BRAIN DEATH: RAPID EVALUATION USING COMPUTERIZED RADIONUCLIDE CEREBRAL FLOW STUDY

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SUMMARY

Demonstration of arrested intracerebral blood flow is the ultimate evidence of brain death. Computerized radionuclide cerebral flow study was done on 18 patients diagnosed clinically as brain dead. Correlation was made with clinical neurophysiological and EEG findings. The criteria for diagnosis of arrested intracerebral perfusion using radionuclide flow study were: non-visualization of blood flow activity in the intracranial arteries during the arterial phase, diffused cerebral activity during the capillary phase and non-filling of venous sinuses during the venous phase; visualization of typical 'hot nasal' activity; the time-activity curve over the cerebral hemispheres lacks a bolus effect and instead shows a delayed gradual rise of activity. These features are pathognomonic of brain tamponade.

Arrested intracranial circulation was seen in 16 patients (ten had electrocerebral silence; one had extremely abnormal EEG with small voltage activity and five had no EEG done). In the remaining two patients, some cerebral blood flow was demonstrated (one had no definite cerebral activity and the other had diffused EEG activity).

Radionuclide cerebral flow study is a very sensitive, accurate, safe, simple, rapid and non-invasive modality in confirming brain death and is especially useful in patients on "brain-protection" regime, in hypothermia or in certain metabolic states where diagnosis based on clinical and EEG criteria is difficult. EEG need not be a required procedure once brain death is established by the demonstration of arrested intracranial circulation.

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INTRODUCTION

Advances in intensive care techniques have made it possible to maintain cardiopulmonary function artificially, in spite of arrested intracerebral circulation and irreversible cessation of cerebral function. This state of intracranial circulatory arrest which occurs when the intracranial pressure is great enough to occlude the flow of blood into the brain while systemic circulation is preserved is termed brain tamponade.[1] This

leads to autolysis and necrosis and the brain at autopsy has a softened and liquefied appearance.[2,3] These changes do not occur under other circumstances of death.

When brain death has occurred further artificial support is futile and should be withdrawn for the following reasons: to reduce "suffering" of the patient, and to spare relatives from further emotional trauma and loss of finance; reduce wasteful drain of limited resources and burden on the hospital bed and the staff which could be used for other patients who may still benefit from them; make available the organs of these patients in the best possible condition for transplantation. Good quality cadaver kidneys are obtainable only in cases where cerebral death occurs before cardiac standstill and the surgeon removes the organs while they are still being oxygenated.[4]

Unconsciousness, absent spontaneous respiration when ventilator is disconnected, absent spontaneous movement (decerebrate or epileptic), non-reacting dilated pupils, absent cephalic reflexes and electrocerebral silence at least 24 hours apart in the absence of hypothermia and depressant drugs are widely accepted as diagnostic of cerebral death.[5] These criteria are open to criticisms as patients may present all signs of irreversible coma including electrocerebral silence and yet actually be in a reversible state. The extensive use of barbiturates, phenytoin and other anaesthetics as "brain protection"[6] or to reduce intracranial hypertension[7] makes the diagnosis of brain death based on clinical and EEG criteria only more difficult. It is now widely accepted that EEG is not necessary for diagnosis of brain death.[8,9] In a few countries, an additional parameter using selective common carotid and vertebral angiography is necessary by law to confirm the absence of intracranial circulation before proceeding with organ removal for transplantation.[2,10,11]

Radionuclide cerebral flow study using a portable scintillation probe or gamma camera[12-15] can rapidly and reliably confirm absent intracranial circulation at bedside in brain dead patients. Recently intravenous and intra-arterial digital subtraction cerebral and neck angiography (DSA) have been used to confirm absent intracranial circulation in the diagnosis of brain death.[16,17] This technique is invasive, fraught with danger of contrast idiosyncracy, albeit low, and cannot be used at the bedside.

This paper describes our experience at the University Hospital, Kuala Lumpur, with radionuclide cerebral flow study (CFS) in the diagnosis of brain death. We find this technique an accurate, sensitive, simple, safe and rapid test to confirm absent intracerebral circulation in clinically diagnosed brain dead patients.

MATERIAL AND METHODS

Eighteen patients with clinical diagnosis of brain death with and without foreknowledge of EEG findings were studied. These patients were admitted to the Intensive Care Unit (ICU) of University Hospital, Kuala Lumpur between 3 February 1981 and 15 March 1986. They were managed on a standard "brain protection" or brain resuscitation regime which included intravenous analgesia and anaesthetics and muscle relaxants; controlled ventilation maintaining adequate arterial oxygenation ($PO_2 > 20$ kPa) and moderate hypocarbia (PCO_2 3.5 to 4.5 kPa); normotension and avoidance of cerebral venous congestion; fluid retention and avoidance of salt-free infusates; mannitol therapy.

This regime was maintained for 48 to 72 hours. Four hours or longer following cessation of central deafferentation agents and reversal of neuromuscular block, neurological examination was performed and repeated 24 hours later.

The clinical diagnosis of brain death was made using the criteria issued by the conference of Medical Royal Colleges and their Faculties in the United Kingdom, 1976.[8] Electroencephalography was performed in 13 patients using standards set out by the American Electroencephalographic Society's "Ad Hoc Committee on EEG Criteria for the Determination of Cerebral Death"[18] In the remaining five patients, EEG was not done due to technical or time constraints

or patient's death. Autopsy was not done due to socio-religious constraints.

The causes of brain death (Table I) were: massive brain injury from traffic accidents, fall and assault; meningitis, encephalitis, and meningoencephalitis; multiple brain secondaries; cardiac arrest from septicaemic shock, post-cardiac surgery, tight mitral stenosis in pregnancy, and anaesthetic induction; asphyxia with respiratory arrest from status asthmaticus and acute epiglottitis; and metabolic encephalopathy in Reye's syndrome and diabetic hypoglycemic coma with disseminated intravascular coagulation (DIVC) and stroke. Respiratory failure and impaired circulation resulting in hypoxia and ischaemia of the brain underlied all these conditions.

TABLE I

CAUSE OF BRAIN DEATH IN 18 PATIENTS

Cause	No.
Massive brain injury:	
motor vehicle accident	2
fall	1
assault	1
Brain infection:	
meningitis	1
encephalitis	1
meningoencephalitis	1
Brain tumour:	
multiple secondaries	1
Cardiac arrest:	
septicaemic shock	1
post-cardiac surgery	1
tight mitral stenosis in pregnancy	1
diabetic gangrene during anaesthetic induction	1
Asphyxia with respiratory arrest:	
status asthmatics	2
acute epiglottitis	1
Metabolic encephalopathy:	
Reye's syndrome	2
diabetic hypoglycemic coma with stroke and DIVC	1
Total	18

The patients included nine males and nine females aged 2 to 60, with a mean age of 20 years.

With manual artificial ventilation maintained, the patient's head and neck were positioned beneath the face of a gamma-scintillation camera with parallel hole, low energy collimation and interfaced with a dedicated computer. 0.1 mCi/kg body weight of Technetium-99m pertechnetate was injected as a bolus with saline flush into an antecubital vein or *via* central venous pressure line. Sequential data in frame mode of tracer blood flow in the neck and head in anterior projection were acquired at 2 seconds interval for 60 seconds in 64 x 64 matrix format and stored in a magnetic disc. Simultaneous analog 2 sec x 30 sequential images were also obtained on X-ray films. The whole procedure took about five minutes. Five patients in coma due to various causes but not clinically brain dead, and five conscious and neurologically normal patients were studied in a similar manner to serve as controls. The digital images were examined and displayed both in static and cine fashion. Time activity (T/A) curves of regions of interest (ROI) over the cerebral hemisphere and carotid artery were created. The bolus was checked and if spread or fragmented, a repeat injection was made and data acquired in a similar manner. The curves were 9 point smoothed, using 1:6:1 filter. Background subtraction was not done.

Correlation was made with clinical and EEG findings and the ultimate fate of the patient and the interval of death from time of cerebral flow study. These patients when confirmed to have brain tamponade were continued on artificial support but transferred from ICU to an ordinary ward.

RESULTS

Radionuclide digital cerebral flow images of arterial, capillary and venous phase acquired in a conscious patient is shown in Fig. 1. Good blood flow activity in the carotid (C), middle cerebral (M) and anterior cerebral (A) arteries during the arterial phase are clearly demonstrated.

Diffuse homogenous symmetrical and equal radioactivity in the distribution of the middle cerebral arteries in both cerebral hemispheres during the capillary phase and prompt emptying into the venous sinuses (S) during venous phase is clearly shown. T/A curve over the cerebral hemispheres in this patient showed the typical pattern with a sharp rise to peak and fall of activity as the bulk of the tracer bolus passed through the brain (Fig. 2). The coma patients without clinical evidence of brain death showed comparable flow images and T/A curves.

In 16 of the 18 clinically suspected brain dead patients, radionuclide flow study showed the neck vessels and scalp circulation to be normal, but there was no visualization of the cerebral arteries and venous sinuses (Fig. 3). The typical "hot-nasal" activity was seen, probably due to hold-up of blood flow in the distal internal carotid vessels at the level of the circle of Willis and diversion of flow to facial bones (Fig. 3). The T/A curves in these patients (Fig. 4) were dramatically different from the normal flow pattern (Fig. 2) in that they showed on bolus effect. There was marked impairment in time and rate of appearance of radioactivity, the level of activity never approached that of the usual peak and there was no definite drip in activity during the one-minute period of imaging. This gradual rise of T/A curve is due to radioactivity from extra-cerebral (scalp) circulation. The T/A curves of the carotid vessels showed normal bolus pattern confirming a good tracer bolus injection. These features are diagnostic of arrested intracerebral circulation.

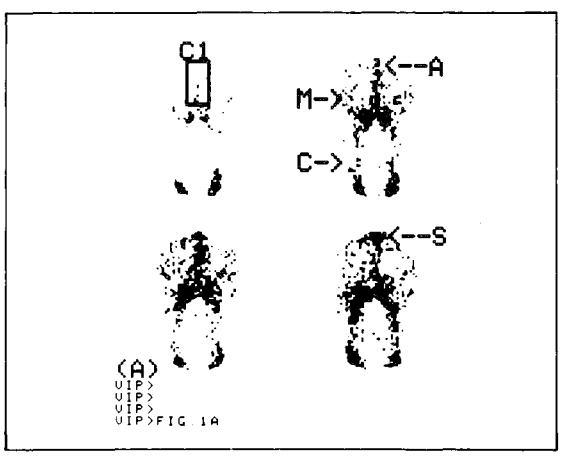

Fig. 1 Normal radionuclide cerebral angiography. During the arterial phase flow radioactivity in the carotid arteries in neck (C), middle cerebral arteries (M) which is equal on both sides and in anterior cerebral arteries (A) is visualized. The arterial-capillary phase show diffuse homogenous activity throughout the cerebral hemisphere. Activity in the saggital sinus (S) and region of jugular bulb is visualized during the venous phase.

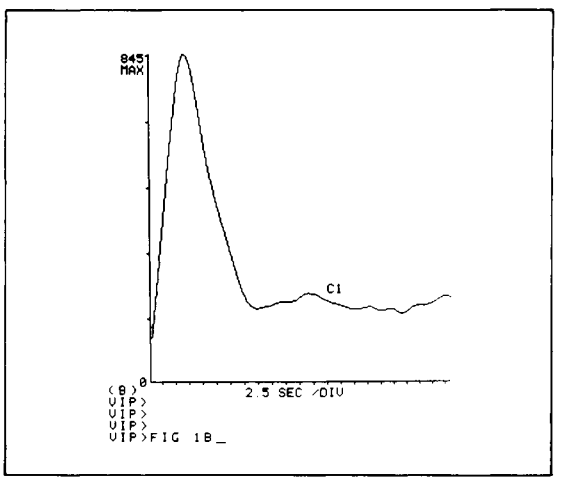

Fig. 2 Normal cerebral T/A curve (C1) clearly shows bolus effect of intracranial flow. This characteristic sharp rise to peak and fall is indistinguishable from curves obtained on comatose but not brain dead patients.

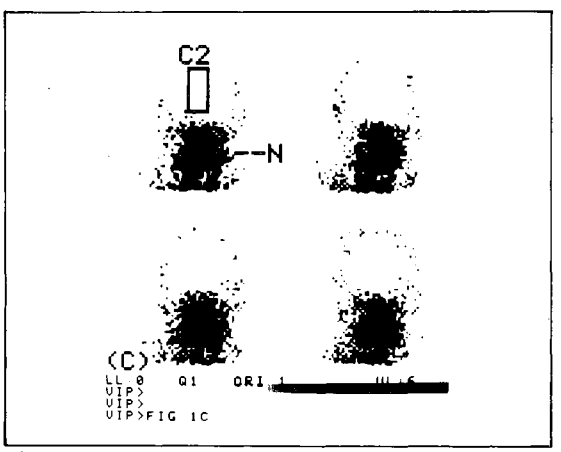

Fig. 3 Flow images in brain death show during arterial phase activity in neck vessels (C) and scalp circulation but no visualization of intracranial circulation. The venous phase show no filling of the saggital sinus. The typical 'hot-nasal' activity (N) is seen.

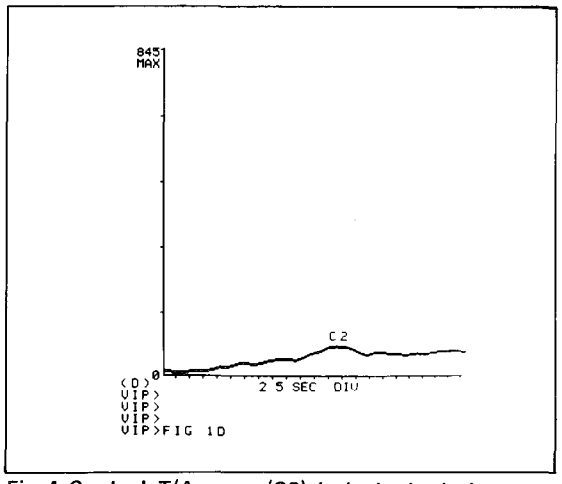

Fig. 4 Cerebral T/A curve (C2) in brain death shows no bolus effect. This delay and gradual rise of activity is from the relatively slower and dispersed extracerebral scalp peripheral type of circulation. EEG in this patient was iso-electric.

Of these 16 patients with absent intracerebral perfusion demonstrated by the radionuclide angiography, ten had isoelectric EEG (Tables II, III). The EEG in another patient done one day prior to radionuclide study was reported as extremely abnormal but not isoelectric. The remaining five patients did not have EEG done due to technical or time constraints or patients' death.

In two patients clinically suspected to have brain death, some intracerebral perfusion was demonstrated: one patient had absent cephalic reflexes but intact spinal reflexes and an EEG with no definite cerebral activity; the other patient had small (1.5 mm) nonreactive pupils but otherwise nonreactive cephalic reflexes and EEG done twice within 24 hours showed diffuse delta activity, some theta and occasional beta activity characterizing diffuse encephalopathy. Both these patients had cardiac standstill three days later. The majority of patients (72%) had cardiac standstill within one day of radionuclide study.

TABLE II

EEG AND RADIONUCLIDE CEREBRAL ANGIOGRAPHIC FINDINGS

	Flow Present	Flow Absent	Total
EEG silent	1	10	11
EEG abnormal	1	1	2
EEG not done	0	5	5
Total	2	16	18

DISCUSSION

The T/A curves over regions of the cerebral hemisphere represent passage of radioactive bolus through two different types of circulation: the large volume of blood flow through the relatively small cerebral blood vessels and cause a characteristic bolus effect with a sharp rise and fall of radioactivity (Fig. 2); the relatively slower and dispersed extracerebral (scalp) peripheral blood flow fed by branches of the external carotid arteries does not show a bolus effect but a gradual rise of radioactivity (Fig. 4).

The criteria for diagnosis of arrested intracerebral perfusion in radionuclide cerebral flow study are: non-visualization of blood flow activity in the intracranial arteries during the arterial phase, diffuse cerebral activity during the capillary phase and non-filling of venous sinuses during the venous phase; visualization of typical "hot nasal" activity; and the time-activity curve over the cerebral hemispheres lacks a bolus effect and instead shows a delayed gradual rise of activity. These features are characteristic and pathognomonic of brain tamponade.

It is important to look for filling of venous sinuses or gradual washout of cerebral radioactivity as in severely impaired but not totally obstructed intracranial circulation, these features may be recognised although faintly, and intracranial arterial blood flow activity may not be obvious due to the 'masking' effect of the extracranial arterial circulation. This is especially important if a computer is not available to create T/A curves. However a computer is not essential

TABLE III

CLINICAL, EEG AND RADIONUCLIDE CFS FINDINGS

Patient Age (yrs)		Cause of brain injury	Neurological examination	EEG	Radionuclide intracerebral flow	Interval in days from scan to cardiac standstill
2	F	MVA with fractured skull and brain contusion	brain death	isoelectric x 1	no flow	1
4	M	Fall, extradural haematoma cerebral oedema and infarct	brain death	isoelectric x 2	no flow	same day
4	M	Encephalitis with respiratory arrest	brain death pupils fixed, dilated reflex plantar equivocal	isoelectric	no flow next day	same day
14	M	Skull fracture with subdural haematoma	brain death spinal reflexes present	not done	no flow	1
20	F	Choriocarcinoma with brain secondaries and intra-cerebral haemorrhage	brain death	not done	no flow	1
4	M	Nephrotic syndrome, uraemia, septicaemic shock, meningitis	brain death	not done	no flow	same day
39	M	MVA with fractured skull, CT scan: cerebral contusion and oedema Respiratory arrest	brain death	isoelectric x 1	no flow	same day
31	F	Pelvic abscess, septi-caemic shock, cardiac arrest	brain death	isoelectric x 1	no flow	1
43	M	Status asthmaticus, asphyxia, cardiac arrest	small (1.5 mm), non-reactive pupils, otherwise cephalic reflexes non-reactive, brain death	diffuse delta activity over both cerebral hemispheres. Some theta and occasional beta activity x 2	some flow in anterior and middle cerebral arteries, saggital sinus visualized	3
38	M	Diabetic hypo-glycemia coma DIVC	brain death	isoelectric x 1	no flow	same day
8	M	Reye's syndrome, hepatic encephalopathy, cardiac arrest	brain death plantar	isoelectric x 2	no flow	1
4	F	Reye's syndrome	absent cephalic reflexes, plantar reflex equivocal ? brain death	not done	no flow	1

Patient		Causes of brain injury	Neurological examination	EEG	Radionuclide intracerebral flow	Interval in days from scan to cardiac standstil
Age (yrs)	Sex					
3	M	Tetralogy of Fallot, Post-cardiac surgery shock. Cardiac arrest	cerebral death Spinal reflexes present	isoelectric x 1	minimal tracer flow in anterior and middle cerebral vessels next day	3
2	F	Acute epiglottitis, asphyxia, respiratory arrest	brain death	isoelectric x 1	no flow	2
27	F	Mitral stenosis with pregnancy, sudden coma, cardiac arrest	brain death	isoelectric x 1	no flow	5
33	F	Status asthmatics, asphyxia, respiratory, arrest	brain death	isoelectric x 1	no flow	6
22	F	Meningoencephalitis	brain death	basically flat except for faint occipital small voltage activity	no flow next day	same day
60	F	Diabetic gangrene for amputation. Cardiac arrest during anaesthetic induction	brain death	not done	no flow	1 day

to make the diagnosis; the analog flow images alone for all our patients were sufficient.

Radionuclide cerebral flow study is very sensitive and provides clinically useful estimation of gross changes in cerebral blood flow. Failure to show intracerebral vasculature may be compared to a non-filling cerebral contrast angiogram. The technique is simple, results are displayed within minutes and arterial punctures are not necessary. Depressant drugs used as 'brain protection' and hypothermia should have no effect on the results. The radiation exposure to the patient and staff is minimal and less than that would be acquired during a portable chest radiograph.

Where definitive aetiology and degree of brain damage is known decision on brain death can be based on a clinical basis alone and EEG is not essential.[8,9] However, EEG is useful when the nature of brain injury is not known provided there is absence of CNS depressant drugs, hypothermia and certain metabolic states.[9] In their paper, Mohandas *et. al.*,[9] reported instances of low voltage fast activity but the brain stem was completely autolysed at autopsy and also patients with isoelectric EEG but did not have histological changes in the brain stem. Again there must be caution in the interpretation of the auditory brainstem response and the loss of brainstem auditory evoked potential after a cerebral insult need not necessarily imply structural damage to the whole brainstem and may occasionally be reversible.[19] Similarly electrocerebral silence soon after a period of, for example, cerebral ischaemia, may only imply temporary 'paralysis' and complete recovery of cortical function can occur.[19] Serial EGG is thus necessary in assessing the degree

and reversibility of brain damage.[19] The presence of modest amounts of artefactual low voltage rhythmic or quasi-sinusoidal activity (usually of greater amplitude in non-cerebral leads) prevented the diagnosis of electrocerebral silence in patients whose brains were found to be totally necrotic at the time of EEG.[20] In our study one patient with absent cephalic reflexes had a basically flat EEG except for faint occipital small voltage activity but an arrested intracranial circulation was demonstrated by radionuclide flow study on the next day. It appears, therefore, in the presence of definite clinical-neurophysiological criteria of brain death and demonstration of arrested intracerebral perfusion by radionuclide flow study the value of an EEG examination is extremely questionable.

"The doctor's dilemma about brain death arises only when patients are put on ventilators, and it is therefore of his own making. When a patient who already has severe brain damage develops respiratory insufficiency or cardio-respiratory arrest, careful thought should be taken before artificial respiration is extended beyond the immediate resuscitation period. Prolongation of such a patient's life, even for 12 hours (it may be much longer in practice), reflects no credit on his doctors, particularly if this is done only so as to postpone the decision to let events take their natural course. It would be unfortunate if the time came when no patient in hospital can decently die without the last rite of modern medicine – a statutory period on the ventilator."[21]

CONCLUSION

Radionuclide cerebral flow study is a very sensitive, accurate, safe and rapid method to demonstrate arrested intracranial circulation in brain dead patients. It is a more practical and useful method than EEG to confirm brain death especially in busy intensive care units such as ours in the University Hospital, Kuala Lumpur where the pressure for bed-space is acute (daily bed-occupancy is greater than 90%). The long duration for EEG examinations (including a repeat EEG in 24 hours); and the occurrence of artefactual voltage activity which prevents diagnosis of electrocerebral silence in EEGs can prolong patients' stay adding burden on ICU bed and the staff which could be used for other patients who may still benefit from them. However where definite aetiology and degree of brain damage are known decision on brain death can be based on clinical basis alone and a second modality such as EEG or radionuclide cerebral flow study is not essential. The doctor's dilemma about withdrawal of further artificial respiratory support is often his own making. In patients with severe brain damage who develop respiratory insufficiency or cardio-respiratory arrest, careful thought should be taken before the decision to provide artificial support is made.

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