Radioisotopic Bolus Technique as a Test to Detect Circulatory Deficit Associated with Cerebral Death

142 Studies on 80 Patients Demonstrating the Bedside Use of an Innocuous IV Procedure as an Adjunct in the Diagnosis of Cerebral Death

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SUMMARY
A portable radioisotopic technique was developed to demonstrate cerebral circulatory deficit, as part of a collaborative study to define and diagnose cerebral death simply and rapidly in comatose, apneic patients with electrocerebral silence. The method involves an intravenous injection of 2mCi of 99mTcO₄⁻ and recording time/activity curves over the cranial cavity and a femoral artery simultaneously, using twin probe radioisotope detector equipment. Eighty comatose, apneic patients had 142 studies in conjunction with clinical electroencephalographic and other laboratory evaluations. The results indicate that the absence of a bolus tracing from the head, as contrasted to the usual bolus seen, is indicative of significant circulatory deficit to the cerebrum. This test may be used as an adjunct in confirming the diagnosis of cerebral death. A normal bolus tracing should be simultaneously observed over a femoral artery and this is used as a control. The method is safe and simple and offers significant information about the irreversibility of cerebral blood flow. Although further studies are indicated, the method appears to be most promising as a fundamental, bedside laboratory test in the diagnosis of cerebral death in conjunction with other clinical and laboratory criteria.

Additional Indexing Words:
Cerebral circulation Electroencephalographic silence

The major problem to which we addressed ourselves was that of obtaining a safe, easily performed and portable test that would detect the cerebral circulatory deficit associated with cerebral death. The need for having such an adjunct to other diagnostic criteria, including electrocerebral silence* (ECS) in the electroencephalogram (EEG), for the pronouncement of cerebral death was evident from earlier studies.¹ In addition, numerous European investigators such as Ingvar, Brock, Hadjigdimos and their coinvestigators²-⁷ have also stressed the need for the use of cerebral blood flow techniques in the diagnosis of cerebral death. We wish to make it clear that the method to be discussed in this report is essentially nonquantitative and is intended for detection of a significant critical decrease of cerebral circulation. The reliability of the technique as an adjunct to the diagnosis of cerebral death would be highly significant if the implied relationship to cerebral blood flow were more fully substantiated. Then the combination of clinical findings, including cerebral unresponsiveness and apnea for an appropriate period, in conjunction with an EEG indicating ECS and a portable cerebral circulatory test, would allow one to arrive at the diagnosis of cerebral death. Trials were relatively simple to perform with a portable bedside apparatus available; initially, equipment with a single detection probe was used. The innocuous short-acting, intravenously (IV) injected radioisotope, technetium 99m pertechnetate (99mTcO₄⁻), which emits a single gamma ray of 140kV was considered suitable for use. These considerations were based on practicality and availability of instrumentation as well as awareness of...
the theoretical concepts of transit time as presented by Oldendorf and his coworkers.\textsuperscript{8-12} The initial study was undertaken despite the difficulties in separating intra and extracranial circulation described by Ingvar and other investigators.\textsuperscript{13-15} Problems such as the differences between blood flow, blood pool volume of the skull, scalp, and intracranial contents, and details of the geometry of the skull were only considered explicitly after pilot trials. The results of using intravenous isotopes by Goodman et al.\textsuperscript{16} and Maynard et al.\textsuperscript{17} indicated the feasibility of developing a technique that might be used in diagnosing cerebral death. The overriding requirement of developing an additional confirmatory technique that was not basically electrophysiological but was based on cerebral blood flow (CBF) was considered sufficient reason to perform the initial studies prior to their inclusion in the CSCS\textsuperscript{*} program by Braunstein and his coworkers.\textsuperscript{18-20}

\textbf{Methods}

\textbf{Pilot Phase}

Although the appearance of time/activity curves of the initial head passage of an intravenously injected radioisotope bolus in noncomatose patients is well established,\textsuperscript{3, 5, 9, 21, 22} we obtained a series of flow tracings in such patients in order to establish our techniques. The preliminary feasibility study by Braunstein et al.\textsuperscript{18-19} was done using a single probe with a thallium activated sodium iodide crystal and a flat field collimator. The output was recorded by a ratemeter and strip recorder. The lower edge of the collimator was placed halfway along a canthomeatal line and angled about 15° cephalad so that the lower edge of the field of view encompassed the cranial cavity only. The probe was placed to one side of the head so that the flow curves could be obtained simultaneously with conventional sequential gamma camera flow images in the anterior projection (figs. 1, 2). After performing this study on a relatively small number of normal individuals and patients with intracranial disease who were not in coma, ten comatose patients were studied. These ten patients met the initial criteria of inclusion into the CSCS project.\textsuperscript{23} They had no spontaneous respirations (on a respirator, not triggering) or cerebral responsivity for 15 minutes. Five had evidence of cerebral activity as determined by the presence of EEG activity while the other five had no evidence of cerebral activity clinically with ECS on EEG (figs. 3, 4). The comparison of the resulting time/activity curves following the injection of 10mCi of 99mTcO\textsubscript{4} was correlated with the clinical picture, the EEG findings and the outcome including observations on the neuropathological findings. In the five patients who had EEG activity there was a clear cut bolus effect (fig. 3). In the five patients with absent EEG activity (ECS) there was a slow, gradual, graded, linear rise in the time/activity curve tracing (fig. 4). These initial studies were done with limited controls which included cerebral angiography and/or brain scan. They yielded results which appeared to be all or none in nature, i.e., the presence of a bolus suggesting the presence of cerebral blood flow (CBF),

cerebral viability. The isotopic technique will be henceforth termed the 'bolus' technique which is descriptive of the tracing found in the presence of significant CBF.

Second Phase

On the basis of the pilot study several modifications were introduced. The original method was altered specifically for bedside use with the addition of a second, control probe for evaluation of the adequacy of the IV injection and systemic circulation. Nearly all patients had an intravenous line in place. Therefore, a syringe containing 2 mCi of 99mTcO₄⁻ diluted with saline to a volume of 2 cc was attached directly to an external connection of the IV line for a rapid, uniform injection. The volume of 2 cc was felt to be appropriate because some intravenous lines may have a dead space of up to 0.5 cc. In practice, a twin probe renogram instrument with balanced probes was adapted for these studies. Sensitivity settings of 100,000 counts/min at full deflection of chart recorder pen, with linear response, were found to be appropriate. The detectors were altered by replacement of the original collimator with others designed to limit the field of view appropriately when the probe is placed in contact with the midline of an adult forehead and pointed directly posteriorly (figs. 5 and 6). Only the lower edge of the collimator is placed in direct contact with the forehead, about 1 cm above the glabella. The upper edge of the front surface of the collimator is kept slightly away from the surface of the forehead. The collimator edge is not aligned with the slope of the forehead so that the probe does not point caudal as well as posteriorly but is directed only posteriorly to avoid the structures below the floor of the skull and to encompass the major arterial vessels entering it (figs. 5 and 6). It should be noted that most or all of the posterior fossa is outside the field of detection.

The fact that the extracerebral circulation alone, which is responsible for a significant proportion of the blood pool of the head, does not give a "bolus" response like that of the cerebral circulation appears to us, above all, to be a reflection of the fundamentally different characteristics of the cerebral and extracerebral circulation (see discussion). An additional factor may be that the truncated cone representing the field of detection is placed in a manner that accentuates detection of radioactivity from the cerebral circulation and minimizes detection of radioactivity from the extracerebral circulation in that the volume of cerebrum in the field of the detector includes the major arterial trunks within a cerebral mass of approximately 600 cc, as opposed to less than 200 cc of skull and scalp that exclude major arterial trunks, in the same field (figs. 5 and 6). The second probe is usually placed directly over a pulsating femoral artery as palpated clinically. This control probe documents the adequacy of the radioisotopic bolus injection as detected in the systemic circulation. In the absence of clear evidence of a good systemic bolus no reliance can be placed on absence of a head bolus. Other possible control probe locations such as one over a carotid artery will also be considered.

Results

Of the 177 patients entered into the study from CSCS Center 4 during the period from 7/15/71 to 5/10/73, 165 adequately fulfilled the criteria for admission to the study. These patients were followed by sequential neurological examinations and EEGs according to the CSCS protocol (tables 1 and 2). Eighty of these 165 patients had 142 portable bolus studies to assess their CBF. A comparison of the findings on the bolus and the EEG findings is presented in table 3. This table does not take into account temporal factors or the sequential relationships and changes of bolus

*Bellevue Hospital Center and NYU Medical Center.
studies in relation to the EEG studies and is therefore oversimplified in several ways. The results presented in table 4 indicate the major etiological factors as related to the EEG and bolus findings in 75 patients. In order to be concise, the results will be discussed by referring to tables 3 and 4 and specific illustrations and examples will be given including some exceptions or cases of special interest.

In considering only those cases in which a satisfactory control was obtained, two dramatically different time/activity curves of the head area were obtained, with the possible exception of four patients with “intermediate” curves who will be discussed separately.

As observed in the initial phase of the study, one type of tracing demonstrated a distinct bolus effect showing a relatively sharp rise and fall of activity (type I) as noted in the patients illustrated in figure 7. The sharp rise and fall of these tracings represents the bulk of intravenously injected bolus passing through a cerebral circulation and is essentially not distinguishable from tracings obtained in noncomatose individuals.8-12, 27 The appearance of the radioisotopic bolus in the femoral artery area in the lower part of the figure is similar but often slightly delayed, when compared to the head tracing. These representative tracings are considered exemplary, and are presumed to reflect sufficient CBF for maintenance of a viable but not necessarily normal cerebrum. The femoral controls indicate that the injection was satisfactory and that sufficient peripheral blood flow is present.

In sharp contrast to type I, the second type of head tracing (type II) displayed a gradual, low magnitude, linear, graded increase in radioisotopic activity with no bolus effect from the head but with a normal femoral control. This is illustrated in figure 8A and B in two different patients (upper tracing) and in figure 8C and D in the same patient. There was no distinct peak during the period of monitoring, which was continued for at least one minute following injection. This type of head time/activity tracing contrasts sharply with the passage of a distinct bolus through the femoral artery (lower portions of tracings, fig. 8). The lack of bolus effect in the head tracings is considered to be evidence of gross cerebral circulatory deficit. The relatively delayed, low level and gradual build-up in activity seen in the head tracings is presumably a reflection of the radionuclide activity in the extracerebral circulation. The evidence for this assumption will be further evaluated in the discussion.

A comparison of the two types of tracings with their concomitant EEGs in two of these patients is illustrated in figure 9.

As stated above, all 80 patients included in this study (table 3) were deeply comatose (i.e., cerebrally unresponsive) and were without spontaneous respirations, fulfilling the criteria for entrance into the CSCS project. Twenty-seven of these patients had evidence on all their radioisotopic flow examinations of the presence of a bolus effect on the head tracing (type I). All but three of these patients had clear evidence of electrical activity on EEG. The exceptions were patients on whom repeated EEGs were technically unsatisfactory because of multiple artifacts such as those caused by muscle, etc. Five of these patients had...
patients survived and are now neurologically normal. These five were originally in drug-induced coma. Autopsies including neuropathological examinations were performed on 12 of the 22 patients who died. General neuropathological results varied and are presented elsewhere (unpublished data, J. Korein and J. Pearson, 1974).23

Thirty-seven patients in this study showed the absence of bolus effect in the head (type II) on radioisotopic IV examination in the presence of an adequate control. In the majority of these cases, the study was repeated at least once after one or more hours at which time they all again showed a type II tracing including satisfactory control. Thirty-one of these 37 patients had EEGs with ECS prior to the radioisotopic tests. The other six had technically unsatisfactory EEGs. In none of these did the EEG activity return although a small number had subsequent technically unsatisfactory EEGs because of artifact. All 37 patients died. Twenty-three had spontaneous irreversible cardiac arrest; in twelve resuscitative procedures were discontinued and in two, it could not be determined whether the resuscitation procedures were discontinued or not. Of these 37 patients, 20 had postmortem examinations including the brain. Although diffuse, congested, edematous fragmented brains with microscopic evidence of anoxic neuronal degeneration were frequent, other findings including multifocal lesions were also common (unpublished data, J. Korein and J. Pearson, 1974).23 Clinical and/or postmortem examinations indicated that 26 patients had intracranial hemorrhage which was either primary or secondary to trauma or other factors. In two patients, there was primary cardiorespiratory arrest and in seven there was secondary cardiorespiratory arrest. Two other patients had intracranial neoplasms (table 4).

In four additional patients with adequately controlled radioisotopic flow studies an "intermediate" response was noted. In figure 10 the response in one such patient is illustrated. Initially, the patient had evidence of a bolus (fig. 10, left) of EEG activity (fig. 11, first panel). The next day the EEG revealed ECS and the flow study tracing from the head region was clearly neither type I nor type II and could be qualitatively differentiated from them by the small

Table 2

<table>
<thead>
<tr>
<th>Primary etiology</th>
<th>Number of patients</th>
<th>Any EEGs with ECS</th>
<th>EEGs never ECS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intoxication</td>
<td>19</td>
<td>5 (1 survived)</td>
<td>14 (12 survived)</td>
</tr>
<tr>
<td>Anoxia†</td>
<td>19</td>
<td>11</td>
<td>8 (1 survived)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>43</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Shock</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Trauma</td>
<td>29</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Metabolic†</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>5 (neoplasm)</td>
<td>1 (postoperative)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (vascular, survived)</td>
</tr>
<tr>
<td>Total</td>
<td>165†</td>
<td>99 (1 survived)</td>
<td>66 (14 survived)</td>
</tr>
</tbody>
</table>

*Includes mainly cases with biological activity and some with technically unsatisfactory records.
†Twelve patients excluded from study: 6 patients died prior to EEG; 6 patients, entered by history of meeting criteria, prior to being seen by neurologist (one of these patients survived).

Table 3

Cerebral Blood Flow (bolus) Study vs EEG: Correlation of 142 Portable CBF Studies on 80 Patients

<table>
<thead>
<tr>
<th>Radioisotopic CBF study</th>
<th>Total patients</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any EEG with ECS</td>
<td>Technically unsatisfactory</td>
</tr>
<tr>
<td>Head bolus present (type I)</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Head bolus absent (type II)</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Unsatisfactory flow study</td>
<td>12</td>
<td>7*</td>
</tr>
<tr>
<td>Intermediate effect</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

*Includes three patients of the initial group in whom no control was available.
rise in activity which occurred concomitant with the femoral artery control (fig. 10 right). ECS was consistently observed on subsequent EEGs (fig. 11, second and third panels) and repeat flow studies continued to show the "intermediate" tracing. Initially, the authors conservatively considered that this might represent some significant degree of cerebral blood flow.\(^{24}\) In another patient, with initial EEG which was ECS and had a type II response, i.e., absent bolus, subsequent flow study revealed an intermediate response in conjunction with another EEG with ECS.

All four of these patients with "intermediate" tracings had EEGs with ECS and died. Three had irreversible cardiac arrest and in one resuscitation was discontinued. Autopsy, including the brain, was performed in three and the neuropathological findings were compatible with cerebral death.\(^{23}\) In the patient with an intermediate response following the type II response, femoral-cerebral (four vessel) angiography was performed and showed no intracranial flow from either the carotid or the vertebral arteries. Detailed studies of the relationship of angiography and the bolus test and the EEG in relation to cerebral death are presented by Kricheff et al. (see addendum).\(^{28}\)

Twelve patients had unsatisfactory flow studies; these included three of the five patients in the pilot study in whom satisfactory control was not performed. Seven of the 12 patients had EEGs with ECS; in three, the EEGs were technically unsatisfactory; and in two, EEG activity was present. All 12 patients died: spontaneous cardiac arrest occurred in ten; in one resuscitation was discontinued; and in one, it could not be determined whether resuscitation was discontinued or not. Autopsy with neuropathological examination was performed in four of these patients (unpublished data, J. Korein and J. Pearson, 1974). Causes of technically unsatisfactory bolus studies included no adequate femoral control, injection of the radioisotope into the femoral artery (fig. 12A) and insufficient rapidity of injection of the radioisotope into the IV line (fig. 12B). In several cases both femoral arteries were inaccessible because they were covered by bandages, casts, etc. In one of these patients, an attempt to use the heart as a control proved unsuccessful as illustrated in figure 13. Subsequently, we introduced the use of the common carotid artery as a

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**Table 4**

<table>
<thead>
<tr>
<th>EEG and Bolus: Etiologies and Results in 75 Patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>EEG with ECS and bolus absent</td>
</tr>
<tr>
<td>TU EEG and bolus absent</td>
</tr>
<tr>
<td>EEG activity and bolus present</td>
</tr>
<tr>
<td>TU EEG and bolus present</td>
</tr>
<tr>
<td>EEG with ECS and TU bolus study</td>
</tr>
<tr>
<td>EEG with ECS with intermediate response</td>
</tr>
</tbody>
</table>

* These patients had cardiorespiratory arrest secondary to the intoxicant. One also had intracranial hemorrhage. Therefore, although intoxication was the initial factor that brought them into the hospital, it was secondary factors which were more important in their entry and outcome in this study. They are listed under the etiological characteristic which brought them into the study.

† Three patients in whom both EEG with flow studies were technically unsatisfactory and two patients with EEG activity and simultaneous technically unsatisfactory flow studies are not included.

Abbreviation: TU = Technically unsatisfactory.

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**Figure 7**

This illustrates the findings in two apneic, comatose patients in whom there was a significant head bolus (top) and normal femoral control, type I (bottom). Note that the head bolus is usually greater in height than that from the femoral artery, occurs somewhat more rapidly, and that there is a distinct maximum. (CPM refers to counts/min and each division is 100,000 counts. However, this measure should be considered entirely qualitative.) The tracings were often run for more than one minute. Both these patients had EEG activity.

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Illustrative Case Reports and Comments

As can be seen from table 4, the major etiological factors in those patients with ECS on EEG and no bolus were increased intracranial pressure due to spontaneous intracranial hemorrhage or trauma (22 of 31 patients). In those patients in whom toxicity was a factor, it was usually not the toxic agent per se which led to ECS and absent bolus effect. Rather, it was secondary to an episode of cardiac and/or respiratory arrest. This was clearly suggested by the temporal sequence of events occurring in these patients. Since many of these patients have a rather complex course, as noted previously, simple tabular presentation of data (table 3) can be misleading. Therefore, several case reports are presented to illustrate the types of patients and the problems encountered.

The first group will be the case reports on two patients in whom ECS was present and head bolus was absent (type II).

Case 84. The patient was a 39-year-old woman who entered Bellevue Hospital Psychiatry Ward on 4/22/72 because of schizophrenia. She was placed on a monoamine oxidase inhibitor and chlorpromazine. Five days later on the morning of 4/27/72, the patient had an episode of cardiorespiratory arrest of unknown cause for a short, undefined period of time and was found unconscious on the ward. She was recovering and was transferred to the Emergency Ward at Bellevue Hospital Center at 12 noon on 4/28/72. She had a second episode which involved only respiratory arrest and was placed on a respirator. At this time, she was cerebrally unresponsive and apneic. The patient was then admitted into the CNS project. Examination at 2:00 p.m. on that day revealed normal pulse and blood pressure although the patient was apneic, with fixed, moderately dilated pupils and absent cephhalic reflexes. There was no papilledema. There were no deep tendon reflexes (DTRs) or spontaneous movements. There were transient decerebrate movements involving the face and upper extremities in response to painful stimuli. Laboratory studies suggested disseminated intravascular coagulation (DIC) and showed no evidence of drug toxicity. EEG was performed twenty minutes after the neurological examination and was severely and diffusely abnormal but did not reveal ECS.

A second neurological examination was performed at 9:15 on 4/28/72, approximately seven hours after the initial examination. The findings were unchanged except that the decerebrate phenomena and withdrawal to painful stimuli were no longer present. EEG at 10:00 p.m. (approximately 8 hours after the first EEG) revealed unequivocal ECS. Subsequent daily examinations and EEGs from 4/29/72 through 5/1/72 showed no changes except for transient return of DTRs in upper extremities. The EEGs still revealed unequivocal ECS. On 5/1/72, portable bolus study with femoral control showed the absence of a head bolus (figure 8B). On 5/3/72, EEG and portable radioisotope studies were repeated with identical results. The last examination at 11:00 a.m. on 5/4/72 showed no change clinically. The patient had ECS for over 130 hours and was never in shock nor was she ever treated with pressor agents to maintain her blood pressure which

control (fig. 14), and the sharp, high amplitude, rapid rise was later shown to be associated with a femoral artery bolus. Thus, this secondary type of control may be of future use. Other reasons for technically unsatisfactory bolus studies include errors in calibration. In one child, a technically unsatisfactory bolus study was performed because the head was small in comparison with the field of detection and vessels in the neck could not be excluded.

In several patients, one to four vessel angiography was performed as a control procedure but this clearly is impractical as a routine. In three of these patients with no bolus and one with an "intermediate" tracing, four vessel angiography showed virtually no intracranial filling except for one case (with type II tracing) in which markedly delayed posterior filling and persistence of the radioisotope material was noted (over 25 sec).

Figure 8

A and B) This illustrates two apneic, comatose patients with no evidence of significant CBF as indicated by the absence of the head bolus (top) and presence of an appropriate femoral control, type II (bottom). Calibration and recording procedure is identical to that of figure 7. Positioning of the collimator on the head in these illustrations is as illustrated in figure 5. These patients had EEGs with ECS. C and D) Two bolus flow studies performed several hours apart on the same comatose, apneic patient. There is no evidence of a head bolus in either tracing (top) with a femoral control (bottom). This patient had EEGs with ECS.
remained within normal range. She died at 3:00 p.m. on 5/4/72 because of spontaneous, irreversible cardiac arrest. Autopsy revealed that the primary cause of the patient's insult was a myocardial infarction with subsequent DIC. Gross examination of the brain showed a fragmented cerebellum and brain stem, portions of which were present at the level of the lumbar spinal cord. The cerebrum was severely softened, swollen, dusky and degenerated diffusely. No major vessels were thrombosed. Microscopic examination showed diffuse severe anoxic degeneration of neurons with almost no gliosis.

This patient represents an example of that category of patient with transient cardiac and respiratory standstill apparently resulting in decreased to absent cerebral flow for a significant period of time with

The bolus study on the left was performed on 8/10/72 at 4:45 p.m. and although the amplitude of the bolus tracing is lower than usual (top), the femoral control is adequate (bottom) and 'significant' CBF is assumed. The study on the right was performed on 8/11/72 at 12:10 p.m. on the same patient. The femoral control is adequate but rather than a bolus effect in the head tracing there is a small but distinct step-function which occurs at the same time as the femoral control. This "intermediate" tracing persisted on repeated testing.
severe anoxia to the entire brain. Although she may have had transient increased intracranial pressure at some time in her course, the possibility of "no reflow phenomenon" as defined by Kowada, Ames, Chang and their coworkers\textsuperscript{29-31} also appears likely. This term is used to define the perivascular glial and endothelial edema which occurs as a rapidly progressive, irreversible occlusive phenomenon without thrombosis after transient cessation of CBF for a relatively short period of time.

In contrast, the second case, is representative of those patients with marked acute increase of intracranial pressure due to a hemorrhagic or traumatic insult.

Case 162. The patient was a 47-year-old woman, a chronic alcoholic, who suffered head trauma and a skull fracture with a subsequent left subdural hematoma. She entered Bellevue Hospital on 3/24/73 and was unresponsive and apneic at 4:40 a.m. Angiography revealed a left subdural hematoma and a left craniotomy was performed. Because of active therapeutic procedures in attempting to evaluate and aid the patient, entry into the study was postponed. On 3/25/73, after surgery, a pressure transducer was inserted between the dura and the skull through a burr hole in order to continuously monitor and hopefully control the intracranial pressure. The range of intracranial pressure for one day was 1500 to 1800 mm Hg with no pressure waves. She was admitted into the study at 10:35 a.m. on 3/26/73 at which time she had no spontaneous respirations or cerebral responsiveness. Vital signs revealed a temperature of 94.4° F and a systolic pressure of 80 mm Hg by palpation while on pressor agents. The left pupil was 5 mm, dilated, and fixed and the right could not be examined. There were no cephalic or deep tendon reflexes. There were no spontaneous movements. She had minimal withdrawal of right leg to painful stimuli. An EEG was done approximately one-half hour after the neurological examination and revealed unequivocal ECS. Two portable radioisotope studies, at 12:40 and 1:40 p.m. on the same day after the EEG, showed no head bolus with normal femoral

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure11}
\caption{Unresponsive Coma With Apnea}
\end{figure}

These are the EEGs in the patient illustrated in figure 9. In the first panel, the EEG activity is that which was seen at approximately the same time as the bolus tracing in 10 left. In the subsequent two panels, one and two days later, the EEG showed ECS and corresponds to the times when the "intermediate" bolus was present.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12}
\caption{A) Technically unsatisfactory bolus tracing because of erroneous injection of radioisotope directly into the femoral artery. The apparent lack of a bolus in the head tracing (top) is artifactual and on subsequent appropriate IV injection of the radioisotope a "normal" head bolus was demonstrated. B) Technically unsatisfactory tracing because the injection in the intravenous line was too slow. Note the inadequate femoral tracing (bottom). Under these conditions no reliance can be placed in the absence of the head bolus (top).}
\end{figure}
control (similar to patient illustrated in fig. 8C and D). On 3/27/73, an attempt was made to measure oxygen consumption and CBF by use of the Kety technique using argon. There was no evidence of significant cerebral metabolic rate of oxygen consumption (CMRO₂) or CBF for a period of three minutes. The patient died at 10:15 p.m. on 3/27/73 and autopsy revealed a skull fracture with left hemicraniotomy and a totally necrotic brain.

In this patient it is significant that the increased intracranial pressure was sufficient to stop cerebral blood flow. In addition, the limitation of reliable measures using the Kety technique in evaluating marked decrease in CBF or CMRO₂ in such patients was evident.

The third patient is an example of a complex situation which occurred early in our study of the bolus effect. She is tabulated under technically unsatisfactory (TU) bolus because of lack of satisfactory control; and under EEG with ECS for reasons which will be more apparent in the case history.

Case 35. The patient was a 20-year-old woman who was hospitalized at Bellevue Hospital in psychiatry for three months because of mental illness. She had been receiving chlorpromazine, trifluoperazine, trihexphenidyl (Artane) and ethchlorvynol (Placidil) and other drugs. She was found cerebrally unresponsive with no spontaneous respirations at 9:00 a.m. on 11/15/71. First neurological examination 1½ hours later also showed total areflexia with fixed, equally dilated (5 mm) pupils. EEG at 11:45 a.m. revealed unequivocal ECS. Toxicology reports revealed large amounts of ethchlorvynol in the serum.

The second examination at 1:00 p.m. on 11/15/71 was unchanged except for presence of muscle tone in the lower extremities. Her pupils were now 7 mm, dilated, equal and unreactive. The next day, after six to eight hours of dialysis, at 10:00 a.m., the EEG showed cerebral activity in the form of suppression bursts. The neurological examination was unchanged except that the pupils were now 4 mm, equal and fixed. Subsequent neurological examinations on 11/17/71 revealed return of pupillary reflexes and EEGs showed increasing cyclic suppression bursts with gradual improvement.

However, on the next day the patient had episodes of congestive heart failure and transient cardiac arrest, and although she still had EEG activity in the form of suppression bursts at 10:30 a.m. on 11/19/71 pupillary response vanished. After the EEG, she went into shock, was totally unresponsive, and was being maintained on pressor agents. Portable radioisotopic study was performed in the afternoon of 11/19/71 and showed no bolus although a control was not yet in use at this time. The patient died at 4:45 a.m. on 11/20/71 from irreversible cardiac arrest. Autopsy was performed but the brain was not examined.

In this patient with initial ECS, minimal recovery followed multiple periods of dialysis. EEG activity returned as did pupillary reflexes but intervening cardiac arrest and congestive heart failure with shock caused her death. Portable radioisotope study showing no head bolus was performed hours after the last EEG which indicated suppression bursts. Further, since there were no controls, she was placed in the category of EEG with ECS (first record) and TU bolus (no control) in table 3. Although the bolus study was done terminally, one may assume the EEG again became
ECS; the potential reversibility of the earlier clinical EEG state related to toxicity is also illustrated in this patient.

The fourth case to be presented may give some insight into the problem of the "intermediate" flow study.

Case 173. The patient was a 26-year-old man who entered Bellevue Hospital because of head and neck trauma and bizarre behavior on 4/28/73. He subsequently developed cardiorespiratory arrest and burr holes were performed. No evidence of subdural or epidural hematoma was found. Patient was admitted into the study on 4/29/73 at 11:40 a.m. in unresponsive coma and apnea with a blood pressure of 90/50 and a temperature of 92.2°F. His pupils were fixed and dilated and he had no cephalic reflexes. EEG at that time revealed ECS. Portable radioisotope study at 1:40 p.m. showed no cerebral bolus. Repeat radioisotope study at 4:50 p.m. on the next day showed "intermediate" flow but no clear bolus (similar to that of patient illustrated in fig. 10 right). The patient then had four vessel angiography which showed no intracranial filling from any vessel.

Repeat EEGs on 5/1/73 showed ECS and repeat radioisotope study on that same day continued to show "intermediate" flow. Patient did not change significantly until time of spontaneous, irreversible cardiac arrest at 10:00 a.m. on 5/4/73. At autopsy, gross examination revealed the primary problem to be related to a massive intracranial hemorrhage secondary to a ruptured aneurysm.

This patient illustrates that the "intermediate" flow group is probably also related to cerebral death, although we are conservatively considering the cerebrum in these cases as potentially "alive" until further data are accumulated (see addendum).

Because of the significance of the "intermediate" bolus, one further case will be presented in which such a flow tracing was obtained.

Case 114. The patient was a 37-year-old man who entered Bellevue Hospital on 8/10/72 because of an intracranial hemorrhage. He was a known chronic user of amphetamines and barbiturates. On the day he was admitted, he was cerebrally unresponsive and apneic at 1:25 p.m. He was accepted into the study after the first neurological examination was performed at 4:30 p.m. which confirmed the above findings and revealed complete absence of spontaneous response or reflexes. There was no papilledema. EEG performed at the same time was only moderately abnormal showing activity which was in marked discrepancy to his clinical picture. Portable radioisotope studies with control at 4:45 showed a bolus.

Second neurological examination at 10:25 on 8/11/72 was unchanged except that there was hyperreflexia in all four extremities and both lower limbs withdrew to painful stimuli. EEG performed at this time revealed unequivocal ECS with some muscle artifact. EEG performed at 12:10 p.m. with adequate control revealed an "intermediate" response. The findings on this patient are illustrated in figures 10 and 11.

Third neurological examination at 3:15 p.m. on 8/11/72 revealed the disappearance of the hyperreflexia and lower extremity withdrawal and subsequent portable radioisotope studies continued to show an "intermediate" tracing. The EEG now revealed unequivocal ECS without muscle artifact.

Patient died because of irreversible cardiac arrest at 11:25 p.m. on 8/12/72. Autopsy, including the brain, revealed an initial hemorrhage in the upper brain stem which became massive and extended into the entire ventricular system.

This last case report suggests that the initial insult in the region of the mid-brain caused the clinical picture as described, including the presence of sufficient CBF for a bolus to be noted, and was compatible with significant EEG activity. The subsequent massive extension of the hemorrhage (and probable increased intracranial pressure) may be assumed to be related to the disappearance of the bolus and EEG activity. Further comments on the "intermediate" tracing will be presented in the discussion.

Discussion

Comments on Results and Goals

The primary goal of this study was to develop an additional, simple, innocuous bedside test that could be used to detect the cerebral circulatory deficit associated with cerebral death. The existence of nonportable qualitative and quantitative techniques has been well documented but they are limited in their practical use as an adjunct in making the diagnosis of cerebral death.2-4, 26-44 The foremost considerations in the development of this technique were safety, simplicity and mobility, and included the concept that the test did not necessarily have to be quantitative, but that it should reflect the significant component of cerebral circulation which was compatible with a living cerebrum; if an error occurred, it was our basic tenet that the sequence of clinical and laboratory events would be judged so that the error would always be made on the side of misdiagnosing a "dead" cerebrum as "alive." The purpose of this principle was to remove any statistical ambiguities and replace them by clinical judgment.1, 26 Thus, any ambiguous result would be considered presumptive evidence of life until the ambiguity was clarified over time or otherwise resolved, e.g., during this aspect of the bolus study the "intermediate" tracing was considered as possibly reflecting some significant cerebral circulation.

The possibility of the presence of cerebral circulation in specific cases of cerebral death as measured by the bolus technique does not diminish the value of the study since the error is in the category of considering a "dead" cerebrum "alive." The probability that a bolus would be present in those comatose, apneic patients who met criteria and had an EEG with ECS related to drug toxicity or other reversible etiologies has yet to be proven but would also increase the value of this test in the adjunct of cerebral death (see addendum). Further, we did not consider that aspect of this technique which did not detect blood flow through the structures of the posterior fossa a disadvantage. Thus, a distinction was made between the cerebral hemispheres in contrast to the brain stem and cerebellum. The terminology of brain death, which
includes the contents of the posterior fossa, and cerebral death, which refers to the supratentorial structures only, is therefore strictly defined\cite{26} and is used in this sense in the bolus study. These definitions have further pragmatic use since we have had experience with patients in whom cerebral death was diagnosed according to previous criteria along with ECS in the EEG and when resuscitative procedures were discontinued, spontaneous respirations resumed after approximately five minutes and persisted for as long as eight hours. Postmortem examination of the brain of one such patient revealed pathological findings in the cerebrum indicative of cerebral death, i.e., "respirator brain,"\cite{23} but microscopic examination of the brain stem uncovered islands of potentially viable neurons. We believe it important for the clinician to be aware of this possibility although its occurrence is rare. Some investigators consider only total brain death as significant and others consider destruction of the brain stem alone as the significant finding in cerebral death.\cite{2, 5, 6, 10, 75} Although the results of this study do not include a large enough population for the high level of statistical significance desired (i.e., there are 37 patients with adequate control studies and no bolus (type II) and four patients with "intermediate" tracing; see table 3), it is noteworthy that thus far no patient who had a head bolus had an EEG with ECS; and in contrast no patient with an absent head bolus or "intermediate" tracing had EEG activity (table 3).

Theoretical Considerations

The limitations of measuring CBF by means of external detection of an IV injected radioisotope has been previously considered and is stressed in the literature.\cite{3, 15, 22} Major problems have been encountered in distinguishing cerebral from extracerebral blood flow using multiple small probes. Furthermore, marked differences of regional circulation, of the grey and white matter for example, have been well documented.\cite{14, 27, 43, 46} These and other factors have led various investigators to conclude that absence of intracranial blood flow only as demonstrated by four vessel angiography is the sine qua non of cerebral (brain) death.\cite{2, 6}

The results of the present study, in using the bolus technique as a qualitative indicator of cerebral circulatory deficit, suggest that under the special circumstances of arrested CBF the extracranial circulation does not pose a significant problem. The reason for this apparent discrepancy with the results of previous investigators may be clarified if one considers that the head flow tracings represent the passage of the radioisotope bolus through two fundamentally different kinds of circulation. First, the cerebral circulation involves a rapid transit of a large amount of blood through a relatively small vascular reservoir. It has been calculated that the CBF normally is about 750 cc/min\cite{47-49} and passes through a blood pool reservoir of about 130 cc.\cite{18} This very rapid transit through the relatively small cerebral blood reservoir causes a distinct registering of the arrival and departure of an intravenously injected bolus which remains reasonably coherent after emergence from the left ventricle. The appearance of such a tracing is essentially comparable to that which might be obtained over any large artery, for example, the femoral. Such a clear bolus effect appears to be absent in the dispersed peripheral type of extracerebral circulation. In contrast, in this second type of circulation, the extracerebral blood flow involves a relatively small amount of blood with a very slow transit through a larger vascular reservoir in the scalp and skull.\cite{47} This may be further illustrated by the studies of Ueda et al.\cite{50} and Obrist et al.\cite{27, 51, 52} In figure 15 the differences in the clearance curves of the internal and the external carotid artery injections of radioisotope illustrate the

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{figure15.png}
\caption{Clearance curves of tracer injection of $^{85}$Kr directly into the common internal and external carotid arteries illustrating the partition of flow compartments of gray matter, white matter and extracerebral circulation. Courtesy of Ueda et al.\cite{50}}
\end{figure}

\textit{Circulation, Volume 51, May 1975}
slow extracerebral flow in contrast to the more rapid flow through cerebral circulation. The cerebral circulation in turn may be separated into two compartments but both appear to be more rapid than the extracerebral component. The model developed by Obrist et al. (fig. 16, table 5) which considers a three compartment analysis of extracerebral and cerebral grey and white matter confirms the major difference between the cerebral and extracerebral circulation. In the situation of arrested cerebral circulation, such as may be found in cases of cerebral death, the differences between white and grey matter are no longer significant and the resultant flow tracing represents only extracerebral circulation, i.e., type II tracing. To further test this hypothesis a bolus study was performed with one probe over the femoral artery and another over the foot (fig. 17). The results confirm the similarity in the rapid transit of blood through a large artery, the femoral, which may be compared to the usual transit of CBF (which is not critically diminished). In contrast, the peripheral blood flow through the foot is similar to that of the extracerebral structures when the blood flow through the cerebrum is absent or critically impaired. In studies performed by Hass and coworkers (unpublished data, 1973) the level of transition from bolus to no bolus tracing would appear to be significantly below 24% of normal CBF (table 6). The transition may be sudden or more gradual with the appearance of the “intermediate” effect reflecting some residual intracranial CBF; more often, however, the intermediate effect appears to be related to extracerebral circulation (see addendum). Further studies are required to identify the nature of

**Table 5**

*Cerebral and Extracerebral Circulation (Adapted from Obrist et al.)*

<table>
<thead>
<tr>
<th>Series</th>
<th>Method 133Xe clearance</th>
<th>Gray fast cerebral component (ml/100 g/min)</th>
<th>White slow cerebral component (ml/100 g/min)</th>
<th>Mean CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingvar et al. (1965)</td>
<td>Internal carotid injection</td>
<td>80</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>Obrist et al. (1967)</td>
<td>Inhalation, 3-compartment analysis</td>
<td>75</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Veall &amp; Mallett (1966)</td>
<td>Inhalation, 2-compartment analysis</td>
<td>53</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>Obrist et al. (1967)</td>
<td>Inhalation, 2-compartment analysis</td>
<td>52</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

Extracerebral blood flow on this basis approximately 25cc/100g/min derived from mean CBF values above (maximal).
the transition as blood flow decreases although evidence thus far suggests that the transition is in the form of a large step function.

Unresolved Problems

Several specific unresolved problems in using the bolus technique require further research. First, validation and correlation of the results of the bolus technique by use of four vessel angiography is required to insure that appropriate interpretation of the absent bolus and the "intermediate" response are valid. Such studies are currently being undertaken (see addendum). In addition patients in several categories must be further studied to evaluate the nature of the bolus response. These include circumstances in which the patient meets all criteria including ECS on their EEGs but are in a reversible condition which may occur in drug intoxication. We would presume that in these situations a head bolus would be present. Another more complex variant would be in a situation where the patient met all criteria including ECS in the EEG and in fact was cerebrally dead because of an intoxicant, and/or anoxia which apparently only destroyed neurons (pathologically verified) and left the cerebral vasculature intact thus resulting in the presence of a bolus. In such a case the patient would be erroneously considered as having a "living" cerebrum. Such an error, of course, is acceptable.

Finally, there are a series of patients in "chronic comas" variously termed "coma vigil," "akinetic mutism," "apallic syndrome" and "persistent vegetative state." Although these patients often have intact respirations, present cephalic reflexes and some measure of responsivity, it has been observed that they may have ECS on EEG. These patients also have markedly reduced CBF and therefore such patients should be studied to determine whether this technique may differentiate them from those patients in which the total cerebrum is irreversibly destroyed. The clinical picture in these patients, however, includes spontaneous movement and respirations and is thus distinguishable. The problem in infants and children must be considered separately since the immature brain has been demonstrated to have greater resistance to CBF and CMRO₂ deprivation and conclusions drawn from studies on adults cannot be applied simply to children and infants.

Conclusions

It is suggested from the results of these studies and on reviewing the literature that "cerebral death" can be reliably and rapidly diagnosed. The first requirement is a combination of clinical criteria including unresponsive coma, apnea and absence of cephalic reflexes, especially unreactive dilated pupils. The second significant ancillary test would be the electroencephalogram which should show ECS at maximal interelectrode distances and amplification. The third most applicable test would be a bedside procedure reliably demonstrating significant deficit of cerebral circulation i.e., absence of a head bolus using the technique described. If these studies are repeated and remain unchanged along with the clinical findings for an appropriate period, e.g. less than three hours, the patient's cerebrum could be considered to be in an irreversible state regardless of etiology, including intoxicants and hypothermia. This conclusion is dependent upon further verification of the significance of the bolus technique as validated by four vessel angiography. Since the application of these principles may have conceivable exceptions in patients in a persistant vegetative state or in infants, clinical judgement must always be used as the final arbiter and one may choose a longer period of observation and testing prior to making the diagnosis of cerebral death.

Addendum

Since the completion of this paper nine additional patients have been studied.* In eight, who were comatose, apneic and had EEGs with ECS and no head bolus, femoral-carotid angiography revealed no intracranial filling of significance. The ninth patient had a TU EEG but otherwise met criteria and bolus study revealed

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"intermediate" response. Four vessel angiography revealed filling of one carotid artery but the flow never reached the venous system; rather it coursed through the internal carotid to the anterior cerebral artery, through the anterior communicating into the opposite anterior cerebral artery and left the cranial cavity via the opposite internal carotid. This was the first demonstrative case in which the "intermediate" response appeared to be related to partial flow through the cerebrum rather than due to extracerebral circulation. All these patients died from irreversible cardiac arrest. An additional patient has been described elsewhere in whom the EEG showed ECS and the radioisotope study was done simultaneously and revealed cerebral blood flow. There was subsequent return of EEG activity although the patient ultimately died.19

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