Impaired cerebral autoregulation may be important in the pathogenesis of both stroke and global cerebral ischemia occurring during periods of hypoperfusion, such as intraoperatively. Risk factors for stroke, such as hypertension, are associated with altered cerebral autoregulation. An acute impairment of autoregulation is also found in a variety of disease states, including head injury, ischemic stroke, and vasospasm secondary to subarachnoid hemorrhage. A profound impairment of autoregulation is found in some patients with carotid artery stenosis or occlusion. This may be associated with increased stroke risk and with increased stroke risk during hypotensive therapy or perioperatively. Conventionally static autoregulation has been measured. Cerebral blood flow itself, or an estimate such as cerebral blood flow velocity (CBFV), is measured during a large change in blood pressure that is usually induced pharmacologically. Such techniques are not suitable for many patients at risk of stroke because the blood pressure change induced could result in cerebral ischemia.

Therefore, most investigators have used an indirect measure of cerebral autoregulation such as the vasodilatory response to hypercapnia. Although this does correlate with cerebral autoregulation, it measures a slightly different physiological response, and the 2 may not always correlate. More recently, noninvasive methods for measuring dynamic autoregulation have been proposed. These study the response of cerebral blood flow or CBFV to small changes in arterial blood pressure (ABP) and therefore are suitable for use in patients at risk of stroke. Aaslid et al suggested the use of bilateral leg cuffs inflated suprasystolically and then suddenly deflated to induce a transient fall in blood pressure, and they correlated the temporal pattern of the change in blood pressure with the change in middle cerebral artery (MCA) CBFV determined using transcranial Doppler. Such a technique may be more clinically relevant than static autoregulation in patients at risk of stroke because the transient blood pressure changes are likely to be more similar to those occurring in patients during periods of hypoperfusion. An alternative method is proposed, based on the spontaneous variability of arterial blood pressure that does not require its manipulation. We compared this method with the established thigh cuff method in patients with carotid artery stenosis.
on a day-to-day basis than the large blood pressure changes induced during static autoregulatory testing. Tiecks et al. have demonstrated an excellent agreement between this method and the classic assessment of static autoregulation.

Transcranial Doppler measurement of MCA CBFV is only a suitable technique if there is no change in MCA diameter during the change in blood pressure. Newell et al. compared internal carotid artery absolute flow values during this step change in blood pressure with transcranial Doppler MCA CBFV changes and found an extremely close correlation, suggesting that transcranial Doppler is an appropriate technique to use in this setting. We have previously shown that this method of assessing dynamic autoregulation may identify a subgroup of patients with carotid stenosis who have significant impairments of cerebral autoregulation. However, in some patients the use of thigh cuffs to induce a fall in blood pressure is not ideal for a number of reasons. First, in ~20% of cases, it is not possible to induce a sufficient fall in blood pressure with this method. Second, inflation of thigh cuffs may be uncomfortable in some patients. Third, particularly in patients with critical cerebrovascular hemodynamics, such as premature newborns and individuals suffering from heart or autonomic failure, there may be a risk associated with the induction of drops in blood pressure. For these reasons alternative methods of providing an assessment of dynamic autoregulation in humans, which do not require induction of ABP disturbances, would be highly desirable.

One attractive possibility is to explore the spontaneous variability in ABP that is observed in most individuals at rest. The feasibility of this approach was demonstrated by Panerai et al. in neonates using a coherent averaging method to improve the signal-to-noise ratio of the CBFV response to transient elevations in ABP. A more general approach is the use of linear systems analysis methods to describe the relationship between fluctuations in ABP and CBFV by the impulse response function (IRF). The IRF represents the CBFV temporal response to a very short, impulselike disturbance in ABP. The usefulness of the IRF is that, once it is known, it can be used to predict the CBFV response to ABP changes of any temporal pattern, including step changes, as induced by the thigh cuff method. Therefore, from baseline, spontaneous fluctuations in ABP and CBFV, it should be possible to estimate the step response and to grade it with the same mathematical model proposed by Tiecks et al.

In a previous study, White and Markus applied the thigh cuff method to assess cerebral autoregulation in patients with carotid artery stenosis. Using baseline recordings from the same study, we have been able to compare the degree of agreement between the autoregulation index (ARI) values obtained by the thigh cuff test with those estimated by the IRF method.

Subjects and Methods
Twenty subjects with carotid stenosis >60% were studied. Grading of stenosis was based on ultrasound Doppler velocities in combination with B-mode imaging with a color-flow duplex ultrasound system (Acuson XP). Eighteen healthy age-matched nonsmoking volunteers with carotid stenosis excluded on duplex ultrasound were also studied as the control group.

Measurements were performed with subjects in a supine position and with their heads slightly elevated. CBFV was recorded bilaterally simultaneously through the transtemporal window with 2-MHz transducers (DNL, Langerach). The MCA was imaged at a mean±SD depth of 50.2±3.5 mm for the control population and 52.6±3.4 mm for the carotid stenosis group. Continuous ABP recording was made with a noninvasive servo-controlled photoplethysmograph (Finapres 2300, Ohmeda), with the subject’s hand maintained at the same level as the head. Baseline measurement of resting ABP was made by automated arm cuff (Omega 1400 series, In Vivo Laboratories Inc). A sudden stepwise drop in ABP was induced by the rapid release of bilateral thigh cuffs that had been inflated suprasystolically for 3 minutes. Drops in ABP of <10 mm Hg were not accepted for analysis. Continuous recordings of bilateral CBFV and ABP were stored on the transcranial Doppler machine for a baseline period of 2 minutes preceding the cuff release and for another 1 minute after the sudden deflation. Five cycles of inflation/deflation were performed per subject with a 3-minute rest interval between cycles. Grading of autoregulation based on the CBFV response to the stepwise drop in ABP was provided by a software program supplied by the transcranial Doppler manufacturers, as described previously. For each integer value of ARI cuff, ranging from 0 to 9, the predicted CBFV response for the mathematical model proposed by Tiecks et al was compared with the actual CBFV tracing and the ARI cuff was defined as the corresponding curve that gave the least square error over a 30-second interval selected as the best estimate. The critical closing pressure (CICP) was manually selected to improve model fitting. We calculated mean values of ARI cuff and CICP cuff for each subject using the individual estimates from each acceptable inflation/deflation cycle.

Data Analysis
Estimation of the ARI with the use of the IRF method was obtained from the baseline recordings preceding the thigh cuff deflation. The 120-second-long records were transferred to a personal computer at a rate of 200 samples per second for subsequent analysis. Each record was inspected visually for the presence of artifact or ectopic beats. Recordings with >4 ectopic beats were rejected. Narrow spikes in the CBFV signals were removed by linear interpolation. Time series of mean values of ABP and bilateral CBFV were obtained by low-pass filtering these signals with a cutoff frequency of 1 Hz (8th order zero-phase Butterworth) and decimating the sampling rate to 5 samples per second.

The IRF was estimated with a fast Fourier transform (FFT) algorithm. Before the direct FFT transform was computed, each signal was normalized by its mean value, and a cosine (Hanning) window was applied to the data. Two segments of data with 256 samples each were used to estimate the cross-spectra and the transfer function between the mean ABP (MABP) and CBFV signals with a frequency resolution of 0.0195 Hz. The amplitude spectra was smoothed with a 3-element triangular window, and the IRF computed from the inverse FFT with a cutoff frequency of 0.5 Hz. Nyquist theorem states that this cutoff frequency is appropriate for signals that have been low-pass filtered at 1 Hz. The final IRF for each MCA was obtained as the average of all IRF available for each side, and it is termed IRFbase. A numerical estimate of the baseline step response can be obtained by integration of the IRF. For technical reasons, however, grading of autoregulation based on baseline recordings was attempted by using the IRFbase rather than the step response. The reasons for this choice will be given in the Discussion.

With the use of the model of Tiecks et al, for each step response a corresponding IRF (IRFmodel) was obtained by calculating the numerical derivative. To compare IRFbase with IRFmodel, it is necessary to take into account the parameter CrCP introduced by Tiecks et al. in their original formulation. As discussed later, this parameter might not reflect the true critical closing pressure of the cerebral circulation. For simplicity, assume that autoregulation is impaired. In
this case, percent changes in ABP will induce velocity changes with unit gain, that is, $D_V = D_P$, where $D_V$ and $D_P$ are percent CBFV and ABP changes, respectively. The model of Tiecks et al.\textsuperscript{6} however, assumes that flow (or velocity) can become 0 for ABP values <0 (ie, when ABP=CrCP), as represented in Figure 4. In this case, percent changes in ABP will lead to percent changes in velocity, as shown in the following equation:

$$D_V = \frac{D_P}{1 - \frac{1}{MABP}}$$

For an impaired autoregulation, the peak value of the IRF is given by the ratio $D_V/D_P$, and the relative amplitude ($A_{rel}$) between IRF\textsubscript{model} and IRF\textsubscript{base} is then

$$A_{rel} = \frac{1}{1 - \frac{1}{A_{ref}}}$$

From Equation 2 it is possible to calculate the equivalent CrCP during baseline measurements, from the relative amplitude of the 2 impulse responses:

$$CrCP_{base} = MABP \left( 1 - \frac{1}{A_{ref}} \right)$$

In summary, $A_{ref}$ was computed from the ratio of peak values of IRF\textsubscript{model} and IRF\textsubscript{base}, leading to an estimate of the equivalent CrCP\textsubscript{base} and also of the relative CrCP\textsubscript{rel} = CrCP\textsubscript{base} / MABP. CrCP\textsubscript{base} estimates were compared with values of CrCP\textsubscript{cuff} manually selected to improve model fitting for the thigh cuff data.

The temporal pattern of IRF\textsubscript{base} was graded by identifying the best fit with 10 model curves, generated with the same set of parameters proposed by Tiecks et al.\textsuperscript{6} providing a value of ARI\textsubscript{base}. Fractional values of ARI\textsubscript{base} were obtained by parabolic interpolation around the point with least square error.

Agreement between parameters derived from IRF\textsubscript{base} and ARI\textsubscript{cuff} was assessed by the correlation coefficient and Bland-Altman plots.\textsuperscript{17} The Mann-Whitney $U$ test was used to test for differences in mean values. ANOVA with Scheffe’s test for post hoc analysis was used to test the relationship between model-derived parameters and the degree of stenosis. Linear regression analysis was performed to test for linear dependence between variables. A level of $P<0.05$ was considered significant.

**Results**

Of the 38 subjects, 1 patient and 1 control subject were rejected because of the high incidence of ectopic beats. As a result, 72 IRF\textsubscript{base} were available for analysis. The mean±SD relative error for fitting the Tiecks model to IRF\textsubscript{base} was 7.2±3.1% of the IRF\textsubscript{base} peak value. Figure 1 shows typical IRF\textsubscript{base} from 1 subject and the corresponding IRF\textsubscript{model} best fits. The negative wave observed after $t=0$ in Figure 1A was present in all control subjects. Similarly, this negative wave was significantly reduced or absent in most patients with carotid artery disease (CAD) (Figure 1B).

Mean±SD values for the main variables studied are given in Table 1 for the control and patient groups, together with the $P$ values for the Mann-Whitney test. Highly significant differences were found between the 2 groups of individuals in relation to ARI\textsubscript{cuff}, ARI\textsubscript{base}, CrCP\textsubscript{cuff}, CrCP\textsubscript{base}, and CrCP\textsubscript{rel}. The MABP was also significantly different for the 2 groups.

**Figure 1.** Representative IRF from a 44-year-old male CAD patient with no stenosis in the right carotid artery and 100% stenosis in the left carotid artery. A, IRF from the right MCA (continuous line) and best-fit model curve (dotted line) obtained with the model of Tiecks et al.\textsuperscript{6} The relative and absolute values of CrCP are 0.46 and 47.6 mm Hg, respectively. The least square error is 6.4% of the IRF peak value. B, IRF from the left MCA. The corresponding relative and absolute values of CrCP are 0.27 and 27.8 mm Hg, respectively. The least square error is 6.0% of the IRF peak value.

**Figure 2.** ARI obtained from baseline recordings (ARI\textsubscript{base} vs corresponding values obtained from the thigh cuff test (ARI\textsubscript{cuff}).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Patient Group</th>
<th>$P$ (Mann-Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP, mm Hg</td>
<td>99.4±12.6</td>
<td>103.2±25.7</td>
<td>0.01</td>
</tr>
<tr>
<td>MCFBV, cm/s</td>
<td>51.1±13.1</td>
<td>57.1±15.0</td>
<td>0.06</td>
</tr>
<tr>
<td>ARI\textsubscript{cuff}</td>
<td>6.35±1.06</td>
<td>3.78±2.32</td>
<td>4×10\textsuperscript{-6}</td>
</tr>
<tr>
<td>ARI\textsubscript{base}</td>
<td>6.68±1.88</td>
<td>3.65±3.11</td>
<td>0.0001</td>
</tr>
<tr>
<td>CrCP\textsubscript{cuff}, mm Hg</td>
<td>62.9±9.36</td>
<td>36.8±27.7</td>
<td>5×10\textsuperscript{-6}</td>
</tr>
<tr>
<td>CrCP\textsubscript{base}, relative units</td>
<td>0.50±0.31</td>
<td>−0.24±1.06</td>
<td>5×10\textsuperscript{-5}</td>
</tr>
<tr>
<td>CrCP\textsubscript{base}, mm Hg</td>
<td>46.7±35.5</td>
<td>−152±94.7</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Values are mean±SD.
the control group, ARI base had a smaller coefficient of variation (16.7%) than ARI ref (28.1%), but the difference was not significant.

Highly significant correlation coefficient values were obtained between the ARI ref and the model-derived parameters ARI base (r=0.764), CrCP ref (r=0.68), CrCP base (r=0.70), and A rel (r=0.69).

Figure 2 presents a scatter diagram between ARI base and ARI ref. A linear regression between these 2 parameters had a highly significant slope (P<0.00001) and residuals that were normally distributed. Figure 2 suggests the presence of 2 distinct groups of arteries. When we performed a linear regression using only data from control subjects, the correlation coefficient was reduced to r=0.406, but the regression slope was still significant (P<0.017). Bland-Altman analysis of the agreement between ARI base and ARI ref indicated a bias value of −0.09 and limits of agreement of −3.89 and 3.71. For the control group, CrCP ref (r=0.484, P=0.004) and CrCP base (r=0.45, P=0.007) were also significantly correlated with ARI ref.

Patients were split into 4 subgroups according to the classification of stenosis15 with the following number of vessels in each subgroup: <60% stenosis (9 vessels), 60% to 79% (8), 80% to 99% (7), and 100% (12). One subject with a carotid artery bypass was not included. The mean±SEM of ARI base and CrCP ref are represented in Figure 3 for these 4 patient subgroups and for the control group, which contained 34 vessels.

ANOVA of the 5 patient subgroups represented in Figure 3 yielded very significant results for both ARI base and CrCP ref (P<10−6). Scheffé’s test also indicated that these parameters can distinguish between some of these subgroups, with the P values given in Table 2. Significant differences between the 5 subgroups were also obtained for the ANOVA of CrCP base (P=1.5×10−3) and CrCP ref (P=7×10−6), but Scheffé’s test indicated inferior discrimination between individual subgroups compared with the results obtained for CrCP ref (Table 2). On the other hand, ANOVA results were nonsignificant for mean CBFV (MCBFV), MABP, and fitting least square error for the different degrees of stenosis considered.

**Discussion**

The possibility of assessing the status of cerebral pressure autoregulation with the spontaneous variability of ABP as the stimulus to perturb CBFV has been demonstrated by previous studies, but hitherto it has been restricted to the dichotomous classification of normal/impaired autoregulation. In the present investigation we have demonstrated that the model proposed by Tiecks et al. to describe the CBFV response to ABP drops induced by the sudden deflation of thigh cuffs, can also be used to grade autoregulation using baseline recordings of ABP and CBFV. The ARI obtained during undisturbed conditions (ARI base) has shown a very high correlation with ARI ref and considerable sensitivity to the degree of stenosis in a population of CAD patients (Figure 3).

In a previous study, Zhang et al. have also shown that baseline estimates of IRF can be used to predict CBFV changes after the sudden release of thigh cuffs in normal subjects, thus suggesting that the same IRF might apply to both situations.

Despite these initially encouraging results, several limitations of the methods adopted need to be kept in perspective. One major limitation of using baseline recordings to grade autoregulatory performance is the lack of ABP variability at the spectral frequency bands, which can stimulate an autoregulatory response. Although the pressure drop produced by the deflation of thigh cuffs is not a perfect “step function” and returns to its original value 10 to 15 seconds after the sudden release of the cuffs, it provides much more low-frequency power (<0.2 Hz) than normally available in a 120-second recording of undisturbed fluctuations in ABP. The amount of signal power available in the pertinent frequency band is important to overcome the noise levels, thus providing reliable estimates of the input-output relationship. This deficiency in low-frequency power becomes
more of a problem if one is estimating the step response because of its higher relative content of low-frequency power compared with the IRF. For this reason, the analysis and fitting of the Tiecks et al. model were performed on the IRF. Although the IRF provides a less intuitive “feeling” of the autoregulatory response corresponding to different values of ARI, its temporal pattern can also reflect grading of autoregulation. At $t=0$, when a hypothetical impulselike disturbance in ABP takes place, there is an immediate direct response in CBFV. If the IRF remains flat, this means a lack of feedback reaction in CBFV that will then tend to follow ABP changes. This situation is characteristic of an absence of autoregulation. On the other extreme, if the positive immediate change in CBFV is counteracted by a negative wave in the IRF (Figure 1A), this will induce a return of CBFV to its original level, representing the case of a perfect autoregulation. Although the occurrence of this temporal pattern was in excellent agreement with the reference values of $ARI_{\text{base}}$, the limits of agreement between this index and $ARI_{\text{base}}$ ($-3.89$ to $3.71$) should be considered inadequate for clinical applications of the baseline method at this stage.

A number of different reasons might contribute to explain this poor agreement. First, it is appropriate to question the accuracy and precision of $ARI_{\text{eff}}$ as a “gold standard” for assessment of dynamic autoregulation. More studies on the reproducibility of the thigh cuff technique are undoubtedly needed, but initial results suggest a possible problem in this area. Second, the transcranial Doppler equipment allows the operator to select values of $CrCP_{\text{eff}}$ to improve the fitting between model and data, but different values of $ARI_{\text{eff}}$ could have been obtained if an objective and automatic procedure was adopted for this purpose, such as we have used to fit the model during baseline recordings. Third, the model of Tiecks et al. is an obvious first choice to fit and grade the IRF$_{\text{base}}$, but we have not explored other alternatives that could lead to better fitting and reduced least square errors. Future research on this topic is important to arrive at more accurate and sensitive mathematical models to describe the dynamic pressure-velocity relationship during baseline recordings. Fourth, and related to this previous point, is the problem of performing the FFT analysis on segments of data that are long enough to yield accurate estimates of IRF and to maximize the low-frequency power spectral content. IRF estimates with higher signal-to-noise ratios than hitherto available are necessary to allow further investigation of alternative mathematical models to fit and grade the IRF$_{\text{base}}$. To summarize this point of the discussion, it is important that more work is performed to understand the sources of variability of both $ARI_{\text{eff}}$ and $ARI_{\text{base}}$, before either is prematurely discarded or uncritically accepted.

Newell et al. have shown that CBFV changes after the sudden deflation of thigh cuffs provide an accurate estimate of the corresponding changes in cerebral blood flow. Their results suggest that the diameter of the MCA does not change significantly during the thigh cuff test, but it is not possible to assume that the same holds true for the spontaneous variability of CBFV recorded during baseline measurements. If the diameter of the MCA remains constant, the observed variability of CBFV is a true reflection of spontaneous or pressure-induced fluctuations in flow. In this case, if autoregulation is intact, the negative transient of the IRF is a reflection of adjustments in small-vessel resistance, possibly involving a metabolic mechanism. On the other hand, as observed by Zhang et al., if flow is constant during baseline and the velocity fluctuations are due to small changes in MCA diameter, then the IRF might be reflecting a myogenic mechanism involving the direct action of ABP variability on large-vessel diameter. Methods based on the power of the reflected Doppler signal might be able to shed light on this problem in the near future.

The CrCP parameter, as introduced by Tiecks et al., is important to explain the finding that IRFs can have markedly different amplitudes. As shown by Figure 4, a sudden change in ABP ($\Delta P$) can produce different $\Delta V$ transients and therefore distinct peak values of the IRF, depending on the CrCP parameter. The peak value of the IRF, represented at $t=0$ in Figure 1, reflects the immediate perturbation of CBFV to a sudden change in ABP, before the few seconds required for the autoregulatory response to be manifested.

The fact that CrCP values required to fit the Tiecks model to IRF$_{\text{base}}$ are spread over a relatively wide range and show extremely high correlation with the degree of stenosis (Figure 3) was not expected at the outset of our study. From the work of Burton, the concept of CrCP has been formulated as the point at which reductions in perfusion pressure lead to a stagnation in blood flow or velocity. For a number of reasons, however, the use of this concept in the model of Tiecks et al. can be misleading, and it is not possible to assume that the resulting values reflect the true critical closing pressure of the cerebral circulation. Values of CrCP $>0$ have been obtained in animals and humans by using the instantaneous pressure–velocity relationship for a complete cardiac cycle. Unfortunately, in humans it is not yet possible to measure the ABP of large cerebral vessels, and this raises questions about the accuracy of CrCP estimates based on ABP measurements in the aorta or radial arteries. This problem becomes worse when the Finapres is used to record the ABP waveform. Note that the CrCP parameter in the formulation of Tiecks et al. bears no relationship to estimates based on instantaneous pressure–velocity relationships, because the signals in Equation 1 represent mean values of CBFV and ABP for each cardiac cycle. In addition, this parameter has not been estimated by the extrapolation of the linear regression of velocity against ABP, as adopted by other studies. Despite these differences and the risk of misleading interpre-
Grading of Cerebral Dynamic Autoregulation

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