

# Current issues in the diagnosis of brain stem death

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## Introduction

The concepts of brain stem death (BSD) and brain death (BD) are not universally accepted. However, many countries do accept these diagnoses although the mechanisms for making the diagnosis vary. Given that the diagnosis of death has such profound implications for the patient, this should be cause for grave concern within the medical profession. In this article, I analyse areas of conflict and, more importantly, identify areas of agreement.

## Medical definitions of death

Defining death can be difficult because of differing concepts based on context; namely religious, cultural, legal or scientific. For BSD, the context is scientific. Defining death as the biological event that marks the transition from being alive to being dead is hard to argue against but is unhelpful because it does not provide criteria that describe what is meant by being alive or being dead. Other definitions have been suggested. Most are similar to 'the permanent cessation of the critical functions of the organism as whole' (1). In the United Kingdom (UK), BSD is defined as irreversible loss of consciousness, irreversible loss of the capacity to breathe and irreversible loss of integrated functioning (2). The UK definition has merit because it permits criteria to be derived that are not only explicit but also testable. The inclusion of irreversible loss of integrated functioning implies death of the organism as a whole, not the whole organism. It is important to recognise that currently, whatever criteria and tests are chosen, we are only able to diagnose the state of being dead, not the event of death.

Worldwide, two distinct mechanisms of death are recognised; namely irreversible cardiopulmonary arrest and BSD (or BD). Scientifically, this distinction is artificial. Cardiopulmonary arrest only causes inevitable death if the brain stem is irreparably damaged due to lack of perfusion with oxygenated blood. Thus, the key feature of both mechanisms is irreparable brain damage. The two mechanisms differ only because death is diagnosed in the presence or absence of a beating heart.

Unfortunately, the general public normally associates death with cardiac standstill. This is an emotive issue and is most easily discussed in the context of heart-lung transplantation

patients receiving extracorporeal membrane oxygenator support. These patients are alive despite the fact that the diseased heart and lungs have been removed. Their brains are capable of integrated function and the patient would be fully conscious were it not for the fact that anaesthesia is administered. Many relatives find brain death easier to accept if it is explained that although the brain relies on the heart to circulate oxygenated blood, this function can be replicated by machines. In contrast brain function cannot be artificially replaced and the heart always stops within days or weeks of the brain stem dying (3). By diagnosing BSD, we have not changed the nature of death. We have, however, improved our diagnostic skills and moved the time that we diagnose the state of being dead closer to the time when death actually occurred.

## Brain anatomy and function

Brain function is complex. A simplistic representation is shown in Figure 1 which is based on standard texts of neuroanatomy and physiology (4, 5). Respiratory and cardiovascular activity is determined by a variety of brain structures. However, the most important control centres reside in the brain stem. The anatomical pathways facilitating consciousness are less well understood. There is a body of evidence (4, 5) suggesting that awareness depends on neuronal integrity in the reticular activating system (RAS) which resides in the core of the brain stem. Coma only occurs if there is disruption at or below the level where the RAS splits to form complex neuronal networks that flow to, from and between the cerebral hemispheres. Anatomically, this occurs at the level of the tentorium cerebelli, a fibrous inflexible structure that divides the cranial vault into anterior and posterior fossae. Trans-tentorial herniation (also known as coning), and the resulting compression of key structures causes coma and a variety of other clinical signs (4). This means that the presence or absence of small groups of living cells in the cortex is irrelevant to a diagnosis of death that relies on irreversible coma as a diagnostic criterion.

The event that precipitates BSD or BD is catastrophic and causes either, direct brain stem injury or cerebral swelling, trans-tentorial herniation and irreversible mechanical damage to brain stem structures. Direct damage to brain cells is important but there is another pathological change that is equally important. The brain stem is supplied by small, short

	Consciousness	Breathing	Cardiovascular integrity	Cranial nerve nuclei
<b>CORTEX</b>	↑ ↑ ↑			
<b>DIENCEPHALON</b>	↔ ↔ ↑ Thalamus ↑ Hypothalamus ↑ Midbrain raphe/Locus ceruleus	↑	↑	1, 2, 3, 4
<b>MIDBRAIN (BS)</b>				
<b>PONS (BS)</b>	↑ RAS			5, 6, 7
<b>MEDULLA (BS)</b>	↓	RAS (rhythmic breathing)	Vagus nucleus	5 (motor), 8, 9, 10, 11, 12

Figure 1. Brain anatomy and function

arteries that derive from the posterior and inferior cerebellar arteries, the superior cerebellar artery, the posterior cerebral artery and the basilar artery. The shifts that occur in association with cerebral swelling and coning certainly disrupt the small arteries and also compromise the main arterial supply. Given that the main arteries contribute to cortical blood flow, it becomes clear that coning induces severe ischaemia of the brain stem and higher structures which compounds mechanical damage. Thus the physiological distinction between death of the brain stem and death of the whole brain becomes blurred.

### Brain stem death versus brain death: International differences

The lack of a clear physiological distinction between BSD and BD is reflected in diagnostic practices. A minority of countries including the UK diagnose BSD. BD is the diagnosis made in North America, Australia and many other countries. Methods of diagnosing BSD and BD vary country by country (Table 1). Wijdicks was able to study 80 countries encompassing a broad diversity of culture and religious belief (6). Only 88% of them have national guidelines and those that do show important variations. Worldwide, the variation is probably even greater than suggested by Table 1 because Wijdicks was unable to obtain any information from another 27 countries and he notes that the United Nations lists a total 189 member states. The variations noted do not correlate with BSD or BD as the final diagnosis.

Death of the organism as a whole is a concept that has been accepted for many centuries and replaced the concept of death of the whole organism (i.e. putrefaction) which was prevalent when religious elders rather than doctors determined that death had occurred. The distinction between death of the organism as a whole and death of the whole organism may be relevant to death of cells within the brain. Within the brain, not all cells die at the same time. Consequently BSD is probably analogous to death of the brain as a whole and BD to death of the whole brain. It is important that all of us understand that whatever diagnosis we use, the criteria and tests are similar and none are capable of determining that all brain cells are dead.

The UK Code of Practice, amplified and explained by Pallis and Harley (2), lists the clinical tests that are used worldwide to diagnose both BSD and BD. The tests are relatively simple to perform but are only the last stage of a complex process that leads to the diagnosis of BSD. The greatest risk of error arises from inappropriate testing i.e. testing patients in whom coma,

apnoea and absent cranial nerve reflexes may be reversible. If the confidence of our patients and especially their relatives is to be maintained, it is vital that we complete the entire process in an exemplary fashion. In the following section, the UK process is described in detail because it is an excellent example of good practice.

### Diagnosing brain stem death in the UK

The diagnosis of BSD has three important components. These are:

- Meeting clearly defined preconditions
- Excluding patients who do not meet the preconditions
- Bedside testing of brain stem functions.

Personnel and safeguards. BSD may only be diagnosed by senior doctors who have training and experience of diagnosing BSD. The entire process is repeated twice by two doctors. Ideally, only two sets of tests are performed observed on each occasion by two doctors. However, variations are permitted. The two doctors may perform the tests independently but each doctor must be present at two sets of tests. Neither doctor should be a member of an organ procurement team.

Preconditions for performing clinical tests. Before tests are performed the patient must have a clinical diagnosis compatible with BSD, usually confirmed by imaging or at operation and the condition must have been treated appropriately. Consequently, the diagnosis of BSD takes time and is not normally made until many hours after admission to the Critical Care Unit.

The patient must be totally unresponsive and dependent on a ventilator. Total unresponsiveness includes absence of seizures and any limb movements (except spinal reflexes). Movement or seizures imply intact pathways between the periphery and the cortex and hence some brain stem activity. Similarly a cough reflex or respiratory effort, no matter how ineffectual, implies residual brain stem activity. All reversible causes of coma and ventilator dependence must be excluded. The influence of all sedative drugs and neuromuscular blockers can be excluded either by direct measurement or by allowing sufficient time before testing to permit metabolism and / or excretion. This includes drugs such as alcohol and other substances of abuse that may have been taken by the patient prior to hospital admission. Metabolic causes of coma e.g. hypernatraemia, hyponatraemia, hyperglycaemia, hypoglycaemia, metabolic acidosis, hypothyroidism and primary hypothermia must also be excluded.

Exclusions. Any patient who does not meet all the preconditions is alive and must be excluded from testing.

Bedside tests. Cranial nerves are tested bilaterally.

- Pupil response to light (II, III)
- Response to painful stimulus applied to the supraorbital nerve (V, VII)
- Corneal reflex (V, VII)
- Vestibulo-ocular reflex (III, VI, VIII)
- Gag reflex (IX, X)
- Cough reflex (X)
- Disconnect patient from the ventilator and observe for signs of respiratory effort in the presence of an arterial carbon dioxide tension of at least 50 mmHg. Prevent hypoxia by preoxygenation and insufflation of oxygen during the apnoeic period.

Attention to detail is important. For example, the caloric test has not been adequately performed if the external auditory canal is blocked by wax. The response of pupils to light must be tested in a darkened room using a bright light. The patient must be disconnected from the ventilator because cardiac contractions can trigger 'breaths' if the ventilator is set to pressure support mode.

Table 1. The diagnosis of brain death and brain stem death: Comparison of 80 countries (after Wijdicks(6))

NATIONAL PRACTICES		NUMBER OF COUNTRIES
National guidelines		70
Physicians required to make diagnosis	1	31
	2	24
	> 2	11
	Unspecified	14
Minimum observation time prior to testing in hours	2	4
	3	2
NB. Many countries specify longer times following anoxic brain injury	6	20
	12	8
	24	8
	Unspecified	38
Cranial nerve assessment		70
Apnoea testing	With PaCO <sub>2</sub> target	41
	Without PaCO <sub>2</sub> target	20
	Not required	19
	Mandatory	28
Confirmatory tests	Not required	
	or optional	52

Diagnosis. The patient is declared dead if, on two occasions there is no respiratory effort and there is total absence of cranial nerve activity. The time of death is legally deemed to be the time when the first set of tests was completed.

Supplementary tests. Clinical testing is the gold standard for assessment of brain stem function and supplementary tests of cortical / whole brain function are normally considered unnecessary in the UK. Supplementary testing, as described below, can however be helpful if extensive facial injuries or high spinal cord injury make some of the bedside tests impossible or difficult to perform.

### Diagnosing brain death

The bedside tests used for BD are similar to those used for the testing of brain stem function. In contrast to bedside tests which assess brain stem function, the supplementary tests employed in some countries are surrogate measures of cortical function. Supplementary tests such as four-vessel angiography are used to demonstrate total absence of brain perfusion. As discussed previously, BSD almost certainly leads to absent perfusion of all brain structures. Electroencephalography (EEG) measures superficial cortical activity. A silent EEG in the absence of metabolic or drug induced coma suggests cortical death but cannot confirm or deny persistent brain stem activity. Equally, electrical activity in a few cortical cells does not mean the brain as a whole is alive.

Newer supplementary tests of whole brain function include transcranial Doppler, evoked potentials, single-proton emission tomography and measurement of jugular venous oxygen saturation. Interestingly, most of these tests have been validated against the gold standard of bedside diagnosis and are not 100% specific or sensitive (7-11). They are recommended as confirmatory rather than absolute tests. Furthermore, some tests such as transcranial Doppler are not universally applicable being subject to technical problems (11).

Although supplementary tests lack sensitivity and specificity and are not uniformly required, they may yet find an important place in the management of BSD and BD. They can be used sparingly to assist relatives who have difficulty accepting the diagnosis made by bedside testing and there is some evidence that they may be useful in facilitating earlier diagnosis of BSD and hence involvement of organ procurement teams (11). Most centres lose a few, precious donated organs each year due to cardiac standstill prior to the team arriving to remove organs.

### The link between the diagnosis of brain (stem) death and organ transplantation

Depending on one's perspective, there is an unfortunate or fortunate link between the advent of BSD as a diagnosis and the development of the organ transplantation programme. BSD has undoubtedly facilitated the procurement of high quality solid organs and hence to the success of the organ transplantation programme. In Australia, BD has been described as a devious mechanism for increasing donation rates (12). In the US some instances of prolonged survival

have been reported (13) but evidence that UK criteria have been fully met is not provided. An American has argued that the diagnosis of BD is not necessary for organ donation and that those who are neurologically devastated or imminently dying should be allowed to donate their organs without being diagnosed as dead (14).

I believe that facilitation of the organ transplantation is just one reason for making the diagnosis of BSD. During a lifetime career, some of us will be unfortunate enough to care for a patient who is ventilated for up to two weeks following the diagnosis of BSD and whose heart continues to beat at a slow rate. Cardiac standstill eventually occurs but not before grieving relatives have been subjected to a prolonged period that encompasses futile hope and intense despair as they watch a loved one dying cell by cell. Loss of brain stem function is associated with more than loss of cardiovascular, respiratory and neurological function. I have personally observed multi-system failure as a consequence of BSD and as cellular function ceases the patient rots, literally. Thankfully, due to greater acceptance of BSD, this is now a rare event. However, it illustrates what could happen if public confidence in BSD testing is lost and reinforces the need for all of us to be meticulous in meeting preconditions and performing the tests.

There are alternative methods for acknowledging that death is inevitable and that active treatment is inappropriate. These are treatment limitation and treatment withdrawal; both on grounds of futility. These options rely on expert medical opinion rather than strict diagnostic criteria and are sometimes even more difficult for families to accept. Although non-heart beating organ donation is becoming more widely available, for the vast majority of families, treatment withdrawal takes away their opportunity to agree to organ donation. In the longer term, many families take comfort from the fact that the death of a loved one was not a meaningless event because after death, their relative gave the gift of life to not one, but many other people.

### Conclusion

Lack of worldwide consensus on the criteria that should be tested in order to diagnose BD /BSD is a serious problem. Our differences are perhaps not as significant as we think and should not be insurmountable.

The diagnosis of BSD / BD undoubtedly contributes to the success of organ transplantation programmes which improve

the both the quality and quantity of life for so many. It is also important for patients who are not organ donors. As critical care physicians, we have a duty to give all our patients the best chance of survival. When death occurs we have a duty to ensure that it occurs with dignity and respect for the views of the patient and his relatives. We must educate ourselves and our patients so that all of us come to share the same concept, definition and criteria for death.

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