Assessment of the Thigh Cuff Technique for Measurement of Dynamic Cerebral Autoregulation

Peter J. Mahony, MSc; Ronney B. Panerai, PhD; Stephanie T. Deverson, MSc; Paul D. Hayes, MBChB; David H. Evans, PhD

Background and Purpose—Dynamic methods of measuring cerebral autoregulation have become an accepted alternative to static evaluation. This article aims to describe a set of data collected from healthy volunteers by a dynamic method, the purpose being to qualify and quantify expected results for those who may be designing a study using this technique.

Methods—Cerebral blood flow velocity (CBFV) (measured by transcranial Doppler) and arterial blood pressure (Finapres) were recorded in 16 normal subjects before, during, and after the induction of a blood pressure drop (release of bilateral thigh cuffs). This procedure was repeated 6 times for each subject. A mathematical model was applied to the data to generate an autoregulatory index (ARI) with values between 0 and 9.

Results—The ARI values for this sample population follow a normal distribution, with a mean±SD of 4.98±1.06 (n=15). Analysis of the cumulative mean ARI values of all subjects showed an exponential-type convergence of ARI toward the sample mean as the number of test iterations increased. The population average blood pressure drop on thigh cuff release was 26.4±7.1 mm Hg (n=16), occurring in 4.6±1.7 seconds. The corresponding population average drop for CBFV was 15.6±5.8 cm/s, taking 2.5±1.0 seconds. No significant trend was noted in the measurements as the number of test iterations increased. The correlation between the predicted and actual CBFV, having a mean value of 0.76±0.19, showed evidence of a nonlinear relationship to ARI values. Significant correlation was also found between ARI and (1) arterial blood pressure before cuff release and (2) the magnitude of the drop in CBFV on cuff release.

Conclusions—The distribution of ARI values is not significantly different from normal. At least 3 iterations of the test procedure are required to achieve an autoregulatory response that can be observed. Tiecks et al 9 entirely passive autoregulation, and ARI

$\text{ARI} = \text{inflated above systolic pressure for } n \text{ seconds before returning to its original level. A simultaneous drop in cerebral blood flow velocity (CBFV), usually estimated with Doppler ultrasound,}^8 \text{ accompanies the fall in ABP. With normal autoregulation, the recovery of CBFV to its resting level will tend to precede that of ABP. This typical response can be quantified with a mathematical model proposed by Tiecks et al}^9 \text{ that assigns an autoregulatory index (ARI) ranging from 0 to 9. A value of } ARI = 0 \text{ corresponds to an entirely passive autoregulation, and } ARI = 9 \text{ represents the fastest autoregulatory response that can be observed. Tiecks et al}^9 \text{ also showed an excellent correlation between the ARI and the more traditional methods of assessing cerebral autoregulation by "static" manipulation of ABP levels. Clinical applications of the thigh cuff technique have included patients with orthostatic hypotension,}^10 \text{ carotid artery disease,}^11 \text{ head injury,}^12,13 \text{ and studies of the effects of anesthetic agents on cerebral autoregulation.}^{15,16} \text{ Despite its increasing use in cerebrovascular research, several aspects of the thigh cuff method have not been described. In particular, the influence of the number of separate thigh cuff maneuvers on test accuracy has not been characterized, with different investigators reporting any number of repetitions between 3 and } 8,1,5,10-13 \text{ In addition, it is not clear whether the amplitude and rate of pressure drop can have an influence on the CBF dynamic response. Using the ARI approach introduced by Tiecks et al.}^9 \text{ we investigated these and other aspects of the thigh cuff technique in a group of healthy volunteers.}

Subjects and Methods
The study involved 16 volunteer subjects (mean age, 31.8±8.5 years; range, 23 to 51 years). Subjects were admitted into the study
if they had no history of cardiovascular disease, hypertension, migraine, epilepsy, cerebral aneurysm, intracerebral bleeding, or other preexisting neurological disorder. The study was approved by the Leicestershire Research Ethics Committee, and informed consent was obtained in all cases.

Recordings were made with subjects in the supine position with the head elevated to ~30°. CBFV was monitored from 1 middle cerebral artery (MCA) with a Scimed QVL-120 transcranial Doppler system in conjunction with a 2-MHz transducer held in position by an elastic headband. Insonation and identification of the MCA was via the transtemporal window. The ABP was measured noninvasively with a finger cuff device (Ohmeda 2300 Finapres BP monitor). The data were collected and stored on digital audiotape with an 8-channel instrumentation recorder (Sony PC108M) and analyzed at a later time. CBFV and ABP were recorded in each subject before, during, and after a step drop in blood pressure. A thigh cuff technique was used to induce the drop. Large bilateral thigh cuffs were inflated, and blood flow in the dorsalis pedis artery was monitored with a Doppler velocimeter (Sonicaid Vasoflo) until circulation to the lower extremities had ceased. The thigh cuff pressure required for this was ≥20 mm Hg above peak systolic ABP, as measured by the Finapres, in all cases. The occlusion was maintained for 2 minutes. A transient blood pressure drop was then induced by rapid simultaneous release of the Velcro fastenings on the thigh cuffs.

The test procedure was repeated 6 times on each subject. An interval of ≥8 minutes was allowed between each cuff release and the next inflation to permit ABP and CBFV to return to their baseline values. CBFV and ABP were recorded continuously throughout the test procedure. The recordings for each subject were carried out in a single session, during which the volunteer remained supine, and took ~90 minutes.

Data Analysis

The Doppler signal was processed by a microcomputer-based analyzer that performed a fast Fourier transform every 5 ms to calculate the maximum velocity envelope. The ABP signal was also transferred from digital audiotape to microcomputer at a rate of 200 samples per second per channel. Further processing was then performed on the data: erroneous spikes from the CBFV and ABP signals were identified by visual inspection of the data and removed by linear interpolation; cardiac cycles were marked, allowing heart rate to be extracted; values for mean CBFV and ABP were calculated; and finally, a common sampling interval of 0.2 seconds was imposed on the data by polynomial interpolation and the results were stored in a computer file.

Cerebral autoregulation was graded by generating an ARI value from 0 to 9 by the method proposed by Tiecks et al.9 The experimentally acquired CBFV response was compared with 10 predicted models. Each model is generated by a specific combination of time constant, damping factor, and autoregulatory dynamic gain. The closest match was selected on the basis of the highest correlation coefficient. Unlike the least-squares error technique used by Tiecks et al.,9 this method does not rely on a specific value of critical closing pressure to select the closest match. A sample window of 30 seconds from the point of cuff release was used in all cases. Each model corresponds to an integer value of ARI (0 to 9). Once a best-fit curve had been selected, a parabolic interpolation was performed to estimate the value of ARI to 1 decimal place. The correlation coefficient between “best-fit” model and the actual CBFV response was also noted for later analysis (“correlation of fit,” COF).

The maximum value of ABP just before cuff release was marked by visual inspection of the ABP signal data. The minimum value after the induced drop was also noted. The magnitude, time taken, and rate of the induced change in ABP were calculated from these 2 points. A similar process was repeated for the CBFV signal.

Statistics

The distributions of ARI and COF values were tested for normality with the Shapiro-Wilks test. ANOVA was performed on the ARI data to test for evidence of physiological accommodation occurring as the number of cuff releases increased, using 6 groups with the corresponding ARI values for each sequential thigh cuff release.

The effect of varying the number of thigh cuff releases on population estimates of ARI was assessed. A cumulative mean value of ARI was calculated for each subject as each thigh cuff release was performed, such that the cumulative mean ARI for a subject at the nth test was given by

\[
ARI = \frac{1}{n} \sum_{i=1}^{n} ARI_i.
\]

The population cumulative mean ARI was then calculated after each cuff release by averaging the cumulative ARIs for all subjects. The mean±SD of the population ARI values were plotted sequentially as the number of thigh cuff maneuvers was increased.

Linear regression analysis was used to assess the dependence of ARI on other variables. Significance was taken as \(P<0.05\).

Results

Seven isolated cuff releases from 4 subjects were excluded from the study because of excessive noise on the original recordings, leaving a sample of \(n=89\) useful thigh cuff maneuvers (see Table). Of the 16 subjects in the study, 12 had a complete data set (ie, 6 thigh cuff releases) in the final analysis. A typical plot of CBFV and ABP is shown in Figure 1a, demonstrating CBFV recovery preceding ABP.

The mean ABP drop of the sample on thigh cuff release was 26.4±7.1 mm Hg, occurring in 4.6±1.7 seconds. The corresponding sample average drop in CBFV was 15.6±5.8 cm/s, taking 2.5±1.0 seconds. The mean ABP and CBFV recorded before cuff release were 117.9±16.4 mm Hg and 66.3±13.7 cm/s, respectively. Individual ARI values for each subject are given in the Table.

On analysis of these initial data, it could be seen that subject 6 showed a markedly different set of ARI values from the rest of the sample population. The mean ARI for subject 6 was 0.5±1.4, and 4 of the 6 cuff releases produced an ARI of zero. By plotting of the mean response of CBFV and ABP on cuff release, subject 6 was also seen to have demonstrated abnormal autoregulatory function during the tests, as shown in Figure 1b. Furthermore, the distribution of the population ARI values was significantly different from normal when subject 6 was included in the analysis (Shapiro-Wilks test \(W=0.957, P<0.02\)). However, removal of subject 6 resulted in the remaining ARI values showing a normal distribution. Subject 6 was therefore excluded from further analysis on the basis of being a statistical outlier to prevent distortion of results. The remaining 15 subjects were included in all subsequent statistical analyses.

For the remaining subjects, the distribution of the population ARI values was not significantly different from normal (Shapiro-Wilks test \(W=0.978, P<0.5\)), with a mean ARI value of 4.98±1.06 (\(n=83\)). The COF data showed significant deviation from normal (\(W=0.817, P<10^{-4}\)), with a mean of 0.76±0.19. Further analysis suggested that the COF distribution could be more accurately described by a rising exponential curve. Of the 83 tests used in the final analysis, 68 showed a COF of ≥0.6, and of these, 49 had a value of ≥0.8. Only 4 of 83 showed a COF of ≤0.4.

ANOVA of sequential ARI values showed no significant differences (Figure 2). A paired \(t\) test using data from the first 2 cuff releases also showed no significant differences. This sug-
gests that no physiological accommodation took place during the course of the test procedure.

The results of the analysis of population cumulative mean ARI values show a convergence of ARI toward the population mean and SD as the number of thigh cuff maneuvers is increased from 1 to 6 (Figure 3). There appears to be little practical improvement in population mean and SD estimates beyond the use of 3 good thigh cuff releases. A subsequent t test, repeated for each individual subject, showed no significant difference between the first 3 and last 3 ARI values recorded. It is therefore fair to assume that there will be no significant difference between the mean ARI after 3 tests and the mean result after 6 tests for any individual within the sample population, confirming the observation that 3 cuff releases are adequate in most cases.

Linear regression was carried out between ARI and selected variables. There was no significant correlation between ARI and blood pressure drop on cuff release, time for blood pressure drop and CBFV drop to occur, rate of blood pressure drop and CBFV drop, baseline CBFV, and baseline heart rate. Significant correlation was demonstrated in 3 cases. The COF showed a correlation coefficient of $r = 0.35$ ($P < 0.01$) for the linear regression with ARI as the dependent variable. However, after visual inspection, a nonlinear relationship between ARI and COF could be clearly observed, and a parabolic curve fitted to the data led to a coefficient of determination $R^2 = 0.55$ ($P < 10^{-4}$). Figure 4 represents the relationship between COF and ARI with the fitted

### Table: ARI Values for Each Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test Iteration</th>
<th>ARI, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6.1 (0.36)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>9.0 (0.43)</td>
</tr>
<tr>
<td>3</td>
<td>Noise</td>
<td>5.9 (0.76)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>7.1 (0.41)</td>
</tr>
<tr>
<td>5</td>
<td>Noise</td>
<td>0.0 (0.75)</td>
</tr>
<tr>
<td>6</td>
<td>Noise</td>
<td>4.8 (0.88)</td>
</tr>
<tr>
<td>7</td>
<td>Noise</td>
<td>7.0 (0.14)</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>2.3 (0.68)</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>7.3 (0.51)</td>
</tr>
<tr>
<td>10</td>
<td>Noise</td>
<td>4.9 (0.83)</td>
</tr>
<tr>
<td>11</td>
<td>Noise</td>
<td>5.7 (0.87)</td>
</tr>
<tr>
<td>12</td>
<td>Noise</td>
<td>3.5 (0.92)</td>
</tr>
<tr>
<td>13</td>
<td>Noise</td>
<td>2.5 (0.80)</td>
</tr>
</tbody>
</table>

Figure 1. Graph of (a) typical and (b) apparently atypical CBFV (continuous line) response to step drop in ABP (broken line).

Figure 2. Mean ARI (○) and SD bars for successive thigh cuff tests. Eleven subjects, each having the maximum 6 thigh cuff releases, were used throughout this analysis.
Results from previous studies using the thigh cuff technique have reported ARI values similar to our own. White and Markus\textsuperscript{11} quoted a mean ARI of 6.3±1.1 in a group of 21 normal control subjects. In the study by Tiecks et al.,\textsuperscript{9} the mean value of ARI was 4.8±1.0 in a group of 10 subjects under propofol anesthesia for elective orthopedic surgery. Junger et al\textsuperscript{13} quoted a mean ARI of 4.7±1.0 in a group of 29 normal volunteers. Our value of 4.98±1.06 compares more favorably with the results quoted by Tiecks and Junger. Two factors might explain the difference in the results of White and Markus and the other studies mentioned above. First, the mean BP drop on cuff release in the study by White and Markus was smaller than that in the other studies (White and Markus: 13.8±5.3 mm Hg; Tiecks et al: 20±4 mm Hg; Junger et al: 22±5 mm Hg; our study: 26.4±7.1 mm Hg). It is plausible that a smaller drop may produce less of a demand on the autoregulatory mechanisms, thus explaining the higher ARI values obtained by White and Markus. Second, the mean age of subjects in our study and the studies of Junger and Tiecks are far closer, perhaps making these studies more suitable for comparison (White and Markus: 67.8±7.8 years; Tiecks et al: 35±10 years; Junger et al: 22±5 years; our study: 31.8±8.5 years).

Previous studies using the thigh cuff technique to generate the ARI by means of Tieck’s method have not mentioned the quality of fitting for the model, which is the criterion used to select 1 out of 10 possible models.\textsuperscript{9,11–13,15} In Tieck’s original publication,\textsuperscript{9} it is implied that a least-squares method was used to find the best fit in each case. The drawback with this approach is that it depends on another model parameter, namely, the critical closing pressure, that Tiecks et al. assumed to be fixed at 12 mm Hg. This parameter influences the amplitude but not the temporal pattern of the velocity response generated by the model. Therefore, unless an optimal value of critical closing pressure is found in each case, it is not possible to obtain the least-squares error on the basis of the difference between the experimental CBFV data and the model-predicted response.\textsuperscript{17} Conversely, if we are interested only in the ARI parameter, it is possible to select the optimal model using the correlation coefficient between the measured and the predicted CBFV curves. Because of its simplicity, we have favored this approach, which provides more robust values of ARI, because it does not depend on a simultaneous estimation of critical closing pressure. The COF values represented in Figure 4 indicate that reasonably high values of correlation are obtained for thigh cuff responses in most cases; this confirms the ability of the Tiecks model to represent the CBFV dynamic response after the sudden release of pressurized thigh cuffs. In a few instances, however, statistically nonsignificant values of COF can be obtained, as shown by the cluster of 3 points (shaded) in Figure 4. These low COF values indicate poor model fitting and raise the question of whether the corresponding values of ARI should be disregarded in such cases. In addition, Figure 4 also shows that COF is reduced for either very low or very high values of ARI. For low values of ARI, the Tiecks model should, theoretically, provide the expected response, but some readjustment of the combination of time constant, damping, and gain might be necessary to improve fitting. At the other extreme, Figure 4 shows that for high ARI, the fitting performance of the model starts to deteriorate, and it is not clear whether this can be solved with simple readjustment of the 3 key parameters or whether it is the mathematical structure of the model that needs to be improved. In light of the need for further work in this area, it is clear that reliable results can be obtained only if due attention is paid to the issues raised above.

The population cumulative mean analysis gives an indication of how many test iterations need be performed to obtain a given level of precision in a normal population and may provide a useful guide for those designing a study. There are diminishing returns in terms of precision achieved as more iterations of the test procedure are performed, and the benefits should be weighed against time, subject discomfort, and so forth. Because there is no evidence for any significant physiological accommodation taking place, it is possible for a degree of redundancy to be built into any test protocol, with more cuff releases being performed than required to achieve the desired level of precision. It is reasonable to use those recordings with a
good signal and/or low noise level and to discard the poorer recordings. Although it may seem logical to select “good” results on the basis of high COF, this is inadvisable in light of the apparent nonlinear relationship between ARI and COF. If high COF is used as a selection criterion, it is possible that measurement bias may be introduced, favoring ARIs that the Tieck method is most capable of modeling, namely, midrange values. Both high and low values of ARI may be discriminated against because of the poorer ability of the method to model these scenarios closely.

The correlation of ARI with baseline MABP and CBV drop on cuff release is small but significant and suggests that these variables should be considered when the ARI data are analyzed. The negative correlation of CBV drop to ARI is perhaps not surprising. A CBV trace that shows only a small drop before returning to baseline level will be modeled best by a curve that rises steeply. Thus, a small drop in CBV may potentially yield a misleadingly high ARI. The correlation of MABP with ARI suggests that a low MABP may give a low ARI value. This is physiologically plausible if considered in light of the static response of CBF to cerebral perfusion pressure. Subjects with low MABP are more likely to be operating close to the lower limit of autoregulation and thus, when there is an induced drop in ABP, may be pushed into the region below the active range of cerebral autoregulation. This suggests that care should be taken in assessing results from the hypotensive patient.

If we are to assume that changes in flow velocity, measured with Doppler ultrasound, are comparable to changes in absolute flow, then the diameter of the insonated vessel must remain constant throughout the measurement procedure. In a study by Newell et al., under surgical conditions, MCA velocity accurately mirrored flow changes in the ipsilateral internal carotid artery when a cuff maneuver was performed. A study by Aaslid et al., also incorporating the thigh cuff technique, supports the notion that any changes in MCA diameter due to vessel-wall elasticity would be approximately constant (Figure 1) and the CBV signal used to estimate ARI would be a good approximation of MCA blood flow, at least during the 10 seconds after cuff release. Although there is no evidence that active changes in MCA diameter take place over the short interval used by the Tieck model, this possibility cannot be discarded. Nevertheless, in the case of the atypical response demonstrated by subject 6 in Figure 1b, it is highly unlikely that the normal fast return of flow to baseline would have been precisely counteracted by a similar rapid change in diameter such that the CBV response would show the same temporal pattern as the ABP drop.

In conclusion, this study has demonstrated that successive applications of the thigh cuff test do not lead to physiological accommodation and that averaging 3 good-quality recordings should lead to an optimal compromise between test precision and patient discomfort. Although highly significant correlations are usually obtained between recorded CBV transient and the response predicted by the Tieck model, more work is necessary to shed light on the relationship between the quality of model fitting and the accuracy of the estimated ARI values.

Acknowledgment

The support of the Engineering and Physical Sciences Research Council, UK (grant GR/L 16163), is gratefully acknowledged.

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Stroke. 2000;31:476-480
doi: 10.1161/01.STR.31.2.476
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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