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Dynamic Computed Tomography of the Brain:
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Rapid sequence computed tomography (CT) scanning has many potential applications in studying intracranial physiologic events. However, visual inspection of these rapid sequence scans fails to extract the large amount of information inherent in the digital data. The concept of corrected mean transit time applied to rapid sequence scans after intravenous bolus injection of contrast material provides quantitative data on relative hemispheric flow. Use of histogram-based areas of interest permits accurate and reproducible identification of anatomic structures including arteries and gray and white matter. Gamma variate curve fit techniques reduce statistical noise. The concept of transit time can be expanded to the creation of functional CT images.

Advances in computed tomography (CT) technology have resulted in scanners with scan times under 5 sec and very short interscan delays. Rapid sequence or *dynamic scanning* offers the possibility of exploring physiologic events such as blood flow and potentially broadens the application of CT, which previously was directed at the detection of structural abnormalities. In the central nervous system, applications for dynamic CT techniques include: (1) examination of the functional significance of extracranial carotid and/or vertebral artery occlusive disease on intracranial blood flow and effects of carotid bypass procedures; (2) recognition of infarction or ischemia and delineation of the extent of infarction by distinguishing between the nonperfused and edematous tissue compartments; (3) evaluation of the effects of vascular spasm in vasculitis or following subarachnoid hemorrhage; (4) evaluation of shunt phenomena associated with arteriovenous malformations; and (5) examination of relative perfusion of tumor compartments.

A research scanner (General Electric Corp.) installed at the University of California, San Francisco has permitted us to explore some of the applications of rapid sequence scanning, the scan technique itself, and approaches to data analysis in studies of the central nervous system.

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Materials and Methods

The Scanner

The research scanner is a versatile instrument capable of a variety of scan modes and reconstruction options [1]. It uses a 360° rotating source-rotating detector geometry with scan duration of 2.4 sec. In addition, the system is capable of producing a 525° scan of 3.5 sec duration. In either mode, the interscan delay time is a nominal 1.2 sec (fig. 1).

The data from a 2.4 sec scan can be processed to yield either a single reconstruction using the full 360° data set or, alternatively, the data can be segmented into two consecutive but partially overlapping 212° segments where each segment yields an image of 1.4 sec effective scan time. Similarly, the 525° scan data can be processed to yield either two 360° reconstructions or three 212° reconstructions (fig. 2). The 525° scan mode yields the highest number of images per unit time and is the mode of choice for performing flow

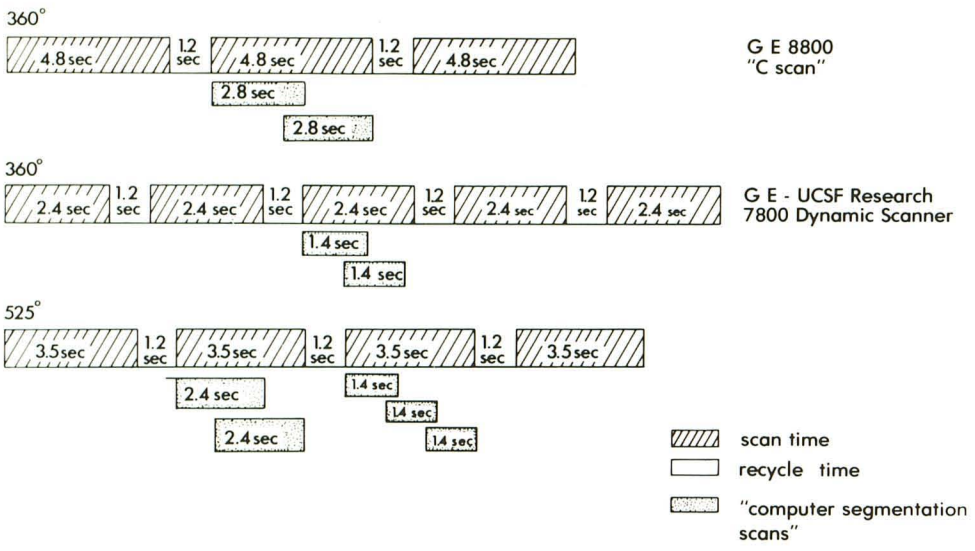
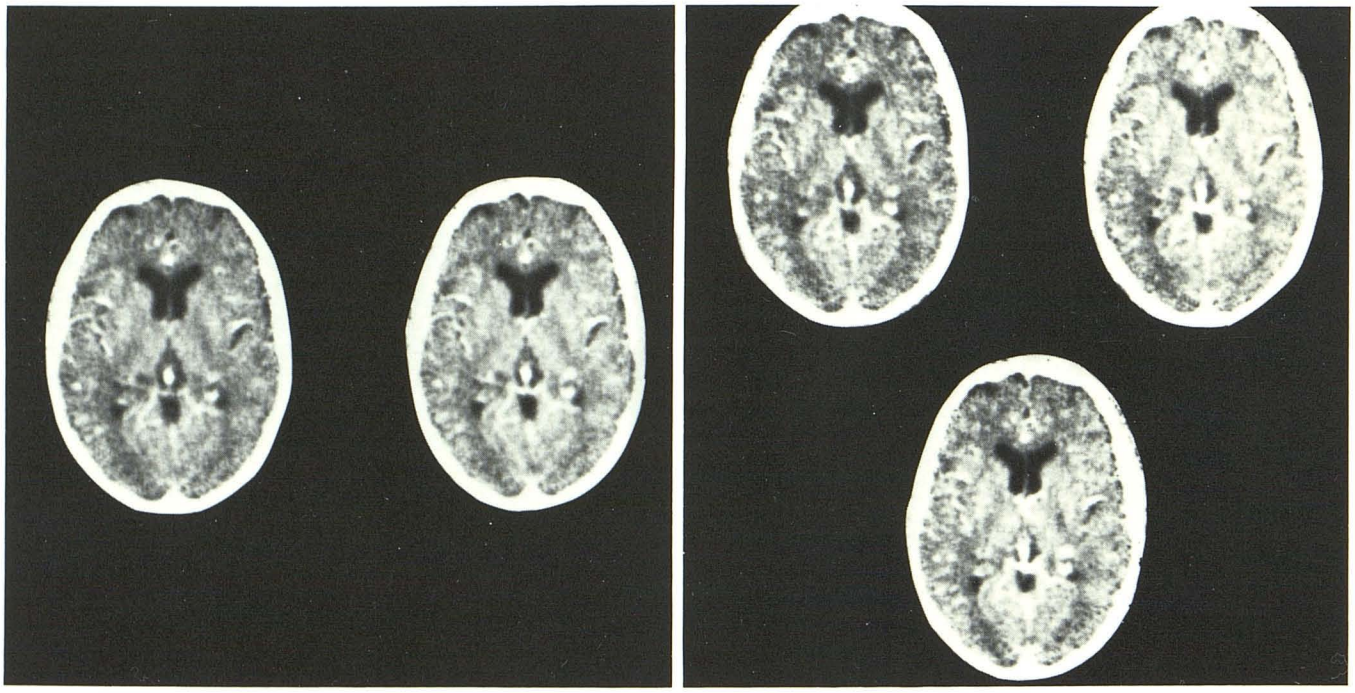


Fig. 1.—Scan speed and segmentation options with clinical GE 8800 and rapid sequence research scanner.



A B

Fig. 2.—**A**, 360° reconstructions (2.4 sec each) from 525° (3.5 sec) scan data. **B**, 212° reconstructions (1.4 sec) from same 525° scan data. Increased image noise accompanies shorter time.

studies. With this mode, for example, up to 18 images can be generated from a scan sequence of less than 30 sec.

Scan Techniques

Xenon and iodinated contrast material are the only two agents that are potentially useful in the evaluation of relative tissue perfusion with dynamic CT. Xenon is expensive, has anesthetic qualities in high doses, and is freely diffusible through the blood-brain barrier. Iodinated contrast agents are relatively inexpensive, can be adminstered as an intravenous or intraarterial bolus, and in the normal brain, do not penetrate the blood-brain barrier. The potential problems associated with the use of an intravenous injection include: (1) poor patient tolerance, (2) contrast dilution in the right heart, and (3) a subsequent relatively prolonged bolus of contrast material in the arterial system. Phantom studies in our laboratory [2] have shown that a relatively prolonged venous injection does not significantly compromise the accuracy of determination of relative flow, provided that the contrast bolus is shorter in duration than recirculation time.

Based on a large number of clinical experiments, the following approach to dynamic CT was established. The scanning procedure

is preceded by a noncontrast study to determine the optimal plane of section. For example, in the exploration of extracranial carotid occlusive disease, a scan plane at the level of the basal ganglia and sylvian fissure is identified. This permits analysis of basal ganglia structures which are relatively artifact-free as they occupy the central part of the scan and have anatomically well-delineated areas of gray and white matter. This scan level also permits analysis of arterial transit by visualization of the relatively large middle cerebral artery branch vessels that lie in the sylvian fissure and have an orientation relatively parallel to the axial scan plane. An 18 gauge angiocath is placed in an antecubital vein, and 50 ml of Conray 400 containing 20 g of iodine warmed to 37° C is injected in less than 5 sec using a mechanical injector. Conray 400 is chosen because of its high iodine content and relatively low viscosity. During injection, the arm is supported in an elevated position and the patient is asked to take a deep inspiration to speed venous return. A series of seven rapid sequence 525° scans is performed in 33 sec beginning immediately after injection.

The rapid injection is well tolerated. In over 50 examinations, ephemeral arm discomfort and occasional nausea were the only subjective complaints. There was no vomiting. Radiation dosage in these studies was about 1 rad (0.01 Gy) per scan.

Scan Data Analysis

A typical series of rapid sequence scans in a patient with a high grade left carotid siphon stenosis is shown in figure 10A. This composite is generated as a nine scan display on the video monitor. Visual inspection of the series shows contrast material appearing earlier in the right sylvian vessels (S3) than in the left (S4) with subsequent delayed passage of contrast media on the left as compared with the right. However, a priori knowledge of the lesion tends to prejudice evaluation. Examination of the scans in this manner yields little more information than that obtained from radionuclide flow scans and is certainly less helpful than a carotid angiogram.

Much more information can be derived if the digital information intrinsic to CT scanning is used. A graph of the change in density over time in any particular region can be generated by the computer. A cursor can be visually placed over a branch of the middle cerebral artery in the region of the sylvian fissure on each side. The arrival time, the relative rise time, and the peak time are some of the parameters that can be examined (fig. 3).

All of these parameters are dependent to a large degree on the character of the input function or contrast bolus. There is uncertainty and subjectivity in choosing specific arrival time due to noise in the data, as well as in deciding at what point the upslope actually begins. The arrival time would be a useful indicator in gross extracranial carotid disease where there are significant differences in flow between the two sides (i.e., a complete carotid occlusion with minimal or no collateral circulation). The rate of rise or rise time is usually defined as the difference between arrival time and the time of peak. The rise time is also influenced by the length of the contrast bolus and is insensitive to perfusion or transit. The peak height of contrast density may be an appealing parameter but is markedly influenced by partial volume artifact in which only part of the vessel is imaged, as well as by total volume of vessels in the region of interest. In comparing sequential exams, it is primarily influenced by volume of contrast bolus and injection rate variations. This assumes the identical level is scanned. More important, these parameters do not provide a measure of relative tissue perfusion, which is the most significant determinant of cerebral function. Basic concepts of brain perfusion determination were well covered by Zierler [3] and were specifically related to dynamic CT by Axel [2].

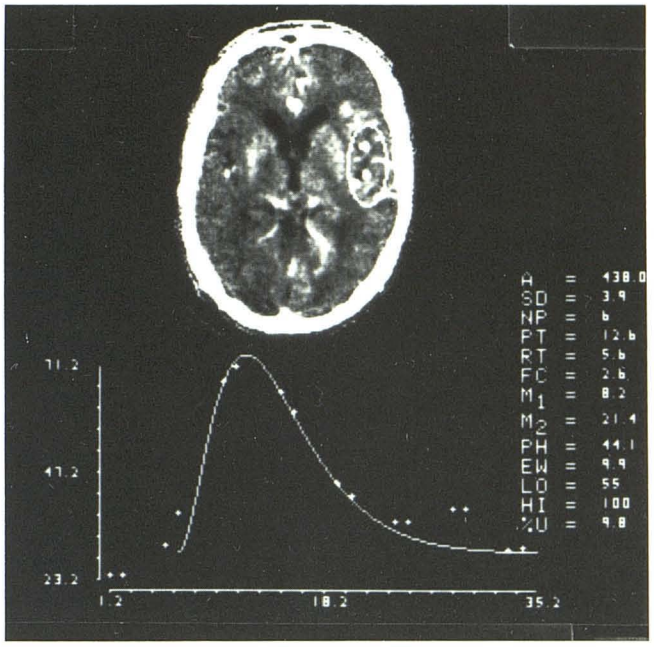


Fig. 3.—Curve fit relating change in density in left sylvian vessels over time after rapid bolus contrast injection. This program permits examination of a number of parameters including: area under curve (A); standard deviation (SD); number of points (NP); peak time (PT) (the time of greatest curve height); rise time (RT) (time between contrast appearance and peak concentration); falling portion of curve (FC) (the exponential decline of a gamma variate); first moment (M1) (measure of mean time); second moment (M2) (measure of curve width); peak height (PH) and equivalent width (EW) (area under curve divided by height, which is another measure of curve width). LO and HI = CT number range; %U = percentage of histogram-selected pixels within total elliptical area selected.

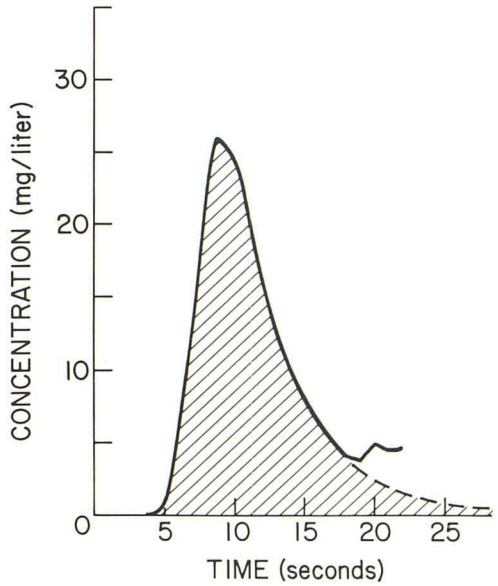


Fig. 4.—Typical indicator dilution analysis curve. (See text.)

They are briefly reviewed below.

The critical parameter is blood flow per unit tissue volume. CT is unique in that it permits identification of specific tissue volumes. However, these sections contain not only cerebral tissue, but also

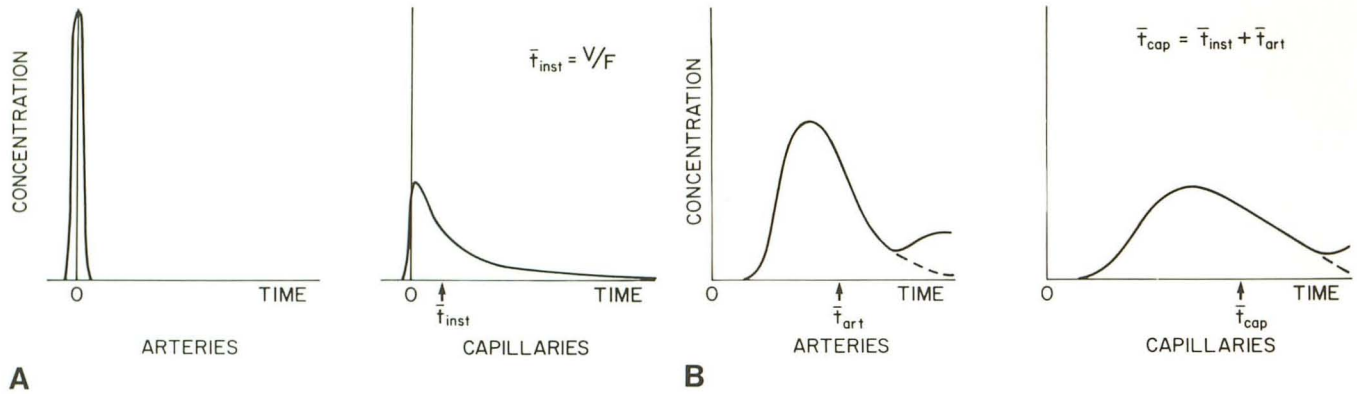


Fig. 5.—**A**, Instantaneous contrast bolus. Washout curve, in which arterial input function is segmented from rest of washout curve. (See text.) **B**, Prolonged contrast bolus. Segmented washout curves with prolonged input function. (See text.)

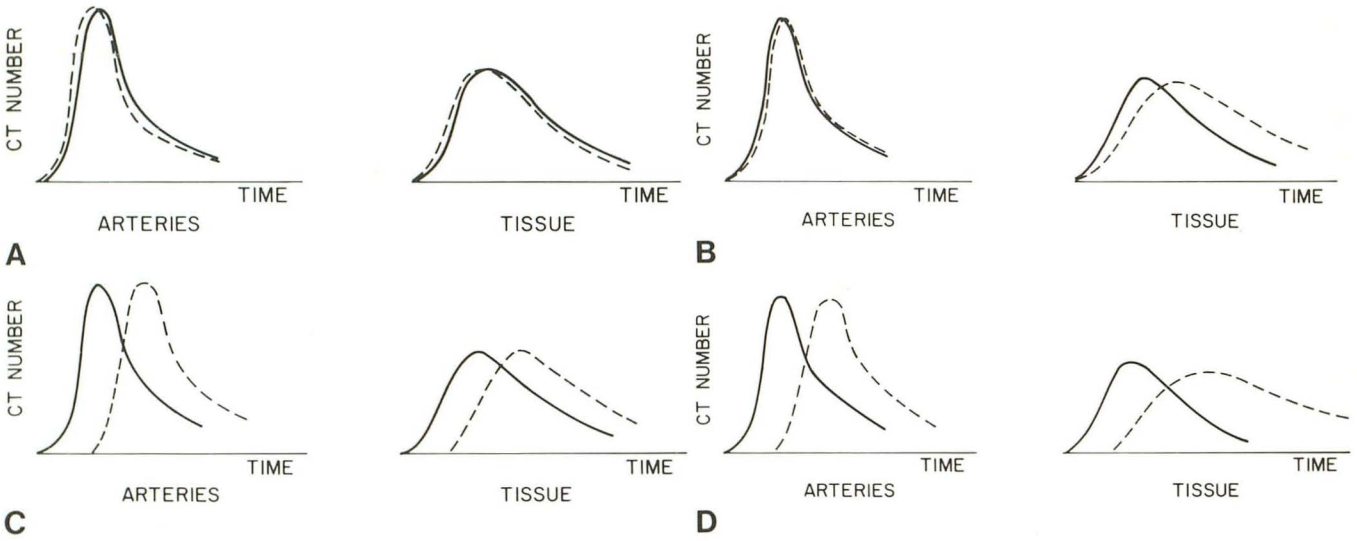


Fig. 6.—Various flow patterns in right and left sides in arteries used to arrive at corrected mean transit time. (See text.) **A**, Normal. Coincident arterial and tissue curves. **B**, Impaired tissue perfusion. Coincident arterial curves; noncoincident tissue curves. **C**, Delayed arrival, adequate tissue perfusion. Noncoincident arterial and tissue curves; equal difference in transit times. **D**, Delayed arrival, impaired tissue perfusion. Noncoincident arterial and tissue curves; unequal difference in transit time.

blood vessels and cerebrospinal fluid spaces.

A typical indicator dilution analysis curve (fig. 4) in which the indicator bolus is small in volume and instantaneous shows a moderately steep rise followed by a relatively prolonged exponential drop with a smaller secondary rise representing recirculation. The area beneath the curve reflects blood volume. The first moment or, graphically, the center of gravity of the curve, is equal to the vascular volume divided by flow, where $V/F = \bar{t}$ or mean transit time [2].

The arterial input function can be segmented from the remainder of the washout curve. This input function shows rapid rise and fall in arterial concentration (fig. 5A). The rise in the capillaries or tissue is less rapid and exhibits a very slow falloff or washout. When the rise and fall of contrast in the artery is extremely fast, it may be neglected. Thus the first moment of the capillary curve reflects the mean transit time through the capillaries and is an indicator of relative tissue perfusion.

With a prolonged input function or contrast bolus, however, both arterial and capillary rise and fall are prolonged (fig. 5B). To determine the mean transit time through the capillary or tissue bed, correction must be made for the prolonged mean arterial transit time. In practice, the mean transit time through the arteries is subtracted from the mean transit time through the capillaries or tissue. The resultant value represents the *corrected* mean transit time (t_c) through the tissues.

For example, in the normal patient (fig. 6A), the mean transit time through the arteries and through the tissues should be equal in the two hemispheres. In a patient with normal carotid flow on both sides but impaired tissue perfusion in a single hemisphere (fig. 6B), the mean transit time in the arteries would be identical, but the mean transit time in the tissue would be prolonged on the abnormal side. The corrected mean transit time on the abnormal side would be longer than on the normal side. In this situation, the arterial rise time would be normal bilaterally.

In contrast to this, a patient with a unilateral carotid stenosis but with normal tissue perfusion bilaterally (i.e., good collateral flow) (fig. 6C), would show a delayed arterial rise on the affected side but equivalent corrected mean transit time on the two sides. Other situations exist in which there is carotid stenosis accompanied by impaired tissue perfusion (fig. 6D). In this situation, the arterial

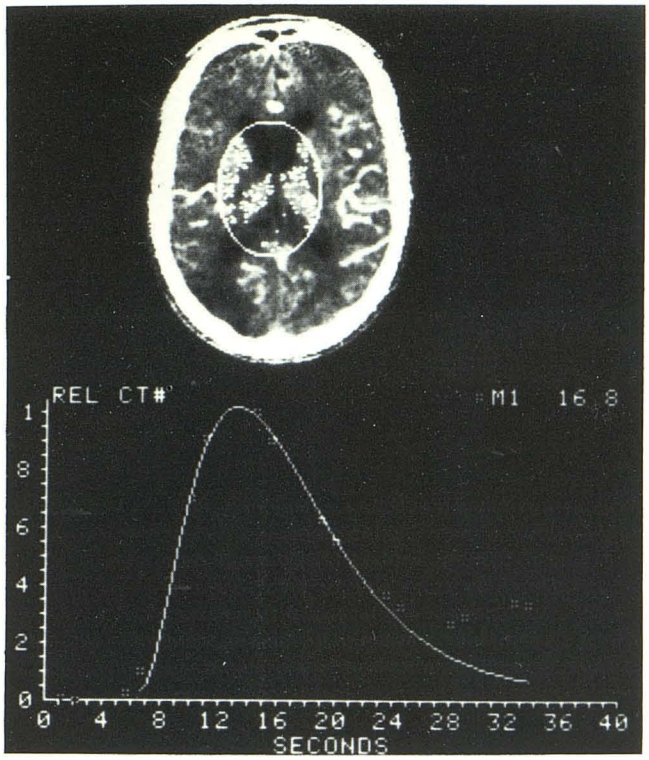


Fig. 7.—Example of histogram-based area of interest. Computer asked to look at change in contrast density over time for pixels representing gray matter only. Many pixels not contiguous. Change in contrast through gray matter only is calculated. In this case, transit time is 16.8 sec. Transit through gray matter in basal ganglia is always more rapid than through white matter.

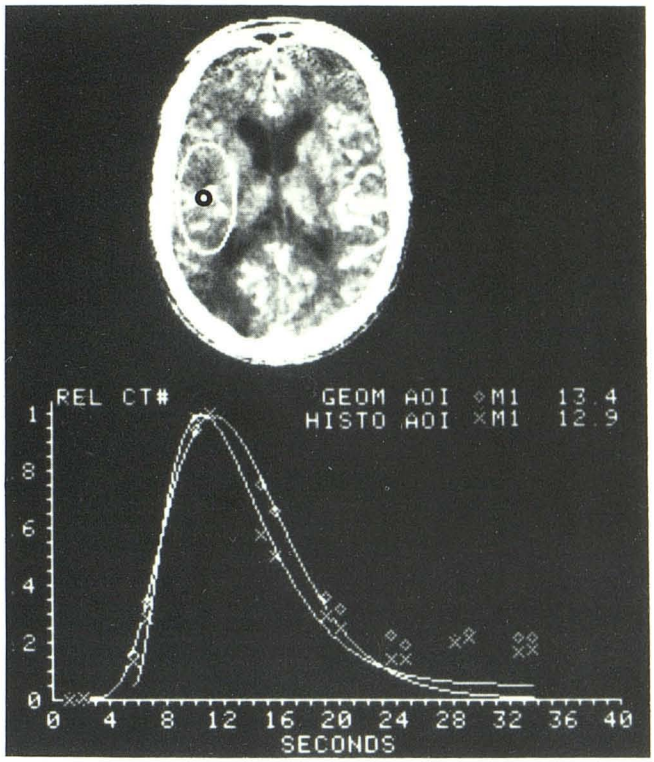


Fig. 8.—Comparison of use of geometric area of interest versus histogram-based area of interest in idenification of vascular transit time. Geometric area of interest (circle) provides transit time 0.5 sec greater than histogram-based area of interest. This is due to lack of precision in identifying vessel and averaging adjacent brain structures.

mean transit would be delayed on the abnormal side, and there would be an even greater prolongation of tissue mean transit as compared with the previous example. The corrected mean transit time on the abnormal side would be longer in duration than on the normal side. Using this technique, it may therefore be possible to identify patients with carotid stenosis in whom tissue perfusion is impaired and those in whom tissue perfusion is preserved, despite the presence of a stenotic lesion.

Additional problems must be considered. If the concept of mean transit time is to have practical application, specific tissue compartments such as vessels and gray matter must be differentiated accurately, reliably, and relatively easily. This differentiation is not possible by the use of a cursor that outlines a simple geometric or irregular area of interest. Volume averaging with adjacent pixels cannot be avoided. For instance, if the structure of interest is a small vessel, there is usually volume averaging with adjacent cerebrospinal fluid spaces or with gray or white matter. Gray and white matter interdigitate in such a way that they cannot be accurately separated from one another with a cursor. This also makes it difficult to obtain a statistically valid number of pixels, and more importantly to be sure that the pixels selected truly represent the absorption value of the anatomic area desired. In addition, a significant amount of unintentional operator prejudice develops. A knowledge of the patient's clinical problem may influence the choice of area and be reflected in the subsequent results. Furthermore, the technique of using geometric areas of interest involves prolonged operator time.

We developed a histogram-based area of interest to overcome these problems (fig. 7). This type of analysis permits the operator to select pixels representing a given range of density values within a relatively large area of interest. These pixels may or may not be

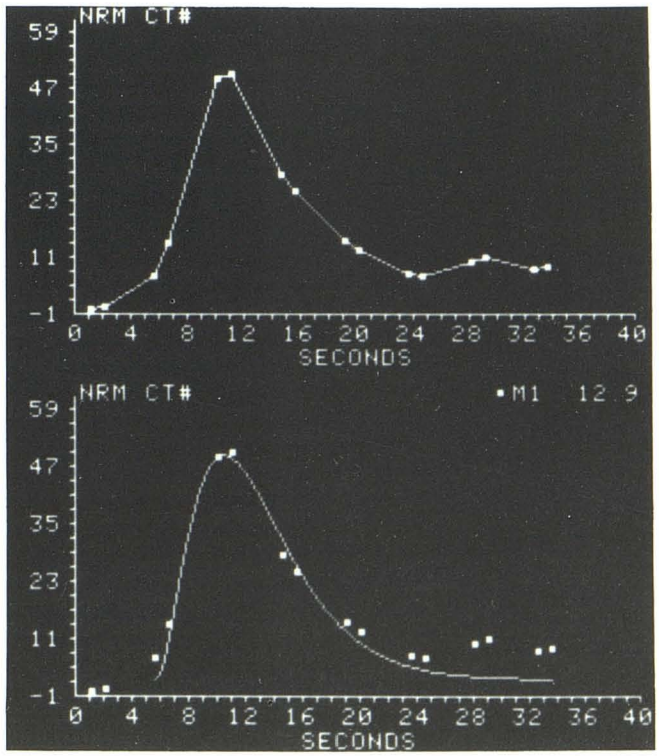
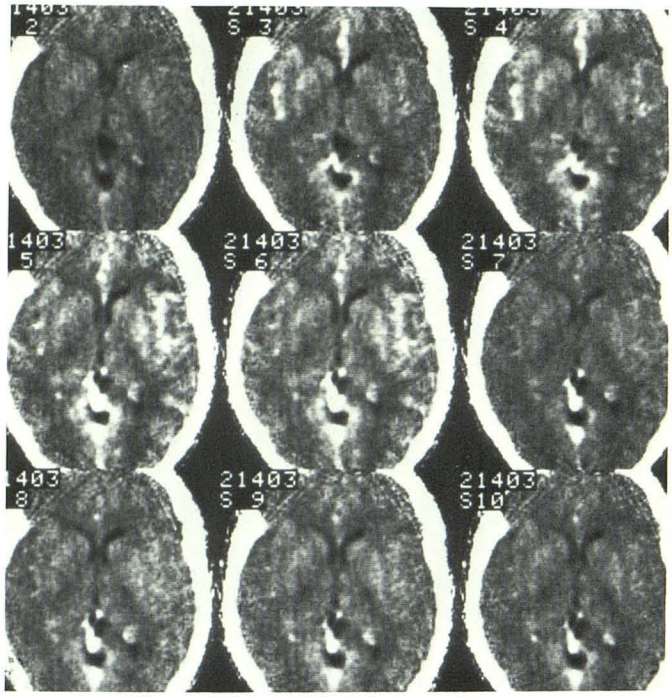
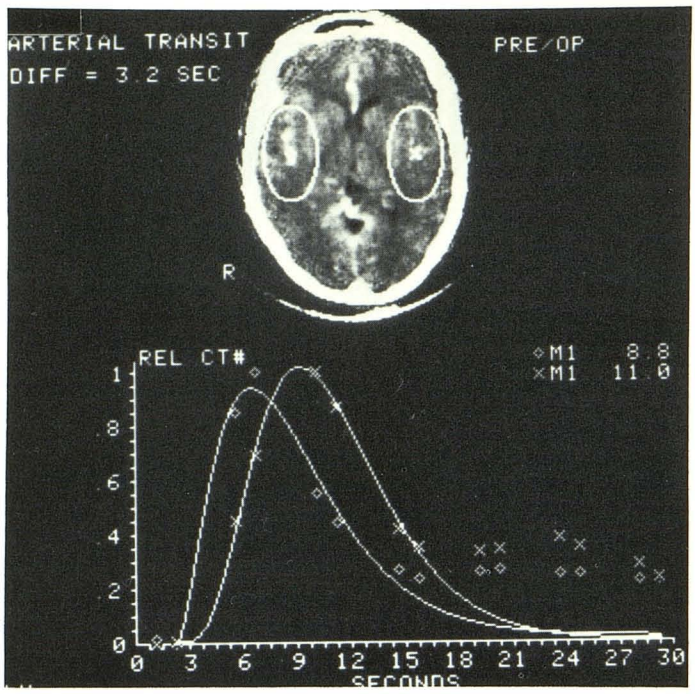


Fig. 9.—Point-by-point fit (above) versus gamma variate curve fit (below) with same data. Cutoff of recirculation with gamma variate curve fit.



A



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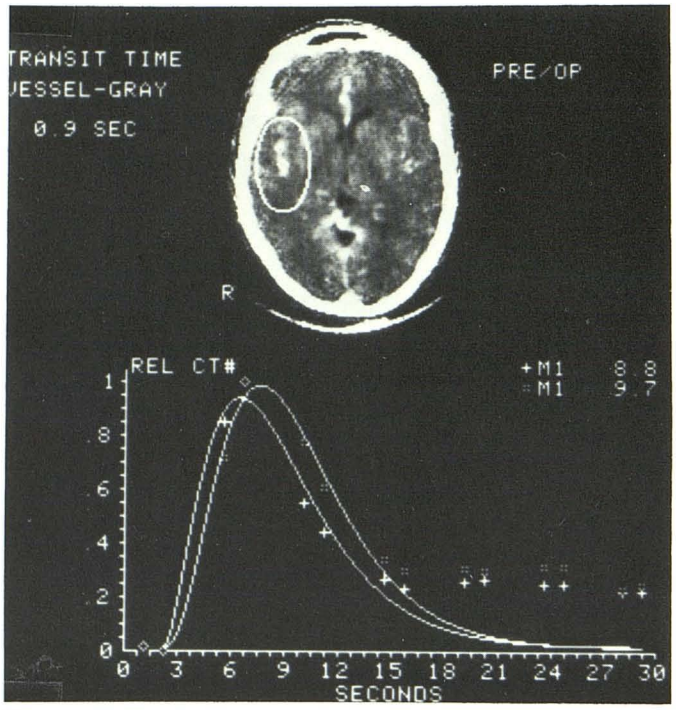
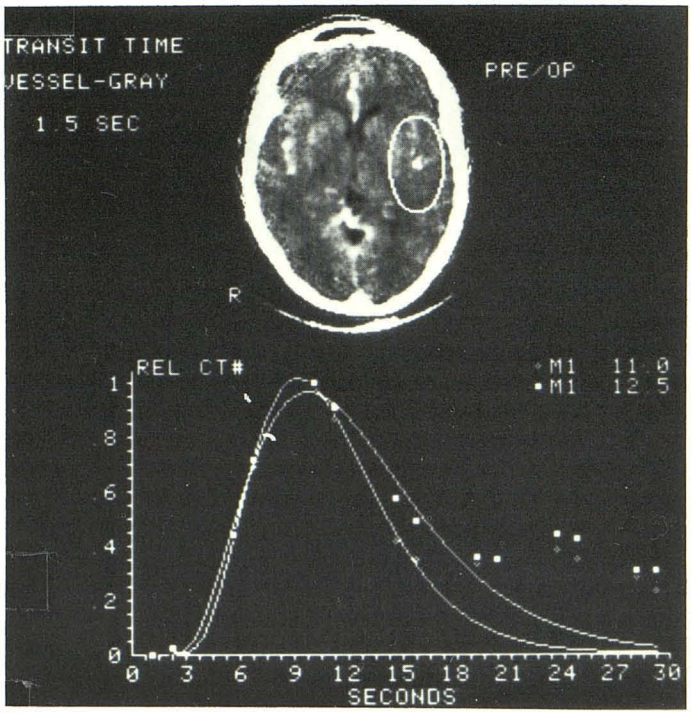


C



D

Fig. 10.—Case 1, 51-year-old woman with left siphon stenosis. **A**, Series of 2.4 sec segmented images from 525° (3.5 sec) scans after intravenous bolus of 50 ml Conray 400. **B**, Difference in arterial transit time ($\bar{t}$) between right (◇) and left (x) hemispheres is 3.2 sec. Corrected mean transit time is 0.9 sec on right (+ = arterial $\bar{t}$, :: = gray matter $\bar{t}$) **(C)** 1.5 sec on left (◇ = arterial $\bar{t}$, ■ = gray matter $\bar{t}$) **(D)**. Corrected mean transit difference between the two hemispheres is 0.6 sec. (See also figure 11.)

contiguous. The pixels representing arteries (i.e., 48–100 Hounsfield units [H]) are selected from the arterial phase. Pixels representing gray matter (40–44 H) or white matter (32–36 H) are identified in the venous phase. Gray and white pixels are not selected in the arterial phase, as pixels thought to represent gray or white matter may, in fact, later in the sequence be shown to be venous structures. The identified pixels are then followed by the computer through the entire sequence of scans, and graphs of relative density change for white and gray matter and vessels are generated. This histogram-based area of interest procedure mini-

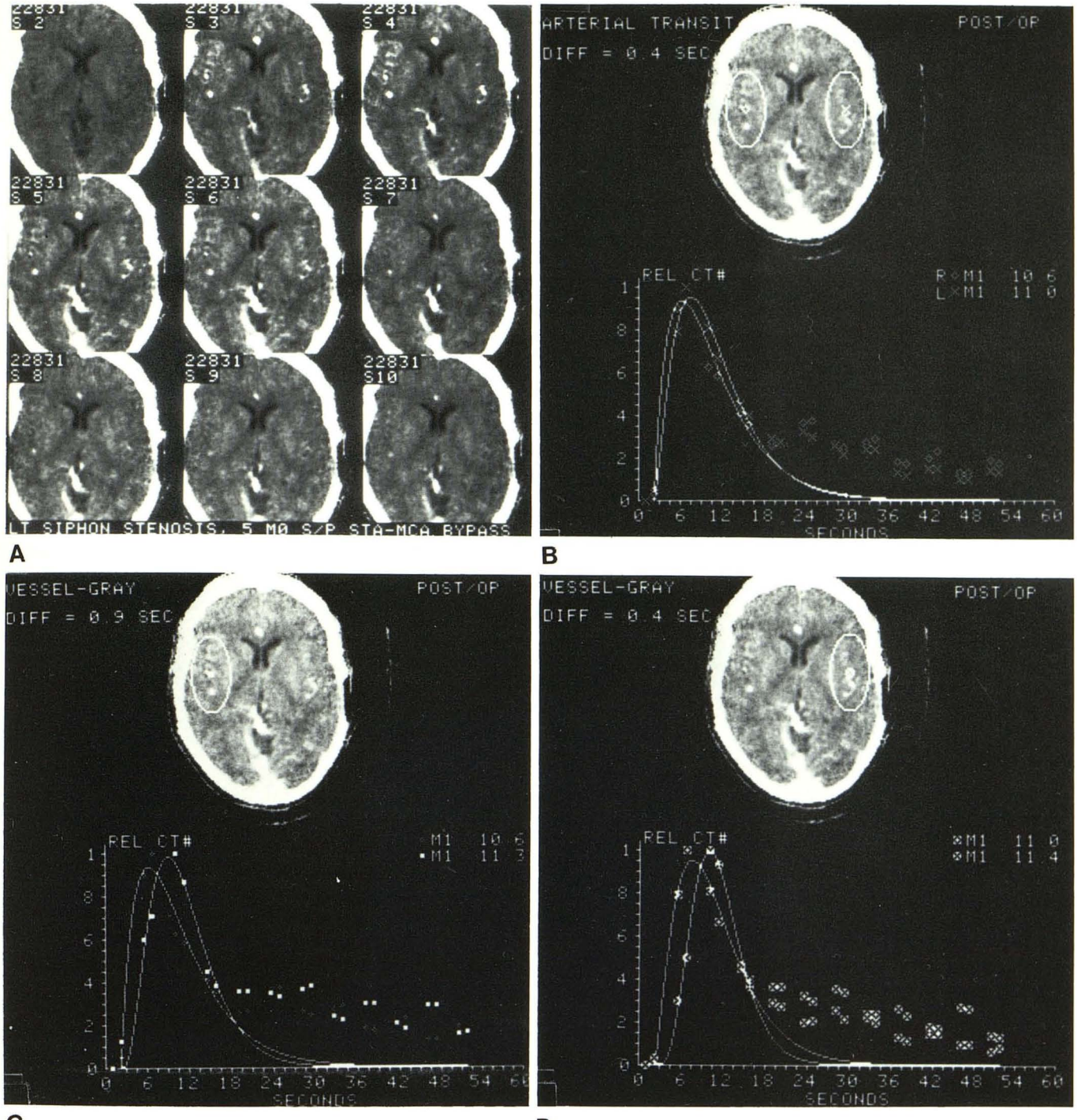


Fig. 11.—Case 1, 5 months after superficial temporal–middle cerebral artery bypass. **A**, Rapid scan series. **B**, Arterial transit (◇ = right, x = left) now differs by only 0.4 sec (versus 3.2 sec on preoperative study). Corrected mean transit time is 0.9 sec on right (◇ = arterial $\bar{t}$, ■ = gray matter $\bar{t}$) (**C**) and 0.4 sec on left (⊞ = arterial $\bar{t}$, ⊗ = gray matter $\bar{t}$) (**D**). Corrected mean transit time difference between the two hemispheres is 0.5 sec.

mizes volume averaging, as well as operator interaction (fig. 8). More importantly, it facilitates a critical identification of specific anatomic areas and significantly improves statistics.

The density changes in these point-by-point graphics are better represented by curve fit techniques, that is, gamma variate (fig. 9) [2]. This curve fit technique diminishes the effect of noise, effective scan time, and data density. It corrects for recirculation as well. These curves can further be exhibited as either direct numeric CT values or as proportional curves.

A further automation of data analysis is the functional image developed by Axel [1] (fig.14), in which uncorrected mean transit time is displayed on a pixel-by-pixel basis. Thus the shades of gray

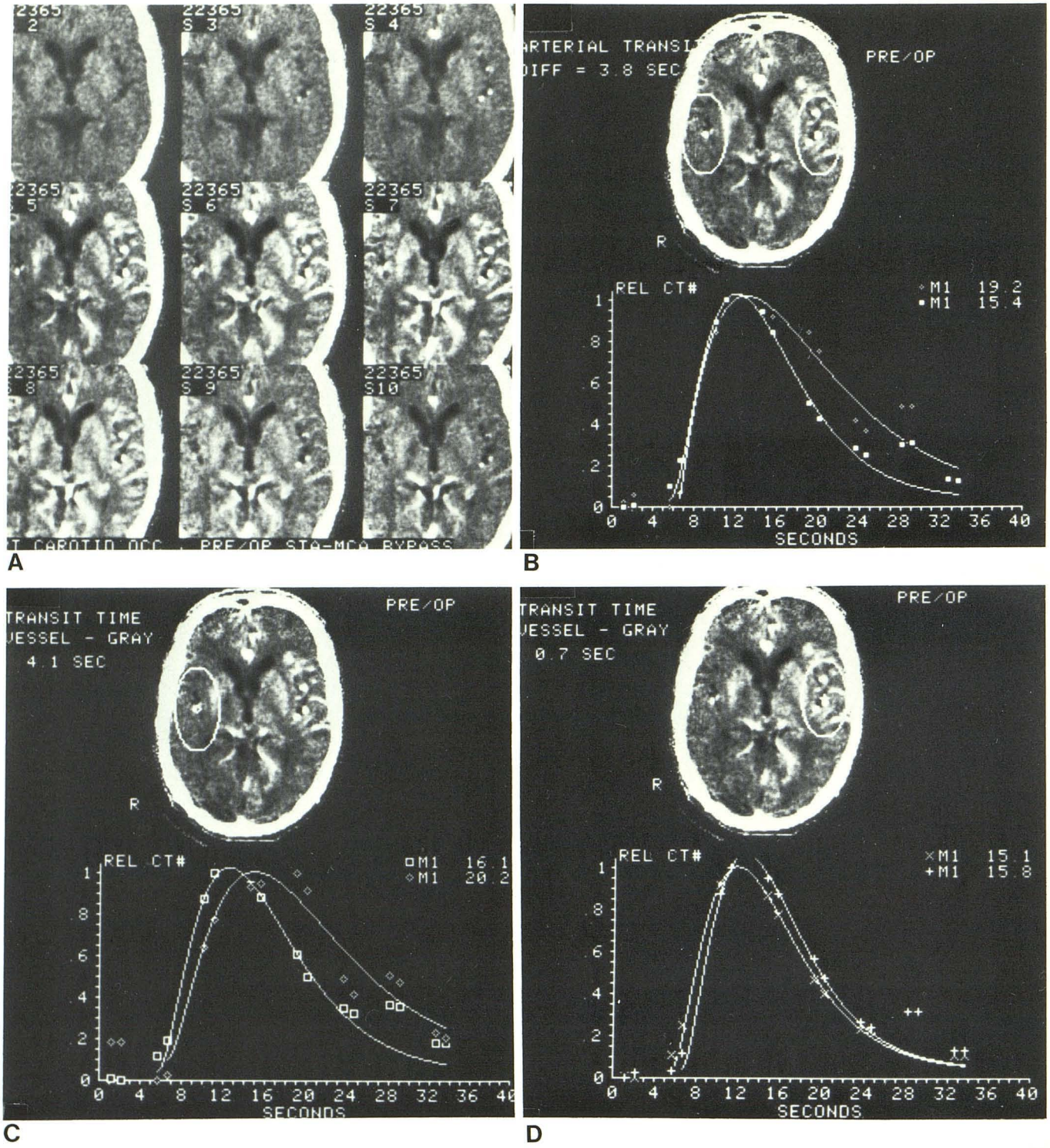


Fig. 12.—Case 2, 56-year-old man with right carotid occlusion. **A**, Rapid scan series. **B**, Difference in arterial transit of 3.8 sec (◇ = right $\bar{t}$, ■ = left $\bar{t}$). Corrected mean transit is 4.1 sec on the right (□ = arterial $\bar{t}$, ◇ = grey matter $\bar{t}$) **(C)** and 0.7 sec on the left (x = arterial $\bar{t}$, + = grey matter $\bar{t}$) **(D)**. Corrected mean transit difference between the two hemispheres is 3.4 sec. (See also figure 13.)

on the CT image reflect not tissue density values, but relative tissue transit. Corrected mean transit time is not displayed, as the specific artery that supplies a particular tissue compartment must first be identified. These concepts are perhaps best understood by application to clinical situations.

Representative Case Reports

Case 1

A 51-year-old woman had several transient ischemic attacks characterized by aphasia, numbness, and weakness of the right

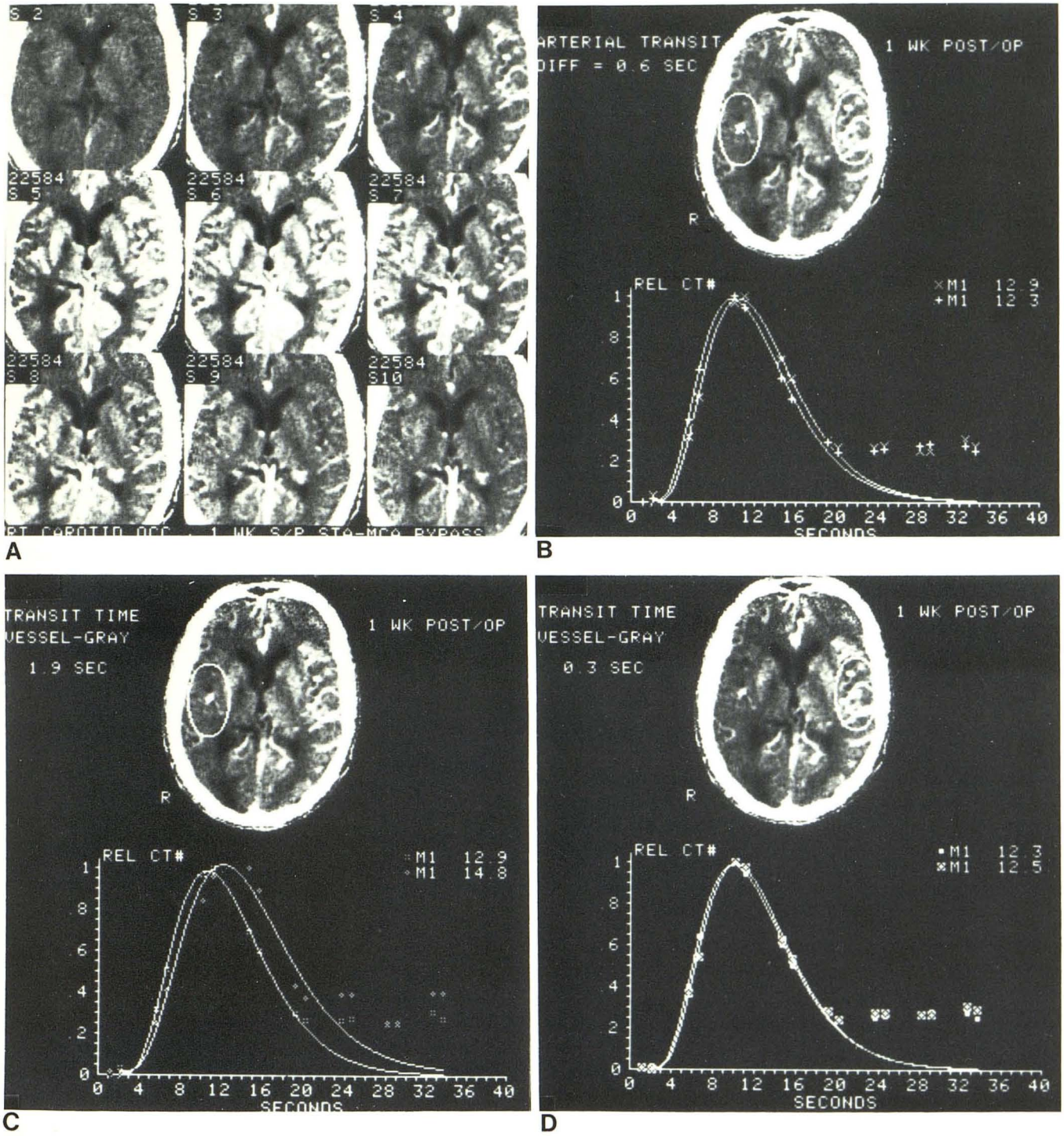


Fig. 13.—Case 2, 1 week after superficial temporal–middle cerebral artery bypass. **A**, Rapid scan series. **B**, Arterial transit difference (x = right, + = left) is now 0.6 sec (versus 3.8 sec on the preoperative study). Corrected mean transit is 1.9 sec on the right (:: = arterial $\bar{t}$, ◇ = gray matter $\bar{t}$) and 0.3 sec on the left (**D**). Corrected mean transit time difference between the two hemispheres is 1.6 sec, which represents a significant improvement from preoperative study.

arm and drooping of the right face (fig. 10A). Angiography revealed almost complete occlusion of the left internal carotid artery siphon with no demonstrable proximal abnormalities. Analysis of relative arterial transit showed a difference between the right and left sides of 3.2 sec, the left slower than the right (fig. 10B). Comparison of vessel to gray matter transit or corrected mean transit time in the two hemispheres showed only a 0.6 sec difference between the left (1.5 sec) and right (0.9 sec), the left being only slightly slower (figs. 10C and 10D). The dynamic CT study suggests that this patient, despite severe internal carotid artery stenosis, had adequate paren-

chymal perfusion, at least when asymptomatic. However, her transient ischemic attacks indicate that cerebral perfusion was only marginally adequate.

Although causes of transient ischemic attacks such as platelet thrombi must, of course, be considered, the dynamic CT suggests the arterial supply to the hemisphere in this instance was the limiting factor and that the transient ischemic attacks could probably be relieved by an adequate surgical bypass procedure. In repeat study after a superficial temporal–middle cerebral artery bypass (fig. 11A), arterial transit differed by only 0.4 sec (fig. 11B) and parenchymal transit by only 0.5 sec (figs. 11C and 11D). The patient experienced relief of symptoms.

Case 2

A 56-year-old man with generalized vascular disease suffered a right carotid occlusion and associated stroke 2 years before admission. He had recovered from the cerebrovascular accident and was under evaluation for a carotid bypass procedure prior to coronary artery bypass surgery. The superficial temporal–middle cerebral artery bypass in this instance was considered prophylactic. Preoperative analysis (fig. 12A) showed a 3.8 sec difference in arterial transit between the two hemispheres (fig. 12B), the right more prolonged than the left. However, analysis of parenchymal corrected mean transit on the right of 4.1 sec and on the left of 0.7 sec (figs. 12C and 12D). These findings suggest that there was impaired perfusion secondary to carotid disease with inadequate collateral circulation.

Postoperative study (fig. 13A) showed marked improvement in arterial (carotid) transit time (0.6 sec) (fig. 13B) and in corrected mean parenchymal transit on the right compared with the left side (difference equals 1.6 sec) (figs. 13C and 13D). Functional images again showed these findings in a composite fashion (fig. 14).

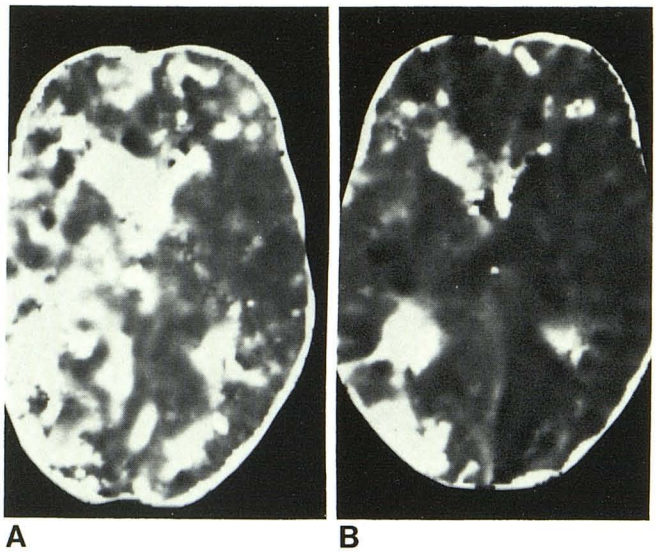


Fig. 14.—Case 2. Pre- (**A**) and post- (**B**) operative functional images. Gray shades represent mean transit; white indicates slow transit; black indicates rapid transit. Significant improvement in right hemispheric transit between pre- and postoperative studies.

Case 3

A 56-year-old woman had an acute left middle cerebral artery stroke. Pre- and postcontrast CT revealed no abnormalities. A dynamic scan (fig. 15A) showed poor filling on the left. More significant was the flow analysis, which showed a 2 sec difference in arterial transit (fig. 15B) and a 1.7 sec difference in corrected tissue mean transit time (figs. 15C and 15D). The functional image (fig. 16) clearly demonstrated the difference in hemispheric perfusion.

Discussion

There are several important limitations inherent in our technique. The information is comparative numeric data about flow in the two hemispheres. Detection of an abnormality depends on a difference between them. For instance, if there is slow flow in both hemispheres, an abnormality may not be detected unless there is a marked reduction in transit bilaterally. Comparative data on corrected mean transit times in a cohort of normal patients is necessary for this judgment.

Although relative hemispheric transit can be detected using this technique, absolute flow cannot. Currently we are working on a modificaton of the technique for determining absolute concentration of contrast material in the sagittal sinus from which a figure for absolute flow can be derived.

The technique works most reliably in patients in whom the blood-brain barrier is intact. In patients in whom it is disrupted (e.g., by infarct or tumor), the technique will usually be useful on the first pass of the contrast bolus as the rate of leakage in most lesions is significantly slower than intervascular transit. However, large blood-brain barrier defects will artificially prolong the mean transit time.

Examination of a single 1 cm thick section of brain is, of course, a limitation even though a level at the basal ganglia has several advantages, as discussed above. However, it will not have application to problems related to posterior fossa or high convexity disease (i.e., peripheral emboli). In addition, accuracy in the posterior fossa is probably significantly reduced due to high spatial frequency artifact inherent in CT scanning of the posterior fossa. Even so, other levels can be studied with current equipment, assuming no gross leakage of contrast material has occurred (i.e., no large blood-brain barrier defect is present).

It is important to remember that with a nondiffusible indicator such as iodinated contrast, corrected mean transit time provides a measure of flow per unit vascular volume as opposed to flow per unit volume of tissue; in order to arrive at this latter value, a measure of fractional total tissue represented by the vascular space would be required. This could be calculated with knowledge of intravascular contrast concentration. By comparison, xenon, which is a diffusible indicator, will provide a measure of flow per unit tissue volume, but to obtain meaningful measurements using this technique, an accurate measure of partition coefficient is required.

An additional potential problem area is statistical error, which might occur if overlapping CT values are selected for identifying different tissue compartments. In our study we were able to use CT ranges separated by at least 2 SD to identify particular anatomic areas of interest. Patient motion

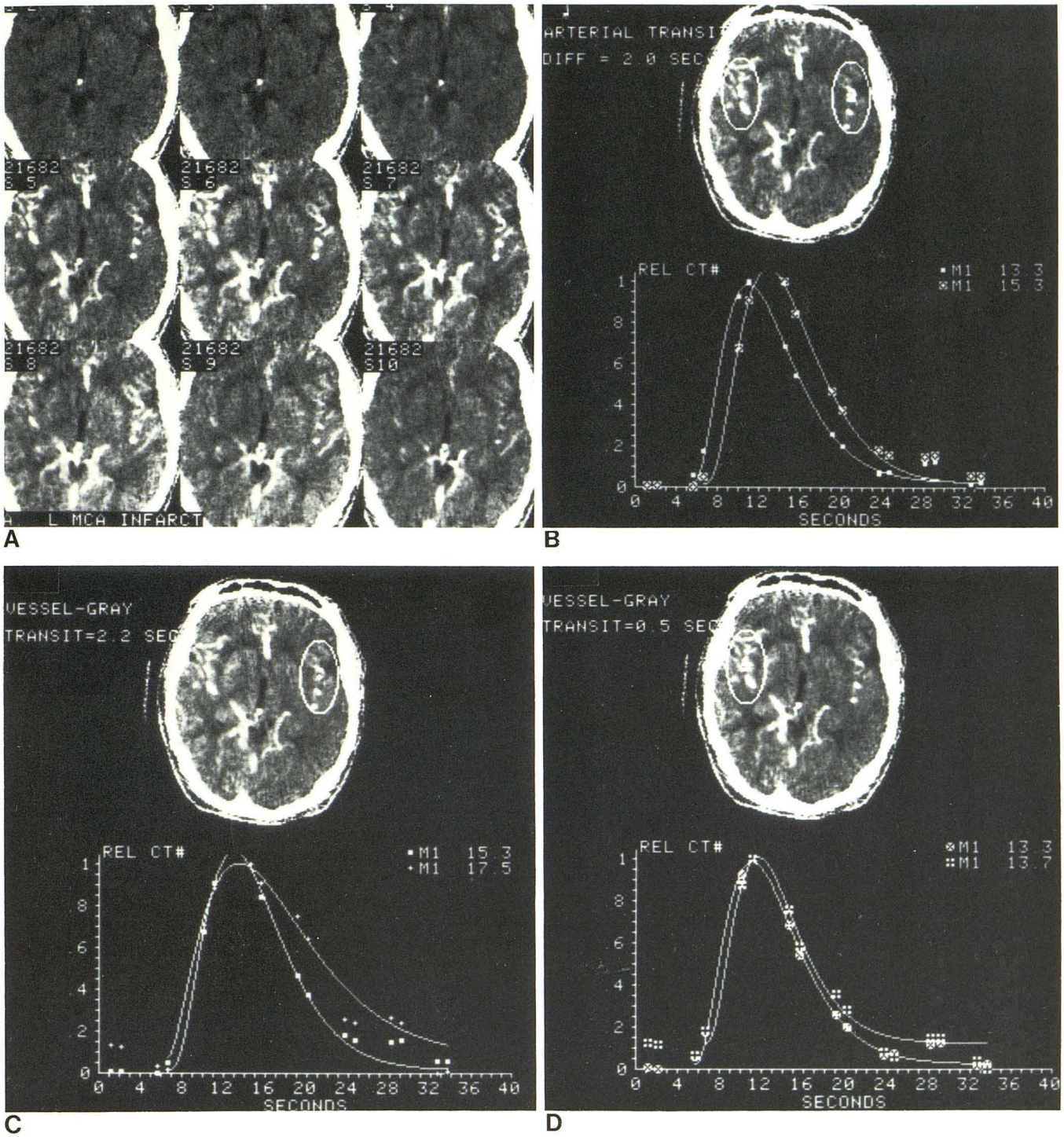


Fig. 15.—Case 3, 56-year-old woman who had acute left middle cerebral artery stroke 3 days before. Pre- and postcontrast static CT scans were normal. **A**, Rapid sequence scan. Relatively less filling on left. **B**, Arterial transit difference is 2.0 sec (■ = right, ⊞ = left). Corrected mean transit time is 2.2 sec on the left (■ = arterial $\bar{t}$, + = gray matter $\bar{t}$) (**C**) and 0.5 sec on the right (⊗ = arterial $\bar{t}$, :: = gray matter $\bar{t}$) (**D**). The difference in corrected mean transit times between the two hemispheres is 1.7 sec.

is also a problem in that a pixel identified on one scan may not be in the same anatomic structure in a subsequent scan. An additional area of concern is the trade-off between temporal and density resolution. Although additional data points might be desired to improve the accuracy of the technique, increased speed results in decreased density resolution due to limited photon flux, which diminishes the gains achieved with increased temporal resolution.

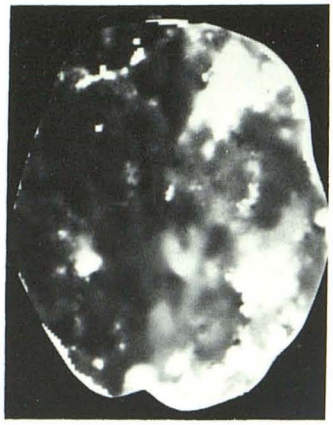


Fig. 16.—Case 3. Functional composite image. White represents slow transit; black represents rapid transit.

If dynamic CT is to have clinical applications, a large series of patients must be examined. Normal controls must be established. Basic experiments confirming data reproducibility, the minimum number of data points required, and acceptable noise levels must be performed. These experiments are in progress.

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