Human Hemispheric Infarction Studied by Positron Emission Tomography and the 15O Continuous Inhalation Technique

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Positron emission tomography (PET) offers an entirely new approach to the study of the pathophysiology of cerebral ischemic disorders. This is so because for the first time it is possible to obtain *functional* tomographic images that represent cerebral perfusion and metabolism in a regional basis. We report here a study of cerebral blood flow and oxygen extraction by means of the ^{15}O inhalation technique in a large number of human hemispheric infarctions.

A. Materials and Methods

We have applied to PET the model developed by Jones (1).A detailed description of the method has been reported by Baron et al (2), and it will be only briefly outlined here. The patient continuously inhales to equilibrium consecutively CO2 and O2labeled with 15O, a positron-emitter with a physical half-life of 123 seconds. Equilibrium axial transverse images (thickness 2 cm ; resolution 1.5cm) of brain tracer distribution are collected at identical levels (at an angle of +5° to the cantho-meatal line) by means of a PET device (ECAT, ORTEC) whose description and physical performances have been reported (3,4).Because of the short half-life of the tracer, a state of "dynamic equilibrium" (1) is reached after 6 to 10 minutes of continuous inhalation of the 15O labeled gas, whereby all blood and tissue tracer concentrations are stable : the input of radioactivity is equal to its egress by radioactive decay and physiological transport. The theoretical model pertains that, because C15O2 inhalation results in blood water labeling (5), the brain distribution of H2 15O in the C15O2 equilibrium image is primarily proportional to perfusion ; this relationship is however non-linear so that at high flow rates the increment of tissue activity is of much smaller magnitude than the real increment in cerebral blood flow (CBF). During 15O2 inhalation, the hemoglobin-bound tracer is taken up by brain (and other tissues)and converted in situ to labeled water in proportion to the oxygen utilisation rate. Locally formed H2 15O is however constantly cleared by tissue perfusion, a process that results in H2 15O recirculation ; the distribution of the tracer in the equilibrium 15O2 image will therefore be dependant on both the oxygen consumption rate (CMRO2) and CBF. The theoretical model however states that division of the 15O2 image by the corresponding C15O2 image eliminates the CBF component, and results in a distribution that is linearly proportional to the regional fractional extraction of oxygen (EO2 = Ca - Cv/Ca where Ca and Cv are the arterial and venous oxygen contents respectively).

Thirty-eight patients were studied ; 33 had a single infarct but 3 were studied twice ; 4 had two and 1 had three infarcts. A total of 47 hemispheric infarcts of age ranging from 30 hours to 20 years were studied. The diagnosis was established on clinical grounds and supported by ancillary diagnostic procedures including CT Scan in 21 patients and autopsy in 1. Of the 47 infarcts, 36 were in the distribution of the middle cerebral artery, 6 in that of the posterior cerebral artery, and 5 were classified as watershed infarcts.

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B. Results

Striking differences in the CBF/EO2 relationship appeared between the recent ($\leq$31 days) infarcts (group I, N=30) and the older ($>$31 days) infarcts (group II, N=17) :

1° - CBF : group I : in 22 cases, CBF was homogeneously decreased (N=15), normal (N=5) or increased (N=2) in the abnormal area ; in the remaining 8 cases, there were heterogeneities with the following associations : normal and decreased (N=4), normal and increased (N=2), decreased and increased (N=2). Thus CBF was normal or increased in part or all of the lesion in 15 of 30 recent infarcts (50%).

group II : CBF was decreased in all 17 infarcts ; in only one case (a 37 days old infarct) there was an adjacent area of hyperemia.

The occurence of normal or increased CBF in both groups of infarcts is summarized in table 1 ; the difference is highly significant ($p<0.01$).

Table 1

Age \ CBF	Decreased	Normal or Increased	TOTAL
$\leq$ 31 days	15	15	30
$>$ 31 days	16	1	17
Total	31	16	47

$X^2 = 9.40$, $p < .01$

2° - EO2 : the EO2 is uniformly distributed in normal brain (2). In group I infarcts, the EO2 was entirely normal in only 3 cases ; it was uniformly decreased (most often profoundly so) in the abnormal area in 17 cases, and uniformly increased in one ; in the remaining 9 cases, there were heterogeneities of the EO2 in the abnormal area with the following associations : normal and decreased (N=5), normal and increased (N=1) decreased and increased (N=2), all three (N=1). Thus the EO2 was clearly disturbed (decreased or increased) in part or all of the lesion in 27 of 30 recent infarcts (90%). The patterns of concomittent perfusion with normal, increased or decreased EO2 are shown in table 2.

Table 2

EO2 \ CBF	Normal	Decreased	Increased
Normal	0	73%	27%
Decreased	37%	53%	10%
Increased	0	100%	0

In group II infarcts, the EO_2 was entirely normal in 11 cases ; in the remaining 6 cases, there was association of areas of normal and of moderately decreased (N=5) or increased (N=1) EO2. Thus, the EO2 was abnormal in part of the lesion in 6 of 17 old infarcts (35%). The occurence of regions of disordered EO2 in group I and II infarcts is shown in table 3 ; the difference is highly significant ($p<0.001$).

Table 3

Age \ EO2	Normal	Increased or Decreased	Total
$\leq$ 31 days	3	27	30
$>$ 31 days	11	6	17
Total	14	33	47

$X^2 = 15.52$, $p < .001$

Typical examples are shown on Figure 1 and 2. Figures 3 and 4 clearly illustrate respectively the inconsistency of CBF and the frequent occurence of disordered EO2 in recent infarcts. They also show the progressive decline of CBF paralleled by a return to a normal EO2 with advancing age of infarct,. Such a course of events is demonstrated in 3 longitudinallystudied cases (represented as broken lines).

C. Discussion

Our results clearly demonstrate that disruption of the CBF/metabolism couple in at least part of the lesion is almost universal in recent cerebral infarction: A focally disordered EO2 indicates that the metabolic demand is not matched by the local perfusion.
The most frequently observed situation was that of a *decreased* EO2 (i.e. a focal decrease in the oxygen arterio-venous difference), indicating Lassens's "luxury perfusion" syndrome (6). Based only on the occurrence of focal hyperemia with conventional CBF technique (7), this phenomenon was thought to be rather unfrequent in recent infarction. However, it is shown from our experience that the luxury perfusion syndrome is almost universal in such as setting, and that it can be associated with normal or decreased CBF as well as with hyperemia, a fact reported in focal experimental ischemia (8). Our results of decreased EO2 in recent infarcts are further supported by the finding of increased internal jugular PO_2 ipsilaterally to human cerebral infarcts 3 to 20 days old (9). Preliminary observations indicate that the areas of decreased EO_2 correlate well with further tissue necrosis as seen on CT Scans (Fig. 1), as mentioned by others (10).

The converse situation of focally *increased* EO_2 in recent infarction was of less frequent occurence, and was always associated with decreased perfusion : this CBF/EO_2 relatioship, that one may call the "misery perfusion syndrome", presumably indicates a beneficial metabolic response in the face of critical but potentially reversible ischemia (10,11). However, in no instance have we observed the hypermetabolic rim surrounding the infarct as reported by users of the ^{18}F -2 Deoxyglucose technique (12), probably because the latter represents increased anaerobic metabolism.

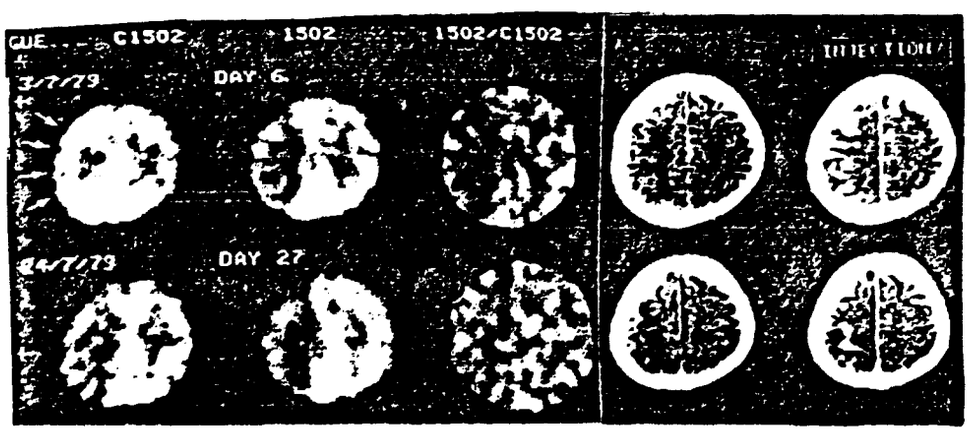

Fig. 1 : Recent left hemispheric infarction studied twice. Hyperemia (arrows) present at day 6 was replaced by decreased CBF at day 27.The area of profoundly decreased EO_2 at day 6 correlateswell with low-absorption areas on CT. Scans performed at days 10 (upper row) and31 (lower row)

Fig. 2 : 2 years old infarction of left deep frontal area. Decreased CBF ($C^{15}O_2$ image) with normal EO_2 (ratio image).

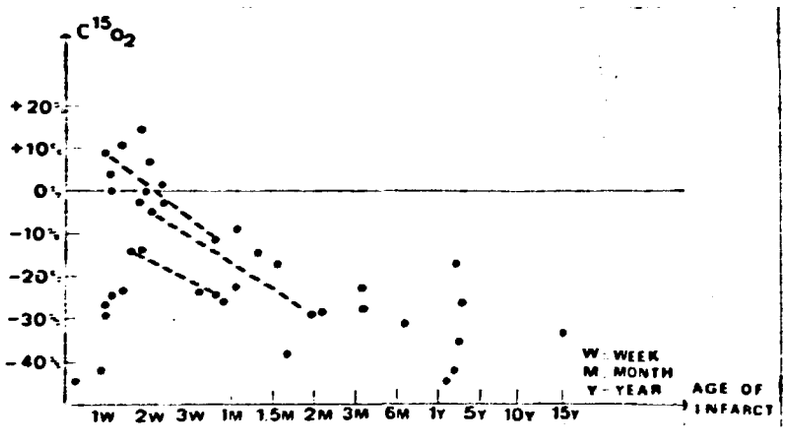

Fig. 3 : Percent difference in $C^{15}O_2$ countrate between the abnormal area and its homologous contralateral area in 39 hemispheric infarctions, i.e. a reflection of the mean change in CBF within the infarct (see text).

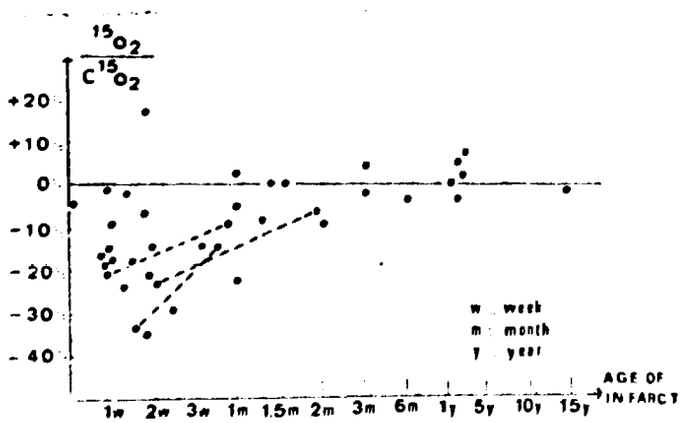

Fig. 4 : Percent difference in the ratios of $^{15}O_2$ and $C^{15}O_2$ countrates between the abnormal area and its homologous contralateral area in 39 hemispheric infarctions, i.e. a reflection of the mean change in EO_2 within the infarct (see text).

Lastly, the occurence of focal *hyperemia* following recent cerebral ischemia does not necessarily imply that the luxury perfusion syndrome is operative, since in 4 of 7 instances it was associated with a normal EO_2, indicating post or peri-ischemic reactive hyperemia (14), with increased aerobic metabolism (15), i.e. a presumably beneficial process (16).

Contrasting with the inconsistency and heterogeneity of CBF together with a disordered EO2 in recent infarcts, older infarcts were characterized by a tendency to associate a uniformly decreased CBF with a normal EO2 : the perfusion is now matched to the low metabolic needs of the infarcted area, probably as a result of partial or total removal of the necrotic tissue. Lenzi et al (15), though using the ^{15}O inhalation technique, however reported a frequently decreased EO_2 in old infarcts : this may reflect inaccuracies due to their non-optimal imaging device.

The 15O inhalation technique is the only presently available procedure that at the same time is non-invasive, allows tomographic imaging, and simultaneously provides information on both CBF and oxygen metabolism. These all constitute major advantages over conventional CBF and other PET techniques that make it particularly suited for the study of ischemic brain disorders. Because they only provide the CBF data, the 133 Xe techniques would have overlooked around 20% of the 30 recent infarcts reported here ; in addition, since a given CBF alteration may have several metabolic counterparts, they are not optimal when physiopathological understanding and hence prognostic correlations are desired. The 15O intracarotid injection technique (17) provides quantitative regional CBF, EO_2 and $CMRO_2$ values but is invasive and does not allow tomographic imaging. PET imaging of $^{13}NH_3$ brain distribution in stroke has been reported (12), but its validity as an index of CBF in diseased brain remains unsettled (18). Lastly, the ^{18}F-2DG method (19) provides PET images, but is not optimal when functional brain damage has occured because focal alteration in both the tracer kinetics (20) and the aerobic/anaerobic metabolism ratio may render interpretation of the results difficult. Such advantages of the 15O inhalation technique in our opinion largely outweight its main criticism, namely the non-linear relationship between C15O2 countrate and CBF that makes this technique poorly sensitive to CBF increases and highly sensitive to measurements errors : from our experience, however, it appears that focal hyperemia is frequently detected and that precision of the C15O2 measurement is reasonably good. That this technique allows imaging of CBF and EO2 is the matter of no discussion, as supported by this and other works (21,22), although definitive experimental verification is still lacking. Finally, regional quantitation of CBF, EO2 and CMRO2 by this technique has been the matter of contradictory reports (22,23), but certainly constitutes a necessary step in its development that will require continuing efforts.

In conclusion, PET imaging with the non-invasive ^{15}O inhalation technique in cerebral infarction has permitted the description of hitherto unreported focal patterns of changes in the CBF/EO2 couple that may have important pathophysiologic and prognostic implications.

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