CHAPTER

Brain Death

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GUIDELINES FOR THE DETERMINATION OF BRAIN DEATH

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SUMMARY AND CONCLUSIONS
Physicians are often asked to make a medical determination of death. In-hospital death requires pronouncement by a physician and, most frequently, occurs as a result of cardiorespiratory failure. It is only relatively recently with the advent of cardiorespiratory support that the determination of brain death has become necessary. In patients not supported by a respirator, failure of the central nervous system invariably leads to failure of the medullary respiratory center, with subsequent respiratory arrest and progressive hypoxia followed by cardiac arrest. In patients who are supported by artificial respiration, progression to brain death is not followed by respiratory and cardiac arrest, and therefore, a determination of brain death is necessary. Many patients, however, who have respiratory support when brain function ceases, if allowed to follow their natural course, will progress to cardiovascular collapse. This is due to the loss of sympathetic activity and the subsequent loss of vasomotor tone and neurohypophyseal failure, which results in massive diabetes insipidus and electrolyte disturbance and ultimately leads to cardiac arrest. In such patients, however, a considerable time may elapse between the cessation of all brain functions and cardiovascular collapse due to its consequences. In this situation, a physician is often required to make the diagnosis of brain death, which has become medically and legally accepted as a criteria for death.¹

The President's Commission for the Study of Ethical Problems in Medicine has established a definition of death that states that an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain including the brain stem is dead. The determination of death must be made in accordance with accepted medical standards.² The need to make the determination of brain death arises when either the interval between cessation of brain function and cardiovascular collapse is prolonged or organ donation for transplant purposes is being considered. It is necessary to make the determination of brain death for several reasons. First, it is important to the patient's family members to be informed of the occurrence of brain death and not to have the family undergo a prolonged interval between the patient's brain death and cessation of cardiovascular function. The time of pronouncement of brain death is recorded in the medical records as the actual time of death despite the fact that cessation of cardiac function has not occurred. Second, in order to expedite the processing of the remains of the patient in addition to allowing the family to proceed with funeral arrangements, it is advisable to make a prompt diagnosis of brain death once it has occurred and then discontinue respiratory support. Third, when organ donation is not planned, it is advisable not to delay the diagnosis of brain death so that hospital staff will not continue to provide cardiorespiratory and other support after the diagnosis is clear. Finally, in cases of organ donation, the unequivocal diagnosis of brain death must be established before organ removal is undertaken. In this situation, however, careful attention must be paid to maintaining adequate cardiac and respiratory function for the optimal preservation of organ function.
GUIDELINES FOR THE DETERMINATION OF BRAIN DEATH

After the development of respiratory support, the need for determination of brain death became obvious. One of the first comprehensive attempts to establish uniform criteria was published in 1968 after the formation and report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. Before this report, there were individual reports on the utility of EEG in helping to make the diagnosis of brain death, but there was no uniformly accepted criteria. Similarly, reports from other countries began to surface to try to establish uniformly accepted guidelines. By 1978, more than thirty sets of criteria for the determination of brain death had been published. Although these were in agreement on many aspects, there was no uniform consensus on the involvement of EEG and other ancillary tests, the specific clinical criteria to be included, and the timing. In 1981, the guidelines for the determination of death were published by the President's Commission in an attempt to provide a more up-to-date consensus of leading physicians studying this problem. The report of the President's Commission is intended to provide guidelines and emphasizes that these guidelines are only advisory. The guidelines are illustrated in Fig. 11-1.

The guidelines provided by the President's Commission are designed to assist qualified physicians in making the determination of brain death. Most states allow considerable leeway in allowing the physician to make the determination of death and only require that a qualified physician make this determination. Professional organizations have also aided by setting forth criteria. The American Medical Association by its judicial counsel has stated that “deaths shall be determined by the clinical judgment of the physician. In making this judgment the ethical physician will use all available currently accepted scientific tests.” There are many legal precedents now recognizing the diagnosis of brain death as a determination of death in many states. The American Bar Association has passed a resolution that recognizes that the physician should be allowed to decide the adequate criteria for death by prevailing standards, and the resolution also makes clear that brain death is a legal as well as medical entity and should fulfill the criteria for death. The resolution states “For all legal purposes, a human body with irreversible cessation of brain function according to usual and customary standards of medical practice shall be considered dead.”

HISTORY AND CLINICAL EXAMINATION

It is essential to obtain an adequate history of events in patients who are being evaluated for brain death. A clear history of injury or sudden ictal event that is consistent with conditions known to cause massive brain destruction
Figure 11-1 Guidelines for the determination of death as established by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. This set of guidelines was compiled after an extensive study of brain death and has been forth as a guide for practicing physicians to make the determination of brain death.

is helpful in establishing a working diagnosis. If there is a history of drug ingestion or hypothermia and no evidence of brain destruction on CT scanning, the physician must be more circumspect in reaching the diagnosis of brain death and must ensure that irreversibility is present. Equally important are the results of imaging studies, particularly CT, which has had a major
is recognized when findings of a and b combine to establish brain death in patients who meet the criteria for diagnosis. The absence of brain stem function confirms death.

Figure 11-1 (Continued)

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impact in allowing an accurate diagnosis to be made in cases of brain death. The CT scan often reveals many important details about the structural pathology in the brain that led to extensive brain destruction. Many cases of brain death will be the result of trauma, gunshot wounds, or spontaneous intracerebral hemorrhage from aneurysms or other causes, and these conditions are accurately revealed by CT scanning. The physician can proceed with the diagnosis of brain death more confidently when there is CT evidence of massive brain destruction.

The clinical examination for brain death should be performed by experi-
enced physicians who are thoroughly familiar with the complete neurologic examination and also with the accepted criteria established for the determination of brain death. The testing should also be performed when the core body temperature is greater than 32.2°C. It should be established that reversible causes of coma, such as alcohol, barbiturate, or other sedative toxicity, are not present. Neuromuscular blockade or other causes of peripheral nerve dysfunction must also be eliminated. The President’s Commission advises that the determination of death must be recognized by the cessation of function as well as by irreversibility. Brain death is recognized when the irreversible cessation of all the functions of the entire brain including the brain stem is determined. Cessation of brain function is recognized when the cerebral functions and the brain stem functions are both absent. To determine the absence of cerebral function, there must be deep coma, unreceptiveness, and unresponsiveness. Absence of brain stem function is recognized when cranial nerve function and respiratory drive are both absent. When certain cranial nerves cannot be tested because of injury or other factors, it is recommended that confirmatory tests be undertaken. Testing of the cranial nerves includes testing of the pupillary light reflexes, corneal reflex, oculocephalic or oculovestibular reflexes and gag reflexes. In addition to these nerve tests, apnea testing should also be performed. Performance of these tests is discussed in the following sections.

**Pupillary Light Reflexes**

To perform this examination, the physician should dim the lights, direct a bright flashlight toward each pupil, and then observe both pupils. The ipsilateral pupil is observed for the direct response, and the contralateral pupil is observed for the consensual response. The process should be repeated on the opposite side. Drugs that can produce pupillary dilatation include scopolamine, atropine, and glutethimide.

**Corneal Reflexes**

Corneal reflexes are tested by applying a wisp of cotton to the cornea on each side while observing for contraction of the orbicularis oculi muscles. No contact lenses must be present during this examination.

**Oculocephalic Reflexes**

The oculocephalic reflexes are tested by forceful turning of the head from a neutral position to 60° off midline to each side while observing the alignment of the eyes. Any deviation of the eyes toward midline with this maneuver indicates the presence of the oculocephalic reflex.
Oculovestibular Reflexes

The oculovestibular reflex can be tested by elevating the head 30° above horizontal and instilling a solution of ice water in the ear with a syringe while the eyelids are held open for 30 s to 1 min to observe any tonic deviation of the eyes, which should be turned toward the cold stimulus in an unconscious patient. The process is then repeated on the opposite side after a waiting period of several minutes.

Gag Reflex

Oropharyngeal reflexes are tested by stimulating the oropharynx with a cotton swab while observing for any gag reflex or oropharyngeal contractions.

Apnea Test

When the testing of the cranial nerves is complete, apnea testing should then be undertaken. The objective of the apnea test is to allow the carbon dioxide level to increase to the point where the respiratory center should be maximally stimulated if it is still functional. When performing this test, adequate oxygenation must be provided, and therefore, an accepted method is to preoxygenate with 100 percent oxygen before beginning the test. Usually a 10-min period of apnea is sufficient to attain a $\text{Pa}_\text{CO}_2$ greater than 60 mmHg, which should stimulate the respiratory center. During this time oxygen is administered at 6 to 12 liters/min through an intratracheal catheter. It is usual to obtain blood gas confirmation of $\text{Pa}_\text{CO}_2$ during the test. If the patient breathes during the apnea test, this indicates that the brain stem is still functioning. If the patient's history suggests chronic lung disease with dependence on a hypoxic stimulus for ventilation, then the $\text{Pa}_\text{O}_2$ should be allowed to fall to less than 50 mmHg. It has been noted during testing in some patients that peripheral movements may occur that may indicate reflex activity but are still consistent with cerebral unresponsiveness. The "Lazarus sign" has been described in patients undergoing apnea testing, which consists of vigorous flexion of the arms to the chest either unilaterally or bilaterally in brain-dead patients. Elicitation of movements of the arms by neck flexion as well as lower extremity flexor responses to stimulation have also been noted but do not invalidate the diagnosis of brain death.

PERFORMANCE OF ANCILLARY TESTS

One of the earliest ancillary tests to be used in the diagnosis of brain death was the electroencephalogram. Some of the first reports of brain death included an EEG as one of the criteria. Subsequent to numerous reports,
however, it is recognized that an EEG can sometimes be difficult to perform in the setting of a ventilated patient in the intensive care unit because of the multiple artifacts that can occur. It has also been recognized that there have been false positive and false negative EEG findings in cases of brain death.\textsuperscript{12-15} It has subsequently been relegated by both the President’s Commission and also by other criteria to an ancillary test rather than a primary requirement for the establishment of the diagnosis of brain death.\textsuperscript{2,6}

The other major category of ancillary tests is cerebral blood flow studies. The gold standard for cerebral blood flow studies to determine the arrest of the cerebral circulation is four-vessel cerebral angiography.\textsuperscript{1,16,17} This procedure has been commonly used in Europe, and the criteria for nonfilling of the intracranial circulation are well defined. Because this test is invasive and time consuming, other methods of cerebral blood flow determination have also been utilized in the determination of brain death. Radioisotope scanning using technetium 99 has been used, and the results of this technique have compared favorably with cerebral angiography.\textsuperscript{17-20} This technique has the advantage of using portable equipment that can be brought to the intensive care unit. The study is relatively rapidly and easily performed, and criteria have been established for the interpretation of intracranial flow cessation to confirm the diagnosis of brain death (see Fig. 11-2). Transcranial Doppler has also emerged as a useful technique for determining the arrest of the cerebral circulation.\textsuperscript{16,19,21-26} Initially, before the development of transcranial Doppler, characteristic waveforms of the velocity tracing were demonstrated by carotid Doppler\textsuperscript{27} in patients with cerebral circulatory arrest. Subsequently,

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{radioisotope_scan}
\caption{Radioisotope scan demonstrating lack of intracerebral blood flow and preservation of blood flow in the face and scalp.}
\end{figure}
Figure 11-3 Example of reverberating blood flow velocity tracing in the middle cerebral artery using transcranial Doppler. This characteristic waveform correlates with arrest of the cerebral circulation due to obstruction of flow at the microcirculatory level with continued patency of the conducting arteries.

similar waveforms have been described using the transcranial Doppler. Reverberating flow velocity patterns found in the middle cerebral arteries have been correlated with radioisotope scanning as well as cerebral angiography in demonstrating a lack of supratentorial cerebral blood flow. An advantage of the transcranial Doppler technique is its portability and the short time required for testing. As with all techniques, however, the results must be interpreted by experienced examiners, and under these circumstances, arrest of the cerebral circulation can be reliably documented.

All the ancillary testing methods that measure cerebral blood flow have been useful in confirming the diagnosis of brain death in suspicious circumstances or under circumstances where examination of the cranial nerves is made difficult. It must be emphasized, however, that although cerebral blood flow studies in most patients confirm brain death, some cases have been reported where confirmatory tests are at variance with the clinical findings of brain death. In such instances, the findings may be due to selective massive destruction of the brain stem from brain stem hemorrhage or posterior fossa lesions that render the patient clinically brain dead by causing impairment of all the cranial nerves and the respiratory center as well as interruption of all descending pathways. However, the supratentorial blood flow may be left
intact, and therefore, because the cortical activity can persist, the EEG may not be flat.\textsuperscript{26} Such patients may demonstrate residual blood flow by any of the methods of testing. Similarly, patients have been reported in which supratentorial blood flow has ceased, yet the patient still demonstrates weak brain stem activity, such as slight residual respiratory drive.\textsuperscript{19} In these instances, the supratentorial structures have been destroyed, but minor residual blood flow to the brain stem probably is present, which accounts for the continued minimal function. These cases, given sufficient time, will all ultimately result in brain death, but at the time of testing, arrest of the cerebral circulation and clinical brain death are not always synonymous. With these caveats in mind, the confirmatory tests can be used intelligently in suspect cases to confirm the diagnosis of brain death or shorten the observation time required to determine irreversibility.\textsuperscript{2}

**MANAGEMENT OF BRAIN-DEAD PATIENTS FOR ORGAN RETRIEVAL**

Once the diagnosis of brain death has been established, the time of this diagnosis can be legally recorded as the time of death, and all support may be discontinued. In cases which qualify for organ donation, however, a significant time may elapse between declaration of brain death and the harvest of organs. As mentioned previously, after cessation of all brain and brain stem functions, failure of the sympathetic tone and the neuroendocrine axis often lead to systemic instability and cardiac arrhythmia followed by cardiac arrest. When the objective is to preserve the central organ functions, such as the heart, kidneys, and lungs for transplant purposes, physiologic function must be maintained. Some of the normal sequelae of cessation of brain function include hypotension, arrhythmia, bradycardia, hypoxemia, diabetes insipidus, hypothermia, anemia, and infection.\textsuperscript{28} It is necessary to develop a management strategy to preserve organ function when this cascade begins to occur. Hypotension will often ensue suddenly following brain death, and this is usually due to neurogenic shock from failure of sympathetic tone and may be aggravated by hypovolemia from diabetes insipidus. If hypotension is due mainly to neurogenic shock, clinically the patients are usually not tachycardic; they have either a normal pulse rate or bradycardia, and the extremities are usually warm. This is in contrast to hypovolemic shock where peripheral vasoconstriction is present, generally accompanied by tachycardia.

**TREATMENT STRATEGIES FOR THE SEQUELAE OF BRAIN DEATH**

**Hypotension**

Central monitoring, such as central venous pressure monitoring or pulmonary artery pressure monitoring, is helpful in guiding hemodynamic management. The initial strategy is to ensure that intravascular volume is adequate and
the EEG may flow by any indicated weak in these in which residual functions for the will ultimately. With these in suspect observation time after this, ionotropic agents can be used. Dopamine or dobutamine can be used initially followed by epinephrine or norepinephrine infusions. When using these agents the physician should have some knowledge of the total peripheral resistance and not be overly vigorous to the point where end organ damage occurs. Intravascular volume expansion can be accomplished with isotonic fluids (normal saline or lactated Ringers solution) in bolus infusions. A reasonable objective is to keep the mean arterial pressure greater than 70 mmHg.

Cardiac Arrhythmias

Electrolyte disturbances can be responsible for arrhythmias, and therefore, should be checked regularly. Bradycardia can be treated with atropine, and in refractory cases, transvenous pacing can be used.

Pneumonia and Hypoxemia

In patients who have been under intensive care for a prolonged period, pneumonia may ensue the onset of hypoxemia. Patients must then be treated with appropriate antibiotics, and adequate oxygenation must be maintained to prevent organ damage.

Diabetes Insipidus

This condition is usually due to neuroendocrine dysfunction secondary to interruption of the hypothalamic pituitary axis and can result in sudden large increases in urine output. Treatment consists of volume replacement and administration of vasopressin, 0.1 unit/min infusion or DDAVP, 0.3 μg/kg intravenously, to maintain a urine output of 1.5 to 3 ml/kg per hour. The electrolytes must also be checked frequently.

Hypothermia

Hypothermia can rapidly ensue after central nervous system failure, and if the central temperature drops too low, the coagulation system may fail. Therefore, the patient's temperature should be maintained at a level greater than 34°C with warming blankets.

Severe Anemia

In patients with multiple injuries or disseminated intravascular coagulation, severe anemia can occur and compromise organ function. As mentioned previously, maintenance of body temperatures is important and a transfusion
may be necessary in order to maintain an adequate intravascular volume and keep the hematocrit above 30 percent.

**SUMMARY AND CONCLUSIONS**

Since the advent of artificial respiration it has become necessary for physicians to make the determination of brain death. Brain death is recognized both medically and legally as being synonymous with death of the patient. The accurate determination of brain death must be made to allow discontinuation of respiratory and cardiovascular support and also to serve as a prerequisite to organ donation for transplant purposes. Many organizations have attempted to reach a consensus on the criteria for determination of brain death. The most comprehensive set of guidelines has been established by the President's Commission, which was formed to establish specific guidelines for the determination of brain death. These guidelines not only state that the irreversible cessation of brain function including the brain stem is synonymous with brain death, but they also set forth the criteria for determining the absence of function as well as irreversibility. Under these guidelines also, clinical criteria are the main determinants of brain death, and EEG and cerebral blood flow studies are considered confirmatory tests. If continued cardiovascular support is necessary for organ donation in patients who have been declared dead, a recognized set of complications and physiologic events are described. The proper recognition and treatment of these physiologic responses will usually result in adequate organ function at the time of removal for transplantation.

**REFERENCES**

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