Dynamic Computed Tomographic Imaging of Regional Cerebral Blood Flow and Blood Volume

A Clinical Pilot Study

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Background and Purpose: The advent of faster computed tomography scanners has evoked considerable interest in using this technology as a more practical method of regional cerebral hemodynamic evaluation than the currently available positron emission and single-photon emission computed tomography. The theoretical concepts have been worked out and validated in the laboratory by several groups. The aim of the present study was the development of a clinically useful system.

Methods: Software was developed for dynamic computed tomography-based calculation and color-coded representation of regional cerebral blood flow and blood volume. Normal values, reproducibility, and sensitivity to acetazolamide challenge were established in 13 volunteers. The method was applied to an additional three patients with internal carotid artery occlusion and known decreased vascular reserve capacity as diagnosed by transcranial Doppler ultrasonography.

Results: Normal regional cerebral blood flow was determined as 50±13 ml/100 ml per minute and normal fractional cerebral blood volume as 58±12 ml/1,000 ml (mean±SD). In five volunteers, two examinations were performed within 15 minutes for determination of reproducibility. Intermeasurement variability of hemispheric blood flow and blood volume was determined as ±23% and ±16%, respectively. Intravenous administration of 1 g acetazolamide resulted on the average in a 75% increase of blood flow and a 65% increase of fractional blood volume. In the patients with decreased cerebrovascular reserve capacity, baseline fractional blood volume in the ischemic hemispheres was significantly increased. Baseline regional cerebral blood flow in the ischemic territories was overestimated. Reactivity to acetazolamide of both regional blood flow and fractional blood volume was clearly reduced in the ischemic hemispheres.

Conclusions: The present results demonstrate that the method is a simple and effective means of determining regional cerebral blood volume. Spatial resolution is superior to that of the radioactive tracer methods. Hemodynamic evaluation of ischemic conditions can be performed on the basis of increased resting cerebral blood volume and a diminished increase after acetazolamide. Accuracy of cerebral blood flow measurements, on the other hand, is affected by abnormal cerebral blood volume, and corresponding adjustments need to be made in pathological conditions. (Stroke 1993;24:591-597)

KEY WORDS • cerebral blood flow • hemodynamics • tomography, x-ray computed

Analysis of the passage of a contrast bolus through the cerebral circulation by computed tomographic (CT) scan theoretically allows for quantitative determination of the hemodynamic key parameters regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV). There are two main principles that can be exploited for rCBF calculation. The first is based on the transit time of the contrast bolus that is inversely proportional to rCBF. The second principle calculates the amount of blood inflow into the parenchyma from the increase of parenchymatous contrast concentration per time unit in relation to the arterial contrast concentration (indicator dilution principle). rCBV can be directly calculated from the increase of the parenchymatous density compared with the increase of the density of a vascular reference after contrast application.

Several difficulties have hampered the clinical application of the method. The relatively discrete parenchymal density increase with contrast requires scanning equipment with a very low photonic background noise. The CT method has a marginal resolution in the temporal domain for exact contrast bolus tracking. Theoretically, this problem has been overcome by new scanners with an acquisition rate of up to 10 scans per second, but the associated high radiation exposure forbids routine clinical application. Furthermore, estimation of fractional cerebral blood volume may be affected by a defect in the blood–brain barrier that causes leakage of the contrast agent into the interstitial space.

The purpose of the actual study was to develop a clinically useful system for measurement and imaging of rCBF and rCBV (hemo-CT). The present report describes the procedure of data acquisition and analysis.
FIGURE 1. Typical cerebral arterial and parenchymatous density curves after intravenous contrast bolus injection. Time scale is given in seconds after beginning of injection. Both curves have a bell-shaped appearance. Phase lag between curves is inversely related to regional cerebral blood flow (rCBF). Maximum up-slope of parenchymatous phase is directly related to rCBF.

and the results of a pilot series of examinations that were performed to define normal values, reproducibility of the method, and sensitivity in detecting pathological conditions.

Subjects and Methods

The dynamic CT sequence was performed on a GE 9800 scanner. Twelve stationary CT scans were done at 4.5-second intervals starting 5 seconds after brachial bolus application of 50 ml 30% meglumine (Telebrix 30, Guerbet AG, Zurich, Switzerland). The data were transferred by magnetic tape to a personal computer (IBM PS/2, model 80) for further processing.

The software package consisted of five main blocks. In the first, a reference vessel (artery or vein) was identified by means of a mouse-driven cursor (Figure 2). The program then determined the maximum density of the reference vessel during the series. The following step determined maximum regional tissue densities and maximum increase of regional tissue densities between scans. For reasons of photonic background noise, these calculations were not performed on single pixels but on

FIGURE 2. Program sequence. Top panel: Selection of window of interest (left) and vascular reference (right). Window of interest has a fixed size of 256 x 256 pixels. Computed tomographic (CT) images can be viewed sequentially on monitor until arteries and veins are well defined. The selected vascular reference (right sigmoid sinus in this case) is then identified using cursor (right panel). The program subsequently determines maximum density of vascular reference during series. Bottom panel: Following determination of maximum density of vascular reference, regional cerebral blood flow (CBF) (left) and regional cerebral blood volume (CBV) (right) are calculated and presented in color-coded fashion. Sixty-four original CT pixels are averaged to eliminate photonic background noise.
TABLE 1. Diamox Challenge in Normal Subjects and in Patients With Diminished Cerebral Vascular Reserve

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vascular pathology</th>
<th>TCD CO₂ reactivity*</th>
<th>Baseline</th>
<th>Diamox</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>hCBF†</td>
<td>hCBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L R L R</td>
<td>L R L R</td>
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<tr>
<td>1</td>
<td>...</td>
<td>...</td>
<td>54 62 38 33</td>
<td>82 114 70 70</td>
</tr>
<tr>
<td>2</td>
<td>...</td>
<td>...</td>
<td>45 43 61 49</td>
<td>98 120 107 96</td>
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<td>3</td>
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<td>...</td>
<td>55 56 60 53</td>
<td>59 58 68 57</td>
</tr>
<tr>
<td>4</td>
<td>L ICA occlusion</td>
<td>1.0</td>
<td>39 46 90 82</td>
<td>42 54 84 81</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>...</td>
<td>54 62 38 33</td>
<td>82 114 70 70</td>
</tr>
<tr>
<td>5</td>
<td>L ICA occlusion</td>
<td>0.1</td>
<td>53 60 68 46</td>
<td>63 73 72 56</td>
</tr>
<tr>
<td>6</td>
<td>Bilateral ICA occlusion (moyamoya)</td>
<td>−0.6</td>
<td>55 56 117 106</td>
<td>58 57 139 110</td>
</tr>
</tbody>
</table>

TCD, transcranial Doppler ultrasonography; MCA, middle cerebral artery; hCBF, hemispheric cerebral blood flow; hCBV, hemispheric cerebral blood volume; ICA, internal carotid artery.

†Values normalized for increased baseline hCBV.

During the third step the program calculated rCBF and rCBV according to the following formulas1,10:

\[
\text{rCBF} = \frac{\max dT}{\max V} \times 100 \tag{1}
\]

\[
\text{rCBV} = \frac{\max T}{\max V} \times 1,000 \tag{2}
\]

where \(\max dT\) is the maximum slope of the tissue density curve during the inflow phase (Hounsfield units per minute) (Figure 1); \(\max V\), the maximum contrast density of the vascular reference; and \(\max T\), the maximum tissue contrast density. Contrast densities are defined as total Hounsfield number minus baseline noncontrast Hounsfield number. Formulas 1 and 2 provide results in terms of partial volumes in contrast to the standard notation, thus giving CBF in terms of milliliters per 100 milliliters per minute and CBV as milliliters per 1,000 milliliters. Both rCBV and rCBF are calculated during the upslope phase of the first contrast passage, thus theoretically eliminating potential errors due to a defective blood–brain barrier.7,18

The fourth step of the program consisted of building up a color-coded representation of rCBF and rCBV, and the last sequence calculated left and right hemispheric (h) mean values (hCBF, hCBV) by averaging.

For evaluation of the program, 13 patients were asked to participate in this pilot investigation 1 week after elective and uncomplicated carotid endarterectomy. The patients ranged from 43 to 80 (average, 67) years of age. None of the patients had suffered a stroke before surgery, and at the time of the study no patient had a significant asymmetry of the middle cerebral artery (MCA) flow velocities as measured by transcranial Doppler (TCD) ultrasonography. The volunteers were subdivided into three groups. In group 1 (n=5), scans were done at the level of the circle of Willis for comparison of the maximum arterial and venous contrast densities. Knowledge of this relation is necessary because the formulas for calculation of rCBF and rCBV are dependent on arterial reference values. Since no major arteries are available at CT planes above the circle of Willis, the superior sagittal sinus must be used as vascular reference. In the second group (n=3), two studies were performed within 15 minutes for determination of the reproducibility of rCBF and rCBV values. In the third group of volunteers (n=3), an acetazolamide challenge was performed 10 minutes after a baseline study (1 g i.v. Diamox; Lederle).

In an additional three patients with internal carotid artery occlusion and diminished CO₂ reactivity as determined by TCD (Table 1), a baseline investigation and a study following administration of 1 g acetazolamide were also performed to compare the new method with TCD in cases of reduced cerebrovascular reserve capacity. In one of the patients, carotid occlusion was unilateral; the other two suffered from bilateral symptomatic carotid disease, due in one to fibromuscular dysplasia and in the other to moyamoya disease. Both patients with bilateral disease had suffered unilateral small parietal infarctions 7 months and 5 years, respectively, before the actual study.

Results

The maximum arterial and venous contrast concentrations analyzed in group 1 were found to be almost identical. The increase of the arterial density during passage of the contrast medium was on the average 151±19 Hounsfield units and the increase of the venous density 146±26 units (mean±SD). The average ratio between venous and arterial density increase was 0.98±0.12. It is therefore permissible to take the superior sagittal sinus values for the denominator in the formulas for calculation of rCBF and rCBV.

Normal rCBF and rCBV values were derived from groups 1 and 2. Normal hCBF was determined as 49.6±13.2 ml/100 ml per minute. Normal hCBV was determined as 58.4±11.6 ml/1,000 ml.

In group 2, in which two studies were performed within 15 minutes, the relative change (hCBF2−hCBF1)/hCBF1 was determined as 4±12% and the relative difference (hCBV2−hCBV1)/hCBV1 as 1±16%. Thus, the average hCBF and hCBV values of the two studies did not differ significantly, and a major systematic error in the second study caused by the already circulating contrast material could therefore be excluded.

Administration of 1 g acetazolamide (group 3) induced a variable increase of hCBF (75±68%) (Table 1, Figure 3), and hCBV was also increased after acetazolamide to a variable degree (65±44%).
FIGURE 3. Normal acetazolamide challenge, computed tomographic plane through centrum semiovale. Top panel: Baseline study. Bottom panel: Repeat exam after intravenous administration of 1 g acetazolamide. Both regional cerebral blood flow (CBF) and regional cerebral blood volume (CBV) are markedly increased.

In the patients with reduced cerebrovascular reserve, baseline hCBF of the ischemic hemispheres was clearly overestimated (average, 88 ml/100 ml per minute). Overestimation of hCBF in these patients appeared to be a consequence of an increased hCBV. Average baseline hCBV in the ischemic hemispheres was measured as 93 ml/1,000 ml (Table 1). Proportional correction of the measured hCBF for the increased hCBV gave reasonable hCBF values (Table 1). After administration of acetazolamide, increase of hCBF and hCBV was reduced or absent in the ischemic hemispheres, comparable to the reduced CO$_2$ reactivity of the MCA flow velocities (Table 1, Figure 4).

Discussion
Cerebral blood volume is currently determined in clinical practice with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) technology using soluble tracers or labeled red blood cells.$^{15-21}$ The hemo-CT method is simpler to use routinely than these techniques. The spatial resolution of approximately 5 mm is also considerably better than the accuracy obtained with PET or SPECT technology. The normal values obtained in our study are in reasonable agreement with the PET and SPECT data. The mixed gray and white matter rCBV values given in the respective literature are approximately 20% lower than our normal hCBV values.$^{21-24}$ A possible difference of the volume of distribution within the cerebral circulation among the tracers may explain the difference.

The normal hCBF values determined with the present method are also in good agreement with the normal values of the standard$^{33}$Xe technique.$^{25-28}$ However, this
FIGURE 4. Acetazolamide challenge in a patient with fibromuscular dysplasia and occlusion of left internal carotid artery and stenosis of right internal carotid (case 4, Table 1). Bottom panel: Baseline study. Cerebral blood flow (CBF) image shows perfusion deficit around a small left parietal infarction (asterisk). Cerebral blood volume (CBV) image shows increased blood volume in border zones of this area. Top panel: Stimulated study. Regional (r) CBF on left side does not significantly respond, whereas contralateral rCBF still increases to some degree. This result is in agreement with bilaterally (but mainly on the left side) reduced CO₂ reactivities as measured by transcranial Doppler. rCBV response is bilaterally absent in this case.

agreement is partially coincidental because both methods do not measure the same physical phenomena. While the xenon analysis is based on gas exchange between capillaries and parenchyma, the hemo-CT method is based on the turnover rate in the entire vascular bed, including the arteries and veins not involved in gas exchange. As known from other methods (e.g., the microsphere method commonly used in animal experiments), conversion factors are usually needed to compare the values obtained with different techniques.3,27,29,30

Different physical principles will result in divergent results in certain situations. A cerebral arteriovenous malformation appears as a low-flow area with the xenon clearance technique. With the hemo-CT method, in contrast, such lesions appear as high-flow areas. Other critical situations are instances of luxury perfusion and disturbed blood–brain barrier. The effect of postinfarction cortical enhancement on the accuracy of hemo-CT measurements is unknown at the present time. It appears likely that the rapid acquisition of both CBF and CBV data makes the method quite insensitive to blood–brain barrier disruption, but this potential limitation needs to be elucidated further.

The reproducibility tests of the actual investigation gave a concordance between two successive measurements within approximately ±20% for CBF and CBV. A systematic bias in favor of the first or second measurement could be excluded. Comparable intermeasurement variations of the xenon methods are reported as ±15%.27 A part of these variations can be accounted for
by true fluctuations of CBF. However, the current software may also be subject to some degree of error; e.g., the maximum vascular contrast concentration may be underestimated if no scan of the series coincides exactly with the peak concentration in the vascular reference. Similar considerations apply to the determination of the maximum slope of the tissue contrast density curve. Fitting a gamma variate curve around the measured densities and basing the further calculations of the gamma variate curve might improve the accuracy of the method.

The present acetazolamide tests in normal individuals gave an approximately 70% increase of both CBF and CBV. In the literature, CBF response to acetazolamide is reported to vary between 25% and 70%, 2,23.34 The ability to measure the reactivity to CO₂ or acetazolamide is considered to be an indicator for the sensitivity of any method of measuring CBF. Our data confirm that the increase of CBF after acetazolamide is associated with a significant increase of CBV and that the dynamics of CBV can be used for the evaluation of cerebrovascular reserve capacity as well as the dynamics of CBF. 4,21,34

The hemo-CT method could adequately identify the expected increased fractional CBV in cases of chronic cerebral ischemia. The high CBV in these instances is well known and corresponds to a compensatory dilatation of the vascular bed. 19,20,34 Baseline CBV in these pathological conditions, on the other hand, was obviously overestimated with the present method. The reason for the falsely high CBV values appears to be a consequence of the high CBV values, which may influence the CBF calculations if relatively long scan-to-scan intervals are used. With the present settings, a tentative correction proportional to the increase of CBV gave reasonable results. The response to acetazolamide in these pathological situations corresponded to the expectations based on the CO₂ reactivities measured by TCD. Reactivity of both CBF and CBV was clearly diminished in the ischemic hemispheres.

In contrast to the good results for CBV, CBF determinations with the present hemo-CT are less adequate than with the standard 19 Xe technique. A reduction of the scan–scan interval to less than 1 second, which has recently become possible with the fast-scanner generation, could theoretically eliminate this disadvantage. However, there are two problems with high-speed scanning. First, the high radiation exposure associated with the necessary 50–100 scans is not acceptable in clinical routine. Second, if the time between scans is reduced below the presently used value, the pulse-wave phase during the scan must be accounted for because flow in most segments of the cerebral vascular bed is pulsatile. To preserve the present simplicity it may be preferable to maintain scan intervals of between 3 and 4 seconds but introduce an rCBV-weighted corrective algorithm.

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References


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