Clinical Experience With the Use of Xenon-Enhanced CT Blood Flow Mapping in Cerebral Vascular Disease


SUMMARY Cerebral blood flow mapping with the xenon-enhanced/CT method has become a useful clinical tool in the management of patients with occlusive cerebral vascular disease. Studies involving 4-5 minutes of inhaling a xenon/oxygen mixture (<35%) can now be performed routinely with acceptable patient tolerance and compliance. Four cases with acute and chronic ischemic injuries are reported here to illustrate the manner in which this method has been used to characterize flow pattern in such patients and the relevance of this flow information to clinical patient management.

Since the Fick principle was first applied to the measurement of global cerebral blood flow by Kety and Schmidt in 1948,† the clinical examination of CBF has evolved rapidly. Scintillation counting of xenon133 introduced by direct carotid injection or inhalation, with washout curve analysis, made regional flow analyses available to many institutions. The inherent lack of spatial resolution and the inability to separate flow values at depth from superficial ones then led to the development of tomographic imaging with xenon133 (Lassen) and other single photon-emitting tracers. The use of positron emission tomography, currently limited to a few centers, added to the capability of examining local flow the important ability of defining local metabolism.13 14 Several groups of investigators, including ourselves, have studied the use of stable xenon gas and transmission tomography for the measurement of local cerebral blood flow. This is a method more readily available than are some others (e.g., PET), and it appears to provide local blood flow information with a relatively high degree of spatial resolution and anatomical correlation. In this report we present four clinical examples of the type of information the xenon/CT method is able to render in cases of cerebral vascular disease.

Methodology

We have successfully completed blood flow studies as of this writing in 36 awake and 6 intubated patients, with xenon/CT gas mixtures of 30-35 and 40-55%, respectively.* Patients and/or their relatives are carefully informed before the study of the radiation dose associated with this method as well as possible transient sensory disturbances and the importance of maintaining head position. An approved consent form is obtained for each study.

A one-way, semi-closed delivery system is used for gas delivery. Before each study, a 60-liter pulmonary function bag (Warren E. Collins, Inc.) containing approximately 50 liters of xenon/oxygen gas mixture is connected to a large-bore three-way valve (Hans Rudolph, Inc.), with the side arm open to room air and a unidirectional T-piece (Instrumentation Industries) connected to the patient via either a face mask (Vital Signs, Inc.) or to a mouthpiece combined with nasal compression (Airlife, Inc.). Distal to the T-piece, an expired air reservoir is created by inserting a 30cc plastic tube connected distally to a one-way flutter valve. A pre-calibrated thermal conductivity analyzer (Gow-Mac Instrument Co.) is used to monitor end-tidal xenon concentration via an 18-gauge needle inserted into the reservoir and connected to the gas analyzer. A capnograph (Puritan Bennett Corp.) monitors PCO2. Both PCO2 and xenon concentration values are continuously recorded. PCO2 values in all our monitored cases have been in the 36-43 mm Hg range.

We have conducted blood flow studies in GE-8800 CT/T and 9800 scanners equipped with dynamic imaging capabilities. Awake patients are positioned in the standard CT head-holder, and the level or levels for blood flow analysis are then selected from a baseline series of CT scans. (Two to three levels may be studied; the number of levels is currently limited by x-ray tube heat loading.) The gas delivery system is connected to the patient, who continues to breathe room air. After the patient has been instructed to remain still, two baseline scans are taken for each level of flow analysis. There is a pause of approximately two minutes to allow for tube cooling and baseline scan review, and xenon delivery is then initiated by rotating the three-way valve. About 1.3 minutes after xenon inhalation is initiated, the first series of images is begun. Dynamic imaging with incremental table movement is used when data from more than one level are desired. The patient’s tolerance to xenon inhalation is monitored throughout this procedure with the use of
predetermined foot movements at the request of the person administering the xenon. If the foot movements are inappropriate or absent, the procedure is terminated. Four to six enhanced scans are obtained at each level during a five-minute inhalation period, after which time the three-way valve is rotated and the patient returned to room air.

A few minutes after gas inhalation is terminated, all our ambulatory patients have been able to sit up and then to leave the CT facility within 10 minutes. The average total time for a single flow study in awake patients has been 40 minutes, with an eight- to 10-minute period of voluntary rigid head fixation. Our success rate in recent studies has increased because of somewhat improved stability and signal-to-noise ratio of our equipment and because of the fact that we perform studies in awake patients at somewhat lower xenon concentrations (30–33%). The radiation dose to the tissue examined is relatively high (15–20 rads). More detailed information on the limitations and problems associated with this method have been described in detail elsewhere. 17  32

Blood flow determinations are made by methods we have described in detail elsewhere. 17  18 In brief, we perform one to three baseline scans before xenon inhalation and average these for reduced noise levels. Four to six enhanced images are obtained at each level during inhalation. The averaged baseline images are then subtracted from the enhanced images, and each voxel is subsequently defined by a series of enhancement values as a function of time \( \Delta CT(t) \). This series is used in conjunction with end-tidal measurements assumed to be proportional to xenon concentrations in arterial blood, to solve for a mono-compartmental Kety equation in which \( \Delta Ca(u) \) and \( \Delta CT(t) \) are used as input data:

\[
\Delta CT(t) = f^2_r \Delta Ca(u)e^{-\sigma_r t} + \omega \Delta u
\]

A weighted and/or nonweighted least square fit routine is used to derive the estimates of two parameters, \( \lambda \) and \( k \) or \( \lambda \) and \( f \). Pre- and post-analysis smoothing routines can be used to reduce pixel-to-pixel variation. We currently use a 3 x 3 pixel bell-shape filter.

Case Histories

Case 1

A previously healthy 50-year-old white male had developed a left-sided weakness and numbness one year before admission. Over the month after he was admitted, he recovered all but fine dexterity of the left hand. At that time, angiography demonstrated a high-grade right middle cerebral artery narrowing suggestive of a dissecting aneurysm. The man was treated with aspirin and persantine satisfactorily for nine months, at the end of which time he awoke with left-sided focal seizure activity. There was no new focal deficit following this episode, but angiography once again demonstrated proximal middle cerebral artery stenosis with delayed filling of the distal middle cerebral artery distribution.

Diphenylhydantoin therapy was initiated, and the patient remained stable for three months, after which time he was referred to us with a question of need for flow augmentation. Physical abnormalities at the time of referral were clumsiness of fine finger movements on the left side and pronation of the left hand. Deep tendon reflexes were also increased on the left side.

A CT scan demonstrated a moderate degree of diffuse atrophy within the distal right middle cerebral artery distribution (figs. 1a, 1b). The xenon/CT blood flow map (34% xenon) showed flow values within the normal range in the lentiform and thalamic nuclei bilaterally. Atrophic regions within the insular cortex had appropriately low flow values, while a central island of retained, normal-appearing gray matter was shown to have normal flow values compared with the left hemisphere (figs. 1a–1c). Consistent flow values were demonstrated in the two brain levels studied.

A repeat angiogram the following day demonstrated a recanalization of the right middle cerebral artery and rapid filling of the distal middle cerebral artery vessels. Following these studies, the patient has remained asymptomatic for 12 months without surgical intervention.

Case 2

A 38-year-old female with a six-year history of recurrent ischemic attacks within the left cerebral artery distribution was admitted. Angiography four and six years previously had demonstrated proximal anterior and middle cerebral artery stenosis and delayed filling of the middle cerebral artery distribution. Until one month prior to admission, this woman had been relatively asymptomatic on anticoagulation therapy with Coumadin. At that time, despite adequate anticoagulant level, the ischemic attacks recurred, and the woman was referred to us for an extracranial/intracranial bypass procedure to augment flow in the left middle cerebral artery distribution.

Carotid and vertebral injections of contrast media failed to demonstrate rapid filling of the middle cerebral artery region on the left side, which filled only in a delayed manner via leptomeningeal and medullary collaterals in a "moya moya" pattern (fig. 2). The preoperative CT scan showed an old and relatively small infarction within the anterior cerebral artery distribution, with a normal-appearing tissue volume and architecture in the remainder of the hemisphere (fig. 3a). Despite the normal anatomical appearance by CT of tissues within the middle cerebral artery distribution and appropriate gray and white matter flow patterns, a xenon/CT blood flow study (33% xenon) showed that flow values were reduced within the entire left middle cerebral artery distribution (figs. 3a, 3b). This patient subsequently underwent an extracranial/intracranial bypass procedure, after which she has remained asymptomatic for six months on antiplatelet therapy alone.

Case 3

A 60-year-old white female who had had a massive middle cerebral artery territory infarction one year earlier was referred for evaluation. Noninvasive studies
had suggested that the left middle cerebral artery might still be patent, although severely compromised. Because this woman had gained a significant degree of independent function, we performed an angiogram, which showed that the left internal carotid artery was, in fact, occluded. One hour later, the patient underwent a grand mal seizure. After six hours, when the patient had not awakened despite the cessation of seizure activity, a CT scan was obtained. There was no new abnormality.

When the patient remained unresponsive for the next 48 hours despite no additional seizure activity, we performed a xenon/CT blood flow study. At this time, the baseline CT scan demonstrated, in addition to the previously found left middle cerebral artery infarction, a new region of low density within the right lentiform nuclei (fig. 4). The xenon/CT blood flow study (35% xenon) verified the absence of flow within this area as well as in the region of the infarction on the left side. There was profound reduction of cerebral blood flow within the frontal lobes, which appeared anatomically intact on the baseline CT scan. Flow values were also markedly reduced within the region immediately behind the area of the old left-side infarction.

Figure 1a. Case I. This transverse tomographic image (top) at the level of the fornix is the baseline image for the derivation of the blood flow map (bottom). The blood flow scale (left) is in ccm/100 cm^2/min. Average blood flow values for the 1 cm x 1 cm x 1 cm-thick region of interest are presented. Note the symmetrically high flow values derived from the basal ganglion and from retained cortical gray matter. Figure 1b. A color display of the flow map in Figure 1a clearly defines the expected high flow (gray matter), regions of the basal ganglia, insular cortex, and cortical gray matter, especially on the normal left side. These high flow values are readily distinguished from the slower flow, presumably within the white matter, of the internal capsule and the deep hemispheric white matter. Figure 1c. This 1-centimeter thick tomographic image through the body of the lateral ventricle was obtained 2 centimeters above the level shown in fig. 1a. Despite diffuse atrophy at this level, all retained tissues have relatively normal flow values.
Figure 2a. Case 2. This left carotid injection during the early arterial filling demonstrates no primary blood flow to the distal middle cerebral artery vessels. Figure 2b. 2.5 sec after the film in 2a, arterial filling into the middle cerebral artery vessels is present via transmedullary collaterals from the lenticulostriate, leptomeningeal, and posterior choroidal vessels.

Case 4

A 37-year-old white male presented with the sudden onset of a severe headache associated with moderate numbness and weakness of his left arm. A CT scan showed retained blood within the deep insular region on the right side, and angiography verified the presence of a right middle cerebral artery aneurysm. There was only moderate narrowing of the vessels.

The patient was referred for surgical management three days later, when it was apparent that the weakness in his left side was becoming more profound. A CT scan at this time demonstrated only a small area of low density within the distal middle cerebral artery distribution. The patient was treated with aggressive blood volume expansion, and his blood pressure was maintained within a normal range over the following three days; this resulted in stabilization and some improvement of the left-sided hemiparesis. However, repeat angiography demonstrated severe vasospasm of the internal carotid artery on the right side, with delayed filling of the distal branches of the middle cerebral artery (fig. 5). A xenon/CT blood flow study (31% xenon) obtained the following morning showed reduced flow throughout the entire right hemisphere and supported the angiographic diagnosis of severe vascular compromise (fig. 6). Flow values were also reduced within the right thalamus and occipital lobe. Surgery was performed five days later, by which time the patients' clinical condition had improved markedly. The aneurysm was clipped in an uneventful fashion, and there was no increase in neurological deficit postoperatively.

Discussion

Methodology

The xenon/CT method possesses a number of attributes that make it a valuable technique for the measurement of LCBF. Blood flow images (maps) correlate to anatomical structures as viewed from CT images. The flow information derived from these maps corresponds to the physiological condition of the patient and has equal validity for superficial and deep brain regions. Flow in gyral gray and white matter (including deep white matter tracts coursing between nuclear masses), tissues with appropriate different flow values, occurs in a ratio of approximately 3.0–3.5:1 as measured by xenon/CT, in agreement with published data derived from other studies. In addition, this method appears to be safe, other than the exposure of a limited brain volume to repeated CT scanning.
symptomatic adult, if exposure to the eyes is avoided, this is probably an acceptable risk.) Finally, cost is not a limiting factor, since the expense for the contrast agent, xenon, is approximately $60 for a five-minute inhalation study.

In the past decade, refinements in computerized transmission tomography and in the computational methodologies used in the calculation of local cerebral blood flow have resulted in additional substantive improvement of the xenon-enhanced CT method of determining blood flow. The signal-to-noise ratio and the stability of current CT scanners have made possible the quantification of xenon movement throughout the brain with clinically acceptable xenon/oxygen concentrations (< 35%) in awake patients. Shorter scanning times and programmed incremental table movements have made possible the acquisition of data from more than one brain level during a single inhalation period.

The resolution of a blood flow image depends on many variables: the xenon concentration, CT technique (kVp, mAs), number of baselines and enhanced scans, time of scanning, the computational methodology used, and the pre- and post-analysis filtering performed. While the determination of flow value for each voxel (0.8 x 0.8 x 5 mm^3) avoids significant tissue inhomogeneities, some mixing and partial volume effects are inevitable. In addition, the existence of artifacts and misregistrations is an important factor in determining the quality of the derived flow map. Typical resolution in our blood flow maps in awake patients has ranged from 5-10 mm (FWHM); the degree of resolution depends heavily on the amount of filtering required to please the viewer. The reproducibility of derived flow values was investigated in a series of repeated studies in nonhuman primates which were maintained under similar physiological conditions. In

**Figure 3a.** Case 2. The CT scan (top) is the baseline image for the blood flow map (bottom). Despite retention of relatively normal tissue volumes within the left middle cerebral artery distribution, blood flow values are diffusely reduced. Note that the value of 9 ccl/100 cc/min is from within the region of old left frontal lobe infarction. Figure 3b. This color display of the flow map in figure 3a demonstrates the reduction of flow values throughout the left middle cerebral artery distribution. The old infarction within the left frontal lobe is evident.

**Figure 4.** Case 3. The baseline CT images are on the left; blood flow maps are on the right. The upper pair of images is derived from axial tomography at the level of the basal ganglion and the lower pair from a level 2 cm above that. An absence of flow is evident from within both old and new (48 hours) areas of injury, along with a far wider disturbance of blood flow than is suggested by the CT image.
FIGURE 5. Case 4. The right internal carotid injection of contrast media displays severe narrowing of the initial intracranial portion of that vessel. The distal middle cerebral artery vessels are also severely narrowed and are seen to fill in a delayed manner.

these studies, the reproducibility of averaged flow values in regions of interest 0.5 × 0.5 × 0.5 cm³ or larger has been ± 11 percent.

Infarction

Although our experience with acute cerebral vascular disease is currently limited to blood flow studies in 10 patients, blood flow mapping with the xenon/CT method does appear to provide clinically useful information. Blood flow information alone may be misleading during the initial days following cerebral infarction, due to the possibility for uncoupling of flow from metabolism, but the ability to compare flow information with anatomy as is defined on the baseline CT scan appears to resolve some of these difficulties.

We believe that a well-defined region which is shown to have no blood flow and which within eight to 24 hours of onset becomes hypodense as shown by computerized tomography defines a tissue which is undergoing the infarction process (cases 3, 4). This has also been a totally consistent pattern in a series of nonhuman primate infarction studies currently underway in our laboratory. Although we have not yet studied cases of partial or total reperfusion of infarcted tissues, described by Olsen et al with xenon¹³³ tomographic imaging and by Lenzi et al with positron emission tomography, the presence of unusually high flow values in a region with an altered partition coefficient (lambda) and lowered baseline CT values may help to define the true nature of this injury. This ability to establish the size and location of an ischemic process, as well as to evaluate the amount of blood flow which results from proposed therapies should be useful in understanding this process and in treating the patient.

Delayed Examination After an Ischemic Event

In the more chronic situation in which a patient is seen months after ischemia occurs and the question arises as to whether an extracranial/intracranial bypass is indicated, xenon/CT blood flow mapping appears to provide a valuable means of comparing retained anatomy directly with its local blood flow. In many cases, this can be done by relating average blood flow values in equally sized regions of interest in both hemispheres to each other or by comparing relative flow imbalances on a pattern basis. The latter technique permits a direct comparison of flow alteration with known vascular distributions.

The retention of some tissue with high flow values within an atrophic region, as was observed in Case 1 above, appears to have suggested correctly that blood flow delivery was no longer the primary problem. In this case, as in three others we have studied in which small but stable strokes occurred following internal carotid artery occlusion, the presence of adequate collateralization was also suggested by the presence of normal flow values within the lentiform nuclei, which...
are primarily supplied by perforating arteries of the proximal middle cerebral artery. The relative need for additional blood flow reserves appears more likely in cases in which structures have been retained, but flow values can be shown by xenon/CT to be diffusely reduced (e.g., cases 2, 4). Because preliminary studies with xenon/CT methodology have demonstrated augmentation of flow with physiological stress (CO₂ variation, motor activation, and sensory stimulation), findings in line with those shown by other methodologies, we anticipate that incorporation of the xenon/CT method will also be helpful in evaluating the blood flow reserve within vascular territories.

**Small Infarction Due to Vasospasm**

Our last case study (Case 4) describes the combination of a small recent infarction and reduced regional perfusion, due presumably to vasospasm which followed the rupture of a middle cerebral artery aneurysm. The xenon/CT method showed that nearly the entire right hemisphere appeared normal anatomically, despite low flow values. This finding, plus the patient's fluctuating neurological deficit, suggested that the primary problem was reduced blood flow delivery due to vasospasm. Treatment was therefore guided toward increased cardiac output and the moderate elevation of blood pressure. In line with this approach, Ferguson et al have reported that the timing of surgical intervention should be guided by flow values. They observed that elective surgical intervention occurring while flow values were severely compromised was associated with a reduced likelihood of successful outcome.

**Patient Tolerance**

Xenon at 80% concentration is a known anesthetic agent, and some alteration of sensorium is commonly associated with its inhalation at the 31–35% level used in these studies. However, we have had no significant difficulty obtaining valuable results due to an intolerance to its inhalation at these levels. The alteration of the senses that occurs is probably due to an early anesthetic release phenomena commonly associated with inhalation anesthetic agents; feelings of tingling, buzzing, or floating are frequently reported but are short lived following the discontinuation of xenon inhalation. Most of our patients have perceived these feelings as pleasant and have expressed the willingness to undergo further studies. Two patients out of 36 have entered an apparent sleeplike state during five minutes of xenon inhalation at a 35% concentration, but they experienced no apparent alteration of blood pressure, heart rate, or breathing pattern and awoke within 30 seconds after the xenon was discontinued, with no apparent sequela.

Two other individuals found the sensory disturbance created by the 35% xenon concentration level to be unpleasant. In one case this was due to a perceived hypersensitivity of all sensory functions and in the other to a fear of lack of control created by a "floating feeling." Our recent experience with newer equipment (GE 9800 scanner) indicates that acceptable data can be obtained with somewhat lower xenon concentrations (30–33%). At these levels, undesirable effects are significantly reduced.

We believe that, in spite of its limitations, the xenon/CT blood flow technique provides a useful and potentially widely available methodology for the study of cerebral blood flow in cases of normal and disturbed physiology. It is now possible to obtain blood flow maps with adequate resolution which also provide the advantage of a direct correlation of flow with anatomy.

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