Assessment of Cerebrovascular Autoregulation in Head-Injured Patients
A Validation Study

Luzius A. Steiner, MD; Jonathan P. Coles, FRCA; Andrew J. Johnston, FRCA; Doris A. Chatfield, BSc; Peter Smielewski, PhD; Tim D. Fryer, PhD; Franklin I. Aigbirhio, PhD; John C. Clark, PhD, DSc; John D. Pickard, MChir, FRCS, FMedSci; David K. Menon, MD, PhD, FRCA, FRCP, FMedSci; Marek Czosnyka, PhD, DSc

Background and Purpose—Cerebrovascular autoregulation is frequently measured in head-injured patients. We attempted to validate 4 bedside methods used for assessment of autoregulation.

Methods—PET was performed at a cerebral perfusion pressure (CPP) of 70 and 90 mm Hg in 20 patients. Cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR O₂) were determined at each CPP level. Patients were sedated with propofol and fentanyl. Norepinephrine was used to control CPP. During PET scanning, transcranial Doppler (TCD) flow velocity in the middle cerebral artery was monitored, and the arterio-jugular oxygen content difference (AJD O₂) was measured at each CPP. Autoregulation was determined as the static rate of autoregulation based on PET (SROR PET) and TCD (SROR TCD) data, based on changes in AJD O₂, and with 2 indexes based on the relationship between slow waves of CPP and flow velocity (mean velocity index, Mx) and between arterial blood pressure and intracranial pressure (pressure reactivity index, PRx)

Results—We found significant correlations between SROR PET and SROR TCD (r²=0.32; P<0.01) and between SROR PET and PRx (r²=0.31; P<0.05). There were no significant associations between PET data and autoregulation as assessed by changes in AJD O₂. Global CMR O₂ was significantly lower at the higher CPP (P<0.01).

Conclusions—Despite some variability, SROR TCD and PRx may provide useful approximations of autoregulation in head-injured patients. At least with our methods, CMR O₂ changes with the increase in CPP; hence, flow-metabolism coupling may affect the results of autoregulation testing. (Stroke. 2003;34:2404-2409.)

Key Words: autoregulation | brain injuries | monitoring, physiologic | tomography, emission computed
TABLE 1. Patient Characteristics

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<td>4.01±0.15</td>
<td>92±4 mmHg</td>
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</table>

Day indicates day after injury; GCS, admission GCS; CT, classification based on CT; GOS, Glasgow Outcome Scale; Paco2, mean±SD of 2 CBF scans; EML, evacuated mass lesion; MD, moderate disability; DII/III, diffuse injury II/III; GR, good recovery; SD, severe disability; NA, outcome data not available; and D, dead.

important to validate the techniques we currently use to determine autoregulation. So far, some of these methods have been compared against each other,3,12–14 and Larsen et al15 have validated TCD for determination of the lower limit of autoregulation in healthy volunteers. However, there has been no validation of these methods in brain-injured patients against a gold standard such as PET.

By simultaneously measuring autoregulation with bedside methods and with PET, we attempted to validate 4 bedside methods to determine autoregulation in acutely head-injured patients: the static rate of autoregulation (SROR) based on TCD, a method based on AJDO2, and 2 methods based on waveform analysis.

Patients and Methods

The local research ethics committee approved this study. Informed consent was obtained from the next of kin of all patients. All patients admitted to our Neurosciences Critical Care Unit with severe (admission Glasgow Coma Score [GCS] ≤8) or moderate (admission GCS ≤12) traumatic brain injury, with secondary neurological deterioration requiring intubation and mechanical ventilation, were eligible for inclusion in this study. Exclusion criteria were rapidly changing requirements of vasoactive drugs and unstable intracranial pressure (ICP). Patients requiring a fraction of inspired oxygen >50% were excluded to avoid a low signal-to-noise ratio during 18O2 PET imaging.

Twenty patients were investigated. Mean patient age was 33±15 years; scans were performed 2.7±1.1 days after injury, and median admission GCS was 6.5. Individual patient data are shown in Table 1. All patients were intubated and mechanically ventilated, sedated with propofol (2 to 5 mg·kg⁻¹·h⁻¹) and fentanyl (1 to 2 μg·kg⁻¹·h⁻¹), and paralyzed with atracurium. Infusion rates of these drugs were not changed during scanning. Patients had variable degrees of therapy for intracranial hypertension, including sedation, moderate hypothermia (34°C to 37°C), surgical evacuation of space-occupying lesions, and barbiturate infusions (2 patients). However, no patient had received mannitol or hypertonic saline within the 6 hours preceding the study. All patients required catecholamines to maintain baseline CPP. Mean arterial pressure (MAP) and ICP were monitored by use of standard kits for invasive blood pressure monitoring (Baxter Healthcare Corp, CardioVascular Group) and intraparenchymal pressure transducers (Codman MicroSensors ICP Transducer, Codman & Shurtleff Inc).

Two sets of PET scans were performed, each assessing CBF and CMRO2. CPP was controlled with an infusion of norepinephrine that was adjusted to reach the desired CPP and then as necessary to keep CPP constant during scanning. The first scan (baseline) was carried out at a CPP of 69±6 mm Hg; the second (intervention), at a CPP of 92±4 mm Hg. Because of the change in CPP, ICP increased from 18±6 to 19±6 mm Hg (P<0.01). Arterial partial pressure of CO2 (Paco2) was measured at 5 time points during each scan, and Paco2 was kept stable by adjusting the ventilator as necessary. Variability of Paco2 during acquisition of CBF data for individual patients is shown in Table 1. The precision of Paco2 control is limited not only by the respiratory status of the patients but also by the precision of the blood gas analyzer. For all blood gas measurements, an AVL Omni blood gas analyzer (AVL Graz, A-8020 Austria) was used. The total precision of this analyzer according to NCCLS document EP0-T is SD <0.27 kPa (personal communication, J. Riegebauer, AVL Graz, 2002). Paco2 during the baseline scan was 4.41±0.33 kPa and during the intervention scan was 4.48±0.34 kPa (P=0.07).

Patient temperature was kept constant with the use of a heating/cooling mattress at the level desired by the team responsible for the clinical management. Patient temperature at baseline and at intervention was 35.4±0.7°C (P<0.04).

PET Methods

The studies were undertaken on a General Electric Advance scanner (GE Medical Systems). The steady-state protocol used has been described in detail previously.16 Emission images were coregistered to spiral CT images obtained immediately after PET scanning. All emission data were normalized to Talairach space.17 CBF and CMRO2 were calculated globally and from the middle cerebral artery (MCA) territory for each hemisphere separately. The MCA territory was defined using high specificity at the cost of sensitivity: All pixels included had a very high probability of being perfused by the MCA, although some pixels that may have been within the MCA territory in individual patients may have been excluded.18

Transcranial Doppler

Bilateral TCD (DWL Multidop X4, DWL Elektronische Systeme GmbH) of the MCA was performed throughout scanning with two 2-MHz probes held in place with a head rack.19 Phantom testing carried out in the PET scanner before the patient studies established that there were no image artifacts caused by the ultrasound probes and head rack.

Determination of Autoregulation

For comparison of PET- and TCD-based determinations of autoregulation, SROR was used.20 SROR is calculated as the percent change in cerebral blood flow divided by the percent change in CPP used to induce the change in resistance. Results are expressed as percentage, with 0% representing complete autoregulatory failure and 100% representing optimal autoregulation. The formula is shown in the Appendix, which is available online at http://stroke.ahajournals.org. For calculation of SROR based on PET data (SRORPET), CBF from the MCA territory and CPP were used as inputs into the formula. SRORPET was calculated using mean flow velocity (FVm) instead of CBF. For comparison of PET and TCD, only FVm and CPP acquired during the phase of the PET scan during which CBF data were acquired were used.
During both scans, AJD\textsubscript{O2} was calculated from paired arterial and jugular blood samples withdrawn immediately before the H\textsubscript{2}O infusion was started and used to calculate the percent change in CBF. According to the Fick principle, if CMR\textsubscript{O2} is constant, then the percentage decrease in AJD\textsubscript{O2} will equal the percentage increase in CBF, which can be compared with the percent change in global CBF as measured by PET. The formula is shown in the Appendix.

Two methods based on waveform analysis were investigated. The first method calculates an index of pressure reactivity from the analysis of spontaneous slow waves of MAP and ICP. Average values of MAP and ICP were calculated for 6-second intervals and used to calculate a pressure reactivity index (PRx) every 60 seconds as the linear moving correlation coefficient between 40 consecutive values of MAP and ICP. Possible values therefore range from −1 to 1. Negative or zero values indicate intact pressure reactivity; positive values indicate disturbed pressure reactivity. Pressure reactivity is a key component of autoregulation, and intact autoregulation implies intact pressure reactivity. The second method calculates a mean velocity index\textsuperscript{*} (Mx). This index is based on changes in FVm in the MCA evoked by spontaneous slow waves of CPP. The same algorithm is applied as described above for calculation of PRx, but FVm and CPP are used as input functions. Possible values range from −1 to 1. Mx = 0 represents intact autoregulation; Mx > 0 implies impaired autoregulation. For comparisons between PET data and PRx or Mx, the last 2 variables were averaged over the complete duration of scanning at the higher level of CPP (≈90 mm Hg), because sampling over longer time periods improves the estimation of these parameters. The value at the higher CPP was chosen because these measures of dynamic autoregulation would clearly have been nonconcordant at the 2 CPP levels and a consideration of cerebrovascular physiology shows that dynamic measures at the higher CPP value more closely represent the SROR that interrogated autoregulatory efficiency across the interval of CPP values that we have been nonconcordant at the 2 CPP levels and a consideration of technical problems prevented us from collecting CMR\textsubscript{O2} data; therefore, CMR\textsubscript{O2} data from 18 patients were available for analysis. For comparisons between PRx and PET CBF, global CBF was used, whereas MCA territory CBF was used for the comparison with Mx.

Data were sampled from the analog output of the hemodynamic monitors, processed through an analog-to-digital converter (DT 2814, Data Translation Marlboro), and stored on a computer using software developed in house. Sampling frequency was 30 Hz. Time-averaged means for MAP, ICP, and CPP (CPP = MAP – ICP) were calculated and stored every 6 seconds. In 1 patient, we were unable to insonate the left MCA; therefore, for comparisons between TCD and PET, data from 39 hemispheres were available. Because of unavailability of monitoring equipment, data from 17 patients were available for comparisons between PRx, Mx, and PET. In 2 patients, technical problems prevented us from collecting CMRO\textsubscript{2} data; therefore, CMRO\textsubscript{2} data from 18 patients were available for analysis. Data are presented as mean ± SD unless otherwise indicated. Linear correlations and Bland Altman plots were used to assess associations and agreement of measurement methods as appropriate. Calculations were performed with SPSS 11.0 (SPSS Inc.). A value of \( P < 0.05 \) was considered statistically significant.

### Results

PET and TCD data are presented in Table 2. TCD FVm correlated significantly with PET CBF in both hemispheres (CPP = 70 mm Hg: left, \( r^2 = 0.24, P = 0.03 \); right, \( r^2 = 0.33, P < 0.01 \); pooled, \( r^2 = 0.23, P = 0.002 \); CPP = 90 mm Hg: left, \( r^2 = 0.33, P = 0.01 \); right, \( r^2 = 0.36, P < 0.01 \); pooled, \( r^2 = 0.34, P = 0.0001 \); Figure 1). However, there was marked variability that limits the usefulness of TCD as an estimator of absolute CBF. The change in CBF correlated with the change in FVm (left, \( r^2 = 0.48, P = 0.001 \); right, \( r^2 = 0.42, P < 0.01 \)). There was a significant correlation between \( \text{SROR}_{\text{TCD}} \) and \( \text{SROR}_{\text{TCD}} \) (left, \( r^2 = 0.53, P < 0.001 \); right, \( r^2 = 0.32, P < 0.01 \)), suggesting that \( \text{SROR}_{\text{TCD}} \) is a useful approximation of autoregulation within the MCA territory (Figure 2a). The Bland Altman plot

### Table 2. Physiological Data

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<tr>
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<th>Baseline</th>
<th>Intervention</th>
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<tr>
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<td>35.9 ± 7.2</td>
<td>38.9 ± 9.3</td>
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<td>CBF (MCA), mL \cdot 100 mL\textsuperscript{−1} \cdot min\textsuperscript{−1}</td>
<td>34.8 ± 7.7</td>
<td>37.5 ± 9.6</td>
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<tr>
<td>FVm, cm \cdot s\textsuperscript{−1}</td>
<td>63.9 ± 19.4</td>
<td>84.1 ± 16.9</td>
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<td>( \Delta \text{CBF} ), mL \cdot 100 mL\textsuperscript{−1} \cdot min\textsuperscript{−1}</td>
<td>2.7 ± 3.9</td>
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<tr>
<td>( \Delta \text{FVm} ), cm \cdot s\textsuperscript{−1}</td>
<td>10.6 ± 7.5</td>
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<tr>
<td>( \text{SROR}_{\text{TCD}} %),</td>
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<td>( \text{SROR}_{\text{TCD}} %),</td>
<td>44.2 ± 29.0</td>
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</table>

Data are presented as mean ± SD. FVm values represent data collected during PET CBF measurements.

(Figure 2b) shows that \( \text{SROR}_{\text{TCD}} \) measurements are on average 30% lower than \( \text{SROR}_{\text{PET}} \) measurements, and again there is a large variability.

AJD\textsubscript{O2} at baseline was normal or low, making global ischemia unlikely. However, increases in CPP resulted in a significant fall in AJD\textsubscript{O2} (4.0 ± 1.2 to 3.2 ± 1.1 mL \cdot dL\textsuperscript{−1}; \( P < 0.001 \)), implying poor flow-metabolism coupling. There was no significant relationship between the estimated percent change in CBF based on AJD\textsubscript{O2} and the percent change in global CBF determined by PET (\( P = 0.6 \)).

PRx was significantly associated with global \( \text{SROR}_{\text{PET}} \) (\( r^2 = 0.31, P = 0.02 \)), with the relationship very close for low values of SROR but less so for those >80% (Figure 3). There was no significant relationship between \( \text{SROR}_{\text{PET}} \) and Mx in either hemisphere.

The correlation between PET and TCD did not appear to be confounded by the presence of lesions within the MCA territory. When MCA territories were grouped as lesioned or not lesioned, the association for each subset was not significantly different from that observed in MCA territories without a lesion.

Global CMR\textsubscript{O2} decreased significantly when CPP was raised (73.2 ± 12.5 versus 69.1 ± 9.8 μmol \cdot 100 mL\textsuperscript{−1} \cdot min\textsuperscript{−1}; \( P = 0.008 \)). Within the MCA territories, CMRO\textsubscript{2} decreased significantly in nonlesioned (79.5 ± 14.0 versus 76.5 ± 10.1 μmol \cdot 100 mL\textsuperscript{−1} \cdot min\textsuperscript{−1}; \( P = 0.03 \)) and lesioned (66.3 ± 13.2 versus 62.8 ± 12.2 μmol \cdot 100 mL\textsuperscript{−1} \cdot min\textsuperscript{−1}; \( P = 0.04 \)) regions of interest. The reduction in MCA territories containing lesions was not significantly different from that observed in MCA territories without a lesion.

### Discussion

We found that some but not all beside measurements provide useful estimates of autoregulation. However, we observed a large variability even when significant associations were present. CMRO\textsubscript{2} was not identical at the 2 levels of CPP; thus, measurements may reflect not only autoregulation but also variable\textsuperscript{25} flow-metabolism coupling.

Our study has 2 major methodological limitations. First, we use a very specific, albeit standard, clinical management strategy. This limits the transfer of our results to centers that use distinctly different management strategies. The second...
important limitation is that, because of the precision of PET, which is strongly influenced by the low signal-to-noise ratio of the method, interpretation of results in patients with small changes in CBF, ie, good autoregulation, may be difficult. Despite reasonable overall agreement of data, measurements in patients with good autoregulation and therefore small changes in CBF are more likely to be influenced by noise. With our PET methods, the SD of repeated CBF measurements under constant physiology from the MCA territory in head injured patients is 1.7 mL \cdot 100 mL^{-1} \cdot \text{min}^{-1} \cdot 100 (unpublished data). This is illustrated in Figure 4, which shows that the agreement between PET and TCD measurements of SROR is better when patients with very low changes in CBF are excluded. This is further supported by Figure 3, which shows that the relationship between PET and PRx is close for low values of SROR but less so for high values of SROR. This suggests that a comparison of methods in patients with good autoregulation is affected not only by the sensitivity of the bedside methods to detect small changes in CBF but also by the precision and signal-to-noise ratio of PET. This also shows that it would be impossible to perform a validation in healthy volunteers with our methods.

Our data suggest that the percent change in AJD{O_2}^{-1} is not a reliable estimator of changes in CBF and therefore not a useful estimator of autoregulation. This may be due in part to the fact that the key assumption of constant CMRO{2} was not fulfilled. These changes in CMR{O_2} associated with norepinephrine-induced CPP increases were often small but may be

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**Figure 1.** Relationship between CBF and blood flow velocity. CBF was measured with PET. All measurements were made at a CPP of \( \sim 70 \) mm Hg. Dashed line represents linear regression function for pooled data.

**Figure 2.** Relationship between static rate of autoregulation measured by PET and TCD. Dashed line represents linear regression function for pooled data. Despite the significant correlation between PET and TCD, the Bland Altman plot (b) shows marked variability. This could limit the usefulness of the TCD-based assessment. However, much of this variability is due to data points in the higher range of SROR. The reason for this could be that measurements of small changes in CBF are strongly influenced by the low signal-to-noise ratio of PET.
particularly relevant with respect to estimates of autoregulation based on metabolism (e.g., AJD O_2 measurements) as opposed to those based purely on an estimate of CBF (e.g., SROR_{TCD}).

We have not been able to validate Mx. There are several possible explanations for this. Earlier work has shown a close correlation between Mx and PRx, which was not present in this group of patients. A selection bias could therefore have influenced our results. Alternatively, the number of investigated patients could be too low to establish this relationship. However, we suspect that our methods have prevented us from establishing a relationship between Mx and changes in PET CBF. Mx depends on spontaneous slow fluctuations of CPP of at least 5 mm Hg to elicit changes in FVm, whereas we tried to keep CPP as stable as possible and possibly suppressed the necessary slow waves to a relevant extent or created overly abrupt changes in CPP with some of the changes in the norepinephrine infusion rate. Our results suggest that an index based on MAP and ICP is more robust than one based on FVm and CPP. This is supported by data from another group that also used waveform analysis for quantification of autoregulation.

The decrease in CMR O_2 that we observed with the increase in CPP is unexpected. For CMR O_2, the SD for repeated scans is 1.3 µmol · 100 mL^{-1} · min^{-1} (unpublished data); therefore, the reductions, albeit small, are likely not to be due to the limited sensitivity or noise of the PET scan. We can only speculate on the reasons for this decrease in CMR O_2. One possible explanation is that the CMR O_2 changes are due to the clinical management, with propofol delivery increased at the higher CPP. Alternatively, it could be a specific effect of norepinephrine or of a disrupted blood-brain barrier. Regard-

Figure 3. Relationship between static rate of autoregulation measured by PET and PRx.

Figure 4. Effect of small changes in CBF. This Bland Altman plot illustrates the effect of small changes in CBF and their influence on the agreement between SROR measured with TCD and PET. Excluding CBF changes <1.7 mL · 100 mL^{-1} · min^{-1} improves the agreement considerably. Axes are scaled as in Figure 2b to enable direct comparison.
less of the underlying mechanism, this reduction in CMRO₂ is likely to lead to a reduction in CBF and thus an overestimation of autoregulation. The extent of the error will depend on the degree of flow-metabolism coupling, which may be disrupted to a variable degree after head injury. Bedside methods do not allow us to quantify this reliably.

In conclusion, the static rate of autoregulation calculated from TCD data and PRx provide useful information on autoregulation in head-injured patients. Studies grading autoregulation on that basis of changes in AJDO2 need to be interpreted with caution. PRx seems to be a more robust estimator of autoregulation than Mx. More data are needed to validate Mx. At least when our methods are used, all measurements may be influenced by flow-metabolism coupling.

Acknowledgments

Dr. Steiner was supported by a Myron B. Laver Grant (Department of Anesthesia, University of Basel, Switzerland), by a grant from the Margaret and Walter Lichtenstein-Stiftung (Basel, Switzerland), and by the Swiss National Science Foundation; he was recipient of an Overseas Research Student Award (Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom). Dr. Colles was funded by a Wellcome Research Training Fellowship and by a Beverley and Raymond Sackler Studentship Award. Dr. Johnston was supported by a grant from Codman. Dr. Czosnyka is on leave from the Warsaw University of Technology, Poland. This project was supported by the UK Government Technology Foresight Initiative and the Medical Research Council (Grant No G9439390 ID 65883). We thank Dr. Neil Harris (Academic Neurosurgery and Centre for Brain Repair, University of Cambridge, UK) for supplying the middle cerebral artery territory templates.

References

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*Stroke*. 2003;34:2404-2409; originally published online August 28, 2003;
doi: 10.1161/01.STR.0000089014.59668.04

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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