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Comparison Study of CT and Positron Emission Tomographic Data in Recent Cerebral Infarction

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To better understand the pathophysiologic correlates of the computed tomographic (CT) scan changes seen in recent cerebral infarction, 17 patients (20 studies) underwent both x-ray transmission and positron emission CT investigations within 18 days after clinical onset of complicated ischemic stroke in the internal carotid artery territory. The density changes before and after contrast study measured within the CT lesion were correlated to the local cerebral blood flow (CBF), oxygen utilization (CMRO₂), and oxygen extraction fraction (OEF) measured with the oxygen-15 steady-state positron technique. Statistically significant linear correlations were found between hypodensity and CBF, hypodensity and CMRO₂, and contrast enhancement and CBF, such that the more CBF and CMRO₂ were depressed, the more marked was the hypodensity; and the more CBF was elevated, the more marked was the contrast enhancement. Although marked contrast enhancement was associated with decreased OEF (luxury perfusion), it was only rarely associated with increased CBF. Various hypotheses are discussed to explain these findings.

In the study of recent cerebral infarction, computed tomography (CT) provides essentially morphologic information, such as location and degree of both density changes and contrast enhancement. On the other hand, positron emission tomography (PET) provides physiologic measurements. For instance, when combined with the oxygen-15 steady-state technique [1], the local cerebral blood flow (CBF), oxygen consumption rate (CMRO₂), and oxygen extraction fraction (OEF) can be obtained on quantitative tomographic images [2-4].

Although a number of studies have been done, the pathophysiologic mechanisms of the hypodensity and contrast enhancement seen in recent infarction have not been fully elucidated. We attempted to correlate the alterations in local CBF, OEF, and CMRO₂ measured with the ¹⁵O-PET technique to the density changes seen on CT in 17 ischemic stroke patients.

Subjects and Methods

Seventeen patients (nine men and eight women, mean age 64.2 years) who had had a single cerebral infarction in the distribution of the internal carotid artery were studied. All patients were evaluated within 18 days of clinical onset and three patients were studied

twice within this time period. Seven infarcts were located in the deep middle cerebral artery (MCA). Embolism, internal carotid artery (ICA) occlusion, and ICA dissection were each presumed to be the mechanism for two of these, and the mechanism for the other was unknown. Six infarcts occurred in the superficial MCA; five presumed caused by embolism, and one by ICA dissection. Three infarcts involved the entire MCA; two presumed caused by embolism and the other by ICA occlusion. One infarct was located in the anterior cerebral artery, presumed caused by embolism.

The studies were all done between day 2 and day 18 after clinical onset (mean, 8.3 days). The model on which the ¹⁵O-PET technique is founded [1, 2], its validity [4-7], its limitations [5, 8, 9], and its application to PET [3, 4, 10] have been reported in detail elsewhere. Briefly, the procedure is this: The patient inhales to equilibrium trace doses of, successively, CO₂ and O₂ labelled with oxygen-15. The labelled gases are continuously delivered by a medical cyclotron at constant flow rate and specific radioactivity. The data are collected by an ECAT II (ORTEC) positron tomographic scanner [11], and tomographic cuts (slice thickness 19 mm, lateral resolution 16 mm) of the tracer quantitative distribution in the head level studied are subsequently reconstructed by the computer.

For each cerebral level studied, three equilibrium images are obtained: a C¹⁵O₂ image, a ¹⁵O₂ image, and a ¹⁵O₂/C¹⁵O₂ ratio image. Pixel-by-pixel transformation of the C¹⁵O₂ and the ratio images into functional CBF and OEF images is then performed according to published equations [2] that relate the pixel ¹⁵O concentration to the equilibrium arterial concentrations of H₂¹⁵O and Hb¹⁵O₂ (the latter are obtained by well-counter measurements on femoral arterial blood samples). Details regarding the operation of quantification have been published elsewhere [10]. Measuring the arterial oxygen content (Ca) then allows the generation of a CMRO₂ image: CMRO₂ (ml O₂/100 g/min) = CBF (ml/100 g/min) × OEF × Ca (ml O₂/ml).

In all but one of the 20 studies (case 11), CT was performed within 5 days (before or after) of the ¹⁵O-PET study, but never in the first 24 hr after onset. The CT device was a CGR (ND 8000) selected at 9 mm slice thickness with a lateral resolution of 0.75 mm. The midcut head levels studied were as close as possible to those used in the ¹⁵O-PET study, and both were obtained using a +5° angle tilt from the orbitomeatal line. All CT studies were done without contrast enhancement, and in 17 instances were immediately repeated after intravenous injection of meglumine ioxithalamate (77% W/V solution containing 0.38 mg/ml of iodine), using

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TABLE 1: Summary of Findings after Cerebral Infarction

Case No.	Study Day		CBF (%)	OEF (%)	CMRO ₂ (%)	Hypodensity (Δ H)	Contrast Enhancement (H)
	PET	CT					
1	2.5	3.5	57	86.7	48.7	-9	+3.5
	9.5	11	79.7	72.8	58.4	-9	+21
2	4	3	47.3	41.8	19.9	-18	+10
3	11	6	91.7	68.8	63.8	-3	+21
4	3	7	40.4	107.5	43.8	-10	+4
	10	14	67.8	66.7	44.7	-15	+6
5	2	4	95.7	43	41	-8	+8
6	3.5	4.5	27.2	76.2	19.2	-9.5	+5.5
7	3	2	40.8	184.2	74.5	-11	0
8	11	12	62.8	35	20	-14	*
9	9	12	79.9	80.4	64.3	+1	+13
10	18	18	94.8	60.2	56.2	+1	+17
11†	6	14	98.3	82	80.7	0	+20
12†	11	16	124.4	66.8	83.1	-3	+30
13†	11	8	62	105.1	64.5	-3	+2
14†	12	17	58.2	126.8	74.0	-6.5	*
15†	5	2	124.7	72.6	86.8	-6	*
16†	3	4	72.3	96.4	69.8	-3	+1
	17	18	84.5	89.4	75.5	-3	+7
17	15	16	81	*	*	-5	+24

Note.—Cases 1, 4, and 16 each had two studies.

* Not performed.

† Small infarct.

a standardized protocol (1 ml/kg as a bolus injection, followed by a slow infusion until the end of image acquisition, without exceeding a total of 150 ml).

Square 4 × 4 cm regions of interest (ROI) were positioned within the center of the lesion on the CT images. Hypodensity was calculated as the mean difference in Hounsfield units (H) between the lesion ROI and the contralateral homologous ROI. Contrast enhancement was expressed as the difference in H between postcontrast and precontrast studies. A circular 4 cm² ROI was then placed in a roughly similar location on the corresponding CMRO₂ image, and the mean ROI values for CBF, OEF, and CMRO₂ were computed for both the lesion ROI and the contralateral homologous ROI. When applicable, the mean CT and ¹⁵O-PET values were calculated across the two or three cuts where the lesion was visible. Linear least-square fitting was then applied to analyze possible correlations between the two CT parameters and the three ¹⁵O-PET parameters. Correlation coefficients obtained were statistically assessed by the Student *t* test. Because of the expected physiologic variations in CBF, OEF, and CMRO₂, both interindividually and from region to region in the same individual [10], only percentage changes relative to the contralateral side were used in the data analysis.

Results

Significant hypodensity (≥ 3 H) was seen on CT in 17 of 20 studies, while contrast enhancement (≥ 4 H) was seen in 13 of 17 studies (table 1). In the ¹⁵O-PET studies, local CBF was decreased ($< 90\%$), increased ($> 110\%$), or unchanged in 14, two, and four of the 20 studies, respectively. The infarct CMRO₂ was consistently decreased (range 19%–87%), while the OEF was decreased ($< 90\%$), increased ($> 110\%$), and unchanged in 14, two, and three of 19 studies, respectively.

Significant positive correlations were found between hypodensity and CBF ($p < 0.02$), hypodensity and CMRO₂ ($p < 0.01$), and contrast enhancement and CBF ($p < 0.01$) (figs. 1 and 2). No significant correlations were found between contrast enhancement and CMRO₂ or OEF, or between hypodensity and OEF. Despite the lack of quantitative correlation between contrast enhancement and

OEF, a significant association between presence of contrast enhancement (≥ 4 H) and decreased OEF ($< 90\%$) was observed ($p < 0.01$ by chi-square analysis). Illustrative examples are shown in figures 3 and 4.

Discussion

The present study suffers from several limitations of methodology. First, because our PET device provides a spatial resolution less detailed than that of the CT scanner used, the local physiologic data obtained are more affected by the partial volume effect [12]. This is especially true in small infarcts, where values from 4 cm² ROI are expected to be grossly distorted [12]. In order to minimize such effects, the six studies of small infarcts (table 1) were reanalyzed using 1 cm² ROI, but this did not alter significantly the correlations observed. Second, due to the limitations of the ¹⁵O model itself, some distortion of the CBF, OEF, and CMRO₂ values measured within infarcts are expected [5, 8]. Third, the topographic identity between the ROI placed on CT and on PET images was only approximate. Fourth, for the sake of clarity, we used mean infarct values even when differences existed between different cuts in the same study; the observed correlations still held when all the single-plane data were analyzed together. Fifth, because motion artifacts were present on the side contralateral to the infarct in two cases, we chose to calculate the infarct contrast enhancement without subtracting the normal-side physiologic contrast enhancement (mean value 2.4 H $\pm$ 1.3); when we did so, the other 15 studies showed similar correlations. Sixth, there was a delay of up to 5 days (8 days in case 11) between CT and ¹⁵O-PET studies, so that some changes may have occurred, although these were probably not dramatic since both studies were carried out more than 24 hr after clinical onset. Although they need to be acknowledged, the above limitations should not alter seriously the validity of the present work.

The four following observations were made. First, and not unexpectedly, severe physiologic abnormalities were consistently seen within the CT-defined lesion. However, it was striking that either CBF or OEF could be unremarkable (in four and three instances, respectively), while infarct CMRO₂ was always markedly decreased, so the latter parameter would stand as the most reliable indicator of

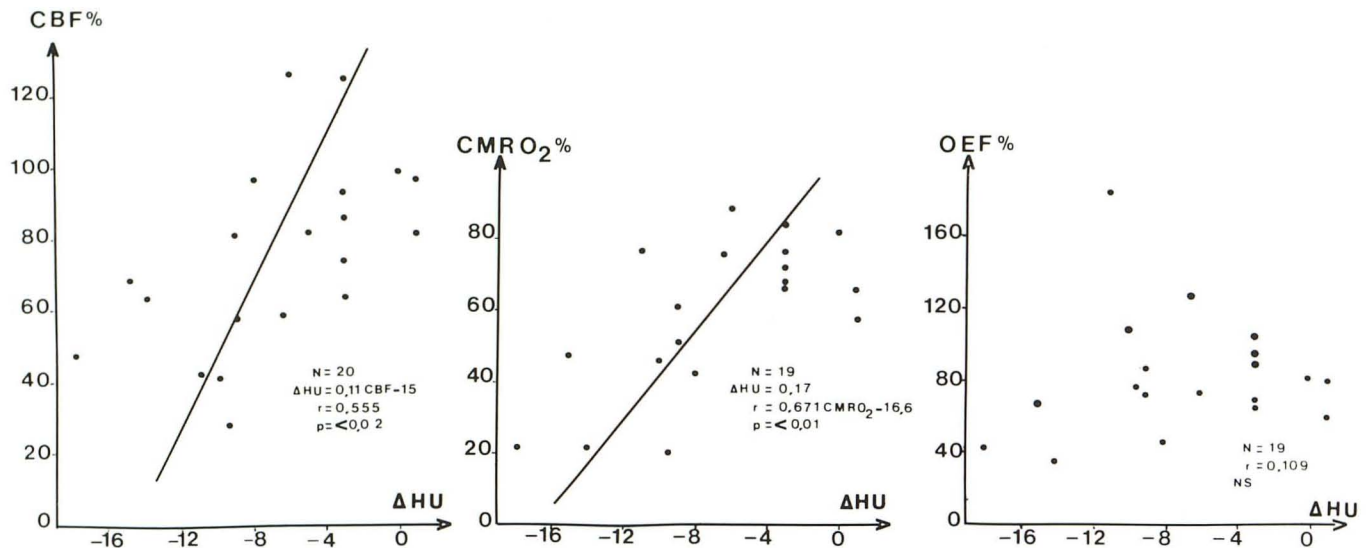


Fig. 1.—Plot of cerebral blood flow (CBF), oxygen utilization ($CMRO_2$), and oxygen extraction fraction (OEF) within infarcted area (all expressed as percentage value relative to contralateral side) versus density changes seen on precontrast CT scan within same area, expressed in absolute difference

in Hounsfield units (H) relative to contralateral side. Each dot represents single patient. Significant positive correlations were found between ΔH and CBF ($p < 0.02$) and between ΔH and $CMRO_2$ ($p < 0.01$).

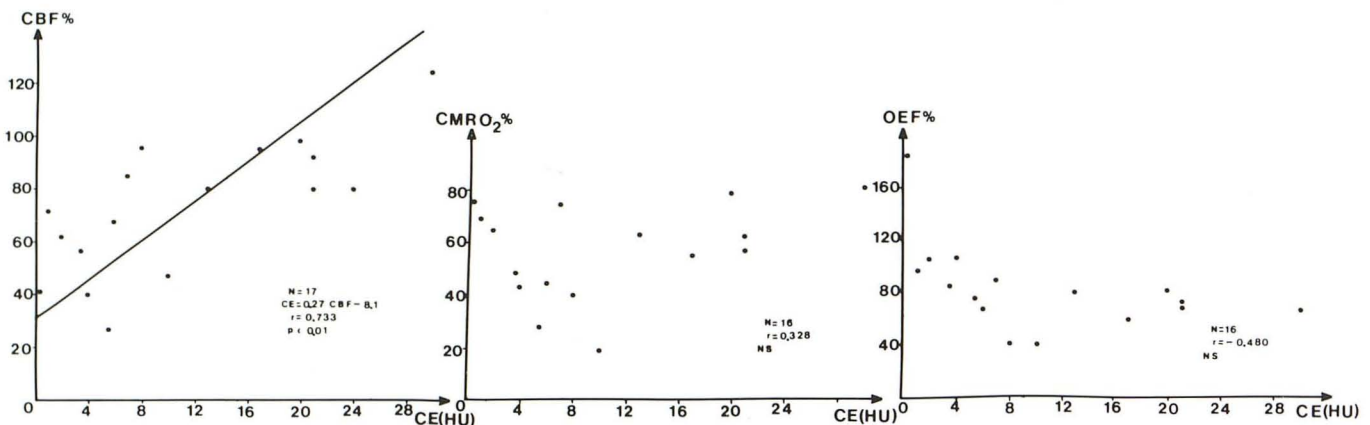


Fig. 2.—Same presentation as figure 2, but relating CBF, $CMRO_2$, and OEF to contrast enhancement (CE), expressed as difference in Hounsfield

units between pre- and postcontrast infusion within infarct area. Significant positive correlation was found only between CE and CBF ($p < 0.01$).

functional alteration, as reported previously [5]. Second, a statistically significant positive correlation between contrast enhancement and CBF was found (fig. 2), indicating that the more elevated the CBF, the more marked was the contrast enhancement, a finding consonant with the recent work of Kawase et al. [13], who used ^{133}Xe intracarotid injection to measure CBF. It must be stressed, however, that contrast enhancement in itself did not mean true hyperemia, since in most cases it was associated with a decreased CBF. Conversely, the absence of any contrast enhancement was not always associated with a profoundly decreased CBF. Third, although there was no significant correlation between contrast enhancement and OEF (the OEF represents the balance between oxygen supply and demand), the association between marked contrast enhancement and decreased OEF (i.e., the "luxury perfusion syndrome" [14]) on one hand, and between absence of contrast enhancement and normal or increased OEF (the latter characterizing the "misery perfusion syndrome" [15]) was highly significant. Fourth, the more the CBF and $CMRO_2$ of the infarct were depressed, the more the hypodensity was likely to be prominent, with significant

correlations (fig. 1), although individual exceptions to the rule existed.

Contrast enhancement of a variable pattern is often seen in recent brain infarction [16–20], with a peak frequency during weeks 2 and 3 after onset [21–23]. Proposed mechanisms for its occurrence include increased CBF and/or local vasodilatation: the former appears at best accessory, as indicated by the present work; while the latter would have to be enormous to induce by itself the contrast enhancement usually seen in infarcts [24, 25]. In the light of comparative studies with postmortem data [13, 20] and with ^{99m}Tc brain scans [16, 17, 26, 27], extravasation of the iodinated medium into the damaged tissue is now accepted as the most contributory factor in explaining the contrast enhancement seen in cerebral infarction, a concept also borne out by dynamic enhancement CT studies [28, 29].

How, then, can the correlation reported here between contrast enhancement and CBF be explained? One hypothesis would incriminate time-dependent but coincidental changes in two otherwise unrelated variables. In support of this hypothesis, both contrast

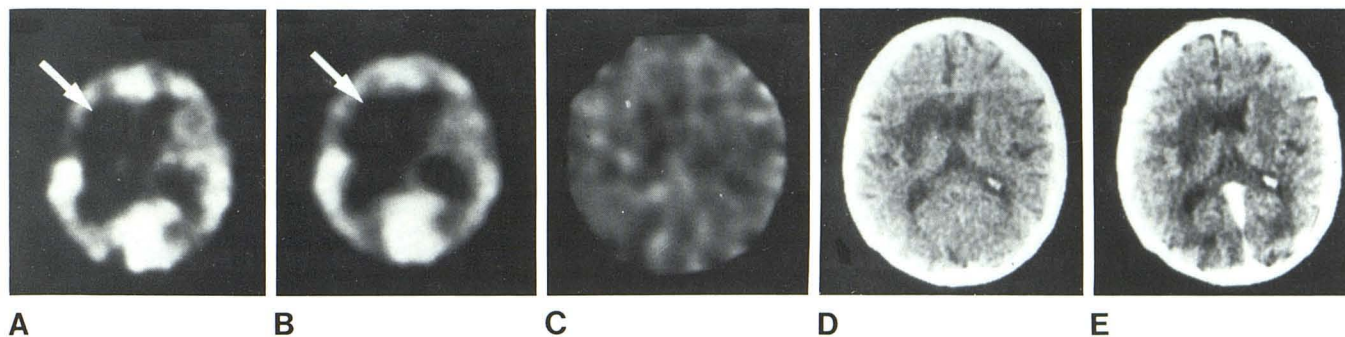


Fig. 3.—Case 1, 77-year-old hypertensive woman. Oxygen-15 PET measurements of CBF (A), $CMRO_2$ (B), and OEF (C) were done 2.5 days after clinical onset of left hemiparesis and Broca aphasia. Directional Doppler study suggested occlusion of left internal carotid artery. CT 24 hr later showed marked hypodensity (9 H) in deep sylvian territory on left side (D),

which enhanced by 3.5 H (same as contralateral side) after intravenous infusion of iodinated material (E). Within this area, PET study disclosed reduction in CBF and $CMRO_2$ (arrows) to 57% and 49% of contralateral values, respectively, with only marginal decrease in OEF (87%).

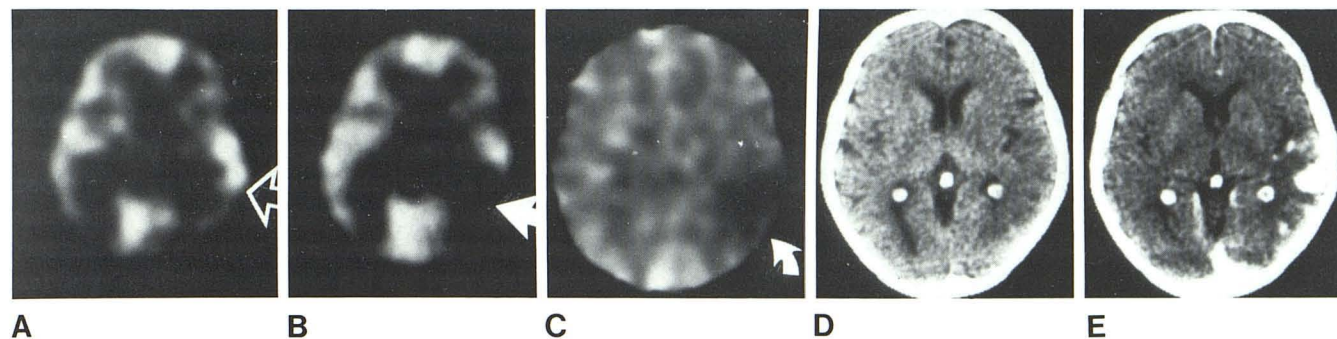


Fig. 4.—Case 10, 75-year-old right-handed woman. Oxygen-15 PET studies of CBF (A), $CMRO_2$ (B), and OEF (C) were done 18 days after sudden onset of crossed expressive aphasia. Directional Doppler study showed no clear abnormality. CT on the same day showed questionable hypodensity in right temporal region (D), with marked but heterogeneous enhancement (+17

H compared with +3 H on contralateral side) after intravenous infusion of iodinated material (E). Within this area, PET showed unchanged or increased CBF (open arrow), but reduction in $CMRO_2$ (straight solid arrow) and OEF (curved arrow) to 56% and 60% of contralateral values, respectively.

enhancement and CBF are known to have a marked tendency to increase during weeks 2 and 3 of infarct evolution [5, 21–23], a trend also seen in the present series where mean infarct CBF and contrast enhancement were 62% and +4 H in the acute (≤ 4 days) phase, and 82% and +16.3 H in the subsequent phase, respectively. Alternatively or additionally, the extravasation of contrast medium could be directly proportional to the local CBF in a causal relationship. In support of this hypothesis, experimental studies have shown that after release of occlusion of the middle cerebral artery, the amount of plasma proteins leaking into the damaged tissue was proportional to the prevailing local CBF [30]. Thus, the degree to which CBF increases and plasma proteins leak would depend on the degree to which perfusion pressure is reestablished in a capillary bed damaged by prior ischemia (i.e., where CBF autoregulation is lost and the blood-brain barrier is leaky). The positive correlation between contrast enhancement and CBF reported here would therefore find a satisfactory explanation.

The association between marked contrast enhancement and decreased OEF can best be explained by an indirect relationship in which CBF acts as the link. Thus, the local vasoparalysis referred to above would allow CBF to be restored to levels above that needed for the (depressed) oxygen demand [5], a situation termed the "luxury perfusion syndrome" [14]. Hence a relatively high CBF would induce simultaneously a decrease in the local OEF and the extravasation of contrast medium.

We also report a weak but statistically significant correlation between precontrast density and CBF. Again, a time-dependent

coincidental relationship may be considered, since the hypodensity frequently vanishes in week 2 or 3 of infarct evolution (i.e., the so-called "fogging effect" [31, 32], presumably due to a combination of decreasing edema, vascular dilatation and proliferation, and petechiae [31, 33], a phase in which a spontaneous increase in local CBF also occurs [5]. In addition, if it is assumed that the hypodensity seen in brain infarction is chiefly due to local edema [17, 20, 33–35], a causal relationship between CBF and hypodensity may then be inferred from several experimental studies on ischemic or cryogenic edema, which showed that the more CBF was decreased, the more the water content of the tissue was elevated [36–38]. These experimental observations would also provide a tentative explanation for the correlation found here between hypodensity and $CMRO_2$, since the latter is known either to determine the CBF in normal (coupled) situations or to be dependent on CBF in ischemic (uncoupled) conditions [5]. Alternatively or additionally, the severity of local (cytotoxic) edema may depend on or aggravate the energy failure of the ischemic tissue.

The present study has provided new functional correlates to the CT density changes seen within cerebral infarction before and after intravenous injection of contrast medium. Although the observations made were statistically significant and could be explained by a pathophysiologically reasonable hypothesis, they should not, as shown by the spread of our data, be applied to the individual patient without extreme caution. In addition, the correlations found may not necessarily apply to conditions other than ischemic cerebral infarction.

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