Can Cerebrovascular Reactivity Be Assessed Without Measuring Blood Pressure in Patients With Carotid Artery Disease?

J. Dumville, PhD; R.B. Panerai, PhD; N.S. Lennard, MBChB; A.R. Naylor, MD; D.H. Evans, PhD

Background and Purpose—Conventional methods of assessing cerebrovascular reactivity (CVR) omit the influence of blood pressure (BP). This study demonstrates the significant influence of BP during the assessment of CVR in patients with carotid artery disease.

Methods—In 56 subjects the CVR was bilaterally assessed by measurement of cerebral blood flow velocity change in response to inhalation of 5% CO₂ in air while BP was continuously monitored. Three methods of calculating the CVR were used: the conventional ratio between relative cerebral blood flow velocity and end-tidal CO₂, simple linear regression, and multiple linear regression analysis (MLRA). The clinical significance of the difference in CVR indices was evaluated. The Bland-Altman test was applied to quantify the comparability and bias between measurements. The magnitude and significance of a change in BP during the CVR assessment were calculated in conjunction with an estimate of the velocity change attributed to the BP. The statistical significance of the data segment length on the variability and magnitude of the CVR index was computed.

Results—The value of the CVR index was reduced by 20% and 6% in comparison to the conventional ratio approach when MLRA and linear regression were applied, respectively. With the use of MLRA, in 96% of cases the value of the BP coefficient was statistically significant, and in four patients the increase in velocity was primarily attributed to the increase in BP.

Conclusions—The influence of BP is significant and requires consideration when the CVR index is calculated in patients with carotid artery disease. (Stroke. 1998;29:968-974.)

Key Words: blood pressure • carotid artery diseases • cerebrovascular reactivity

Patients with a compromised CVR are more likely to develop ischemic events.¹ These patients may benefit from therapeutic measures improving large-vessel flow, such as CEA or other revascularization techniques. Distal to a severe internal carotid artery stenosis, the brain is usually able to maintain normal CBF by recruitment of the cerebral collateral circulation. When this fails, the brain is usually still able to maintain perfusion by progressive dilation of low-resistance arterioles, albeit at the expense of an increasingly compromised CVR.

Investigation of the CVR capacity by regional CBF measurements and positron emission tomography is used to evaluate the efficiency of the collaterals.² Another simple noninvasive technique is the Doppler CO₂ test. Typically, a CVR index is expressed that characterizes the response of the CBF to a change in ETCO₂ with several segments of steady state data.³ Frequently no reference is given to the change in systemic BP, which is inevitable from the positive inotropic effect of CO₂ on the heart.⁴ However, some authors record the BP changes and then dismiss the effect as nonsignificant.¹⁵⁶ In contrast, Gur et al⁷ acknowledge the potential influence of the BP by removing any large changes in BP.⁷

This study questions the conventional methodology of assessing the CVR index with the purpose of highlighting the influence of BP.

Subjects and Methods

Clinical Subjects
Fifty-six patients undergoing CEA in the vascular unit of the Leicester Royal Infirmary National Health Service Trust were included in the study. The study was approved by the Leicester Health Authority Ethical Committee, and informed consent was obtained from all patients. The patients’ mean age was 67±8 years, and 70% were men. From a potential total of 112 MCAs, 85 arteries were studied. The remaining 24% of arteries were not included in the study because of the absence of an acoustical window in the temporal bone or technical problems. The study includes patients with unilateral and bilateral stenoses and occlusions of the contralateral extracranial internal carotid artery (18 stenoses with ≤50% diameter reduction [non–flow limiting], 56 stenoses with >50% diameter reduction [of which 24 arteries had >80% stenosis], and 11 occlusions). The grading of stenosis was based on Doppler velocities in combination with B-mode imaging.

Doppler Examination
TCD was used to assess the blood flow velocity in the MCA by insonating the transtemporal window. Ultrasonic gel was used to...
acoustically couple the Doppler probe to the skin. MCA Doppler signals were identified at depths of 45 to 55 mm and characterized by flow toward the transducer. Optimization of the Doppler signal was achieved by slight lateral and angular shifting of the probe in the anterior direction. A bilateral TCD examination was performed with a Sci-med Doppler instrument with 2-MHz Doppler probes with the patient in the supine position and head elevated. Both TCD probes were securely fixed in position throughout the assessment with the use of separate head probe systems (elasticized head bands attached with a hook and loop faster). The audio outputs of the TCD were continuously recorded onto DAT throughout the assessment.

BP Assessment

The arterial BP was indirectly measured throughout the test with the noninvasive Finapres (Ohmeda 2300). The finger cuff was positioned on the side of the patient common to the site of the subsequent CEA operation.

CVR Assessment

To avoid feelings of suffocation, the patients were asked to fit the mask tightly by themselves so that they would be able to remove it if fearful. The face mask is characterized by two nonreturn valves that allow the entrance of the inhalation gases and the outlet of exhaled gas. In addition, a sampling line was attached to the front of the face mask to enable constant monitoring of the CO2 level by an infrared CO2 analyzer (Datex Normocap 200).

For each patient a 6-minute cycle of recording events took place. The patient initially breathed ambient air to provide a 2-minute baseline, then an equal period of elevated ETCO2 was followed by an additional 2-minute air baseline. All four signals (right MCAV, left MCAV, BP, and CO2) were continuously recorded onto DAT for off-line analysis.

Data Processing

In-house software facilitates the extraction of the peak velocity envelope from the recorded quadrature phase signal and the simultaneous downloading of the recorded signals from DAT. The recorded signals were converted to a digital format at a rate of 200 samples per second onto a microcomputer. Data were low-pass filtered (20 Hz), and narrow spikes in the signals were detected and removed by linear interpolation. The filtered BP signal was used to estimate the RR interval and mark the beginning and end of each cardiac cycle. The mean values of CBFVs and BP were calculated for each respiratory cycle. The resulting beat-to-beat sequence of all four variables was interpolated with a third-order polynomial and resampled at intervals of 0.2 second to produce signals with a uniform time axis. Signals were further low-pass filtered at 0.5 Hz with the use of a Butterworth low-pass filter.

Calculation of the CVR Index

Three methods of measuring the CVR index (percentage per millimeter of mercury) were used. All methods use the ratio between the percent change in mean velocity relative to the air baseline velocity and the difference in ETCO2. Common to all methods, a pulse-seeking algorithm was used to detect the foot of both the CBFV and BP waveforms. The estimated time delay from the first 100 beats was used to realign the signals before analysis.

Method 1

The conventional ratio approach of utilizing two segments of data ( ~ 80-second duration) at constant levels of ETCO2 was adopted. The minimum accepted change in ETCO2 was 3.9 mm Hg: differences below this value produced distorted results because of the low signal-to-noise ratio. In addition, the distribution of changes in BP due to the elevation of ETCO2 was considered.

Method 2

The two additional methods of calculating the CVR index both use the complete 6-minute data segment and use regression analysis. This incorporates calculating cerebrovascular changes during rapid changes in ETCO2. In addition, Shapiro et al reported on the presence of hysteresis due to the delayed response of CBFV to a step change in PCO2. Hence, for each artery the time delay was estimated by the cross-correlation function peak position between CBFV and ETCO2. The estimated time delay was used to realign the CBFV and ETCO2 time series before analysis was performed.

The second method of assessing CVR utilizes simple regression analysis when CO2 is the independent variable and CBFV is the dependent variable.

Method 3

Finally, MLRA was performed when MABP and ETCO2 were used as independent variables and CBFV was used as the dependent variable.

The CVR indices were characterized by three categories of CO2 reactivity: sufficient, diminished, and exhausted.

To identify the extent to which the three methods agree, a correlation coefficient associated with a simple regression fit between data sets was calculated. In addition, the Bland-Altman procedure was applied to quantify the comparability and possible bias between measurements. First, the Bland-Altman procedure estimates a mean intermethod error (or bias), which is the mean (Dm) of all the individual errors (Di) within each pair of measurements of the same quantity. Second, if a normal distribution of the differences is assumed, a 95% confidence interval of Di is expressed by Dm ± 1.96(2Dm/ n)1/2. In addition, values for interindividual variability of CVR (mean±SD) are presented.

Further analysis was performed on the MLRA data. The magnitude of the BP coefficients was examined. In addition, the significance of the BP coefficient was determined by comparing the BP coefficient value to zero and applying the t test. A value of P < 0.05 was adopted as the criterion for statistical significance. In addition, the partial MABP-CBF, ETCO2-CBF, and MABP-ETCO2 correlation coefficients were estimated from the data. Also, for each data segment the contribution to the change in velocity attributed to the change in ETCO2 was calculated as the product of the absolute change in ETCO2 and the ETCO2 coefficient. A similar calculation was performed with the use of the BP data.

In addition, for a random subsection of patients (n=10) the conventional approach of extracting the CVR index was further investigated with respect to the length of the data segment utilized. Reactive indices were extracted with the use of different data segments (10, 20, and 40 beats), and a t test was adopted to assess the effect of data segment length on mean CVR index and its variability.

Results

A typical data segment is described in Figure 1. The MCAVs responded to a positive step in ETCO2, as did the BP. The distribution of the rise in BP resulting from the inhalation of 5% CO2 in air is described in Figure 2 and characterized by a mean±SD (range) increase of 7±7 mm Hg (−13 to
20 mm Hg). The CBFV response to hypercapnia began after an estimated delay of 4 seconds. The mean time delay between the pulse foot of the MABP and MCAV cardiac cycles was 90 ± 26 milliseconds when the first 100 beats in each individual data segment were compared.

The majority of patients had sufficient CVR ($\geq 84\%$) (Table 1). When the conventional ratio was used, 8 patients had compromised CVR; however, with the introduction of BP into the calculation, 6 more patients were identified to be hemodynamically at risk. The 8 patients with diminished and exhausted CO$_2$ reactivity as assessed by the conventional ratio all had severe carotid disease ($\geq 90\%$ stenosis). The 8 patients showing diminished CO$_2$ reactivity from the simple regression were not the same 8 patients showing deficient CO$_2$ reactivity as calculated by the conventional ratio. Indeed, only 2 patients were common to each group; however, both these patients had bilateral disease ($\geq 90\%$ stenosis).

Scatterplots showing the relationships between the CVR distributions as calculated by the three different methods are described in Figure 3 and characterized numerically in Table 2. The Bland–Altman test was applied to compare methods (Figure 4). The resultant mean error and confidence intervals are described in Table 3. MLRA and the conventional ratio were the least comparable methods: replacing the conventional ratio by the MLRA could decrease the CVR index by $-0.67\%$ (mean). The mean error values reflect the change in the mean CVR from the three analysis methods: conventional ratio (3.43 ± 1.50%/mm Hg), simple linear regression analysis (3.22 ± 1.28%/mm Hg), and MLRA (2.76 ± 1.20%/mm Hg). The use of simple linear regression and MLRA resulted in a 5% and 19% reduction in the resultant CVR index, respectively.

From the MLRA, the mean ± SD (range) value of the pressure coefficient was 0.49 ± 0.34%/mm Hg (2.14 to 1.40%/mm Hg). In 96% of cases the value of the BP coefficient was statistically significant. The partial CBF-MABP, CBF-ETCO$_2$, and MABP-ETCO$_2$ relationships yielded mean ± SD (range) partial correlation coefficients of $0.41 \pm 0.23$ (−0.41 to 0.78), $0.71 \pm 0.18$ (0.13 to 0.93), and $0.41 \pm 0.29$ (−0.41 to 0.79), respectively. The mean values of the partial correlation coefficients were statistically significant ($P < 0.001$). In addition, with the use of the individual MLRA equations, the changes in velocity induced by BP and ETCO$_2$ changes are described in Figure 5. A mean ± SD (range) increase in velocity of $19 \pm 11\%$ (2% to 70%) was induced by the change in ETCO$_2$, whereas the increase in BP contributed a mean ± SD (range) velocity increase of $4 \pm 5\%$ (−6% to 20%). The velocity increase introduced by the different mechanisms was significantly different ($P = 0.0000$). Some of the BP effects were negative (Figure 5). In 4 patients the

<table>
<thead>
<tr>
<th>CO$_2$ Reactivity</th>
<th>CVR, %/mm Hg</th>
<th>Conventional Ratio</th>
<th>Simple Regression</th>
<th>MLRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>$\geq 1.54$</td>
<td>77</td>
<td>77</td>
<td>71</td>
</tr>
<tr>
<td>Diminished</td>
<td>&lt;1.54</td>
<td>7</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Exhausted</td>
<td>&lt;0.77</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 2. Distribution of the change in mean BP induced by the inhalation of 5% CO$_2$ in air relative to air.

Figure 1. A typical data segment describing the cycle of events used to characterize the CVR. The right MCAV (RMCAV), left MCAV (LMCAV), and BP all responded to the enhancement of ETCO$_2$. 

Table 1. Classification of CO$_2$ Reactivity
increase in velocity was primarily attributed to the BP increase: 3 patients had bilateral disease (≥85% stenosis both sides), and 1 patient was characterized by a unilateral stenosis of 80%.

The effect of the data segment length on the CVR index was investigated (Table 4). The duration of the data segment did not affect the CVR index magnitude ($P_0.66$) but did influence the variability. An extension of the data segment from 10 to 40 beats significantly reduced the variability of the CVR index ($P_0.02$).

**Discussion**

Typically, it is the relationship between CBF and ETCO$_2$ that characterizes the CVR. Impairment of the collateral blood supply,\textsuperscript{15,16} status of pressure autoregulation,\textsuperscript{17} and intracranial pressure\textsuperscript{18} all affect the physiological response to a change in ETCO$_2$. The contribution of the BP to the CVR index is considered below.

When the CVR is assessed by a change in CBF relative to a change in P$_CO_2$, the influence of BP is not considered. Typically, a slight increase in mean BP of 7 to 12 mm Hg during CO$_2$ inhalation is reported in the literature.\textsuperscript{6,15,19–21} This is consistent with a mean rise in BP of 7 mm Hg (range, 213 to 20 mm Hg), as reported in this study. Smielewski et al\textsuperscript{22} reported an MABP increase of 13%; however, in one case the MABP rose by 193% of its baseline measurement.

The relationships between MABP and CBF\textsuperscript{23} and between CBF and P$_CO_2$\textsuperscript{24} are extensively documented. However, it is the interplay between CBF, BP, and P$_CO_2$ that requires further investigation. Harper and Glass\textsuperscript{25} described a greater reactivity in dogs with MABPs of 150 mm Hg than in dogs with

**TABLE 2. Comparison of the Three Tests by Simple Regression Fit and Correlation Coefficient**

<table>
<thead>
<tr>
<th>Tests Compared</th>
<th>Simple Regression Fit</th>
<th>Correlation Coefficient</th>
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</thead>
<tbody>
<tr>
<td>MLRA/conventional ratio</td>
<td>$y=1.00x+0.67$</td>
<td>.64</td>
</tr>
<tr>
<td>Simple regression/MLRA</td>
<td>$y=0.84x+0.07$</td>
<td>.79</td>
</tr>
<tr>
<td>Simple regression/conventional ratio</td>
<td>$y=1.02x+0.16$</td>
<td>.75</td>
</tr>
</tbody>
</table>

Figure 3. Comparison of CVR as estimated by three different methods: (A) MLRA vs conventional ratio, (B) simple regression vs MLRA, and (C) simple regression vs conventional ratio. All CVR indices describe the change in relative velocity per unit change of ETCO$_2$ (%/mm Hg).
MABP of 100 mm Hg. Since canine BP is similar to that of humans, it was translated that hypertensive patients would yield a greater CVR index in comparison to analogous normotensive counterparts.

To include BP in the calculation of CVR, MLRA was adopted from Menke et al,13 who applied the technique to preterm infants. MLRA facilitates the simultaneous evaluation of cerebral autoregulation and CO2 reactivity.

The use of MLRA for the assessment of CVR results in a 20% mean reduction in the CVR index. The clinical relevance of introducing the BP must be justified. In a healthy person (no vascular disease, intact cerebral autoregulation, intact collateral flow, normal intracranial pressure) the CVR assessment as determined by the relative changes in velocity and ETCO₂ will be independent of pressure provided that the pressure change is contained within the autoregulatory plateau (of constant gradient) and the change in ETCO₂ displaces the velocity reading along a constant gradient line. However, if any of these conditions is violated, the influence of pressure is potentially relevant. For example, in patients with carotid artery disease, the resistance arteries of the brain become maximally dilated above a critical stenosis. Breathing increased levels of inspired CO₂ may increase the CBF as a consequence of passive autoregulation and not active vasodilation.17 Indeed, in 4 patients in this study the increase in velocity on breathing 5% CO₂ in air was primarily attributed to BP. In addition, the effect of removing the influence of the MABP to the rise in CBFV identifies an additional 6 patients at hemodynamic risk (Table 1). The distinction between active vasodilation and passive autoregulation would identify patients at risk of hypoperfusion and stroke in the face of reductions in arterial BP.26 In addition, the status of pressure autoregulation and CVR would aid the comprehension of

<table>
<thead>
<tr>
<th>Tests Compared</th>
<th>Mean Error</th>
<th>Confidence Interval</th>
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<tbody>
<tr>
<td>MLRA/conventional ratio</td>
<td>-0.67</td>
<td>-0.87 to -0.47</td>
</tr>
<tr>
<td>Simple regression/MLRA</td>
<td>0.46</td>
<td>0.34 to 0.58</td>
</tr>
<tr>
<td>Simple regression/conventional ratio</td>
<td>-0.21</td>
<td>-0.37 to -0.05</td>
</tr>
</tbody>
</table>

Mean error relates to a mean intermethods error (bias). Confidence interval is defined as the 95% confidence interval of the bias.
post-cea hypertension and hyperperfusion syndromes, which are a cause of postoperative morbidity. Indeed, the influence of BP can define the condition. After traumatic brain injury, the influence of BP on CO2 reactivity was used to distinguish between ischemia and hyperperfusion.

The delay between end-tidal and CBFV response (4 seconds) compares favorably with a 6-second delay described previously by Poulin et al. The time delay between the pulse foot of the MABP and MCAV cardiac cycles is due to the different sites of variable detection: a site of synchronous detection would result in zero delay.

From the calculations of CVR in which data segments of different lengths were used, it was demonstrated that the longer segments reduce uncertainty in the CVR index as a result of the smoothing of fluctuations in the MCAV. Additionally, uncertainties in the CVR are inevitable because of the indirect measurement of the CBF, arterial BP, and arterial blood gas during changes in PCO2. Although the noninvasive finger pressure measurement was applied previously to monitor BP during inhalation of 5% CO2 in air, its validation during vasodilation can only be extrapolated from its accuracy during vasoconstriction. Further uncertainty regarding the value of the CVR index may be introduced if assumptions fundamental to the accurate application of TCD are violated, ie, the angle of incidence between the probe and the associated coefficient from the MLRA divided by the cross-sectional area of the MCA remains constant. Intraindividual variability removes the necessity of having segments of steady state data. In patients with carotid artery disease the influence of BP was statistically significant in 96% of patients, and in 4 subjects it primarily caused the increase in velocity. Indeed, the application of MLRA identified 6 additional patients as hemodynamically compromised. Furthermore, the application of MLRA would potentially allow the dissociation between cerebral autoregulation and CO2, thus allowing those patients most at risk of stroke and post-cea hypertension and hyperperfusion syndromes because of a hemodynamic compromise to be identified and managed accordingly.

TABLE 4. Mean CVR and Cumulative Variance for Measurements With the Same Data Segment Length

<table>
<thead>
<tr>
<th>Estimation Window, beats</th>
<th>CVR Index, %/mm Hg</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3.57 ± 1.06</td>
<td>28.70 ± 11.76</td>
</tr>
<tr>
<td>20</td>
<td>3.65 ± 1.01</td>
<td>20.60 ± 6.85</td>
</tr>
<tr>
<td>40</td>
<td>3.45 ± 0.97</td>
<td>17.00 ± 9.09</td>
</tr>
</tbody>
</table>

Variability is defined as the SD relative to the mean. Values are mean ± SD.

Figure 5. Comparison of the relative velocity changes (%) induced by a change in ETCO2 and BP. Relative velocity changes were calculated as the product of the absolute change and the associated coefficient from the MLRA divided by the mean baseline CBFV and expressed as a percentage. The graph describes patients with sufficient (○) and deficient (■) CO2 reactivity.

References


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