed the dynamic relationship between continuous measurements of CBFV and ABP at rest and during brain stimulation with cognitive and motor tasks in a group of young, healthy volunteers to test the hypothesis that the CrCP-RAP model can provide greater insight into CBF regulatory mechanisms than the classical approach of relying only on CVR estimates.

**METHODS**

**Subjects and measurements.** Fifteen healthy subjects (7 men), aged 21–43 yr, were recruited. Acceptance into the study required a score of ≥70% for right-handedness as assessed by the Edinburgh handedness inventory (26). No subject had any indication of cerebrovascular disease. The Leicestershire Local Research Ethics Committee (Two) approved the study, and fully informed, written consent was obtained from each subject. The data collection protocol has been described previously (24). Subjects avoided alcohol, nicotine, and caffeine-containing products for 24 h before attending a temperature (23°C)- and lighting-controlled laboratory. Measurements were performed with subjects in the seated position. One hand was kept at heart level and was used to record ABP noninvasively with an arterial volume-clamping device (Finapres 2300, Ohmeda). The other hand was kept free and was used to perform the tasks (“active hand”). An ECG signal was monitored using three surface chest leads. EtCO2 was measured via a closely fitting mask and an infrared capnomograph (Capnogard, Novametrix). The middle cerebral arteries (MCA) were insonated bilaterally using 2-MHz TCD (SciMed QVL-120). The transducer probes were placed over the temporal bone window and locked in position using a specially designed head frame. All physiological signals were continuously recorded onto digital audiotape (DAT, Sony PC-108M).

**Activation paradigms.** Two different paradigms were adopted involving the use of the right or left hand to activate the contralateral hemisphere (40). After random assignment the ABP transducer was placed on the middle finger of the nonactive hand, the servo-correcting mechanism of the Finapres was turned off, and the ABP calibration was recorded. Subjects were asked to breathe normally and relax with eyes closed during a 10-min baseline recording, after which, the Finapres servo was switched back on and then off again and a new calibration was performed before the first paradigm was started. After changing the Finapres transducer to the other hand, a similar procedure was adopted to record another 10-min baseline segment of data before the second paradigm was performed.

The paradigm controlled by the right hand involved the random presentation of a letter on a computer screen for 30 s. During this time, subjects were asked to write down as many words as possible beginning with the letter displayed. Subjects were asked to stop writing when the letter disappeared and to relax for the following 30 s while waiting for the next letter. The 10 letters selected correspond to the 10 most common initial letters in the English language. The paradigm controlled by the left hand was a simplified three-dimensional (3-D) puzzle using multi-colored building blocks of different shapes. Ten different puzzles were previously constructed and were displayed in random order on the computer screen for 30 s. Using their left hands, subjects had to select and pick up the individual blocks and assemble the puzzle as a two-dimensional (2-D) pattern on the bench top. Subjects stopped as soon as the puzzle photograph disappeared from the screen and were asked to relax for the next 30 s before the next picture was displayed. The total duration of the word or puzzle paradigms was 10 min each. A pulse of synchronism, indicating the beginning and end of each activation task was also recorded on tape.

**Data analysis.** Data recorded on tape were downloaded onto a microcomputer in real time. A fast Fourier transform (FFT) was used to extract the maximum frequency velocity envelope with temporal resolution of 5 ms. The ABP, ECG, EtCO2 and stimulus marker signals were sampled at a rate of 200 samples/s, and ABP was calibrated at the start of each recording. All signals were visually inspected to identify artifacts or noise, and narrow spikes were removed by linear interpolation. The two CBFV signals were subjected to a median filter with a window width of five samples, and all signals were low-pass filtered by a zero-phase Butterworth filter with a cutoff frequency of 20 Hz. The distance between the heart and the Doppler probe was used to calculate ABP at MCA height.

The beginning and end of each cardiac cycle were detected on the ECG, and mean beat-to-beat values were calculated for the two CBFV channels, ABP, and heart rate. The heart-MCA distance was used to obtain estimates of ABP in the MCA (ABP-MCA).

The end-tidal position was detected in the capnographic signal and linear interpolation was used to obtain estimates of EtCO2 synchronized to the end of each cardiac cycle. An index of cerebrovascular resistance (CVRi) was estimated by the ratio meanABP/meanCBFV for each heartbeat, for both MCA's (14). The CrCP of the cerebral circulation was estimated by extrapolation of the linear regression CBFV = a + b·ABP as described previously (3, 4, 6, 8, 32). The RAP was obtained from the inverse of the regression slope (RAP = 1/b). The CrCP can then be obtained from the value of ABP where CBFV = 0, that is CrCP = −a/b. Figure 2 gives examples of CBFV-ABP scatterplots and corresponding regression lines at rest and during activation. From the expressions of CrCP and RAP, CBFV can be expressed as 

$$\text{CBFV} = (\text{ABP} - \text{CrCP})/\text{RAP},$$

where all parameters should reflect dynamic regulation of CBF induced by changes in ABP, arterial PO2 (PaO2), and mental activation. All beat-to-beat estimates were interpolated using a third-order polynomial and resampled at 0.2-s intervals to generate a time series with a uniform time base. Suffixes R and L are used with abbreviations to denote right and left side variables, respectively.

**Components of CBFV responses.** A novel approach was adopted to weight the separate contributions of ABP, CrCP, RAP, and CVRi to the CBFV responses induced by activation tasks. At rest, the previous expression of CBFV can be written as:

$$\text{CBFV}_0 = \frac{\text{ABP}_0 - \text{CrCP}_0}{\text{RAP}_0} \quad (1)$$

during activation, all variables in Eq. 1 can change, leading to:

$$\text{CBFV}_0 + \Delta v = \frac{(\text{ABP}_0 + \Delta p) - (\text{CrCP}_0 + \Delta c)}{\text{RAP}_0 + \Delta r} \quad (2)$$

where $\Delta v$, $\Delta p$, $\Delta c$, and $\Delta r$ represent small changes in CBFV, ABP, CrCP, and RAP, respectively. Assuming that $\Delta r \ll \text{RAP}_0$,
Substituting in Eq. 2:

\[
\frac{1}{\text{RAP}_0 + \Delta r} = \frac{1}{\text{RAP}_0} \left( 1 - \frac{\Delta r}{\text{RAP}_0} \right)
\]

(3)

and the total change in CBFV, \( \Delta v \) is now approximated as the sum of the three components, reflecting the separate contributions of parallel changes in ABP, CrCP, and RAP. The great advantage of Eq. 9 is that each component has the same units of CBFV (cm·s⁻¹). In other words, the transformations expressed by Eqs. 1–9 allow us to have a uniform “currency” to compare different contributions to the CBFV response. Reference values of the quantities in Eq. 1 were obtained by averaging data for the 10-s interval preceding the beginning of activation. The differences \( \Delta v \), \( \Delta p \), \( \Delta c \), and \( \Delta r \) were obtained by subtracting reference values from the total values during activation. Equation 9 was used to calculate \( \Delta v^* \) as a “checksum” to compare this approximation with the true change \( \Delta v \).

For the analysis of CVRi, the same set of equations above was used by replacing RAP with CVRi and removing CrCP0, \( \Delta c \), and \( \Delta v \). In this case,

\[
\Delta v^* = \Delta v_{\text{ABP}} + \Delta v_{\text{CrCP}} + \Delta v_{\text{RAP}}
\]

(9)

In addition to the analysis of changes due to brain activation, spontaneous changes in ABP were also analyzed to study changes in CBFV, CrCP, RAP, and CVRi at rest. This approach has been described previously (29, 30). Recordings at rest were scanned for spontaneous ABP transients with peak amplitude >2% of the mean baseline value. Transients were inspected visually to reject artifacts or ABP transients shorter than 8 s. The minimum time interval between transients was 20 s. The component analysis described above was also applied to changes in CBFV, ABP, CrCP, and RAP (or CVRi) during spontaneous transients. Mean values during the 10 s preceding the foot of the ABP transient were used to calculate reference values (Eq. 1).

Statistical analysis. Averages of each variable, synchronized by the beginning of each activation task or by the foot of spontaneous ABP transients, were calculated for each subject and then averaged for the entire population. Subjects with \( \text{V}_{\text{RAP}} \), \( \text{V}_{\text{CrCP}} \), or \( \text{V}_{\text{CVRi}} \) averages with consistent displacement from the population mean of more than two standard deviations were treated as outliers and removed from the study. Multi-way analysis of variance (MANOVA) with repeated measures at \( t = 0, 5, 10, 15, 20, 25, \) and 30 s after activation (7 levels) was performed to test for the effects of hemispheric dominance (dominant vs. nondominant) and paradigm (word vs. puzzle) for CrCP, RAP, and CVRi. Statistical significance was set at \( P < 0.05 \).

**RESULTS**

All subjects completed the word and puzzle paradigm. Due to a technical fault, data from a 29-year-old male subject was lost during one baseline recording. The number of spontaneous transients contributed by this subject at rest was reduced but did not affect the analysis because transients from both baseline recordings were pooled as discussed below. Two subjects showed large displacement from the population mean for their mean \( \text{V}_{\text{CrCP}} \) for both paradigms and were removed from the study. The mean ± SD age of the remaining 13 subjects was 27.7 ± 6.3 yr.

Previous analysis of the same data set (24) did not show any significant differences between the two recordings at rest (“baseline”), except for mean RAP, which was reduced for the second baseline recording. Because the present analysis is not based on mean values but on changes from the mean, spontaneous transients detected in the two baseline recordings were pooled together, leading to a total of 79 transients that were averaged, synchronized by the foot of the ABP transient. Table 1 gives the mean ± SD reference values for the three different situations (rest + 2 paradigms). No significant differences were observed between the right and left MCA recordings.

Figure 1 shows the averaged CBFV change (\( \Delta v \)) for the spontaneous transients (Fig. 1, A and B) as well as for the word tasks (Fig. 1, C and D) and puzzle paradigm (Fig. 1, E and F), compared with the checksum of components (\( \Delta v^* \)), given by Eq. 9. The largest differences were observed for the word paradigm, corresponding to mean square values of 0.23 cm²s⁻¹ and 0.19 cm²s⁻¹ for the left and right MCAs, respectively. Qualitatively similar results were obtained for the CVRi.
model. From these results, it is possible to conclude that Eq. 9 provides an acceptable approximation to describe the change in CBFV (Δv) by the sum of two (CVRi model) or three separate components (CrCP-RAP model).

A representative example of instantaneous pressure-velocity relationships is shown in Fig. 2. Activation with the word paradigm rotates the regression line clockwise, leading to a reduction in CrCP and an increase in RAP. As a result, Eq. 9 will show that activation leads to a positive VCrCP and a negative VRAP. These components can be better visualized by their time-dependent plots as presented in the next three figures.

The breakdown of Δv in its components is presented in Fig. 3 for the spontaneous transients. For simplicity, only the averages of the 79 transients are shown. Information about the scatter of these values is given below. For both models, results are almost identical for the right and left MCA (Fig. 3). On the other hand, there are substantial differences between the two models, involving the amplitude and temporal pattern of the CBFV components. To highlight only the main differences, VABP shows a greater contribution in the CrCP/RAP model, in relation to the CVRi model, due to the fact that CVRi > RAP. In Fig. 3, A and B, VCVRi is showing a sharp rise immediately after t = 0, but that has no equivalent change in the VCrCP and VRAP components in Fig. 3, C and D. Both of these figures show that VRAP and VCrCP decrease after the sudden rise in VABP (t = 0), but VCrCP reaches a minimum before VRAP. Finally, for values of t > 10 s, there is a reduction in VCVRi, but VRAP continues to show a sustained contribution up to t = 30 s (right MCA) and t = 50 s (left MCA). Possible reasons for these different patterns will be discussed later.

Fig. 1. Comparison between measured values of Δv (continuous line) and the estimated sum of components given by Eq. 9 (Δv*, dashed line) for spontaneous transients (A, B), word tasks (C, D), and puzzle paradigm (E, F).
Figure 4 contains the same information for the word paradigm. Again, the contribution of VABP is more pronounced in the CrCP/H11001 RAP model (Fig. 4, C and D) compared with the CVRi model (Fig. 4, A and B). VCVRi also shows a peak coinciding with the rise in VABP but has a distinct pattern for the two sides, being biphasic for the right MCA but almost entirely positive for the left MCA. These changes suggest a combination of vasoconstriction with vasodilatation on the right side and predominant vasodilatation in the left MCA territory. Noteworthy, VCVRiL remains elevated after the end of activation (Fig. 4B). For the CrCP-RAP model, the contribution of VCrCP is almost entirely positive for both sides (see Fig. 2), with a continuous rise during activation, indicating a vasodilatory effect. VRAP remains negative during activation, suggesting maintained vasoconstriction. Hemispheric lateralization is reflected by the larger change in ΔvL, compared with the right side. This was achieved mainly by an upward shift of VRAPL (Fig. 4D).

The puzzle paradigm led to more similar behavior in VCVRi (Fig. 5, A and B) compared with VRAP (Fig. 5, C and D) mainly due to reduced values of VCrCP. In general, the relative contribution of VABP was also reduced in relation to the two other situations in Figs. 3 and 4. Predominance of the right hemisphere is also confirmed by the larger change in ΔvR (Fig. 5, A and C) compared with ΔvL (Fig. 5, B and D). Again, this was achieved by upward shifts of VCVRiR and VRAPR compared with left-side values. For the right MCA, both VCVRiR and VRAPR show a predominantly vasodilatory response, whereas some suggestion of vasoconstriction can be observed in the left-side plots (Fig. 5, B and D), mainly for VRAPL after the main peak in VABP (Fig. 5D).

Figure 6 depicts the temporal changes in the population average EtCO2 during mental activation and also at rest, corresponding to the spontaneous transients represented in Fig. 3. Mean values of EtCO2 were higher during the puzzle paradigm in relation to rest and the word test (Fig. 6), but differences were not significant (Table 1). As reported previ-
ously (24), both paradigms induce a significant reduction in EtCO₂, with a minimum around 10 s after stimulation. This pattern was not observed for the spontaneous fluctuations at rest, which showed a relatively constant value of EtCO₂. Possible influences of EtCO₂ changes during mental activation will be discussed below.

For clarity, Figs. 3–5 do not include information about the scatter of synchronized averages. Tables 2 and 3 give the mean SD of the main components of the CrCP/RAP model for activation with the word and puzzle paradigms at selected time intervals after activation, as adopted for the repeated-measures MANOVA. Standard deviation values for the rest data (Fig. 3) and the CVR𝑖 model (Figs. 4, A and B, and 5, A and B) are of similar magnitude to the corresponding values in Tables 2 and 3. Repeated-measures MANOVA showed significant trends in CrCP (P = 0.025), RAP (P = 0.046), and CVR𝑖 (P = 0.002) as suggested by Figs. 4 and 5. CrCP also had a significant effect of paradigm (P = 0.045) but not hemispheric dominance. On the other hand, both RAP and CVR𝑖 had significant effects of hemispheric dominance but not for the tasks (P = 0.039 and P = 0.0008, respectively). In general, the results of the MANOVA confirm the significance of differences that can be inferred by visual inspection of Figs. 4 and 5 and Tables 2 and 3.

**DISCUSSION**

**Subcomponent analysis.** Signal decompositions, such as Fourier transform or principal component analysis, can shed light on the structure of physiological measurements and their inter-relationships. The principle of subcomponent analysis is fairly general and can be easily extended to many different areas of physiology. The method we proposed to breakdown the CBFV response into meaningful subcomponents is original and allows the identification of the different hemodynamic contributions to the CBFV response using standardized units of measurement. The main advantage of this approach is to identify the relative contribution of the different determinants of CBFV at any instant of time, according to different models of the passive pressure-velocity relationship.

The demonstration that subcomponents associated with separate variables (ABP, CrCP, RAP, or CVR𝑖) can reproduce the CBFV response (Δv) with reasonable accuracy during spontaneous transients at rest or induced by mental activation tasks is particularly relevant.

In a previous analysis of the same data (24), we concluded that significant changes in ABP induced by brain activation paradigms led to a more complex cerebral hemodynamic response than hitherto assumed, probably involving the interaction of myogenic and metabolic pathways. The breakdown of the CBFV response to activation into standardized components allows further insights into the interpretation of those early findings and facilitates a critique of different models of the passive pressure-velocity relationship.

**Determinants of cerebrovascular resistance and critical closing pressure.** When using subcomponent analysis to study the behavior of different models during mental activation, it is important to take into account previous evidence about the physiological information conveyed by the CVR𝑖, RAP, and
CrCP parameters. Historically, CVRi has been widely used in studies of static autoregulation, mainly in situations where both mean ABP and mean CBF varied simultaneously (33, 42). Zhang et al. (45) suggested that CVRi reflected myogenic regulation in response to infusions of phenylephrine and L-NMMA. Tiecks et al. (42) derived an index of static autoregulation from relative changes in CVRi in response to changes in mean ABP. Dynamic changes in CVRi were reported by Aaslid et al. (2) in response to sudden changes in ABP induced by the thigh cuff test. The same authors showed that the amplitude of the CVRi change was modulated by arterial CO2 (2). Edwards et al. (14) used spontaneous fluctuations in ABP and CBFV to derive beat-to-beat time series of CVRi, which were then used to estimate step responses of CVRi to a sudden change in ABP. The amplitude and rise time of these step responses were also shown to be sensitive to arterial CO2 (14). The RAP+CrCP model stems from early observations that instantaneous flow (or velocity)-pressure relationships in the brain, like in many other organs, intercept the pressure axis at values of ABP (7, 9, 12, 13, 22, 23, 32, 35, 37, 39, 44). A two-parameter model has the potential to convey more information about the cerebral circulation than a single parameter such as CVRi and, ideally, the potential to discriminate between different regulatory pathways. Some evidence seems to support this possibility, but there are still more questions than answers. The ideal method to obtain beat-to-beat estimates of RAP and CrCP remains controversial (4, 32, 39). A simple model of the cerebral microcirculation shows that in most cases what can be estimated from pressure-velocity curves is only an “apparent” CrCP that is usually greater than the “real” CrCP (32). Nevertheless, this model also shows that estimated values of the apparent CrCP are influenced by intracranial pressure (ICP), cerebral venous pressure, and vasomotor activity (32). Hitherto, the largest body of evidence that has been accumulated about CrCP is its greater sensitivity to changes in PaCO2, in relation to corresponding changes in RAP (3, 12, 17, 19, 21, 28, 32, 35, 44). CrCP was also shown to vary with ICP (6), intrathoracic pressure (10, 35), vasospasm (39), and hyperemia.
resulting from ventricular fibrillation (4). These results suggest that CrCP might be influenced by transmural pressure (ICP, venous/intrathoracic pressure) and metabolic regulation of CBF (PaCO2, hyperemia, vasospasm). Not much is known about specific determinants of RAP. A study in neonates showed that RAP reflected disturbances in dynamic autoregulation, whereas CrCP did not (28). Unlike CVRi, there have been very few studies of beat-to-beat changes in RAP and CrCP, and this gap was one of the motivations behind the present investigation.

**Contribution of arterial blood pressure.** Although our main objective was to compare the consequences of using either the CVRi or the RAP+CrCP model, some findings are common to both models. The VABP component expresses the fraction of the Δv change that can be attributed exclusively to the direct effect of ABP. At rest, spontaneous ABP transients led to Δv changes in agreement with previous reports (30, 31). Despite different model-dependent amplitudes (Fig. 3), VABP was considerably reduced 10 s after the foot of the transient and had limited influence thereafter. On the other hand, the contribution of VABP was maintained throughout the duration of activation for both the word and puzzle tasks (Figs. 4 and 5), and represented a substantial portion of the Δv change. In our previous communication (24), we suggested that the initial rise in ABP could lead to a vasocostricting myogenic response at the beginning of activation, say for t < 10 s (Figs. 4 and 5), but this would be gradually overcome by a vasodilatory metabolic response to match the need for additional O2 supply. What the new results in Figs. 4 and 5 are suggesting is that the metabolic response could be even less significant than originally thought, including instances where Δv ≈ VABP during late activation, as in Fig. 4A. The relevance of these findings deserves further investigation to assess the extent to which they can be generalized to different activation paradigms.

**Contribution of EtCO2.** The well-known effects of PaCO2 on CBF suggest that some of the changes observed in CBFV and model parameters could be caused by the significant reductions in EtCO2 observed during mental activation (Fig. 6). During spontaneous fluctuations at rest, EtCO2 remained relatively constant and hence was not likely to have influenced the time course of Δv and the model-derived parameters in Fig. 3. Poulin et al. (34) have shown that the CBFV response to sudden controlled changes in PaCO2 is delayed by ~6 s and then rises or falls with a time constant of 45.3 s for the “on” response and 6.1 s for the “off” response (34). With the gradual changes in EtCO2 observed during mental activation, it is important to take into account that any effects would not be manifested before a delay of ~10 s (34), thus resulting in noticeable changes around 20 s into the response (Fig. 6). With that in mind, we could expect the reduction in EtCO2 to be reflected as a delayed reduction in Δv, resulting from reductions in VRAP, VCrCP, or VCCP (2, 3, 4, 12, 14, 17, 29, 32, 44). For the word paradigm, the pattern of Δv does not suggest an association with EtCO2. VCCP also remains positive, but VRAP shows negative values that could be reflecting some influence of EtCO2, although the main downward shift, occurring before 10 s (Fig. 4) suggests a different influence. For activation with the puzzle, the contribution of EtCO2 is even less likely because VRAP and VCrCP show positive trends during most of the response and the slight dip in VRAP takes place before t = 10 s. If measurements of EtCO2 are reflecting the true changes in PaCO2 during mental activation, the observed transient hypocapnia should have a measurable influence on Δv and hence on model parameters. One possible reason why such influences

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### Table 2. CBFV change and its components (Eqs. 6–8) at selected time intervals after activation (t = 0) with the word paradigm

<table>
<thead>
<tr>
<th>Time After Activation, s</th>
<th>Δv</th>
<th>VABP</th>
<th>VCCP</th>
<th>VRAP</th>
<th>Δv</th>
<th>VABP</th>
<th>VCCP</th>
<th>VRAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.96 ± 1.15</td>
<td>0.02 ± 1.44</td>
<td>0.30 ± 1.09</td>
<td>0.62 ± 1.21</td>
<td>0.76 ± 0.94</td>
<td>0.06 ± 1.42</td>
<td>0.55 ± 0.69</td>
<td>0.12 ± 1.24</td>
</tr>
<tr>
<td>5</td>
<td>3.46 ± 1.95</td>
<td>6.19 ± 3.91</td>
<td>0.35 ± 3.11</td>
<td>-2.93 ± 4.16</td>
<td>5.26 ± 1.62</td>
<td>6.15 ± 4.13</td>
<td>1.63 ± 2.61</td>
<td>-2.31 ± 2.88</td>
</tr>
<tr>
<td>10</td>
<td>1.42 ± 1.71</td>
<td>3.83 ± 3.55</td>
<td>0.92 ± 4.11</td>
<td>-3.39 ± 4.77</td>
<td>4.27 ± 1.90</td>
<td>3.88 ± 3.43</td>
<td>2.32 ± 3.90</td>
<td>-1.96 ± 4.16</td>
</tr>
<tr>
<td>15</td>
<td>2.59 ± 3.14</td>
<td>5.14 ± 3.83</td>
<td>1.25 ± 5.85</td>
<td>-3.71 ± 4.57</td>
<td>5.90 ± 2.82</td>
<td>5.04 ± 3.62</td>
<td>2.88 ± 5.27</td>
<td>-1.87 ± 3.84</td>
</tr>
<tr>
<td>20</td>
<td>2.93 ± 4.72</td>
<td>5.06 ± 4.96</td>
<td>2.25 ± 6.71</td>
<td>-4.06 ± 5.46</td>
<td>6.39 ± 4.48</td>
<td>5.16 ± 4.53</td>
<td>3.46 ± 6.29</td>
<td>-1.94 ± 4.89</td>
</tr>
<tr>
<td>25</td>
<td>3.17 ± 5.22</td>
<td>4.48 ± 5.52</td>
<td>2.25 ± 6.98</td>
<td>-3.33 ± 5.73</td>
<td>6.29 ± 4.46</td>
<td>4.60 ± 4.91</td>
<td>3.70 ± 6.65</td>
<td>-1.78 ± 5.20</td>
</tr>
<tr>
<td>30</td>
<td>3.88 ± 5.68</td>
<td>4.18 ± 5.93</td>
<td>2.09 ± 7.00</td>
<td>-2.15 ± 6.65</td>
<td>6.61 ± 4.87</td>
<td>4.31 ± 5.17</td>
<td>3.61 ± 6.69</td>
<td>-1.09 ± 5.57</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 13) in cm/s⁻¹. CBFV, cerebral blood flow velocity.

---

### Table 3. CBFV change and its components (Eqs. 6–8) at selected time intervals after activation (t = 0) with the puzzle paradigm

<table>
<thead>
<tr>
<th>Time After Activation, s</th>
<th>Δv</th>
<th>VABP</th>
<th>VCCP</th>
<th>VRAP</th>
<th>Δv</th>
<th>VABP</th>
<th>VCCP</th>
<th>VRAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.06 ± 1.68</td>
<td>0.06 ± 1.38</td>
<td>0.21 ± 1.18</td>
<td>0.78 ± 0.88</td>
<td>0.73 ± 1.54</td>
<td>0.038 ± 1.33</td>
<td>-0.01 ± 1.48</td>
<td>0.69 ± 1.73</td>
</tr>
<tr>
<td>5</td>
<td>5.30 ± 3.27</td>
<td>6.44 ± 4.71</td>
<td>-0.54 ± 4.20</td>
<td>-0.61 ± 2.72</td>
<td>4.05 ± 2.27</td>
<td>6.78 ± 5.19</td>
<td>-0.61 ± 4.79</td>
<td>-1.95 ± 3.70</td>
</tr>
<tr>
<td>10</td>
<td>5.58 ± 3.51</td>
<td>3.75 ± 3.43</td>
<td>0.62 ± 5.33</td>
<td>1.01 ± 3.77</td>
<td>3.47 ± 1.88</td>
<td>3.87 ± 3.60</td>
<td>0.49 ± 5.53</td>
<td>-0.85 ± 4.15</td>
</tr>
<tr>
<td>15</td>
<td>6.76 ± 3.57</td>
<td>4.64 ± 3.68</td>
<td>0.54 ± 5.48</td>
<td>1.21 ± 5.21</td>
<td>4.85 ± 2.91</td>
<td>4.55 ± 2.94</td>
<td>0.49 ± 6.17</td>
<td>-0.18 ± 4.98</td>
</tr>
<tr>
<td>20</td>
<td>6.02 ± 3.44</td>
<td>3.98 ± 2.70</td>
<td>0.05 ± 2.60</td>
<td>1.61 ± 5.00</td>
<td>4.24 ± 3.76</td>
<td>4.22 ± 4.91</td>
<td>0.21 ± 7.48</td>
<td>-0.25 ± 6.56</td>
</tr>
<tr>
<td>25</td>
<td>7.44 ± 3.80</td>
<td>4.41 ± 6.05</td>
<td>0.61 ± 7.34</td>
<td>1.97 ± 5.48</td>
<td>5.71 ± 4.07</td>
<td>4.60 ± 5.93</td>
<td>0.38 ± 8.72</td>
<td>0.64 ± 6.56</td>
</tr>
<tr>
<td>30</td>
<td>7.42 ± 3.87</td>
<td>4.51 ± 10.11</td>
<td>0.64 ± 12.25</td>
<td>1.95 ± 6.96</td>
<td>5.33 ± 4.51</td>
<td>4.75 ± 10.13</td>
<td>-0.83 ± 12.56</td>
<td>1.33 ± 7.03</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 13) in cm/s⁻¹.
are not obvious is the relatively small change in EtCO\textsubscript{2} and the fact that other influences, such as ABP and increases in metabolic demand during activation, are more likely to dominate and overshadow smaller influences like the EtCO\textsubscript{2} transient. Future studies, including changes in the CO\textsubscript{2} content of inspired air, should be able to quantify the influences of hyper-ventilation during cognitive and sensorimotor stimulation.

**Model-dependent findings.** Before discussing the appropriateness of different models of the passive pressure-velocity relationship, a word of caution is needed, regarding two different aspects. First, due to the lack of detailed human data on dynamic control of vasomotor activity in the microcirculation, a “gold standard” is not available to be used as a reference to guide the selection of different macroscopic models. Most research involving brain activation mechanisms in humans has been performed with positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), but no simultaneous data on the dynamic effects of ABP changes are usually available. Consequently, at this stage our assessment and interpretation of the performance of different models can only be speculative. Second, we are considering only two relatively simple models. It is likely that the true passive pressure-velocity relationship is considerably more complex, showing nonlinearities and viscous effects (32, 43), but the search for practical alternatives has not been successful (27). Nevertheless, consideration of two different models can provide clues about their benefits and limitations, and, above all, can show the extent to which the interpretation of CBFV responses can be model dependent. The CVR\textsubscript{i} and RAP+CrCP models generated very distinct standardized components at rest and during activation with the word paradigm but less so during the puzzle tasks. A sudden spontaneous change in ABP at rest is expected to induce a myogenic compensatory response. Due to the initial change in CBFV, however, it is likely that a metabolic response will also be triggered by the transient unbalance between O\textsubscript{2} supply and demand (1, 2, 33). In Fig. 3, CVR\textsubscript{i} does not seem to reflect these different mechanisms and there is a vasodilatory peak simultaneous with the ABP rise that is difficult to explain, unless it is assumed to represent a large passive arterial dilatation due to the ABP transient. Such a large initial vasodilatation is not observed for the RAP+CrCP model, and in this case the small peak in V\textsubscript{RAP} could be explained by the preceding drop in V\textsubscript{ABP}. Due to their pattern and temporal evolution, it is tempting to assume that V\textsubscript{RAP} is reflecting the myogenic response while changes in V\textsubscript{CrCP} are due to metabolic influences. Previous investigators have shown that CrCP is much more sensitive to Pa\textsubscript{CO\textsubscript{2}} than RAP (4, 12, 13, 17, 19, 21, 29, 32, 44), but this cannot be generalized to other metabolic pathways. In the same fashion that \(\Delta v\) peaks before V\textsubscript{ABP} (24, 30, 31), the trough in V\textsubscript{CrCP} precedes the corresponding trough in V\textsubscript{RAP}. This could be interpreted as CrCP responding to \(\Delta v\) (metabolic), with RAP representing the response to the ABP change. Finally, as soon as \(\Delta v\) reaches its original level (t \sim 15 s), V\textsubscript{CrCP} also oscillates around zero, but the vasoconstrictive effect of V\textsubscript{RAP} is maintained to counteract the residual influence of V\textsubscript{ABP} (Fig. 3, C and D).

During activation, V\textsubscript{CVRI} shows a similar temporal pattern for both the word and puzzle tasks, suggesting gradual vasodilatation with the progress of activation, with the exception of the right MCA during the word paradigm (Fig. 4A), where there is the indication of initial vasoconstriction. In these curves, left hemispheric dominance for the word tasks and right dominance for the puzzle paradigm (24, 40) are reflected as an upward shift of V\textsubscript{CVRI}, and this was confirmed by the repeated-measures MANOVA. More diverse patterns were observed for the RAP+CrCP model. Starting with V\textsubscript{CrCP}, Figs. 4 and 5 represent population averages showing marked between-task differences but less interhemispheric variation. These visual indications were confirmed by MANOVA. The predominantly positive values of V\textsubscript{CrCP} (vasodilation) during activation with the word paradigm (Fig. 4, C and D), suggest that this component is mainly influenced by metabolic pathways. On the other hand, V\textsubscript{RAP} is predominantly negative, this indicating vasoconstriction, possibly of myogenic origin, because V\textsubscript{ABP} maintains a significant contribution throughout activation. Nevertheless, left hemispheric dominance is reflected as an upward shift in V\textsubscript{RAPL} (Fig. 4D), thus showing some metabolic influence on this component as well. These differences were confirmed by the repeated-measures MANOVA.

For the puzzle paradigm, V\textsubscript{CrCP} shows smaller values in relation to the word tasks and the temporal pattern of V\textsubscript{RAP} approximates to the corresponding patterns of V\textsubscript{CVRI} (Fig. 5). Again, hemispheric dominance is reflected by an upward shift in V\textsubscript{RAP} (Fig. 5C) as confirmed by MANOVA. Differences in the pattern of CBFV responses between different brain activation paradigms have not been previously reported with the same richness of information as afforded by the RAP+CrCP model, and it is not clear why there are marked differences in V\textsubscript{CrCP} and V\textsubscript{RAP} between the puzzle and word tasks. Most studies in this area are performed with fMRI or PET and mainly describe differences in topographical intensities based on number of activated pixels. Animal studies have shown regional differences in vessel structure between cerebrum and brain stem and their myogenic responses (5), but we are not aware of similar findings involving different cortical regions. What is well known is that cognitive and spatiotemporal paradigms activate different cortical regions (11, 16), but at this stage it is premature to suggest that differences in V\textsubscript{CrCP} and V\textsubscript{RAP} components are related to regional heterogeneity of vessel structure and/or sensitivity to myogenic and metabolic mechanisms (5). Another possible cause of differences in cerebral hemodynamic responses to word and puzzle paradigms could be the extent of sympathetic activation elicited by different mental activation tasks (20).

**Limitations of the study.** Although the MCA can supply 80% of the blood flow to each hemisphere, it is likely that the word and puzzle paradigms also stimulated other regions of the brain not supplied by the MCA. Both paradigms had a visual component that would only be detected in brain supplied by the posterior cerebral artery (1, 3, 40). This effect may be more intense for the puzzle paradigm and could explain some of the differences found between the two kinds of response, for example, regarding the contribution of V\textsubscript{CrCP}. The use of the right hand to write during the word paradigm and the left hand to assemble the puzzle does not allow for the separation between cognitive and motor components of the responses. This is one aspect that needs to be refined in future studies with the use of more selective paradigms. Using recordings of CBFV as a surrogate of CBF can lead to misleading results if there are significant changes in the MCA cross-sectional area. The accumulated evidence shows that the MCA diameter...
remains relatively constant at rest and during large changes in ABP and PaCO₂ (25, 37), but there is less evidence that this is so during cognitive and/or sensorimotor stimulation. Because both RAP and CVRi represent cerebrovascular resistance multiplied by MCA cross-sectional area, any changes in MCA diameter taking place during activation tasks would be reflected as a modulation of these parameters, but would not affect CrCP estimates (3, 4, 32). The use of the Finapres device to record ABP continuously in the finger is also of concern because of the different morphology of the peripheral ABP waveform in relation to the ascending aorta, which is probably closer to the morphology that would be expected in the MCA. The larger systolic pressures recorded in the finger can lead to underestimates values of CrCP and overestimates of RAP. For this reason, we paid great attention to the stability of measurements and removed occasional artifacts in individual ABP and CBFV waveforms. Estimates were also improved by averaging a large number of spontaneous transients at rest and the 10 separate activation tasks for each subject. Despite these precautions and careful data analysis, CrCP estimates had the highest coefficient of variation and two subjects had to be removed due to values of VcrCP well outside the 95% confidence band. Nevertheless, the population values obtained for baseline values of CrCP are in very good agreement with the results of several previous studies (32). In general, the high variability of the subcomponent estimates in Tables 2 and 3 suggest that future studies might benefit from a larger number of subjects, mainly in research designs testing for differences between subgroups of patients or subjects.

In conclusion, a new approach to describe the CBFV response to spontaneous ABP transients and mental activation with cognitive and motor paradigms allows the quantification of the relative contribution of different hemodynamic variables as expressed by models of the passive pressure-velocity relationship. Independently of the model selected, ABP contributes significantly to the CBFV response during activation, and consequently some degree of myogenic vasoconstriction would be expected. The classical model of the ABP-CBFV relationship based on a single parameter (CVR) does not seem to fully reflect the influence of ABP. On the other hand, a two-parameter model of the ABP-CBFV relationship, consisting of a resistance element (RAP) and a critical closing pressure element, can reflect the presence of both vasoconstriction and vasodilatation, with a consistent interpretation of the CBFV response at rest and during activation. Similarly to CVR, the contribution of RAP changes with hemispheric lateralization, but it is not sensitive to the different tasks performed. On the other hand, CrCP is dependent on the task but does not reflect interhemispheric differences. More research is needed on the extent to which these findings can be extended to other activation paradigms. The method of subcomponent analysis was useful to shed light on the physiological interpretation of CBFV responses to mental activation and might also be useful in different areas of cardiorespiratory physiology. The main conclusion of this study is that interpretation of CBFV responses induced by mental activation tasks is dependent on the underlying model of the passive ABP-CBFV relationship. More research is needed about the performance of the CrCP+RAP model in different physiological conditions and activation paradigms, and for this reason it is recommended that future research in this area should take both models into account.

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REFERENCES


