Critical closing pressure explains cerebral hemodynamics during the Valsalva maneuver

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Dawson, Suzanne L., Ronney B. Panerai, and John F. Potter. Critical closing pressure explains cerebral hemodynamics during the Valsalva maneuver. J. Appl. Physiol. 86(2): 675–680, 1999.—The Valsalva maneuver (VM), a voluntary increase in intrathoracic pressure of ~40 mmHg, has been used to examine cerebral autoregulation (CA). During phase IV of the VM there are pronounced changes in mean arterial blood pressure (MABP), pulse interval, and cerebral blood flow (CBF), but the changes in CBF are of a much greater magnitude than those seen in MABP, a finding to date attributed to either a delay in activation of the CA mechanism or the inability of this mechanism to cope with the size and speed of the blood pressure changes involved. These changes in CBF also precede those in MABP, a pattern of events not explained by the physiological process of CA. Measurements of CBF velocity (transcranial Doppler) and MABP (Finapres) were performed in 53 healthy volunteers (aged 31–80 yr). By calculating beat-to-beat values of critical closing pressure (CCP) during the VM, we have found that this parameter suddenly drops at the start of phase IV, providing a coherent explanation for the large increase in CBF. If CCP is included in the estimation of cerebral vascular resistance, a temporal pattern more consistent with an autoregulatory response to CBF to normal during phase II, accounting for the fall in MABP and heart rate; phase III is associated with release of the strain and a sudden fall in MABP due to the release of the intrathoracic pressure influence on the arterial tree; and, finally, phase IV sees a rapid rise in CBF, which is quickly returned to baseline values by dynamic CA, before MABP returns to normal.

Greenfield et al. (12) examined nine male subjects (demographics unknown) 10–20 days after neurosurgery for resection of malignant cerebral tumors. Cerebrospinal fluid pressure (CSFP), internal carotid artery blood flow (QICA), and intra-arterial MABP were measured during the VM (20 mmHg for 15 s). The changes detected were as follows: during phase I, MABP increased by 17 mmHg, CSFP by 7 mmHg, and QICA by 23 cm3/min; in phase II, MABP fell 28 mmHg, CSFP rose a further 3.5 mmHg, and QICA fell 21% below baseline; during phase III MABP fell more, CSFP rose to baseline values, and QICA increased to 16% below baseline; and, finally, during phase IV MABP increased to 18% above baseline, with CSFP at 21% and QICA at 22% above baseline. Cerebrovascular resistance (CVR) was calculated to assess CA from the equation

\[
\text{CVR} = \frac{\text{MABP} - \text{CSFP}}{\text{QICA}}
\]

As expected, resistance fell during phases II and III, then increased in phase IV, implying that the autoregulatory mechanism was intact, but this change was considered to be both slow, compared with the MABP change, and also not of sufficient magnitude to return CBF to normal during phase II, accounting for the fall in cerebral perfusion pressure.

Tiecks et al. (23), studying normal volunteers (mean age 30 ± 9 yr), measured middle cerebral artery (MCA) cerebral blood flow volume (CBFV) by using TCD, CBFV being regarded as a valid surrogate marker of CBF (2). Similar results were found with a fall in MABP of 10.2% and in CBF of 35% in phase II and a
rise of 29.6 and 56.5%, respectively, during phase IV. CA during phase IV was calculated by using the formula

\[
CA = \frac{\text{CBFV}_{\text{IV}}/\text{CBFV}_{\text{I}} - 1}{\text{mABP}_{\text{IV}}/\text{mABP}_{\text{I}}} = \text{CA intact}, <1.0 = \text{CA impaired}
\]

Again, it was thought that CA was occurring and that the larger overshoot in CBFV occurred because of the time delay in the onset of CA.

Because of this disparity in the magnitude of changes between mean cerebral blood flow volume (MCBFV) and MABP, and the temporal pattern of events seen during the VM, our goal was to find a more physiological explanation for these results by examining the temporal evolution of instantaneous pressure-velocity relationships throughout the VM. We studied a group of volunteers with a wide age range because this technique may find a clinical application in subjects with, e.g., cerebrovascular disease.

METHODS

Subjects and study design. We examined 53 healthy volunteers (29 men), mean age 66 yr (range 31–80 yr), mean blood pressure 134/79 mmHg (range 108–164/63–108 mmHg), and mean body mass index 26.2 kg/m² (range 20–35).

Subjects were recruited from respondents to local newspaper advertisements, patients awaiting routine elective orthopedic surgery, and outpatient attendants. All were independent in their activities of daily living and free from cardiovascular disease as determined by history, physical examination, and 12-lead electrocardiogram. None were taking any medication known to affect the autonomic nervous or cardiovascular systems.

Subjects were studied after a strict protocol. They were asked to arrive at the laboratory in the morning, at least 2 h after a light breakfast, and having refrained from alcohol-, nicotine-, or caffeine-containing products for a minimum of 12 h. The study was performed in a quiet, dimly lit room at a constant ambient temperature (23°C) to minimize external stimulation. They were placed supine on a couch with their head supported by two pillows and their right arm supported at atrial height. Left and right MCA velocities were measured by using a dual-channel TCD (SciMed QVL120); 2-MHz probes were held immobile in a purpose-built head frame, and the MCA was identified by using the technique described by Aaslid et al. (1). Blood pressure was measured by using a Finapres noninvasive blood pressure monitor (Ohmeda 2300), an appropriate-sized cuff being attached to the middle finger of the right hand; heart rate was monitored by using three standard surface chest leads, and PCO₂ was monitored by using the TINA transcutaneous blood gas analyzer (Radiometer, Copenhagen, Denmark), which has been shown to be valid compared with arterial and arterialized blood samples (5, 14). The VM was explained to the subjects: they were asked to achieve an intrathoracic pressure of 40 mmHg for 15 s by blowing into a syringe attached to a pressure transducer with an integral bleed device after taking a normal-sized inspiratory breath; the intrathoracic pressure was displayed as a visual output by the transducer to aid subject cooperation. This was repeated a total of three times, with a minimum of 60 s between recordings to allow readings to return to baseline values. Data were recorded onto digital tape (Sony digital instrumentation cassette recorder PC-108M). During the recording the servo adjust mechanism on the Finapres was disabled, and an arterial blood pressure (ABP) calibration signal was recorded before each maneuver.

Data analysis. Off-line recordings of CBFV and ABP signals were continuously transferred to a microcomputer at a rate of 200 samples·s⁻¹-channel⁻¹. These signals were low-pass filtered with a cutoff frequency of 20 Hz, and the beginning and end of each cardiac cycle were detected from the ABP waveform.

Assuming that the dynamic relationship between the ABP and CBFV waveforms is linear, this can be modeled by partial differential equations with distributed parameters reflecting the vascular resistance (blood viscosity), inductance (blood inertia), and elastance (vessel compliance) (17). In the frequency domain, the relationship between these two quantities would then reflect the arterial vascular impedance (4, 17). As discussed in DISCUSSION, the effects of inductance and elastance can be neglected to provide a simpler, yet more robust, model of the instantaneous pressure-velocity relationship, according to the equation (6, 21)

\[
\text{CBFV}(t + \Delta t) = a + b \cdot \text{ABP}(t)
\]

Equation 1 applies to each cardiac cycle, with \( \Delta t \) representing a time lag between the CBFV and ABP waveforms. When CBFV is plotted as a function of ABP (Fig. 1), the parameter \( b \) represents the slope of the straight line that intercepts the pressure axis at a value \(-a/b\). This pressure-axis intercept has been defined as the critical closing pressure (CCP) (3, 6, 16, 19–21), whereas the inverse of the slope represents the resistance-area product (RAP) due to the dimensional relationship between pressure and velocity (rather than absolute flow) (7).

Parameters \( a \) and \( b \) in Eq. 1 were estimated for each cardiac cycle by linear regression after compensating for the time lag \( \Delta t \) between CBFV and ABP. For each cardiac cycle, the beginning of the pressure pulse and the corresponding upstroke of the CBFV signal were detected, and the time difference between these two points was obtained to provide an estimate of the lag \( \Delta t \). Before the linear regression was performed, the CBFV waveform was shifted by the corresponding lag, which is typically on the order of 75–100 ms. From the regression parameters, CCP and RAP_c are then given by

\[
\text{CRCP} = \frac{-a}{b} \quad \text{and} \quad \text{RAP_c} = \frac{1}{b}
\]

where RAP_c represents the RAP estimate that takes the CCP into account. We have also studied the more conventional estimate of CVR that ignores the pressure-axis intercept (RAP_z, i.e., CCP = 0) or

\[
\text{RAP_z} = \frac{\text{MABP}}{\text{MCFBV}}
\]

where MABP and MCFBV are the mean values of ABP and CBFV over a complete cardiac cycle, respectively.

These estimates were obtained for both right and left MCA. Because of the variability in the duration of the cardiac cycle, beat-to-beat estimates of parameters were converted to a uniform time base with a sampling interval of 0.2 s by using a
third-order polynomial interpolation. For each subject, the beginning of phase IV of the VM was manually marked, and a computer algorithm was used to locate the maximum rate of rise in the MABP overshoot during phase IV. To estimate representative temporal changes in these parameters for the population studied, this point was used to synchronize the calculation of the mean and SD of all waveforms at 0.2-s intervals.

**RESULTS**

A representative recording of ABP and CBFV changes during the VM is given in Fig. 1A, and instantaneous pressure-velocity relationships for a single cardiac cycle in phases II and IV are represented in Fig. 1B. The pressure-axis intercept of the linear regression that is used to estimate the CCP shows a clear shift between the two phases; the complete evolution of the CCP during the VM is depicted in Fig. 1C.

The increased CCP during phases I and II, and its sudden fall after phase IIb, as observed in Fig. 1C, could be observed in most subjects. In a small number of cases the linear regression extrapolation becomes less reliable as the result of noise in the pressure-velocity relationship (Fig. 1B). Nevertheless, this temporal pattern of CCP during the VM was confirmed for the whole group of subjects studied by the average results displayed in Fig. 2, A-D, for the right MCA. Similar results were obtained for the left MCA (Table 1), although the CCP during phase IV tends to be lower than for the right MCA.

The changes in MABP and MCBFV that we detected were not unlike those found previously (12, 23), i.e., a 15 and 20% fall from baseline in MABP and MCBFV, respectively, during phase II, and a 5 and 20% overshoot from baseline in phase IV. However, the rise in MCBFV precedes the increase in MABP, as does the change in RAPZ (Fig. 2D, dotted line). It would appear that CCP mirrors the changes in intrathoracic pressure and that the fall in CCP leads to the unexpected sudden...
We have confirmed the characteristic changes in CBF and MABP seen during phase IV of the VM described in previous studies (12, 23). However, by taking into account CCP and calculating a measurement of cerebrovascular resistance (RAPC) that includes this parameter, we have provided a more physiological explanation for these changes than have previous reports, which implies an inability of the CA to cope with changes in MABP of the magnitude recorded.

The early studies of Burton (3) and Dewey et al. (6) suggest that CCP probably reflects the interplay between active arteriolar tone and extravascular pressure. This needs to be interpreted with some caution in the present study. We have defined the CCP as the pressure-axis intercept of instantaneous pressure-velocity relationships after compensating for the time lag between these two waveforms. The main determinant of the time lag (70–100 ms) is the additional time required for the pressure wave to reach the finger, compared with the time it takes for it to reach the MCA. We have found that this parameter is not critical; without lag compensation, the pressure-velocity relationships represented in Fig. 1B tend to form a loop rather than a straight line, but the linear regression still provides CCP values that are significantly >0. Our conclusions only apply, however, to the model adopted in this study (Eq. 1), corresponding to a vascular resistance (RAP) in series with a back pressure (CCP).

If more complex models were considered, e.g., including compliance and inductance parameters, different results could have been obtained. First, it is important to compare the CCP model with the more simplistic representation of the cerebral circulation by a single vascular resistance parameter (RAPC). This model assumes that pressure-velocity relationships intercept the pressure (and velocity) axis at the origin. From Fig. 1B, which can be generalized to all our subjects, this approach is obviously in error and leads to temporal changes in resistance that are not only very distinct from RAPC but also more difficult to interpret physiologically, as indicated by the sudden reduction in RAPC during phase III (Fig. 2D). It could be argued that pressure-velocity relationships, as depicted in Fig. 1B, can become nonlinear for smaller values of ABP and therefore pass through the origin. This explanation is more physiologically acceptable (3) and should be pursued in the future in the search for more realistic models. The incorporation of cerebrovascular compliance as a model parameter would represent the next step forward in the attempt to develop more realistic models. Giller and Aaslid (9) have obtained evidence suggesting that cerebral vessels are less compliant than those of the systemic circulation. This observation is supported by the relatively flat impedance ratios obtained by Giller et al. (11), using carotid artery pressure waveforms. However, when ABP measurements are obtained with the Finapres device, the contribution of the peripheral circulation needs to be taken into account. More complex models are likely to reflect the compliance of peripheral arteries and the inertia of blood between the aorta and the finger, rather than the input impedance of the MCA. In addition, the incorporation of more parameters frequently leads to instability and unacceptable variability in parameter values. Using intra-aortic ABP measurements, Panerai et al. (19) studied pressure-velocity relationships in neonates, examining the significance of different mathematical models. The most robust model obtained was the RAP + CCP model adopted in the present study. Higher-order dynamic models, which can represent the contribution of compliance and inductance, or quadratic static models, frequently fail to produce statistically significant parameter values, which tend to have very large coefficients of variation (19). These problems stem from the fact that these models depend on the calculation of first- and second-order derivatives of the pressure and velocity waveforms, which are frequently corrupted by noise. Nevertheless, a parameter equivalent to the CCP can also be extracted from these models, albeit with a much higher coefficient of variation (19). The robustness of the two-parameter model adopted is well expressed by the correlation coefficient of the linear regressions, exemplified in Fig. 1B, which
is typically in the range 0.85–0.95. The consistency of the RAP + CCP model is reflected in the population values presented in Table 1.

Increases in CCP, as estimated during phases I and II (Fig. 2C), are equivalent to a reduction in perfusion pressure (i.e., MABP − CCP). This reduction in the effective perfusion pressure can be caused by different factors, the most obvious being an increase in intracranial pressure (ICP); Fry et al. (8) demonstrated a significant reduction in perfusion pressure at the Vein of Galen (i.e., the collapsible interface between the intracerebral venous system and the “rigid” venous sinuses linking with the extracerebral venous circulation) in studies using baboons in situations of raised ICP. However, Greenfield et al. (12) observed relatively small changes in ICP during the VM, compared with the large changes observed in CCP (see Fig. 2C). Also important is whether the peripheral MABP we are measuring with the Finapres reflects the true arterial pressure in the MCA. With the increase in intrathoracic pressure and subsequent reduction in stroke volume during phase II, it is conceivable that MCA pressure will fall more than aortic pressure. However, Greenfield et al. (12), who measured MABP invasively via a catheter in the common carotid artery (i.e., centrally), found changes of similar magnitude to the peripheral values obtained in this study. It is also conceivable that cerebral venous pressure will consequently rise above ICP, further contributing to a fall in perfusion pressure; both of these factors will lead to a substantial increase in the value of CCP that is calculated.

Furthermore, it is conceivable that posture might modify the responses we have observed. Because of the TCD measurement, we placed our subjects in the supine position with the head elevated. However, if the VM is performed in the upright position, the corresponding changes in venous return, transmission of the intrathoracic pressure to the cerebral circulation, and autonomic nervous system responses might lead to significant differences in the time course of CBFV, CCP, and RAP. Future work will be necessary to estimate the relative contribution of these different factors; it is clear, however, that the contribution of the effective perfusion pressure, and hence CCP, in the hemodynamic changes seen in the cerebral circulation secondary to the VM cannot be ignored.

Other possible confounding factors include the influence of changes in PCO2 during the VM. We monitored PCO2 by using the TINA (5, 14) (Radiometer), and this did not detect any change, but its temporal resolution may not be sufficient to detect changes over 1–2 min in keeping with the blood pressure findins during the VM; however, Myer et al. (15) previously found that, in the time window of 15–20 s, there is a 2-mmHg change in PCO2, which might be expected to trigger vasodilation and could explain the gradual reduction in RAP during phases I–III (Fig. 2D). We have also not considered whether the diameter of the MCA is constant during the VM, i.e., whether changes in MCA volume to reflect changes in CBFV are a valid methodology in this situation. During validation studies of TCD, no change was found in MCA diameter during CA, and therefore changes in velocity are extrapolated to represent changes in CBF (10). However, to our knowledge, the effect of the VM in particular has not been assessed; because we used noninvasive methods, we are unable to comment on this.

The physiological changes we are detecting may also be altered by advancing age (the majority of our subjects being elderly); however, Tiecks et al. (23) studied younger subjects and found the same MABP and CBF changes, although CCP per se was not assessed.

In conclusion, CCP of the cerebral circulation has been previously studied in animals (6) and humans (16, 19–21) because it provides a more accurate model for instantaneous pressure-velocity relationships that tend to intersect the pressure axis at values significantly > 0 (3, 16). We have demonstrated, in a large group of subjects, that this parameter provides a coherent explanation for the dynamics of CBFV in response to the VM and that, unless this parameter is taken into account, assessment of autoregulation on the basis of the VM will lack a sound physiological basis and might produce misleading results. In addition, estimates of cerebral vascular resistance (or RAP) (RAP(z)) do not show the aberrant sudden changes displayed by classical estimates (RAP(z)), which ignore this parameter. Because of its close relationship to physiological changes of the cerebral circulation, the RAP(z) parameter has potential to grade the performance of CA during the response to the MABP overshoot in phase IV of the VM (21).

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