Brain SPECT in Neonates Following Extracorporeal Membrane Oxygenation: Evaluation of Technique and Preliminary Results

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Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure in neonates with refractory respiratory failure that has been used at our institution since 1985. In an attempt to study its clinical value, regional cerebral blood flow (rCBF) alterations were measured using SPECT and ^{99m}Tc-HMPAO in 13 newborns following ECMO. Eight infants were studied after ECMO with reanastomosis of the right common carotid artery (RCCA), two with the permanent ligation of the RCCA, and three after veno-venous ECMO. Brain SPECT was technically satisfactory in all newborns using a triple-head SPECT system. Altered rCBF was found in 7 of 13 infants. In five newborns, there was a decrease in rCBF within the ipsilateral hemisphere, and in one infant, contralateral hemisphere was involved. In one infant, there was bilateral hemispheric involvement. The infant underwent cardiopulmonary resuscitation prior to ECMO and exhibited clinical features of hypoxic-ischemic encephalopathy at the time of SPECT. Only 2 of 13 newborns demonstrated morphologic changes on neuroimaging modalities such as cranial ultrasonography, computed tomography and magnetic resonance imaging. Our study demonstrates that: (1) functional brain imaging is feasible in neonates after ECMO; (2) SPECT has potential for demonstrating rCBF deficits not detectable by neuroanatomic imaging modalities; and (3) SPECT has potential clinical value in long-term follow-up of neurodevelopmental outcome after ECMO.

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Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure in refractory neonatal respiratory failure. During veno-arterial ECMO, a modified form of heart-lung bypass is used until transient pulmonary compromise is recovered. The infant's blood is shunted from the right atrium of the heart, via the right internal jugular vein, where it is oxygenated through the membrane oxygenator and returned to the systemic circulation via a catheter in the right common carotid artery (*1–3*). For veno-arterial ECMO, most commonly the right internal jugular vein and right common carotid artery are ligated. Recently, veno-venous ECMO is performed by ligating only right internal jugular vein for less critical newborns. This technique differs from veno-arterial bypass in that the oxygenated blood is returned to the inferior vena cava instead of the aortic circulation. At our institution, veno-venous bypass is accomplished by a double-lumen catheter placed in the right atrium. In this technique, venous blood is drained into the outer lumen and oxygenated blood is returned to the right atrium via the inner lumen.

Approximately 80%–90% of newborns treated with ECMO have survived. However, if they are treated with maximal conventional therapy, the survival rate is less than 20%. Therefore, the benefit of ECMO is far greater than the potential risk of right-sided ischemic brain lesions associated with the right common carotid artery ligation performed for ECMO (*4,5*).

Only brain SPECT and positron emission tomography (PET) can provide rCBF or brain perfusion, although neuroimaging modalities such as ultrasound (US), color Doppler, computed tomography (CT) and magnetic resonance imaging (MRI) as well as magnetic resonance arteriography (MRA) are sensitive and noninvasive methods in assessing vessel patency and brain parenchymal changes of neonates during and after ECMO (*6,12*). Recently, brain PET has been used following ECMO (*10*). However, its clinical application is limited to certain centers. On the other hand, brain SPECT is widely available and indeed, brain SPECT using ^{99m}Tc-hexamethyl propylene amine oxime (HMPAO) is an established technique to measure brain perfusion of various disease states in adults and children (*6,9*). In an attempt to study the technical feasibility and clinical value, rCBF alterations were measured using SPECT and ^{99m}Tc-HMPAO in 13 newborns after veno-arterial or veno-venous ECMO.

MATERIALS AND METHODS

Clinical Findings

From January 1992 to May 1992, 13 consecutive newborns treated with ECMO were evaluated by brain SPECT. All 13 neonates were suffering from persistent fetal circulation (PFC) or

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primary pulmonary hypertension of the newborn (PPHN). The duration of ECMO ranged from 4 to 14 days with a mean of 8.6 days. The right common carotid artery and right internal jugular vein were used for ECMO in 10 newborns. Two newborns had permanent ligation of the right common carotid artery and in the remaining eight neonates, reanastomosis was performed upon completion of ECMO. The reanastomosis was surgically successful in seven of eight neonates. In three infants, veno-venous ECMO was performed after ligating the right internal jugular vein. In general, clinical conditions of the newborns and blood gases were stable when SPECT was performed. SPECT was performed just prior to the neonates' discharge from the hospital. Other clinical parameters such as sex, birth weight, gestational age and Apgar scores of 1 and 5 min are listed in Table 1.

HMPAO Brain SPECT Procedure

Each neonate received 2 mCi of ^{99m}Tc-HMPAO (Ceretec® Amersham International) through an existing peripheral intravenous line followed by a saline flush in the intensive care nursery (ICN) at least 1 hr prior to SPECT. The neonates were subsequently sedated with oral administration of chloral hydrate (50 mg/kg) given approximately 30 min prior to the imaging procedure. The sedation would not alter rCBF as the brain uptake of the tracer occurs within 4–5 min after the injection. The neonates were then transported to the imaging room located on the same floor as the ICN about 60 min after the injection of ^{99m}Tc-HMPAO and positioned on the head-holder attached to the imaging table in the most comfortable position. This usually consists of the supine position with the head turned to the left side, which was not affected by the surgical procedure for ECMO. The most comfortable positioning of each neonate is very important for successful acquisition of SPECT images without motion artifacts. SPECT was performed using a triple-head system (Triad, Trionix research laboratory Inc., Twinsburg, OH) interfaced to a Sun microsystems based computer. A low-energy, ultrafine, parallel-hole collimator was used on each detector. The system resolution of the triad was measured about 7–8 mm using the Jaszczak SPECT phantom. Each neonate was scanned with 120 frames (40 frames per detector) lasting 35–45 sec, depending on count rate, for a scan duration of approximately 30 min. This was sufficient time to acquire a minimum of two million total counts. A 1.4x zoom mode was used to compensate for the neonates' small head. The scans were performed with the smallest scanning radius of 13.5 cm. Attenuation correction and filtered backprojection methods were used for image reconstruction. A Hanning filter at a cutoff frequency of 0.9 cycles/cm was used. Orthogonal tomographic slices of transaxial, sagittal and coronal images were reconstructed using a 128 × 128 matrix after correcting for head tilt incident to the most comfortable position during the SPECT procedure. The transaxial slices were parallel to the orbitomeatal line.

Interpretation of Brain SPECT Images

Visual Interpretation. An interpretation was based on visual inspection of asymmetry between the right and left cerebral hemispheres as well as by detection of any focal abnormalities.

Quantification. In addition to the visual inspection of the tomographic images, quantification of SPECT data was made. The most abnormal transaxial or coronal slices were selected for quantification. Eight regions of interest (ROIs) were semi-automatically placed over the transaxial slice or slices and were symmetrically distributed about the mid-line (Fig. 1). In some cases, a selected coronal slice or slices was divided equally into two ROIs (Fig. 2). A calculation of more than 10% differences in ROI of counts of the cerebral hemispheres was considered significant.

RESULTS

Brain SPECT was successful in all 13 newborns after ECMO, and the image quality was excellent in all newborns studied. The SPECT findings after ECMO along with neuroradiologic findings in the 13 neonates are summarized in Table 2.

Normal Neonatal SPECT Pattern

Six newborns demonstrated symmetrical hemispheric blood flow, which was highest in the sensorimotor cortex, thalami, brain stem and cerebellar vermis. Physiologically low rCBF was noted in the frontal, parietal and temporal cortices (Fig. 3). This "normal pattern" closely parallels PET brain findings in newborns (*14*). Of the six newborns with the "normal pattern," three had a successful reanastomosis as shown by color Doppler imaging (CDI) and

TABLE 1
Clinical Findings

Patient no.	Sex	BW (kg)	GA (wk)	Apgar	ECMO (days)	RCCA
1	F	3.6	40	3/5	6	Repaired
2	M	3.9	40	8/10	5	Repaired
3	F	3.4	38	5/8	4	Repaired
4	F	3.44	40	5/7	8	Ligated
5	M	4.0	40	4/6	11	Repaired
6	F	4.0	38	7/8	12	Repaired
7	M	3.1	39	2/6	12	Veno/Veno
8	M	3.18	37	8/9	4	Repaired
9	M	4.3	40	1/5	6	Veno/Veno
10	M	2.27	39	3/8	10	Repaired*
11	M	3.59	40	8/9	14	Ligated
12	M	2.87	39	6/6	14	Repaired
13	M	3.8	40	4/9	6	Veno/Veno

* Failed repair.
BW = body weight; Apgar = 1/5 min and RCCA = right common carotid artery.

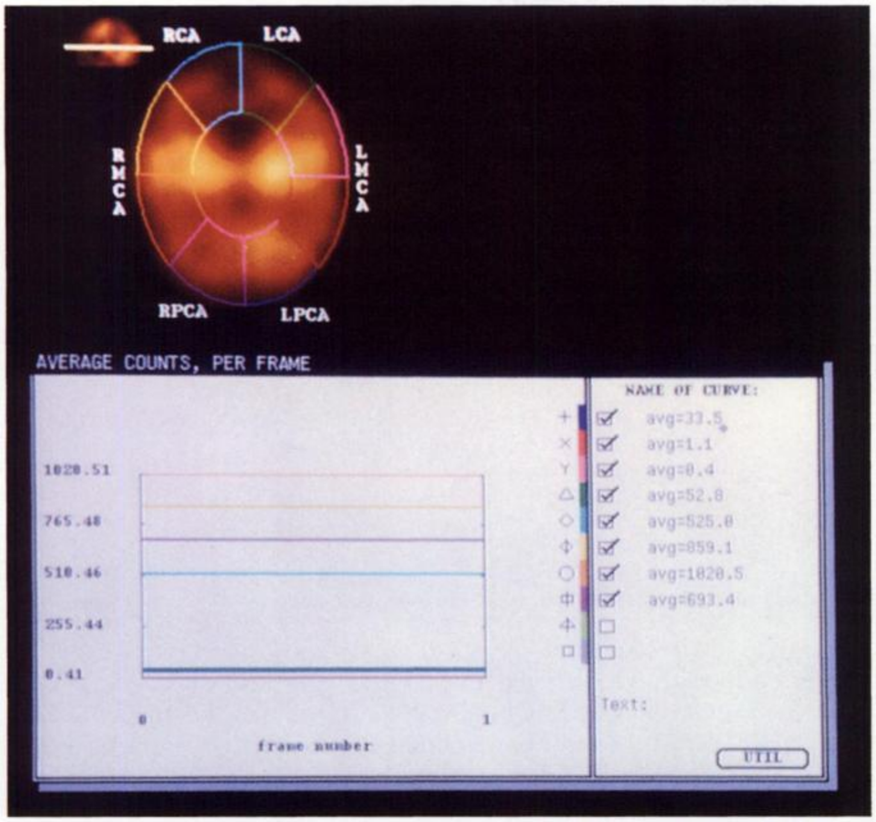

FIGURE 1. ROIs on transaxial slice (Patient 3). Eight ROIs are symmetrically distributed about the mid-line. Thalami are excluded from this semi-automatic ROI method but can be quantified by using two ROIs as shown in Figure 2. Two frontal cortical sectors represent anterior cerebral arterial (ACA) distribution, while two posterior sectors represent posterior cerebral arterial territory (PCA). Two lateral sectors on each side represent middle cerebral arterial territory (MCA). RCA = right anterior cerebral artery and LCA = left anterior cerebral artery.

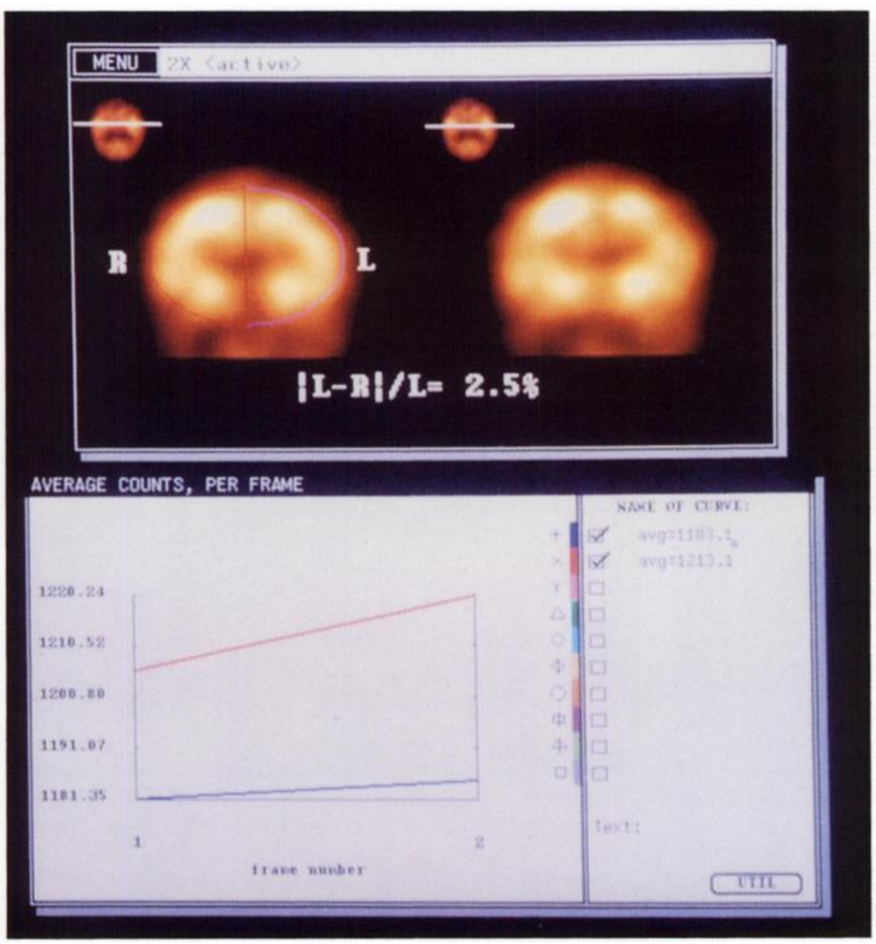

FIGURE 2. Two ROIs on coronal slice (Patient 3). The coronal slice is divided equally into two ROIs placed symmetrically about the mid-line, if this slice depicts more abnormality than the transaxial slice.

TABLE 2
Brain SPECT and Neuroradiologic Findings After ECMO

Patient no.	Sex	BW (kg)	Age at SPECT (days)	SPECT findings	L-R/L or R-L/R (%)	US	MRI	CT
1	F	3.6	15	Normal	5%	Normal	—	—
2	M	3.9	23	Decreased R	28%	Normal	Normal	—
3	F	3.4	26	Normal	2.3%	MVD	Normal	—
4	F	3.44	16	Decreased R	75%	MVD	—	—
5	M	4.0	20	Decreased R	16%	Normal	—	—
6	F	4.0	33	Normal	1.5%	Normal	Normal	—
7	M	3.1	23	Normal	2%	Normal	Normal	—
8	M	3.18	16	Decreased R	24%	Normal	Normal	—
9	M	4.3	14	Decreased R (focal)	2%	1.6 cm cyst	HI	—
10	M	2.27	28	Normal	3%	Normal	—	—
11	M	3.59	47	Decreased L	13%	MVD	Normal	—
12	M	2.87	24	Decreased R&L	3.5%	Normal	—	IE
13	M	3.8	10	Normal	2%	Normal	—	—

BW = body weight (kg), R = right, L = left, MVD = mild ventricular dilatation, IE = ischemic encephalopathy and HI = hemorrhagic infarct.

one had an unsuccessful surgical repair. The other two with "normal patterns" had veno-venous ECMO without ligation of the right common carotid artery.

Abnormal SPECT Findings

In 7 of 13 newborns, SPECT was abnormal. Four had a diffuse decrease in rCBF within the ipsilateral hemisphere in relation to the carotid ligation (Fig. 4). One had an ipsilateral focal decrease in rCBF (Fig. 5). One had a diffuse decrease in rCBF within the contralateral hemisphere (Fig. 6) and one had focal areas of decreased perfusion in both hemispheres (Fig. 7). The neonate with bilateral focal defects underwent cardiopulmonary resuscitation prior to veno-arterial ECMO and exhibited clinical features of hypoxic-ischemic encephalopathy at the time of SPECT. Three of this group had a successful repair of the ligated right common carotid artery after ECMO as shown by CDI, two had a permanent ligation of the right common carotid artery, and one had veno-venous ECMO.

SPECT versus Neuroradiologic Findings

All six newborns with a "normal SPECT pattern" had normal CT or MRI studies. Only two of seven abnormal SPECT studies correlated well with morphologic images; one had focal hemorrhagic infarct seen on US and MRI (Fig. 8), and the other had multiple ischemic encephalopathy demonstrated on CT (Fig. 9). In the remaining five newborns with abnormal rCBF, US or MRI was unremarkable.

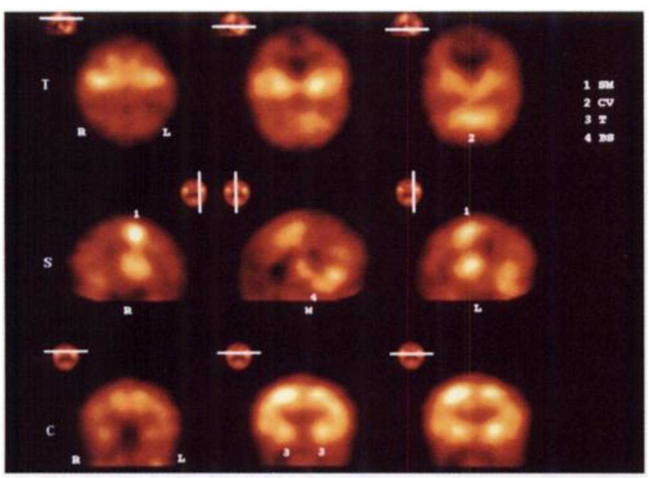

FIGURE 3. Normal neonatal rCBF pattern (Patient 3). Three representative slices of transverse (T), sagittal (S) and coronal (C) planes depict symmetrical rCBF, highest in the sensorimotor (SM) cortex, thalamus (T), brain stem (BS) and cerebellar vermis (CV). Note physiologically low rCBF in the frontal, parietal and temporal cortices. US and MRI were unremarkable. Small reference images with a straight line depict tomographic level of each slice. Sagittal slices through the right (R), left (L) and mid-line (M) are shown.

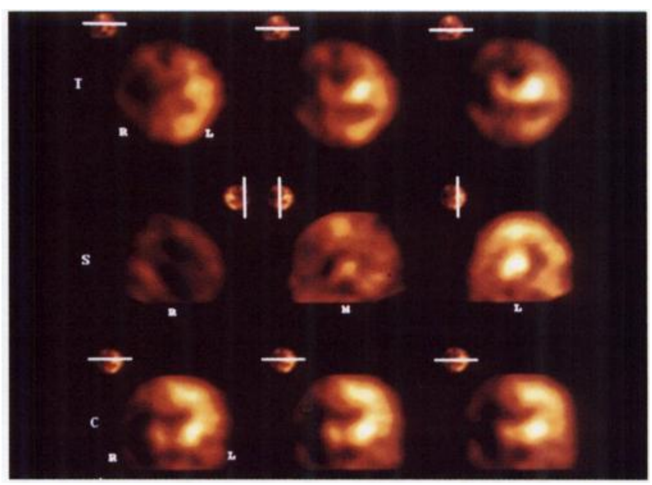

FIGURE 4. Diffuse decrease in rCBF in ipsilateral hemisphere (Patient 4). Note marked decrease (75%) in rCBF within the right cerebral hemisphere on transverse, sagittal and coronal slices. US showed only mild ventricular dilatation with an interhemispheric fluid collection which is also seen on transverse SPECT slices.

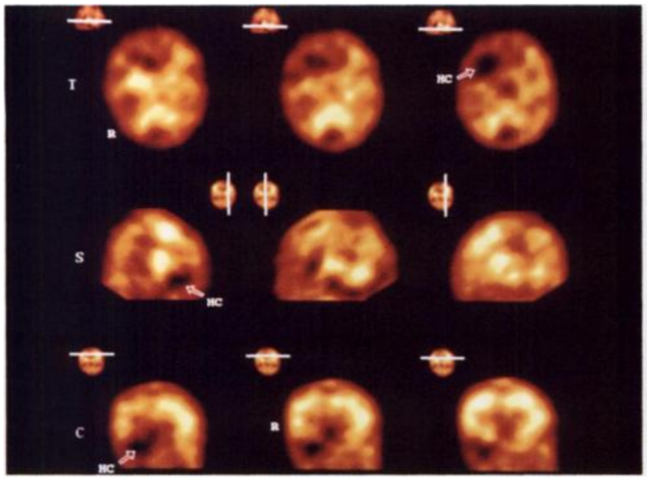

FIGURE 5. Focal decrease in rCBF in ipsilateral hemisphere (Patient 9). SPECT following veno-venous ECMO demonstrated an area of decreased perfusion (open arrow) in the right fronto-temporal region. US and MRI (Fig. 8) showed hemorrhagic infarct in the same region.

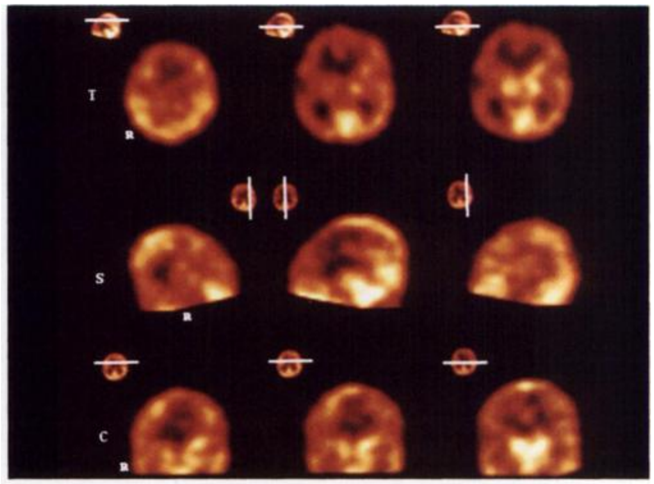

FIGURE 7. Multiple defects involving both hemispheres (Patient 12). This newborn had cardiac arrest prior to ECMO, necessitating cardiopulmonary resuscitation. SPECT reveals multiple areas of decreased perfusion in the right frontal, temporo-occipital, left frontal, parietal and right thalamus. The neonate had clinical features of hypoxic-ischemic encephalopathy and CT depicted multiple hypoxic regions, which was more obvious than SPECT (Fig. 9).

DISCUSSION

The ECMO procedure most commonly requires ligation of the right common carotid artery and right internal jugular vein for cannulation (*3*). For this reason, altered blood flow following ECMO is one of the major concerns associated with ECMO therapy. In an attempt to improve ipsilateral hemispheric CBF, at our institution, the ligated right common carotid artery is reanastomosed at termination of ECMO whenever possible. Veno-venous ECMO is now being performed more often for less critical newborns without ligating the right common carotid artery.

An assessment of intracranial blood flow in newborns had been limited to CDI and MRA until recently, when PET was used effectively in measuring rCBF after ECMO (*10–12*). Although CDI and MRA provide blood velocity and vessel patency, rCBF cannot be measured using these techniques. US and MRI, however, are excellent parenchymal imaging methods in these neonates. PET, on the other hand, is an accurate method for measuring rCBF in absolute terms, but the technique is expensive and is available at only a few medical centers. Brain SPECT maps relative rCBF and is available even at community hospitals throughout the United States. By utilizing flow-specific agents such as ^{99m}Tc-HMPAO or ^{123}I-iodoamphetamine along with SPECT, an accurate rCBF can be mapped in patients of all age groups (*6–9*). Indeed, brain SPECT has been used successfully in the evaluation of stroke, seizure disorders and dementias (*7,8,13*). In neonates, brain SPECT has also been successful by wrapping

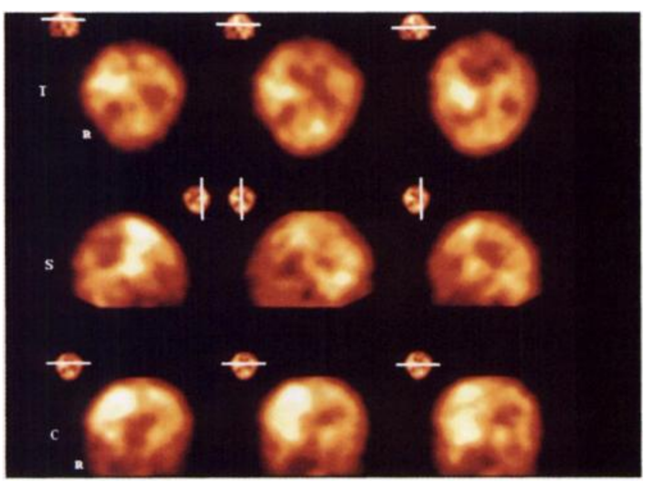

FIGURE 6. Diffuse decrease in rCBF in contralateral hemisphere (Patient 11). Contralateral hemispheric abnormality may be related to high flow state at the time of the right common carotid artery ligation for ECMO. MRI the day before and MRA the day after SPECT were normal.

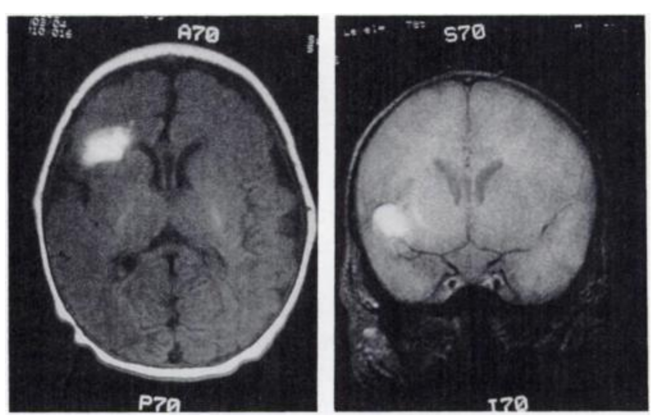

FIGURE 8. MRI of Patient 9. Transaxial and coronal slices demonstrate hemorrhagic infarct in the right fronto-temporal region. US was abnormal as well.

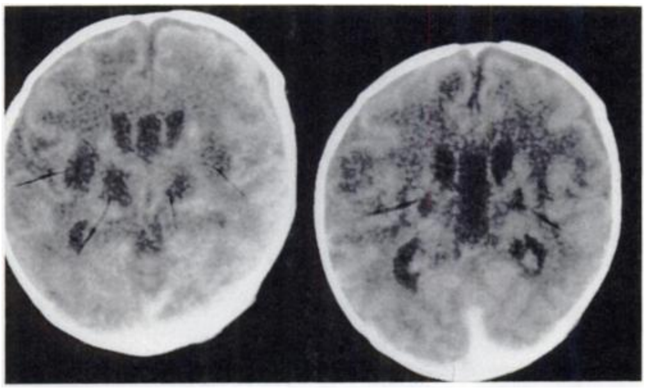

FIGURE 9. CT of Patient 12. Transaxial slices depict multiple areas of low density lesions consistent with hypoxic-ischemic encephalopathy.

the head and trunk in a specifically designed polystyrene vacuum cushion (*9*). Our ECMO infants were kept in the most comfortable position in an acrylic cradle for optimal comfort during SPECT. In addition, sedation with chloral hydrate was very useful for successful SPECT imaging in these infants after ECMO. The 30-min sedation period after ^{99m}Tc-HMPAO administration will not affect rCBF because tracer distribution within the brain is completed within 4–5 min after the injection.

Brain maturation patterns in the neonatal period have been evaluated by PET and SPECT (*14–16*). Both modalities have demonstrated prominant rCBF or metabolism in the thalamus, sensorimotor cortex, brain stem and cerebellar vermis. Physiologically low metabolism or rCBF is noted in the frontal, temporal and parieto-occipital cortices (*14–16*). This "normal pattern" was seen in 6 of 13 newborns after ECMO; 4 after reanastomosis and 2 after veno-venous ECMO. This pattern is expected if there is sufficient collaterals through the circle of Willis or if repair of the ligated right common carotid artery is successful.

Perlman and Altmen reported that the ratio of right-to-left hemispheric CBF was not significantly different in newborns with an reanastomosed or occluded right common carotid artery, and a maximum asymmetry of 8% was observed only in 2 of 23 newborns studied with PET (*10*). However, in our SPECT study, 7 of 13 neonates had a significant decrease in rCBF (13%–75%) after veno-arterial or veno-venous ECMO. Neonates with insufficient collateral circulation through the circle of Willis at the time of ECMO will likely have an ipsilateral decrease in rCBF regardless of the patency of the right common carotid artery. A focal area of decreased rCBF is probably due to embolism. One newborn demonstrated a contralateral decrease in rCBF, a finding probably related to increased flow through the contralateral hemisphere during the ipsilateral carotid ligation at the time of the ECMO procedure. One infant underwent cardiopulmonary resuscitation prior to ECMO and the infant showed clinical features of hypoxic-ischemic encephalopathy. Both CT and SPECT revealed multiple areas of hypoxic injury of both hemispheres.

In summary, brain SPECT using ^{99m}Tc-HMPAO provides very useful information after ECMO that may not be apparent on neuroimaging modalities such as US, CT and MRI. The technique is being used in the evaluation of the long-term effect of permanent ligation versus reanastomosis of the right common carotid artery. It may also prove to be useful in long-term follow-up of neurodevelopmental outcome after ECMO.

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