Positron Emission Tomography in the Study of Regional Cerebral Blood Flow in the Premature Infant with Major Intraventricular Hemorrhage and in the Term Newborn with Asphyxia

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The two major causes of neurological morbidity and mortality related to definable events in the neonatal period are intraventricular hemorrhage (IVH) with hemorrhagic intracerebral involvement in the preterm infant, and hypoxic-ischemic encephalopathy in the asphyxiated term infant. This chapter reviews studies of regional cerebral blood flow (CBF) by positron emission tomography (PET) in these two important groups of infants.

INTRAVENTRICULAR HEMORRHAGE WITH HEMORRHAGIC INTRACEREBRAL INVOLVEMENT IN THE PRETERM INFANT

Periventricular-intraventricular hemorrhage (PVH-IVH) is the most common serious neurological lesion encountered in the premature infant (1). The incidence of PVH-IVH is high, approximately 35% to 45% (2). A recent prospective study by serial real-time ultrasonography in 460 infants with a birth weight below 2,000 gm revealed an incidence of PVH-IVH of 39% (3). Of all patients with PVH-IVH, those with hemorrhagic intracerebral involvement exhibit the highest rates of mortality and neurological morbidity and account for the vast majority of all neurologically impaired infants with PVH-IVH. To prevent this lesion, an understanding of its pathogenesis and basic nature is necessary.

Two possibilities concerning the pathogenesis and basic nature of the hemorrhagic intracerebral involvement with severe PVH-IVH seem most worthy of consideration. First, the intracerebral blood could represent localized extension of
blood from the germinal matrix or lateral ventricle into previously normal white matter, or second, the intracerebral blood could represent a component of a larger, primary parenchymal lesion. We reasoned that assessment of regional CBF could provide highly valuable information for the evaluation of these hypotheses. However, until now elucidation of regional CBF in the newborn has not been possible. Positron emission tomography has been recently shown to be highly effective in the study of regional CBF in older patients (4).

In this study, we utilized PET to measure regional CBF in six premature infants with severe IVH and hemorrhagic intracerebral involvement to obtain insight into the basic nature of the parenchymal involvement. The findings demonstrate the value and feasibility of PET for the determination of regional CBF in the newborn with severe IVH and hemorrhagic intracerebral involvement and clarify the basic nature of the parenchymal involvement.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN THE ASPHYXIATED TERM INFANT

Hypoxic-ischemic encephalopathy in the term newborn is the most frequently recognized cause of the subsequent nonprogressive motor deficits often grouped under the rubric, cerebral palsy (1). These deficits consist most commonly of spastic weakness of proximal extremities, usually symmetric. The magnitude of the problem of hypoxic-ischemic encephalopathy relates not only to the gravity of the lesions, but also to the relatively high and unchanging prevalence of the encephalopathy (5). Indeed, unlike the decline in neurological sequelae attributable to hypoxic-ischemic encephalopathy in the premature infant with the advent of neonatal intensive care, there has been little or no decrease in such sequelae in the term infant (6).

Further insight into the basic nature and pathogenesis of the major brain injury associated with neonatal hypoxic-ischemic encephalopathy is needed to devise interventions to decrease the high prevalence of the neurological sequelae. Obtaining such insight from neuropathological observations has been difficult because relatively few infants, that is, approximately 10% to 15%, die in the neonatal period, and these as expected represent the most severely affected infants. Diffuse cerebral changes, confirmed by computerized tomography (CT) (7), are common and obscure critical elemental lesions. We reasoned that insight into the basic nature and pathogenesis of the brain injury in surviving infants could be provided by measurements of regional CBF in the acute period of illness. Recently, we have demonstrated the feasibility and value of PET in the study of regional CBF in the newborn (8). Thus, we undertook the present study to measure regional CBF during the acute period of illness in term infants with hypoxic-ischemic encephalopathy and to provide insight into the basic nature and pathogenesis of the associated brain injury.
METHODS

Measurement of Regional Cerebral Blood Flow by Positron Emission Tomography

Positron emission tomography was performed with the PETT VI tomograph. The design and performance characteristics of this system have been described (9,10). Data are recorded simultaneously from seven slices with a center-to-center separation of 14.4 mm. The in-plane resolution is 11.7 mm. Each PET slice is performed in the horizontal plane parallel to the orbitomeatal line. Head positioning is accomplished with the aid of a vertical laser line, which indicates the level of the lowest PET slice.

For the measurement of regional CBF, an emission scan, 40 sec in duration, is obtained following an intravenous bolus injection of $^{15}$O-labeled water, 0.7 mCi/kg, in 0.5 ml of saline. In those studies in which an arterial catheter had been placed for the infant's intensive care, collection of arterial samples was carried out approximately every 5 sec. These samples were weighed and counted and the radioactivity corrected for the physical decay of $^{15}$O, as previously described (8). Calibration of the tomograph to obtain the regional isotope concentration in brain from the reconstructed image was carried out as previously described (8).

The scan data and blood curve were analyzed according to the general principles of inert gas exchange, developed by Kety (11) and later embodied in a tissue autoradiographic technique for the measurement of local CBF in laboratory animals (12,13). We have described the details of this analysis (8) and have established the validity of this technique in the adult baboon (14). The correlation between CBF determined by PET, and with $^{15}$O-labeled water and standard tracer principles, was excellent. Because of the near linear relationship between local tissue counts and CBF obtained with the PET autoradiographic approach, it is possible to measure accurately relative differences in local blood flows in different brain regions. This is particularly important because the majority of the infants studied herein did not have arterial lines in place and thus absolute blood flow quantitation could not be performed.

The total absorbed radiation dose, in a representative 1 kg subject receiving an intravenous bolus injection of 0.7 mCi of $^{15}$O-labeled water, is 63 mrem for the whole body. The critical organs, that is, those receiving the largest radiation exposure, are the brain, heart, kidney, liver, and gastrointestinal tract. These high-flow organs receive 76 mrem.

Other Measurements

Continuous measurements of arterial blood pressure were made from an indwelling umbilical artery catheter. Intracranial pressure was determined at the anterior
fontanel with the Ladd monitor. Cranial ultrasonography was performed with an Advanced Technology Laboratories (ATL) sector scanner. Computerized tomography and technetium radionuclide brain scanning were performed by standard techniques.

RESULTS

Intraventricular Hemorrhage with Hemorrhagic Intracerebral Involvement in the Premature Infant

Clinical Features

The birth weights of the six infants studied ranged from 920 to 1,200 gm. Four of the six infants sustained varying degrees of perinatal asphyxia, since their 1 min Apgar scores were 3 or below, and their 5 min scores below 6. Each of these four infants experienced probable intrauterine insults, for example, fetal bradycardia, worsening maternal hypotension, precipitous delivery, and second born of twins. Two infants had large patent ductus arteriosus at the time of the PET study, and all six had severe respiratory distress syndrome. The PET scans were performed on the fifth day of life in two of the infants, on the sixth day in one, on the tenth day in two, and on the seventeenth day in one. The latter infant had a second PET study on the ninetieth day. Four infants expired in the neonatal period.

The cranial ultrasonographic abnormalities are illustrated in a typical case (Fig. 1). The cranial ultrasound scan shows bilateral subependymal hemorrhage and IVH, much more marked on the left, and marked hemorrhagic intracerebral involvement on the left (Fig. 1A). The left sagittal scan (Fig. 1B) demonstrates that the hemorrhagic intracerebral involvement was confined to frontal white matter.

PET Determinations of Regional Cerebral Blood Flow

Each patient exhibited the essential PET findings. These are illustrated in Fig. 2 and include (a) on the side opposite to the intraparenchymal lesion, highest blood flows laterally in the region of adjacent and overlapping frontal-temporal cortex, that is, sylvian cortex, and in some slices, basal ganglia; (b) anteriorly and posteriorly, in the midline, highest blood flows in adjacent, right, and left medial frontal and occipital cortex; and, most significantly, (c) in the hemisphere containing the intraparenchymal blood, decreases in regional blood flow that are much more extensive in distribution that can be accounted for by the locus of the intracerebral blood. Indeed, in the involved left hemispheres marked diminutions of regional CBF are apparent not only anteriorly in frontal white matter, the site of the hemorrhagic intracerebral involvement, but also in posterior cerebral white matter and, to a lesser extent, in frontal-temporal-parietal cortex (especially sylvian cortex).
Structural Correlate to the Extensive Impairment of Cerebral Blood Flow in the Involved Hemisphere

Neuropathological study of three of the cases defined the structural correlate of the extensive impairment of CBF in the hemisphere containing the intraparenchymal hemorrhagic involvement. Thus the blood clot in the left frontal white matter was found to be continuous with extensive nonhemorrhagic softening of the posterior frontal, parietal, and occipital white matter.
Hypoxic-Ischemic Encephalopathy in the Asphyxiated Term Infant

Clinical Features

The essential clinical features of the 14 infants were characteristic of neonatal hypoxic-ischemic encephalopathy (1). The severity of the asphyxial insults is emphasized by Apgar scores of <4 at 5 min in 11. The likelihood that the Apgar scores reflected depression secondary to intrauterine asphyxia is supported by the findings of fetal distress in 10 of the 12 infants for whom adequate intrauterine data were recorded. One infant sustained a primarily postnatal hypoxic-ischemic event, that is, cardiorespiratory arrest at 4 hr, of unknown etiology.

The neurological features were similar and conformed to the neurological syndrome previously described (1). Eight of the infants experienced neonatal seizures, with onset consistently on the first postnatal day. All infants were treated with phenobarbital (1).

Twelve of the infants exhibited proximal limb weakness. Affection of upper more than lower extremities was consistent (1). The two infants who did not exhibit definite proximal limb weakness also did not exhibit seizures and, on the basis of clinical course, appeared to be the least affected patients in the group.

The PET studies were performed on postnatal days 3 to 5 in twelve infants, on day 7 in one, and on day 20 in one. At the time of the PET studies, all infants had normal blood gases, hematocrit, intracranial pressure, and systemic blood pressure.

PET Determinations of Regional Cerebral Blood Flow

The normal or near normal pattern of regional CBF in the term newborn is apparent in the PET scan obtained from the infant least affected on the basis of clinical findings (Fig. 3A). (For ethical considerations, no clinically normal infants have been studied thus far.) The major PET findings include an external ribbon of relatively higher flows in regions of cerebral cortex. Cerebral blood flow to frontal and parietal cortical regions are approximately 50% higher than to corresponding cerebral white matter. Of the cortical regions, relatively higher flows are especially apparent anteriorly and posteriorly in the midline, in adjacent right and left medial frontal and occipital cortex. Laterally, CBF to adjacent and overlapping fronto-temporal-parietal cortex, that is, sylvian cortex, is approximately 10% higher than CBF to adjacent frontal or parietal cortex. In addition to cerebral cortical regions,
relatively higher flows are also observed centrally, in the region of thalamus and basal ganglia.

The abnormalities of regional CBF in the infants constitute a continuum of deviation from the normal or near normal pattern just described (Fig. 3B–D). The consistent and apparently unifying abnormality was a relative decrease in CBF to parasagittal regions, generally symmetric and more marked posteriorly than anteriorly. The spectrum of this abnormality is apparent in the illustrated PET studies (Figs. 3B–D). In the least affected patients, CBF to posterior parasagittal regions is approximately 25% lower than CBF to sylvian cortex, and in the infants with the most severe affection, parasagittal CBF values are approximately 40% lower than those to sylvian cortex. The relative decreases in parasagittal CBF are slightly less marked in the anterior parasagittal regions. A consistent feature in the affected para-
sagittal areas is a loss or even reversal of the cortical gray matter versus white matter gradient of regional CBF.

The number of infants who were studied with arterial lines in place and for whom, therefore, absolute values for CBF are available is too small to permit generalizations about the severity of the deviation of parasagittal CBF from normal. In three such infants, the absolute values in the posterior parasagittal regions ranged from 30 to 50 ml/100 gm/min, and in the corresponding sylvian regions, 60 to 80 ml/100 gm/min.

Correlates of the Parasagittal Abnormality in Regional Cerebral Blood Flow

To determine the structural correlates, if any, of the decrease in CBF in parasagittal regions, we initially turned to the CT scan. However, clear topographic correlation of the CT findings with the PET findings was not possible. Thus CT scans obtained within several days of the PET scans showed more diffuse abnormalities, usually diffuse hypodensity of cerebral white matter, as described in previous studies of asphyxiated term infants (7).

We next evaluated correlation with the radionuclide brain scan. Thus far, the two infants evaluated by technetium brain scan have exhibited nearly identical findings (see Fig. 4). A striking pattern of increased uptake of the radionuclide in the parasagittal regions, bilaterally and posteriorly more than anteriorly, was observed. The close correlation of this abnormality with the abnormality of regional CBF is apparent.

Neuropathological correlation of the parasagittal abnormality in CBF was ob-

FIG. 4. Technetium brain scan (right lateral view) from asphyxiated term infant. Note the increased uptake of technetium in the parasagittal region, posteriorly more than anteriorly.
tained in the one infant who died. At postmortem examination, softening was apparent in parasagittal parietal cortex bilaterally. Coronal sections of the fixed brain revealed regions of softening in the parasagittal cerebral cortex and subcortical white matter, especially posteriorly. The involvement extended into periventricular white matter. Microscopic sections of the affected areas showed occasional cortical neurons with faintly eosinophilic cytoplasm or pyknotic nuclei and pyknotic nuclei in cerebral white matter; there was no definite tissue reaction, which was not unexpected in view of the short duration of survival. (Similar cellular changes were also observed in the caudate nucleus, ventral pons, and Purkinje cell layer of the cerebellum.)

DISCUSSION

Intraventricular Hemorrhage with Hemorrhagic Intracerebral Involvement in the Premature Infant

The current observations indicate that the hemorrhagic intracerebral involvement in infants with severe PVH-IVH is a component of a larger, primary ischemic lesion. This conclusion is based on consideration of the topography of the abnormality of CBF, shown by PET, and on the nature of the anatomic abnormality, shown by neuropathological study. The lesion involves periventricular white matter and, apparently, frontal, temporal, and parietal cortex, although because of the limits of resolution of PET it remains possible that the lesion involves only white matter. Periventricular white matter is a vulnerable region to ischemic injury in the premature newborn (1). Thus, DeReuck and co-workers have demonstrated the presence of periventricular arterial border zones and end zones, that is, watershed regions, at the sites of occurrence of ischemic neonatal periventricular white matter injury (15). Within the periventricular region, two sites, one anterior and one posterior, are especially likely to be affected by periventricular leukomalacia (16), and in this regard, it is of particular interest that in the infant with the least severe parenchymal involvement, separate anterior and posterior lesions appeared to be present. Our conclusion that the hemorrhagic intracerebral lesion observed in these patients is a component of a primary ischemic lesion is compatible with our own neuropathological observations and those reported by Flodmark et al. (7), who concluded that virtually all of the hemorrhagic parenchymal lesions in their series of preterm infants with severe PVH-IVH were hemorrhagic infarcts. In keeping with this formulation is our demonstration, in the single patient who had a second PET scan, that the relative extent and severity of the decreased CBF in the left hemisphere persisted (data not shown); thus, the ischemia was not a transient acute event, but rather a reflection of a fixed structural lesion.

The etiology and timing of the ischemic injury in our infants remain unclear. The ill preterm infant is considered to be especially susceptible to ischemic cerebral
injury, often secondary to systemic hypotension, because of the occurrence of a pressure-passive cerebral circulation (17). In this regard, it is noteworthy that four of six infants experienced perinatal asphyxia, as judged by depressed Apgar scores, and two had a large patent ductus arteriosus, which has been associated with decreased CBF velocity (18). It also remains possible that the ischemic lesion present in the patients was not caused by prior systemic hypotension but rather by the secondary effects of blood in the lateral ventricle, the cerebral parenchyma, or subarachnoid space. Thus, the topography of the lesion is compatible with ischemia in the distribution of the middle cerebral artery. Such a formulation raises the possibility of spasm of this artery, secondary to subarachnoid or intraventricular blood, the former a well-documented event in older patients, or of compression of its branches by local brain swelling.

Why does the intracerebral hemorrhage occur principally anteriorly in a primary parenchymal lesion that also extends far posteriorly? The consistent relation between the laterality of the intraparenchymal blood and the laterality of the more extensive degree of IVH may provide a clue. Thus, as observed in this study of six cases and in our previous ultrasonographic study of 33 cases (3), the hemorrhagic intracerebral component almost invariably occurs on the side of the most marked IVH. This relation raises at least three potential explanations for the anterior placement of the hemorrhage. First, as noted above, the large amount of intraventricular blood could impair venous drainage in the affected hemisphere, and the resulting increased venous pressure, with a propensity for hemorrhage into an infarcted area, would be greatest at the anterior site because of the previously described anatomic peculiarities of the deep venous drainage anteriorly (19). Second, the intracerebral blood may emanate from the anteriorly placed germinal matrix and extend into the periventricular white matter because the latter is infarcted. Third, the intracerebral blood may emanate from the blood-laden lateral ventricle and extend into the infarcted white matter through the external angle of the lateral ventricle because of a combination of pressure effects, related to the large volume of intraventricular blood, and a relative weakness of the ependymal barrier, related to the presence of the anteriorly placed germinal matrix.

Hypoxic-Ischemic Encephalopathy in the Asphyxiated Term Infant

These observations, the first measurements of regional CBF in the term newborn, are of particular importance with regard to the basic nature and probably pathogenesis of the major brain injury in the asphyxiated infant. In addition, the data provide important new information concerning normal regional CBF in the newborn.

Regarding normal regional CBF in the newborn, the data define approximately 50% higher flows to cerebral cortex than to subcortical white matter. It is likely that the true difference between CBF to cerebral cortex and to subcortical white matter is greater than this because of the partial volume averaging effect of the PET tech-
nique. Thus, because of the current spatial resolution of PET, 11.7 mm in the image plane, it is not possible to sample pure gray or white matter, and measurements of local tissue radioactivity will receive contributions from both gray and white matter. As a consequence, blood flow is slightly underestimated in cerebral cortex and slightly overestimated in subcortical white matter. In addition to the cortical gray matter–white matter differences, our data indicate that CBF in basal ganglia and thalamus is at least as high as to cerebral cortex. These observations are compatible with regional differences in CBF measured in neonatal animals by tissue autoradiographic techniques (20).

Regarding the major brain injury in the asphyxiated infant, a consistent abnormality has been identified, specifically, a relative decrease in CBF to parasagittal regions, posterior regions being more affected than anterior. A continuum of this abnormality was observed. The absolute severity of the defects in parasagittal CBF is difficult to quantitate precisely because of our lack of normal values for CBF and the relatively small number of the asphyxiated infants in whom absolute values of CBF could be obtained. However, we consider the parasagittal deficits in CBF to be indicative of tissue injury. In support of this conclusion are, first, the findings on the delayed radionuclide brain scans in the two patients studied, the increased uptake of the radionuclide in the parasagittal regions, posteriorly more than anteriorly, correlating closely with the findings on the PET scans; and second, the identification in the single patient studied at postmortem examination of injury to parasagittal cerebral cortex and subcortical white matter, especially posteriorly. It is similarly noteworthy that the few available neuropathological studies of long-term survivors with “cerebral palsy” emphasize and illustrate the parasagittal distribution of cerebral cortical and subcortical white matter injury (21,22).

Our CBF findings suggest that parasagittal cerebral injury is an extremely common feature of neonatal hypoxic-ischemic encephalopathy, at least in patients who survive the perinatal insult. Previous studies of asphyxiated term infants by radionuclide brain scans (23,24) showed that this distribution of injury, although the most common single type, nevertheless is demonstrable in only the minority of asphyxiated infants. It is reasonable to speculate that the less marked degrees of disturbance of parasagittal CBF, defined by PET, reflect degrees of tissue injury that would not be detected by radionuclide brain scan. Whether such injury is associated with neurological deficits will require long-term follow-up for resolution.

The pathogenesis of the parasagittal brain injury in these asphyxiated infants is not established by our measurements, but the characteristic parasagittal topography is indicative of ischemia as the principal pathogenetic factor. Thus the parasagittal cerebral injury occurs in the border zones between the end fields of the major cerebral arteries, that is, the anterior, middle, and posterior cerebral arteries. This characteristic topography was defined initially by Meyer in a series of mainly adult patients (one out of his series was an infant who had experienced birth asphyxia) and was related by Meyer to systemic hypotension (25). Experimental support for this watershed concept was provided in the monkey by Brierley and co-workers who reproduced similar parasagittal lesions by producing rapid, profound systemic hypo-
tension while preventing hypoxemia (26). As we observed in our asphyxiated infants, more marked injury was demonstrable in the monkeys in the posterior cerebrum, an observation also made by Brierley and co-workers in affected adult human patients (27).

Our observations emphasize the critical importance of ischemia in the pathogenesis of the brain injury with neonatal hypoxic-ischemic encephalopathy, but do not establish the timing or precise cause of the ischemia. At least one major component of the ischemia may be systemic hypotension in association with the intrauterine asphyxia. Thus, evidence for fetal distress was common in our patients, and the occurrence of systemic hypotension (28), impaired CBF (29), and parasagittal cerebral injury (30) in asphyxiated fetal animals is well-documented. However, the additive role of postnatal hypotension, perhaps in association with difficulties with resuscitation, as evidenced by the depressed Apgar scores, could be considerable. In addition, the possibilities that postnatal hypoxemia, hypercarbia, acidemia, or brain edema could play additive roles in impairing cerebral perfusion, energy metabolism, or both must be considered. Further studies of regional CBF, coupled with the determinations of regional oxygen metabolism, could provide considerable insight into several of these issues. Clearly, PET should be of great value in such subsequent studies.

REFERENCES


