The Role of Xenon CT Measurements of Cerebral Blood Flow in the Clinical Determination of Brain Death

Frank Pistoia[1]
David W. Johnson[1]
Joseph M. Darby[2]
Joseph A. Horton[1]
Laura J. Applegate[1]
Howard Yonas[3]

The demonstration of absent blood flow to the brain is often used as a confirmatory test of brain death. Traditionally, cerebral angiography and dynamic radionuclide brain scanning have been used for this purpose. Recently, xenon CT cerebral blood flow techniques have been developed and applied to a wide variety of clinical problems, including the confirmation of brain death. We report our experience with xenon CT studies performed over a 7-year period (1983–1989) in 30 patients with brain injuries. These patients met clinical criteria for brain death within 24 hr of the study. Twenty patients had average global flow values of less than 5 ml/100 ml/min. Seven patients demonstrated mixed flow patterns, whereby large areas of brain showed flow values of <5 ml/100 ml/min and residual pockets of flow greater than 5 ml/100/ml/min. Globally symmetric normal to hyperemic flows were seen in three patients.

Our study suggests that the demonstration of average global flows of <5/ml/100 ml/min is confirmatory of brain death. Demonstration of persistent flow to the entire brain or regions of the brain is not diagnostic of brain death but also does not exclude such an outcome in patients with severe brain injuries. Xenon-derived flow information may be clinically useful in determining the patient's prognosis and in counseling the patient's family.

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Modern medical technology has forced reconsideration of definitions of death, which for centuries were based on the irreversible loss of cardiac or pulmonary functions. The advent of effective cardiopulmonary life support permits sustenance of circulation and respiration in patients who have temporarily or permanently lost these functions, including those patients who have sustained irreversible brain injury. This has resulted in a shift from the heart-lung criteria to the concept of brain death as equivalent to the death of the individual.

Clinical criteria for brain death have been outlined in the President's Commission report [1]. This report also states that demonstration of "complete cessation of circulation to the normothermic adult brain for more than 10 minutes is incompatible with survival of brain tissue." Documentation of absence of blood flow to the brain is therefore confirmatory evidence of brain death. This has been assessed by several imaging studies, including four-vessel cerebral angiography, radionuclide brain scanning, contrast-enhanced CT, transcranial Doppler sonography, and recently, stable xenon CT [2–5].

We review our experience with xenon-enhanced CT cerebral blood flow (CBF) studies in patients with severe brain injuries who, within 24 hr of the xenon study, met established clinical criteria for brain death (coma and absent brainstem reflexes). We were interested in relating the xenon CT CBF data with more conventional determinations and clinical outcomes in these patients.

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[1] Department of Radiology, Division of Neuroradiology, University of Pittsburgh School of Medicine, Presbyterian-University Hospital, DeSoto at O'Hara Sts., Pittsburgh, PA 15213. Address reprint requests to D. W. Johnson.

[2] Critical Care Medicine, Department of Anesthesiology, University of Pittsburgh School of Medicine, Presbyterian-University Hospital, Pittsburgh, PA 15213.

[3] Department of Neurosurgery, University of Pittsburgh School of Medicine, Presbyterian-University Hospital, Pittsburgh, PA 15213.

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TABLE 1: Summary of Patients, Clinical Histories, Adjunctive Studies, and Xenon CT Cerebral Blood Flow (CBF) Data

Group/Case No.	Age (years)	Sex	Diagnosis	Adjunctive Studies	Xenon CT CBF (ml/100 ml/min)
Group 1: Global low flow					
1	28	M	ICH	EEG (ECS), RN brain scan (no flow)	2.3
2	30	F	AVM rupture	EEG (ECS)	1.5
3	30	M	SAH	RN brain scan (no flow)	2.3
4	23	F	Head trauma	Two-vessel angiography (no flow), EEG (ECS)	0.9
5	32	M	SAH	EEG (ECS)	0.3
6	28	M	Hepatic coma	EEG (ECS), RN brain scan (no flow)	3.2
7	57	F	SAH	Four-vessel angiography (no flow), EEG (ECS)	1.2
8	9 mo	F	Head trauma	None	1.5
9	29	M	Hepatic coma	EEG (ECS)	2.6
10	38	F	ICH	EEG (ECS)	3.0
11	8	F	MVA	EEG (ECS)	1.0
12	30	M	Liver failure	EEG (ECS)	2.1
13	14	M	Hepatic coma	EEG (ECS), RN brain scan (no flow)	2.4
14	8	F	Hepatic coma, liver transplant	EEG (technically inadequate)	0.3
15	3	F	Liver transplant	EEG (artifacts)	2.1
16	26	M	Hepatic coma	EEG (ECS)	3.1
17	47	F	Cardiorespiratory arrest	EEG (ECS)	2.5
18	74	M	SAH, IVH	None	2.9
19	23	F	Hepatic coma	EEG (ECS)	1.7
20	34	F	SAH	None	2.1
Group 2: Mixed flow					
21	19	M	GSW to head	EEG (ECS)	1.9 (global) 10.5 (cerebellum)
22	40	M	Head trauma	None	4.1 (cerebrum) 52.7 (cerebellum) 4.1 (brainstem)
23	34	F	GSW to head	None	1.8 (global) 12.0 (PCAs)
24	5	M	Shaking injury	EEG (artifacts)	2.4 (L cerebrum) 25.7 (R cerebrum) 41.7 (cerebellum)
25	51	F	SAH	Angiography (no flow in carotid, slow flow in vertebral arteries)	3.5 (global) 16.0 (R ACA) 24.3 (R BG) 13.7 (L BG)
26	64	M	ICH	None	2.6 (global) 24.4 (L PCA) 10.4 (cerebellum)
27	60	M	SAH	EEG (ECS)	3.5 (global) 12.0 (L PCA)
Group 3: Globally normal to hyperemic flow					
28	18	M	Hepatic coma	EEG (ECS), RN brain scan (no flow 24 hr after xenon CT CBF study)	25.8
29	31	M	Drowning	None	57.4
30	28	M	Stab wound to chest, cardiorespiratory arrest	EEG (ECS) (at same time as second xenon CT CBF study)	45.7 (first study) 1.7 (2 days later)

Note.—ICH = intracerebral hemorrhage; EEG = electroencephalogram; ECS = electrocerebral silence; RN = radionuclide; AVM = arteriovenous malformation; SAH = subarachnoid hemorrhage; MVA = motor vehicle accident; IVH = intraventricular hemorrhage; GSW = gunshot wound; PCA = posterior cerebral artery; ACA = anterior cerebral artery; BG = basal ganglia.

Materials and Methods

During a 7-year period (1983–1989), xenon CT CBF evaluations were performed in 30 patients who met clinical criteria for brain death within 24 hr of being studied. Their medical records were reviewed for pertinent clinical history and adjunctive studies (Table 1). Eight of our patients (cases 1–8) have been described previously [2].

CBF data were determined with the General Electric 9800 Xenon Blood Flow System (General Electric, Milwaukee, WI). Detailed descriptions of this method have been published [2, 6–8]. Blood flow examinations were obtained at three levels spaced up to 20 mm apart. These were chosen to evaluate the basal ganglia, the centrum semiovale, and in certain cases, the brainstem and cerebellum. Usually, the scanning angle was 20° above Reid's baseline. However, some patients were examined with the head in flexion to better evaluate the posterior fossa with reduced bone artifact. Once the levels were selected, the patient's endotracheal tube was connected to a mechanical ventilator that delivered oxygen-enriched room air

during acquisition of the baseline images and a 33% xenon/67% oxygen mixture during xenon inhalation. Two baseline scans and four xenon-enhanced scans were obtained at each level. Dynamic scanning with table incrementation allowed acquisition of data at separate levels during the study. Before 1987, the duration of xenon inhalation was approximately 4½ min. Since then, an effort has been made to prolong the duration of xenon inhalation to 6 min for patients in whom brain death is suspected. The prolonged duration would increase the opportunity for xenon to diffuse into brain tissue, thereby increasing the sensitivity and accuracy at low flow states.

At our institution, xenon CT CBF studies are filmed at 50 ml/100 ml/min, with a window of 100 ml/100 ml/min. For the purpose of publication, all figures in this article were filmed at 50 ml/100 ml/min, with a window of 150 ml/100 ml/min to demonstrate extremely low flows.

Flow map images were derived from calculations of the time-dependent change in pixel density, whereby the averaged baseline pixel data were subtracted from the pixel data on the enhanced images. An assumption was made that the end-tidal xenon concentration as measured by a thermistor could be used to derive the percent xenon in arterial blood [9]. The xenon-enhancement data and the accumulation of arterial xenon were used to solve the Kety-Schmidt equation to calculate the blood flow for each voxel [8].

Average flow values in cases of globally low flow rates and global hyperemia were determined by using region-of-interest (ROI) areas including the entire hemisphere, but excluding areas that normally

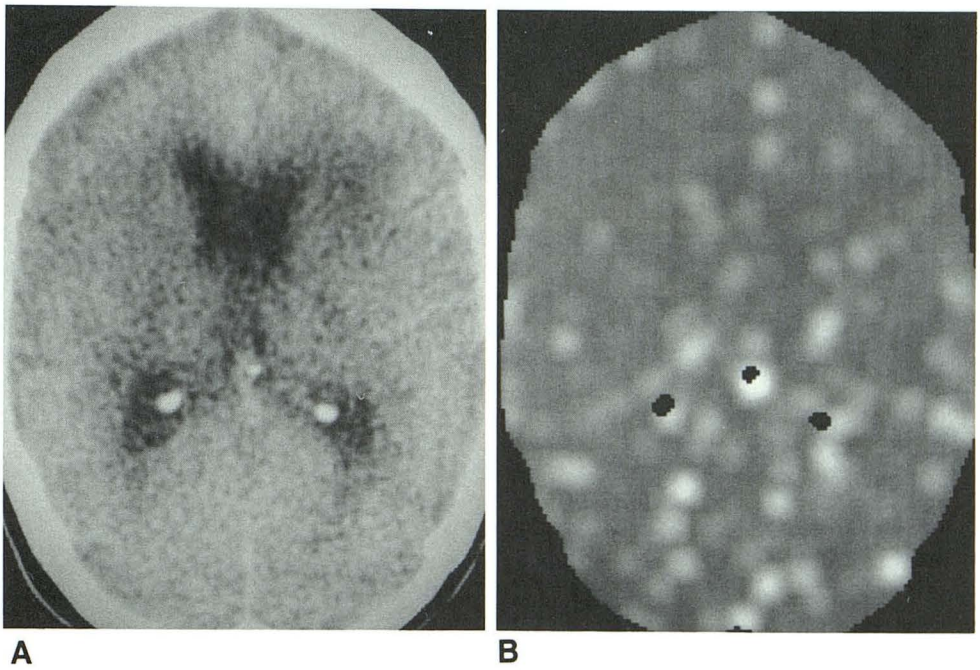

Fig. 1.—Case 17: 47-year-old woman with history of metastatic breast carcinoma who had a seizure. On reaching the emergency room, she was comatose, with absent brainstem reflexes.

***A*, Unenhanced CT scan shows area of edema in left frontal lobe suggesting a metastatic focus.**

***B*, Corresponding xenon CT cerebral blood flow scan shows no flow (average global flow, 2.5 ml/100 ml/min). Criteria for clinical brain death were met shortly after this study.**

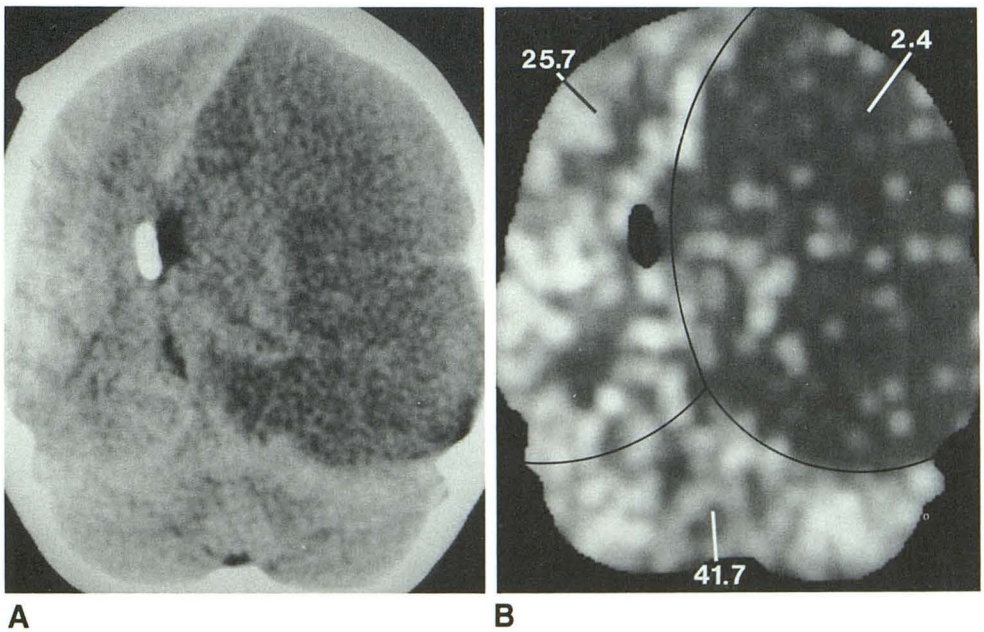

Fig. 2.—Case 24: 5-year-old boy with shaking injury resulting from abuse.

***A*, Unenhanced CT scan the day after admission shows edema of left cerebral hemisphere with massive midline shift from left to right. Shunt catheter is seen in right lateral ventricle.**

***B*, Corresponding xenon CT cerebral blood flow map shows flows averaging 2.4 ml/100 ml/min in the left cerebral hemisphere, 25.7 ml/100 ml/min in the right cerebral hemisphere, and 41.7 ml/100 ml/min in the posterior fossa. Although the patient was not brain dead at the time of this study, full criteria for brain death, including an isoelectric electroencephalogram, were met the next day.**

have no blood flow such as the ventricular system and hematomas. Flow values obtained at each level were then averaged to estimate total brain blood flow. When mixed flow patterns (large areas of low flow with persistent areas of preserved flow) were identified, multiple ROIs were placed in areas with similar flow to obtain average regional blood flow rates.

Results

Data on the 30 patients who met clinical criteria for brain death within 24 hr of the xenon CT CBF study are summarized in Table 1. Three main groups of patients were identified: Group 1 comprised 20 patients (cases 1–20) in whom there was complete absence of blood flow at each level (xenon CT CBF criteria define flow values of <5 ml/100 ml/min as equivalent to no flow) (Fig. 1). Eight patients in this group (cases 1–8) have been reported previously [2]. Group 2 comprised seven patients (cases 21–27) in whom a mixed flow pattern (large areas of no flow and areas of persistent flow) was present (Figs. 2 and 3). Group 3 comprised three patients (cases 28–30) in whom symmetric flow patterns with flows ranging from above ischemic threshold to hyperemia were observed (Fig. 4).

Discussion

So uncertain is men's judgment, that they cannot determine even death itself.

—Pliny, cited in [10]

The concept of brain death is widely accepted as equivalent to the death of the individual. Defining this state, however, can be problematic, as brain death may be seen as the lowest extreme in a continuous spectrum of comatose states [11]. Considerable effort has been expended during the past 20 years toward the clarification and definition of the concept of death by physicians, lawyers, and philosophers. Clinical criteria proposed to define the brain-dead state in the United States originated with the Harvard criteria (1968) [12]; more recent guidelines have been provided by the President's Commission report (1981) [1]. Such criteria will likely continue to change with the advent of new technologies and evolving social and ethical policies.

Current guidelines, as proposed by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, endorse the "whole brain" criteria—that is, both cortical *and* brainstem functions must be absent, and reversible causes of coma must be excluded from the diagnosis [1]. Clinical criteria by themselves often are sufficient in diagnosing brain death. In practice, the absence of brainstem functions is assessed by clinical examination, whereas absence of cortical functions is established by unresponsiveness and an electroencephalogram (EEG) demonstrating electrocerebral silence. The EEG may be unreliable in cases of drug or metabolic intoxication or hypothermia. These cases, as well as shock, brain death in children, and medicolegal cases, may make the use of blood flow studies both necessary and desirable. Absence of circulation to the brain is presumed to result in infarction of the entire brain; therefore, it is synonymous with brain death.

The xenon CT method of calculating blood flow is a noninvasive, practical tool that has found applications in a variety of neurologic problems [2, 6–8, 13]. Positron emission tomography (PET) can provide similar data, as well as measurements of local metabolism, but it is costly and available at only a few centers. In contrast, the xenon CT CBF method has been adapted by several CT manufacturers and can be added on to existing hardware, thereby making this a potentially widely available and relatively cost-effective technique. An advantage of xenon CT CBF is that it allows the coupling of anatomic information with measurements of local CBF for a chosen CT level. Blood flow values determined by this

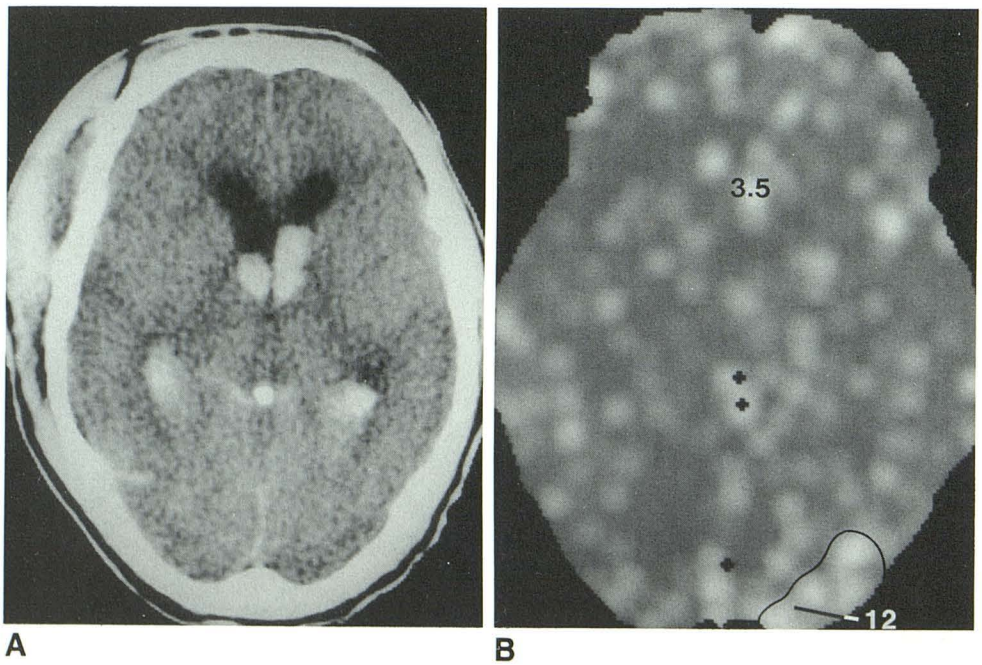

Fig. 3.—Case 27: 60-year-old man admitted with subarachnoid hemorrhage secondary to ruptured basilar tip aneurysm.

***A*, Unenhanced CT scan shows intraventricular hemorrhage. His course deteriorated rapidly.**

***B*, Xenon CT cerebral blood flow study shows global flow values measuring 3.5 ml/100 ml/min, except for an area in left posterior fossa measuring 12 ml/100 ml/min. Full clinical criteria for brain death, including an isoelectric electroencephalogram, were met that same day.**

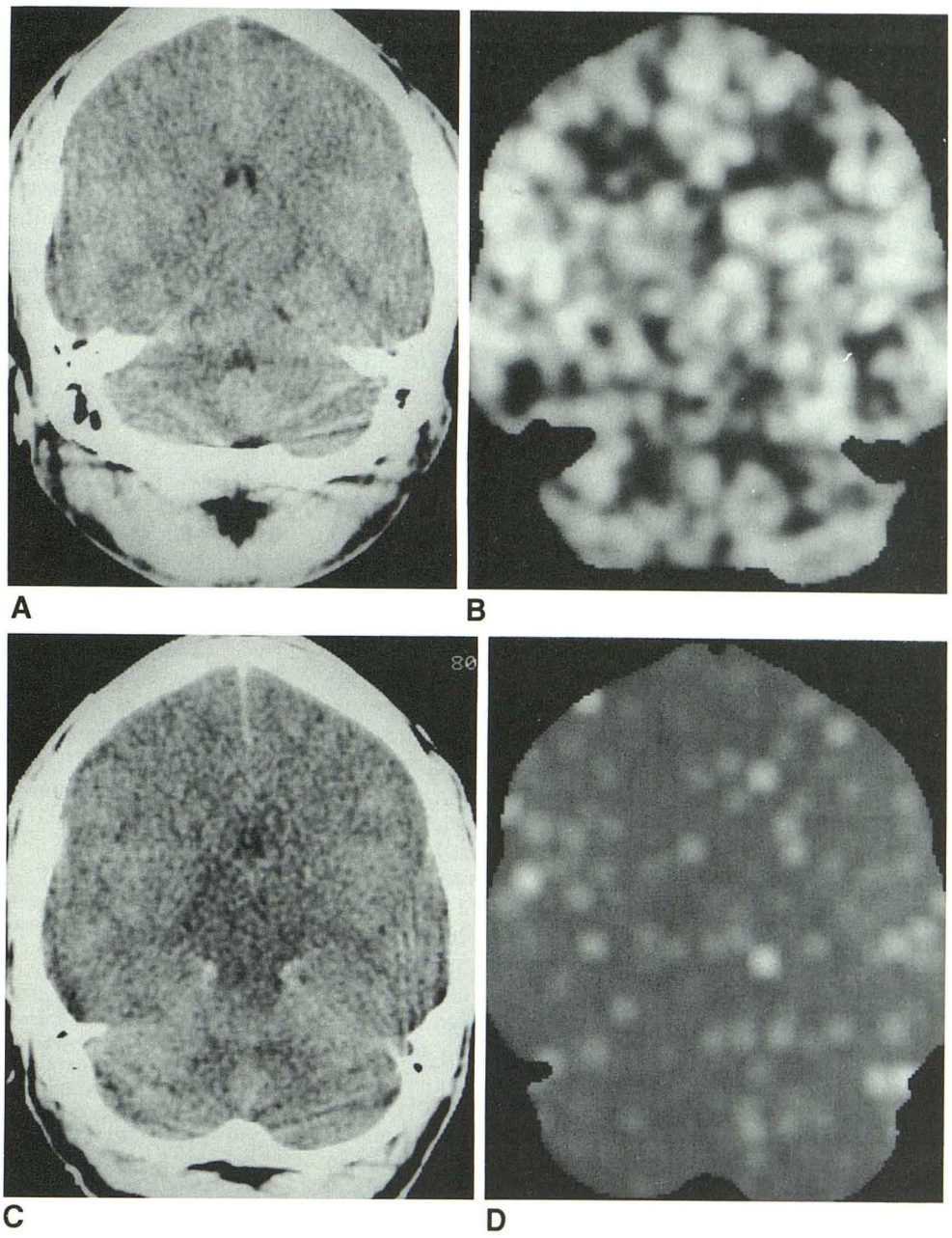

Fig. 4.—Case 30: 28-year-old man with stab wound to the chest, resulting in a penetrating wound to the heart. He was found in cardiorespiratory arrest of unknown duration. The patient was resuscitated, but the next day was in a deep comatose state.

***A*, Baseline CT study shows generalized brain swelling with effacement of lateral ventricles and sulci.**

***B*, Corresponding xenon CT cerebral blood flow study shows average global flow values of 45.7 ml/100 ml/min, believed to be slightly hyperemic in the presence of profound coma and a carbon dioxide tension of 24 mm Hg.**

***C*, Unenhanced CT scan 2 days later shows evidence of increased brain swelling with effacement of sulci and ventricles.**

***D*, Corresponding xenon CT cerebral blood flow map shows global flows of 1.7 ml/100 ml/min. The electroencephalogram was isoelectric, and full criteria for brain death were satisfied.**

method have correlated with values obtained by other methods, including microspheres [14, 15] and radioactive xenon-133 [9]. Many studies have suggested that inhalation of 35–40% xenon may lead to a 15–40% rise in CBF [16, 17]. It has been suggested that this effect can be useful, because it would increase the sensitivity of identifying areas of low flow [18, 19].

We reviewed our experience with xenon CT CBF imaging in patients who progressed to brain death within 24 hr of the study. As suspected, the majority of patients (n = 20) met criteria for brain death by xenon CT CBF (global flow values of <5 ml/100 ml/min); average flow values ranged from 0.3 to 3.2 ml/100 ml/min (mean, 2.0 ± 0.9 ml/100 ml/min). These flow values are not significantly different from previously reported data: In eight patients, the mean CBF was 1.6 ± 2.0 ml/100 ml/min [2] (these eight patients are included in the present study also); in 10 pediatric patients, the mean CBF was 1.3 ± 1.6 ml/100 ml/min [4]. We consider these values to be equivalent to zero flow.

The accurate measurement of extremely low flow values against background noise is a problem in many blood flow measurement systems. Certain factors specific to the xenon CT CBF technique result in values slightly greater than zero even in the total absence of flow. System noise will result in a range of values assigned to voxels with no flow; the range of values will be distributed around the value of zero. Any voxel in which the flow value would calculate as negative is assigned a value of zero in the General Electric system, since

such a value is not physiologic and necessarily results from system noise. When measuring average flow within an ROI, values just above zero may be obtained in areas of no flow, since positive values resulting from system noise are not canceled [18].

The system's error is dependent on the flow value and size of the ROI. Acceptable errors (<20%) can be achieved when ROIs exceeding 120 mm^2 are used in tissues with high or low flow values [8]. A recent study by Wolfson et al. [20] showed close correlation of xenon CT CBF data and the ^{14}C-iodoantipyrine method in an animal model at both normal and low flow states.

Despite theoretical concerns of measuring low flow states, studies have shown a close correlation between xenon CT CBF data and clinical outcomes in patients with cerebral ischemia [19, 21]. PET studies have shown that the minimal blood flow required for neuronal viability ranges from 15 to 20 ml/100 ml/min [22, 23]. These values compare with a xenon CT study that showed flow values of <12 ml/100 ml/min to be invariably accompanied by either concurrent or later infarction by CT [21]. Therefore, xenon CT CBF–derived values of <5 ml/100 ml/min are believed to be consistent with irreversible infarction.

The presence of persistent flow to regions (group 2) or the whole brain (group 3) is *not diagnostic* of brain death by flow criteria. In patients with severe brain injuries, such flow patterns may still portend a poor eventual outcome, including brain death [4, 24]. Persistent flow to small regions of the brain cannot predict a good prognosis when large areas of brain show no flow. In certain cases, the areas of persistent flow were located in the posterior fossa in the region of the transverse sinuses. It is possible that persistent *venous* flow may have accounted for these cases, similar to the occasional superior sagittal sinus activity seen on radionuclide brain scans. Venous flow may represent persistent collateral flow from emissary scalp veins. Whenever sinus flow was present, such activity was identified as parenchymal flow to reduce potentially false-positive diagnoses.

In patients with severe brain injury, the presence of globally symmetric normal to hyperemic flow patterns may be a form of global luxury perfusion following global anoxia. Such a phenomenon is well known with focal ischemia, and has been demonstrated with xenon CT CBF studies in both animal models and human clinical studies [18, 21]. An experimental model of cerebral reperfusion following brief (10 min) cardiac arrest in dogs resulted in survival with brain damage; immediate postresuscitative hyperemia was followed by a generalized global reduction in flow over the next 5–6 hr (Wolfson SK Jr, presented at the International Conference on Stable Xenon/CT CBF, February 1990). Obviously, timing of studies following the insult would be critical for determining CBF patterns (early high flows resulting from luxury perfusion, late low to absent flows resulting from eventual infarction and edema). The exact prognostic significance of global hyperemia or sparse residual flow following global insult cannot be determined by a single study, although we suspect that such findings would portend a grave prognosis in patients with severe brain injury and coma.

One limitation of the xenon CT CBF technique in the determination of brain death is that an assumption is made that flow to the entire brain can be approximated by sampling three levels. Although three 10-mm-thick levels represent only 20–25% of total brain volume [8], these levels are representative of a much larger volume for anatomic reasons (a vascular territory showing no flow on one level would be predictive of no flow in the "downstream" territories, excepting, of course, the potential presence of leptomeningeal collaterals). It is possible that patients identified as having patterns of low flow globally may have small islands of cerebral perfusion that may be missed if they are outside the chosen level. In fact, xenon CT CBF maps of the lower pons and medulla are not obtained because of severe bone artifacts at these levels. The ability to image large portions of the midbrain and upper posterior fossa is an attractive feature of this technique, which addresses the "whole brain" criteria currently endorsed in the United States. Flow maps that show large areas of supra- and infratentorial brain without flow cannot be expected to carry a good prognosis.

CBF data obtained by the xenon CT CBF method can be useful as an additional confirmatory test of brain death. Correlative anatomic CT levels are obtained with corresponding blood flow maps. Absence of blood flow to the brain is diagnostic of brain death; the presence of partial or global flow is not diagnostic of, but also does not exclude, such an eventual outcome. This information may nonetheless prove beneficial in patient management and family counseling.

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