Tumor volume, luxury perfusion, and regional blood volume changes in man visualized by subtraction computerized tomography

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Computer and photographic methods for producing subtractions of computerized axial tomographic (CAT) scans have been developed. By subtracting point for point a normal scan from one taken after intravenous infusion of contrast material, a picture of the contrast in the cerebral vessels is created. By this method, tumor size and degree of vascularity may be assessed. Furthermore, abnormalities in perfusion and changes in blood volume due to mass effects and edema may be detected. Subtracting scans should add to the diagnostic potential of CAT and provide a noninvasive way to study vascular changes in cerebral disease.

KEY WORDS • computerized tomography • luxury perfusion • cerebral blood volume • tumor vascularity • brain edema

COMPUTER analysis of transaxial tomograms has, in the few years since its introduction, established itself as an extremely useful clinical diagnostic tool. By providing density values of the tissue scanned, it complements other diagnostic methods such as radioisotope scanning and arteriography. The first step in interpretation of the data provided by computerized axial tomography (CAT) has been identification of normal tissue, bone and fluid densities, and then the cataloging of densities associated with pathological processes. So far, the major clinical application has been in scanning the intracranial contents, and papers are now appearing that illustrate normal values for brain tissues, cerebrospinal fluid (CSF), and bone, and also for brain tumors, intracerebral and extracerebral hematomas, infarctions, and edema. From this information, it is apparent that the densities of normal brain tissues and some pathological processes, such as low-grade gliomas and white matter, may sometimes be in the same range; also, different pathological conditions, such as edema from trauma and a glioblastoma, may have the same abnormal density range.

To help distinguish tissues of the same density that are functionally or pathologically different, the intravenous infusion of iodinated contrast material, i.e., material of high x-ray absorption, has been employed. Often lesions, because of increased vasculature, accumulate the dye and "light up" due to their
higher density on CAT scanning. To take full advantage of this enhancement technique, the pre- and postinfusion scans should be compared; the difference in density of the two scans represents uptake of the dye in the abnormal area. For this purpose, we have developed photographic and computer methods to create a subtraction computerized tomogram.

Although the subtraction method was originally designed to enhance infusion CAT scans, the general principle can be used in many ways. For example, the subtraction scan can be used to quantify tumor size. The normal brain parenchyma does not increase in density with infusion as much as glioblastomas and many metastatic tumors, so the subtraction scan accurately delineates the tumor edge. Since borders of the mass can be defined, the total tumor volume can be calculated. When the increase in density within the tumor is compared to that in normal tissue, the degree of breakdown of the blood-brain barrier (BBB) and increased vascularity can also be assessed. In the same way, the response of the tumor to therapeutic intervention such as radiation therapy or chemotherapy may be followed by serial subtraction scans.

Another use of the subtraction scan is in measurement of regional cerebral blood volume. Normally, the iodinated contrast material stays within the cerebral vessels due to the BBB. The subtraction scan, therefore, displays only the contrast within the blood vessels since the density of the brain tissue has been eliminated. If the concentration of contrast material in the blood is known, the amount of blood in the brain and its regional distribution may be calculated. The details of this measurement are described in a recent article.9

The subtraction method need not be limited to infusion studies. It may be used to compare two scans through a region in which a change has occurred, whatever the cause of the change. Thus, evaluation of pathological processes that affect the density of cerebral tissue may be followed by subtraction of serial scans. The difference between scans will give the true course and spatial characteristics of the process.

Materials and Methods

Photographic Method

The most straightforward way to obtain a subtraction is by use of negative transparencies of the pre- and postinfusion scans. The first negative is reversed by contact printing to produce a positive. This positive of the preinfusion scan is then placed over the postinfusion negative and a final contact print is made. Thus, only the change in densities due to the infusion is represented in the final print. In practice, the highest densities, such as those of bone or calcified tissue, subtract least precisely so that the calvaria and sometimes the pineal gland are seen. The brain parenchyma, on the other hand, is an even gray tone. An area of increased density due to uptake of dye appears lighter on the final print.

Another photographic method has been developed which avoids the several steps in creating reversals and prints. With a computer routine, a "negative" is created on the cathode-ray viewing screen. Figure 1 left
Subtraction computerized tomography shows a "negative" of the plain CAT scan, and Fig. 1 center the "positive" of the infused scan. These two transparencies are then superimposed and the effect of any slight motion between scans may be eliminated by careful alignment of the calvaria in each. The result is a subtraction, which, for purposes of illustration, has been made with a positive contact print (Fig. 1 right). The abnormal region, a tumor, in the right frontal region along the falx, stands out more clearly on the subtraction than on the pre- or postinfusion scans. Note that the ventricles subtract and that the brain tissue has an even gray tone. The precision of this subtraction depends on the linearity of the film’s response to intensity over the range of densities displayed on the viewer, so the characteristics of the emulsion used must be known.

**Computer Method**

The only way to quantify the subtraction and to make possible regional cerebral blood volume calculations is to employ a computer subtraction technique. Two of the authors (R.W. and L.A.) have developed a software system for the EMI Tronics CAT scanner* which not only produces a subtraction scan but also isolates the brain, sets the scan periphery to a uniform gray level, verifies that the pre- and postinfusion scans are at the same location in the horizontal plane, and calculates histograms for the pre-, post-, and subtraction scans. The system was developed for the Data General 820 computer and is written in FORTRAN. For computational purposes, the 160 X 160 EMI array is reduced to 80 X 80.

The first step in the program is retrieving the pre- and postinfusion slices from magnetic tape. Then the interior edge of the skull is located for each slice by initiating a search from the center of the scan outward for a matrix point greater than 100. Once a density of bone value is found, an edge-following routine delineates the inner border of the skull. The brain tissue is defined by an analogous procedure in which absorption densities greater than 10 but less than 100 are located within the previously marked bone edge. The center point of each skull is computed and a 1.5-cm midline strip is eliminated from the subsequent statistical analysis. This is done to exclude the large midline sinuses along the falx from estimates of blood volume. A scaled histogram and mean absorption density for each slice are calculated and are printed along with the pre- and postinfusion pictures and center coordinates.

The final step in the program is to subtract the brain tissue located on the preinfusion scan from the brain tissue plus contrast in the postinfusion scan. Once again a midline strip is excluded for computations and the mean density of the subtracted scans, i.e., the mean increase in density due to contrast material, is computed as well as the histogram of densities. The 80 X 80 subtraction picture, the mean, and the histogram are then printed and the program is completed.

To check the programming routines, a phantom that consists of a skull filled with tap water was scanned twice. The first scan was subtracted from the second and the subtraction printed in the usual manner. The presubtraction histogram of the tap water showed a mean density of 2.7 units. The subtraction of the two scans is seen in Fig. 2 right. The inner table of the skull is clearly outlined and the interior space consists of densities varying around zero. The histogram of the subtraction scan (Fig. 2 left) has a mean of -0.001 and a symmetrical spread of values on both sides with a standard deviation of 2.48. This variation is inherent in all CAT scans and comes from the photon noise in the x-ray beam and approximations in the reconstruction algorithms.

It is crucial to the concept of subtracting scans to have CAT density values that are linear with x-ray absorption over the range being subtracted. This lineation has been demonstrated by others and it was checked on our own scanner with sucrose solutions of varying concentrations. Figure 3 shows that from 3 to 80 EMI units strictly linear values are obtained.

**Illustrative Cases**

**Tumor Vascularity and Size**

Infusion scanning combined with subtraction allows the accurate delineation of tumor size and provides an estimate of increased

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*CAT scanner manufactured by EMI Tronics, Incorporated, 3605 Woodhead Drive, Northbrook, Illinois 60062.
blood volume within the mass plus breakdown of the BBB.

Case 1. This 69-year-old man had right-sided headaches and a mild left hemiparesis. The regular CAT scans (Fig. 4 left) show mass effect with a right-to-left shift, collapse of the right lateral ventricle, and areas of marked variation in density from 11 to 22 in the right parietal region. The second set of scans (Fig. 4 center) were taken immediately following the intravenous infusion of 300 cc of sodium diatrizoate (Hypaque).* The lesion in the parietal area now lights up and clearly stands out as a tumor of high vascularity. On biopsy, it proved to be a Grade III astrocytoma. A series of computerized subtractions of the regular CAT scans taken from the infusion scans show the tumor well separated from the brain tissue and regions of edema (Fig. 4 right). Once the borders have been accurately defined, the volume of the tumor mass may be approximated by adding all the matrix points within the edge. In this case the tumor mass volume was 25.3 cc.

Since the contrast material is all that is seen on the subtraction scans, the increased density in the region of the tumor is directly proportional to the amount of contrast material within the mass. In this Grade III astrocytoma, the concentration of the contrast material was 11 times higher than in the normal contralateral hemisphere. The subtraction in Fig. 4 right, second from top, is notable because a ring of increased density is seen around a central region of much lower average density; this demonstrates that the contrast material does not penetrate the deeper areas of the tumor mass.

*Hypaque-25 manufactured by Winthrop Laboratories, 90 Park Avenue, New York, New York 10016.
Subtraction computerized tomography

Fig. 4. Case 1. Brain scans in a patient with a biopsy-proven Grade III astrocytoma. Left: Regular CAT scan. Center: Infusion CAT scan. Right: Subtraction CAT scan. Second scan from top shows ring sign of increased vascularity at edge of tumor.
Blood Volume Changes with Pathology

Subtraction CAT has been extremely useful in differentiating hemorrhagic from ischemic strokes.

Case 2. This 69-year-old woman developed a right-sided headache and then a left hemiparesis; on examination her eyes were tonically deviated to the right and a left homonymous hemianopsia was present. A regular CAT scan done 3 days later showed a large lesion in the right hemisphere of below normal density consistent with an ischemic cerebral vascular accident of the middle cerebral distribution (Fig. 5 left). The infusion was performed (Fig. 5 center), and then a subtraction computed (Fig. 5 right). In the region of infarction, well defined on the regular CAT scan, the average density is 0.94, compared to an average of 3.0 in the corresponding region of the left hemisphere. Thus, the relative blood volume is 69% less in the area of infarction. Of particular interest is the region just adjacent to the infarction fed by the posterior cerebral circulation. On the subtraction scan, this area lights up and density calculations show an increase of 3.5 times compared to a corresponding normal area.

Serial Subtraction Scans

Variations in relative blood volume can be followed in a serial fashion by subtraction CAT scanning.

Case 3. This 62-year-old man had a large tentorial meningioma. In the preoperative scan (Fig. 6 left) the calcified mass is seen in the left occipital region. The patient’s only symptom was headache, and neurological examination, including visual fields, was entirely normal. The tumor was removed by way of a left occipital craniotomy and he did well until the fifth day postoperatively when he developed a complete right homonymous hemianopsia. A repeat scan (Fig. 6 center) showed edema in the left calcarine region. After 10 days the field defect had cleared and a final scan (Fig. 6 right) showed resolution of the edema. Along with the regular scans, infusion scans were performed and a subtraction computed for each. Figure 7 shows the printout for the third subtraction. The areas of the medial occipital lobe along the falx have been outlined for analysis of blood volume. Preoperatively, the blood volume was 8% less on the left than on the right. Because of the postoperative edema, the relative blood volume on the left dropped to 27% of the right. Finally, when the hemianopsia had resolved, the blood volume of the two sides became nearly equal to the preoperative state, 7% less on the left. Thus, the reduction in relative blood volume parallels the development of edema and the cortical dysfunction indicated by hemianopsia.

Discussion

Subtraction techniques in angiography have substantially enhanced radiographic images, and so it is a natural step to apply the same idea to CAT scanning. The basic concept of subtracting out interfering structures,
so the location of the contrast material may be better visualized, is the same in both techniques, but the products are quite different. Computerized tomography scanning requires 4 to 5 minutes, and angiographic pictures may be taken in fractions of seconds. The spatial resolution of CAT scanning is also much less precise than angiography. For example, the large arteries at the base of the brain are rarely delineated on CAT infusion scans. On the other hand, the CAT scan is able to measure extremely small changes in overall tissue density. The infused contrast material distributed in all the blood vessels of the central nervous system is detected even though the blood volume is only 3.0% of the brain parenchyma. Thus, the subtraction CAT scan is a picture of the distribution of the blood in the entire cerebral circulation.

Fig. 6. Case 3. Regular CAT scans. Left: Preoperative scan shows a left occipital calcified tentorial meningioma (white area). Center: Five days after operation. The tumor has been removed but there is edema (darker area) in the left calcarine region producing a right homonymous hemianopsia. Right: Ten days postoperatively the field defect is no longer present and the edema has resolved.

Fig. 7. Case 3. Computer printout of subtraction scan shown in Fig. 6 right. Calcarine regions are outlined for regional blood volume analysis.
In normal patients, the contrast material stays within the vascular system due to the BBB. Obviously, anything which interrupts this barrier could allow contrast to escape into a nonvascular space. Therefore, in diagnosing cerebral pathology, care must be taken not to equate regions of increased contrast with increased vascularity. For example, the 11-fold increase in contrast found within the glioma in Case 1 would represent an unusually high blood volume of approximately 30% if the BBB were assumed to be intact. Biopsy studies of brain tumors using 51Cr-labeled red blood cells as an intravascular marker showed lower blood volumes than would be predicted by contrast material accumulation on CAT scans. On the other hand, in a series of benign tumors, serial scans demonstrate a direct relationship between blood level of contrast material to level in a tumor. The contrast material clears as rapidly from the tumor as from the blood, which suggests that little contrast material is trapped within the tumor. Furthermore, regions of cerebral edema with a known breakdown of the BBB have a decreased, not increased blood volume, as in Case 3. The apparent discrepancy between the 51Cr study and the serial measurements of the ratio of blood to tumor contrast material may relate to differences in tumor types studied and, consequently, to the degree of breakdown in the BBB. One way to differentiate between contrast material in blood vessels and leakage into brain or tumor tissue is to follow the time course of contrast accumulation. The blood vessels will fill immediately with the infusion and only later will contrast material diffuse through the BBB. The newer scanners with a better time resolution of 20 seconds or less per scan should make such serial measurements possible.

Of interest in Case 1 is the ring of vascularity around a large core of tissue having a low uptake. This ring sign frequently occurs with tumors but has been seen with other lesions. Its presence suggests a core of tumor that is not in connection with the normal vascular pool and, consequently, has a low oxygen tension. The existence of this core of poorly vascularized neoplastic tissue may be important in explaining failure of chemotherapeutic agents and radiotherapy. Subtraction scans should allow serial assessment of changes in overall tumor volume as well as inner core size and, hopefully, guide therapeutic intervention.

Case 2 demonstrates how the subtraction technique can delineate regions of infarction by decreased relative blood volume. Also shown is an area of increased blood volume around the infarction that could be due to luxury perfusion. Until now only regional cerebral blood flow studies have been used to quantitatively define this condition. The subtraction CAT scan should complement the flow studies by adding measurements of increased regional blood volume. An advantage of the CAT method is that anatomically identifiable areas deep within the brain may be studied.

Case 3 illustrates the usefulness of serial scans in understanding the pathophysiology of cerebral edema. The regular CAT scans show the evolution of edema associated with objective changes in neurological function. The subtraction scans add information about regional decreased blood volume that accompanies the edema. By studying similar cases, it should be possible to determine the minimum decrease in blood volume that causes loss of neuronal function. The 23% reduction in relative volume seen in this case probably reflects a more dramatic decrease in blood flow since small changes in volume have been associated with large changes in flow. For example, in one study in monkeys, a 28% increase in blood volume doubled the cerebral blood flow. The decrease in regional blood volume with edema suggests that pressure within cerebral tissue will collapse the vascular system. Conversely, the amount of collapse, as measured by decrease in blood volume, should be proportional to pressure. Once the normal distribution of blood is known, the subtraction scan could provide a map of pressure variations within the intracranial vault.

References

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