Xenon and Iodine Enhanced Cerebral CT: A Closer Look

David Gur, Sc.D., Howard Yonas, M.D., Sidney K. Wolfson Jr., M.D., David Herbert, M.B.B.S., William H. Kennedy, Burton P. Drayer, M.D., Leonard Shabason, Ph.D.

SUMMARY Xenon and iodine enhanced dynamic computerized tomography (CT) have been used experimentally to obtain both qualitative and quantitative information on local cerebral blood flow in both normal and infarcted tissue. Direct comparisons between Xenon enhancement, iodine enhancement and pathological findings demonstrate significant differences between results derived from each of the 2 in vivo techniques. While iodine enhanced dynamic CT yields valuable information concerning the patency and density of vasculature, xenon enhanced studies can provide highly focal information on cerebral tissue perfusion.

INTRODUCED as a morphologic technique, computerized tomography (CT) can be used to derive in vivo physiologic information which was previously the sole domain of radionuclide studies.14 The spatial resolution provided by CT permits anatomical specificity previously unachievable from external scintillation counting techniques of blood flow. Fast scanners allow rapid, serial imaging required for monitoring rapid changes of tracer concentrations within physiological systems.4-7 The clinical role of dynamic CT imaging is being explored for a number of applications.8

One of the more promising applications of CT lies in its ability to qualitatively visualize and quantitatively characterize time dependent changes on serial CT images of the brain, after either intravenous iodine injection or non-radioactive xenon inhalation. It is proposed at this time that this type of information can be used for non-invasive, in vivo evaluations of local cerebral blood flow and possibly the quantitative measurement of this variable.5-7 Both techniques have clear advantages and limitations.9 The major advantages of an iodine enhanced CT are a high degree of CT enhancement that can be evaluated and the fact that delayed scanning provides qualitative diagnostic information on blood-brain barrier permeability defects.11-13 Its major disadvantages are the difficulties in obtaining meaningful quantitative blood flow estimates and in correlating such data with tissue perfusion. In addition, only one brain level can be studied at a time.14 The major advantage of the xenon enhanced dynamic CT is the ability to quantitatively estimate tissue perfusion and to do so at more than one brain level during a single inhalation study.14 Its major drawback is a limited maximum attainable enhancement when non-anesthetic xenon concentrations are inhaled.

In this study we report the results of a direct comparison between xenon and iodine enhanced CT studies on the identical brain level of a baboon 19 days post infarction. Direct evaluation with the appropriate pathological specimen is then made.

Method

A. Animal Preparation

The study was carried out on a baboon (Papio cynocephalus/anubis) weighing 9.8 kg. A cerebral infarction had been created 19 days previously by directly occluding only the animal's right lateral lenticalostricate arteries (LLS) at their origin from the middle cerebral artery. This was done through a retro-orbital approach in which the lateral and posterior inferior orbital wall was surgically removed, and the vitreous of the posterior chamber of the eye aspirated. The dura over the middle cerebral artery was then incised and folded inferiorly, allowing an arachnoidal dissection anterior to the middle cerebral artery without brain retraction. The lenticalostricate arteries were then identified and selectively coagulated with a fine, insulated bipolar forceps. The dura was then reaproximated, the vitreous reinjected into the eye and the incision closed. Although the animal rapidly returned to full alertness and independent activity within its cage, a left hemiplegia was apparent with the greatest deficit in the use of the left arm and intrinsic hand muscles. Further details of this technique and its reproducibility are given elsewhere.14

After sedation with phencyclidine hydrochloride (Sernyol, Bio Centric Labs, St. Joseph, MO) a cuffed endotracheal tube was inserted and connected to a semi-closed ventilation apparatus (Harvard respirator) controlling the inhalation of xenon and oxygen. Ketamine hydrochloride (Ketalar, Parke-Davis, Morris Plains, NJ) and pancuronium bromide (Pavlon, Organon Pharm., West Orange, NJ) were then administered intravenously as needed throughout the experiment to keep the animal sedated and immobile. Continuous cardiac and respiratory monitoring were routine. An arterial catheter was placed in the femoral artery to permit rapid arterial blood sampling. In addition, to enable the rapid intravenous injections of contrast media, a venus catheter was placed in the inferior vena cava. A multi-channel Corning Analyzer
was used to measure Pao\(_2\), Paco\(_2\), and pH of samples drawn from the arterial line. A Gow-Mac gas leak detector was used to measure the end tidal xenon concentrations\(^*\) from the end of the endotracheal tube. This information was used to provide a continuous record of alveolar and, therefore, (indirectly) arterial xenon levels.

B. Xenon Study

Pure oxygen was inhaled by the animal for about 10 minutes until nitrogen was washed out of the respiratory system and tissues, as indicated by stable arterial and expired oxygen concentrations. CT scans were performed using a CT/T 8800 General Electric scanner with 320 x 320 matrix and 5 mm collimation. Exposure factors were a 4.8 second scan time, at 90 kVp, and 160 mA. Subject motion did not interfere with the study, as a surgical plane of anesthesia was maintained. A non-enhanced, baseline CT scan was obtained before each study in order to locate the optimal level for the xenon and iodine enhanced measurements.

Following the baseline scan, a mixture of 61% xenon/39% oxygen was inhaled for 6 minutes and serial CT scans were performed at the same level at 2, 4 and 6 minutes during xenon buildup. The clearance phase was begun by abruptly discontinuing xenon inhalation and initiating 100% oxygen inhalation.

A visual evaluation, which was based on the CT images with routine window settings, permitted a gross analysis of the temporal changes in tissue attenuation coefficients during xenon enhancement. The visual review was utilized in choosing specific anatomic locations to be used for the derivation of numeric information concerning xenon build up.

Several specific anatomic regions of interest (ROI) were selected for analysis within the CT slice under investigation. Each of these locations were assumed to be homogeneous and the tissue volume investigated in each locale was 4 x 4 x 5 mm\(^3\). A partition coefficient and regional cerebral blood flow value was estimated from the inhalation (build up) phase.

In tissue locales where saturation was confirmed by stable enhancement at 4 and 6 min scans, a direct method was used to derive partition coefficients (\(\lambda_i\))\(^*\). In all other locations, estimates were made from either hematocrit corrected tables or from estimated enhancement values at equilibrium.\(^*\) These were extrapolated by multivariable analysis (curve fitting) from a 15 min inhalation study (38% xenon/62% oxygen). Once the partition coefficient for each ROI was estimated, the in vivo autoradiographic technique was used to derive flow rate constants (\(k_i\)). The governing relationship used here is based on the principle set forth by Kety:\(^*\)

\[
C(t) = \lambda_i f_i \int_0^t C(u) e^{k_i(t-u)} du
\]

where flow is \(f_i = \lambda_i k_i\).

The derivation of the flow constant (\(k_i\)) is performed by several iterations of equation, one using the partition coefficient (\(\lambda_i\)), the xenon concentration in arterial blood \(C_a(u)\) and the CT enhancement of the tissue of interest \(C(t)\) as the input data. Enhancement values from the 2 minute and 4 minute scans were used in the calculations of flow within tissue with fast or slow flow, respectively.

C. Iodine Study

The iodine enhanced study at the same level (slice) was carried out using data from 6 scans performed in the rapid sequential mode, 4.8 sec scan time with 1.2 sec interscan delay, and identical exposure factors. Scanning was initiated approximately one sec following intravenous injection of 0.9 grams of iodine/kilogram of body weight in 5 seconds. Limitations of the scan times precluded quantitative analysis of the iodine enhancement patterns, however, a plotting routine was used for display of the time dependent iodine enhancement in the same locales for which quantitative xenon analyses were made.

D. Pathologic Studies

Twenty-four hours following the CT studies, while under barbiturate anesthesia, the abdominal aorta and vena cava were cannulated and the animal infused with saline followed by 10% buffered formalin. The head was then selectively perfused with radio-opaque silicone rubber (Microfil, Canton Biomedical Products, Inc., Boulder, CO) injected via a common carotid cannula. The brain was then removed and placed in 10% buffered formalin solution for one week. The brain was then studied for external anatomical detail under 15 and 25 power magnification following which it was sectioned into 4 mm thick slices. Xeroradiography of the silicone injected sections was employed to obtain images of the entire vascular system.

Results

A series of images showing the baseline scan and 3 xenon enhanced scans (2, 4 and 6 min) are shown in figure 1. Figure 2 displays typical time dependent patterns of xenon enhancement in selected regions; tissue with fast flow (gray), slow flow (white) and infarcted tissue. Progressively increasing brain enhancement is readily noted. Tissue with fast flow (gray) shows a rapid build up reaching equilibrium at 4 min while tissue with slow flow (white or infarcted) shows a continuing increase in xenon concentration even at 6 min. The table contains a summary of blood:brain partition coefficients and blood flow estimates for several representative locales. Estimated CBF in gray and white matter is easily differentiated.

Time dependent iodine enhancements following bolus injection in selected locales used in the xenon analysis are presented in figures 3, 4 and 5. No attempt has been made to quantitatively analyze these results at this time. Prominent enhancement is observed in tissue with fast flow (gray), slow flow (white) and infarcted tissue.
TABLE Local Cerebral Blood Flow in Selected Locales

<table>
<thead>
<tr>
<th>Locale</th>
<th>Flow Rate Constant, k (min⁻¹)</th>
<th>Partition Coefficient, x</th>
<th>Cerebral Blood Flow Rate (ml/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Lobe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Gray</td>
<td>0.80</td>
<td>0.82</td>
<td>66</td>
</tr>
<tr>
<td>White</td>
<td>0.12</td>
<td>1.4</td>
<td>17</td>
</tr>
<tr>
<td>Left Gray</td>
<td>0.82</td>
<td>0.90</td>
<td>74</td>
</tr>
<tr>
<td>White</td>
<td>0.11</td>
<td>1.6</td>
<td>18</td>
</tr>
<tr>
<td>Infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.20</td>
<td>0.48</td>
<td>10</td>
</tr>
<tr>
<td>B</td>
<td>0.10</td>
<td>0.6¹</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
<td>0.06</td>
<td>0.6¹</td>
<td>&lt;5²</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Gray</td>
<td>0.77</td>
<td>0.95</td>
<td>73</td>
</tr>
<tr>
<td>White</td>
<td>0.09</td>
<td>1.5</td>
<td>14</td>
</tr>
<tr>
<td>Left Gray</td>
<td>0.86</td>
<td>0.92</td>
<td>79</td>
</tr>
<tr>
<td>White</td>
<td>0.12</td>
<td>1.5</td>
<td>18</td>
</tr>
</tbody>
</table>

¹Partition coefficient in these locales was assumed that of water.
²Due to the rapid increase in the errors associated with such low flow only an upper limit for flow was derived.
³The overall estimated error in derived partition coefficient and cerebral blood flow in normal tissue is estimated to be 15 and 30%, respectively.

Cerebral tissue perfusion. The penetration of highly lipid soluble xenon gas in brain tissues is observed as an increase in CT number and its rate of build up or washout can then be used to directly calculate local tissue blood flow. Because the rate of tissue saturation is a relatively slow process, taking 2 to 3 min in tissue with fast flow and 15 min or more in tissue with slow flow, xenon enhanced CT studies do not require rapid scanning and can be adequately performed with slower scan times. However, rapid scanning technology has allowed us to perform flow studies at several different brain levels during a single inhalation study. Xenon build up methodology has been chosen because it is less biased by potential anesthetic effects.
of the gas itself. It is possibly somewhat less expensive than washout methodology because a shorter study may be permitted. Although a high xenon concentration (61%) was utilized in this study, quantitative information can be obtained with lower xenon concentrations (35–40% range). The latter will be required for studies involving awake patients voluntarily respiring through a face mask.

A bolus injection of intravenous iodine does provide a striking enhancement of the cerebral vasculature during the initial arterial transit. Because CT visualization of iodine transit through the vasculature (not actual tissue penetration) is highly time dependent, scan times of 1 sec or less are necessary to obtain several data points during the 6 to 8 sec of the cerebral
transit time. Variations of cardiac output, injection technique and dilutional variables are inherent sources of errors associated with quantitative blood flow determinations using this technique.\textsuperscript{11, 14} The correlation of increased iodine enhancement in gray matter with its evidently dense vasculature is readily apparent from the comparison with the xeroradiographs. White matter and infarcted tissues are poorly differentiated in these studies because of their relative lack of blood vessels. Although time dependent iodine enhancement has been utilized to study blood flow within areas of gray matter, white matter and areas of infarction, we are unable to make a clear separation with our equipment. We have, however, noted a consistently higher maximum enhancement in tissues with fast flows with peak arrival time observed somewhat earlier than slow flow tissue. Other authors have suggested that these patterns may be more distinguishable in other types of diseased tissues.\textsuperscript{11}

It is apparent that although both xenon enhanced and iodine bolus enhanced CT studies demonstrate alterations of cerebral blood flow, they do this by different mechanisms. At this time we believe that xenon enhanced CT actually extends the hope of non-invasively obtaining quantitative, clinical data of tissue perfusion with a high degree of tissue specificity. Iodine studies, in conjunction, provide valuable additional information about the density of vasculature, as well as information about blood-brain barrier permeability defects.

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Treatment Program and Comparison Between Anticoagulants and Platelet Aggregation Inhibitors After Transient Ischemic Attack

ANDREW BUREN, M.D., AND JOHAN YGGE, M.D.

SUMMARY Transient cerebral ischemic attacks (TIA) are an important warning symptom of threatening stroke from cerebral infarction (CI). A local treatment program aimed at identifying as many individuals with TIA as possible and treating them in a uniform manner is desirable. Platelet aggregation inhibitors with a combination of acetylsalicylic acid and dipyridamole (ASA + DP) has been compared with anticoagulants (AC). The average length of treatment was 24 months and all patients received the treatment for at least 6 months. Sixty patients received AC and 65 ASA + DP. Four patients in the ASA + DP group (6 percent) and 2 in the AC group (3.3 percent) sustained cerebral infarction. These figures are essentially lower than the expected incidence of 15-20 percent.

TRANSIENT ischemic attacks (TIA) occur in 25-40 percent of patients who subsequently sustain a cerebral infarct. But not all of those afflicted consult a doctor before a stroke occurs. To identify as many individuals as possible with TIA and treat them in a uniform manner within our health service district, a special program to evaluate treatment was designed and put in operation in February, 1974. The clinical definitions for TIA and stroke are those proposed by the Joint Committee for Stroke Facilities. The diagnosis of TIA is based solely on the clinical evaluation. Angiography was reserved for patients with carotid TIA who were believed to be possible candidates for carotid surgery. The treatment program comprised 3 possibilities: anticoagulation, antiplatelet aggregant therapy and carotid endarterectomy.

Methods

One hundred and twenty-five patients with a clear history of TIA were included in the study. Sixty were given anticoagulants (AC) and 65 acetylsalicylic acid and dipyridamole (ASA + DP). All the patients were evaluated at the Department of Neurology at Borås Central Hospital. Patients with possible or suspected TIA were excluded, as were patients with minor symptoms and signs which persisted for more than 24 hours, which included patients who fell into the TIA + IR (incomplete recovery), RIND (reversible ischemic neurological deficit), and PNS (partial non-progressing stroke). The symptoms of the patients included in the study are listed in table 1. All patients found to have TIA were immediately put on one of the 2 treatment regimes, depending on whether they were born on odd or even dates. Patients with several ischemic attacks in the acute phase, so-called malignant or excessive TIA, were also allocated to treatment.

Five patients with TIA in whom a non-atherosclerotic etiology (e.g., hemodynamic factors) was considered likely, were excluded. Three of these had intracerebral vascular anomalies which may have caused TIA, one had kinking in the internal carotid artery without atherosclerotic lesions of the vessel wall and one patient with vertebrobasilar TIA was believed to have symptoms due to severe cervical spondylosis. Three patients with TIA with known collagen disease and 2 with advanced cancer were excluded, as were patients (n = 17) in whom AC were contraindicated.

Six patients born on odd dates stated that they had not taken their medicine according to directions; they had only taken one of the drugs. Two patients stopped taking the medicine owing to diffuse gastrointestinal discomfort, one patient felt "funny in his head" and one patient stated a basic fear of tablets as the reason for failing to comply with directions. These 8 patients were excluded from the study.

The concentration of acetylsalicylic acid in serum was analyzed and measurable levels found in 85 percent of random samples. This evidence of the level of...
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