

## Diagnosis of brain death

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### Abstract

Brain death (BD) should be understood as the ultimate clinical expression of a brain catastrophe characterized by a complete and irreversible neurological stoppage, recognized by irreversible coma, absent brainstem reflexes, and apnea. The most common pattern is manifested by an elevation of intracranial pressure to a point beyond the mean arterial pressure, and hence cerebral perfusion pressure falls and, as a result, no net cerebral blood flow is present, in due course leading to permanent cytotoxic injury of the intracranial neuronal tissue. A second mechanism is an intrinsic injury affecting the nervous tissue at a cellular level which, if extensive and unremitting, can also lead to BD. We review here the methodology of diagnosing death, based on finding any of the signs of death. The irreversible loss of cardio-circulatory and respiratory functions can cause death only when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain. The sign of such loss of brain functions, that is to say BD diagnosis, is fully reviewed.

### Introduction

Long before modern technology, everyone agreed that death occurred when heartbeat and breathing ceased, and the soul abandoned the body. Nonetheless, a new concept of death evolved as technology progressed, forcing medicine and society to redefine the ancient cardio-respiratory diagnosis to a neurocentric diagnosis of death.<sup>1,4</sup> In the meantime, the technical and scientific advances of the last century provided effective mechanical ventilators, and cardiopulmonary resuscitation ("reanimation") compelled physicians in the late 1950s to confront a condition impossible even to imagine previously, a state in which the brain is massively damaged and nonfunctional while other organs remain functioning. Was such a patient alive or dead? This radically changed the course of the debates about human death, marking a turning point when brain-oriented definitions of death started to be formulated, and brain death (BD) was gradually accepted as death of the individual.<sup>5-12</sup> However, it is commonly believed that the con-

cept of BD evolved to benefit organ transplantation. A historical approach demonstrates that both brain death and transplantation had fully separate origins. Organ transplantation became possible with technical advances in surgery and immunosuppressive treatment. The concept of BD evolved with the introduction of intensive care units.<sup>12,13</sup>

BD should be understood as the ultimate clinical expression of a brain catastrophe leading to a complete and irreversible neurological stoppage, characterized by irreversible coma, absent brainstem reflexes, and apnea.<sup>14</sup> Most authors affirm that the diagnosis of BD is just a clinical assessment, and after the Harvard Committee Report,<sup>15,16</sup> most countries and states designed their BD diagnostic criteria.<sup>6,7,17-21</sup> BD diagnosis should be carried out following a certain set of principles; that is to say, excluding major confusing factors, establishing the cause of the coma, determining irreversibility, and precisely testing brainstem reflexes at all levels of the brainstem.<sup>22</sup>

### Pathophysiology of brain death

Increased intracranial pressure (ICP) is considered the most important pathophysiological mechanism of BD leading to a complete cessation of intracranial blood flow. Upholding of oxygenation and hemodynamics by vasopressor drugs as well as mechanical ventilation can sustain somatic organs while the brain suffers an ongoing necrosis process. However, this is not the only pathophysiological mechanism of BD.<sup>1,23</sup> Palmer and Bader studied a series of brain-dead patients by brain tissue oxygenation (PbtO<sub>2</sub>) and described two pathophysiological patterns regarding cerebral blood flow (CBF).<sup>23,24</sup> The most common pattern is manifested by an elevation of ICP to a point beyond the mean arterial pressure (MAP), and hence cerebral perfusion pressure (CPP) falls to zero and, as a result, no net CBF is present, in due course leading to permanent cytotoxic injury of the intracranial neuronal tissue.

In addition, there may be circumstances where an ICP increment does not lead to CBF cessation. This may occur when ICP augmentation is compensated in infants with open fontanelles and soft, deformable skulls, and in patients whose skulls are open owing to multiple fractures, ventricular drainage, or decompressive craniectomy.<sup>25-35</sup> Moreover, diffuse intracranial parenchymal swelling is the main reason for a markedly elevated ICP, but swelling is not an indefinite phenomenon, and it may decrease progressively, and if MAP is maintained at reasonable values, CBF might ultimately return.<sup>25,28</sup>

The second pattern described by Palmer and

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Bader is characterized by preserved CBF, because normal ICP does not exceed MAP, and sufficient CPP is maintained leading to CBF preservation, which supplies the nervous tissue with necessary oxygen, glucose, and nutrients to permit its survival.<sup>24</sup> In this pattern the mechanism causing PbtO<sub>2</sub> to fall to zero is an intrinsic catastrophe affecting the nervous tissue at a cellular level which, if extensive and unremitting, can also lead to BD.<sup>23,25,36</sup> It is clear that in this pattern the lack of oxygenation of the brain is not a failure of the delivery system, and hence it stands for end organ breakdown of the brain at the capillary or tissue level.<sup>23,36</sup>

### Diagnosis of brain death

BD diagnosis should be carried out following a certain set of principles;<sup>6,21,37-46</sup> that is to say, excluding major confusing factors, establishing the cause of the coma, determining irreversibility, and precisely testing brainstem reflexes at all levels of the brainstem.<sup>47</sup> Nonetheless, most criteria for BD diagnosis do not mention that this is not the only way of diagnosing death. If a concept of death on neurological grounds is accepted, then BD diagnostic criteria can be applied only in patients under life support assistance in ICUs. Does it mean that when a physician diagnoses death in a regular ward (the patient is not under life support), applying cardio-circulatory and respiratory diagnostic criteria, or when a forensic specialist diagnoses death in a body under criminal circumstances, we are denying a brain-oriented concept of death?<sup>48</sup>

Recently Cuba has passed a law for the determination and certification of death. The National Commission for the Determination

and Certification of Death has accepted a neurological view of death and emphasized that any legislation of death should be completely separated from any norm governing organ transplants.<sup>49,52</sup> Hence, the Commission enumerated three possible situations for diagnosing death:

i) Outside the intensive care environment (without life support), physicians apply the cardio-circulatory and respiratory criteria.

ii) In forensic medicine circumstances, physicians utilize cadaveric signs. (They do not even need a stethoscope.)

iii) In the intensive care environment (with life support) when cardio-circulatory and/or respiratory arrest occurs, physicians utilize the cardio-circulatory and respiratory criteria. When physicians suspect an irreversible loss of brain functions in a heart-beating and ventilatory supported case, BD diagnostic criteria are applied.

This methodology of diagnosing death, based on finding any of the signs of death, is not related to the concept that there are different types of death. The irreversible loss of cardio-circulatory and respiratory functions can cause death only when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain. According to the Commission, there is only one kind of death, based on the irreversible loss of brain functions.<sup>1,48-52</sup>

## Signs of death

The diagnosis of death was based on the finding of any of the following signs of death:

- I Irreversible loss of respiratory function.
- II Irreversible loss of cardio-circulatory functions.
- III Algor mortis (postmortem coldness).
- IV Livor mortis (postmortem lividity).
- V Rigor mortis (postmortem rigidity).
- VI Cadaveric spasm.
- VII Loss of muscle contractions.
- VIII Putrefaction.
- IX Irreversible loss of brain functions.

Signs I and II correspond to the classical respiratory and cardio-circulatory functions. Signs III to VIII are related to forensic circumstances, and beyond the scope of this review.

## Irreversible loss of brain functions (diagnosis of brain death)

As has already been emphasized, when physicians suspect an irreversible loss of brain functions in a heart-beating and ventilatory supported case, BD diagnostic criteria are applied. To assess brain functions during BD diagnosis, the clinical neurological examination is the accepted standard.<sup>8,12,13,22,48,52-54</sup>

## Preconditions or pre-requisites

1. Coma owing to irreversible acute brain damage of known etiology, affecting both hemispheres and brainstem. What is demanded is to have clear and definite clinical and/or neuroimaging evidence of an acute central nervous system (CNS) insult that is consistent with the irreversible loss of neurological function.<sup>1,7,22,47,55</sup>

2. At the time of beginning the neurological examination, it is essential to exclude confounding factors that mimic BD:<sup>1,22,56,57</sup>

*Unresuscitated shock.* This is indispensable to applied BD criteria only when blood pressure has a minimum value of 90 mm Hg.<sup>22,58-62</sup>

*Hypothermia* (core temperature <34°C). An inability to regulate temperature, or poikilothermia, is often present in BD. Core temperature results should be obtained through central blood, rectal, esophageal, or gastric measurement. Most sets of criteria for BD diagnosis demand a body temperature of at least 32.2°C.<sup>1,17,22,43,55,61-64</sup>

*Severe metabolic disorders capable of causing a potentially reversible coma.* Severe metabolic or endocrine abnormalities make BD unreliable.<sup>22,55-57,65</sup> Metabolic or endocrine derangement including glucose, electrolytes (including phosphate, calcium, and magnesium), inborn errors of metabolism, liver or renal dysfunction, etc. may cause a potentially reversible coma.<sup>1,22</sup>

*Peripheral nerve or muscle dysfunction and neuromuscular blockade* potentially play a role in inducing unresponsiveness in patients, and it could be a confounding factor in BD diagnosis.<sup>66-72</sup>

*Clinically significant drug intoxications* (e.g. alcohol, barbiturates, sedatives, hypnotics). CNS-depressant drugs should be ruled out if the clinical history is indicative.<sup>55,72-76</sup> Clinicians in the emergency department are often confronted with coma patients owing to poisoning or intoxication. Several authors recommend using naloxone in a titrated way when an opiate intoxication is suspected.<sup>77</sup> In the same way, flumazenil has been advocated as a benzodiazepine antagonist in coma of unknown etiology.<sup>77,78</sup>

## Diagnostic criteria

1. Deep unresponsive coma. The diagnosis of deep unresponsive coma demands a comatose patient showing a lack of spontaneous movements in addition to an absence of motor responses mediated by stimuli applied within the cranial nerve distribution.<sup>17,22,47,49,53,65</sup> CNS-mediated motor response to pain in any other distribution, seizures, and decorticate and decerebrate responses impede BD diagnosis. Some brain-dead individuals may present spinal reflexes or motor responses, confined to spinal distribution, which do not preclude the BD diagnosis.<sup>22,55,61,62,79,80</sup>

2. Absent brainstem reflexes. The reflexes mediated by the cranial nerves are main indicators of brainstem function. Hence, to prove their absence is indispensable to BD diagnosis. The individual significance of each brainstem reflex varies in BD diagnosis according to an intrinsic sensitivity of the cranial nerve networks and to the effect of some accompanying factors in brain-dead patients, such as trauma, local edema, dried tissues, and intracranial tubes affecting the exploration of reflexes.<sup>17,79</sup>

*Pupillary reflex.* This reflex, direct and consensual, is considered one of the most discriminant reflexes in BD diagnosis.<sup>17,22,55,57,61,62,79,81</sup> Mydriatic, small, or medium-sized pupils are found in brain-dead cases.<sup>17,43,63,64</sup>

*Corneal reflex.* Unilateral corneal stimulation with a throat swab induces a bilateral closure of the eyelids, is an easy response to elicit and, if present, is readily observed. This is also one of the most discriminant reflexes in BD diagnosis. A bilateral or unilateral response of eyelid closure and upward deviation of the eye (Bell's phenomenon) indicates preserved brainstem functioning. However, edema or drying of the cornea, and severe facial and ocular trauma may preclude a satisfactory stimulus for this reflex. Moreover, the threshold for excitation decreases markedly if the lids are kept closed.<sup>1,4,17,22,47,79,82,83</sup>

*Oculo-cephalic and oculo-vestibular responses.* The oculocephalic reflex, also known as Doll's eyes response, is elicited upon brisk turning of the head from middle position to 90° on both sides. In comatose patients without lesions of the brainstem, the eyes normally conjugately deviate to the other side. In BD no eye movements are observed. The neural pathways of this reflex are mediated through arcs involving the vestibular mechanisms, medial longitudinal bundle, and ocular nerves. This is a reflex easy to obtain and moderately discriminative. The oculo-vestibular response is elicited by irrigating the tympanum in both sides with iced water. In a comatose patient without lesions of the medial longitudinal bundle, and/or ocular nerves, the elicited response is a slow deviation of the eyes directed to the cold caloric stimulus. The head of the patient should be elevated 30° above the horizontal plane, and 50 cc of iced water is irrigated into the external auditory canal using a small suction catheter. To confirm lack of eye movement may be very difficult; it has been suggested pen marks are placed on the lower eyelid at the level of the pupil to facilitate the detection of slight eye movements. The examiner should observe for one minute after irrigation, and wait an interval of five minutes before stimulating

the opposite side. It is essential that the examiner confirm that the external auditory foramen and tympanic membrane are undamaged, because clotted blood or cerumen in the external auditory canal may impair this response. Moreover, a rupture of the eardrum usually augments caloric responses. The presence of severe facial and ocular trauma, eyelid edema, and chemosis of the conjunctiva may limit movement of the globes, making it very difficult to elicit and observe eye movements. Basal fracture of the petrous bone abolishes the caloric response unilaterally and may be identified by the presence of an ecchymotic mastoid process (Battle's sign). There are also some drugs that can lessen this reflex, such as tricyclic antidepressants, aminoglycosides, antiepileptic drugs, anticholinergics, and chemotherapeutic agents, etc.<sup>1,6,48,62</sup>

**Gag and cough response.** Pharyngeal (gag), cough, and swallowing reflexes are often difficult to explore because of the presence of tubes in the throat and dryness of the mucosa. Hence, in suspected brain-dead cases the cough response is usually explored by passing a catheter through the endotracheal tube and suctioning with negative pressure for several seconds. As these reflexes have their arcs through the medulla oblongata, it is desirable to explore them.<sup>17,22,64,84</sup>

3. Negative atropine test. The atropine test (AtT) assesses bulbar parasympathetic activity on heart activity in brain-dead patients.<sup>85</sup> Ouaknine first proposed including this as a criterion for the so-called brainstem death.<sup>85-89</sup> The method for this test consists in injecting 2 mg atropine under continuous monitoring of the ECG during 10 minutes. The AtT is considered negative if heart rate is not augmented by more than 3% compared with basal ECG records.<sup>1,58,86,90-95</sup>

4. Absent respiratory effort confirmed by the apnea test. The apnea test (AT) has been considered by some authors as the "condition *sine qua non*" for determining BD, because it provides an essential sign of a definitive loss of brainstem functions. Nonetheless, several authors have expressed their concern about the safety of this procedure, owing to potential complications such as severe hypotension, pneumothorax, excessive hypercarbia, hypoxia, acidosis, cardiac arrhythmia, or asystole, which may constrain the examiner to abort the test, thereby compromising BD diagnosis. Nevertheless, when an appropriate oxygen-diffusion procedure is used, this technique is safe.<sup>1,96-105</sup>

5. Periods of observation. If BD determination is only based on clinical evaluation, the following periods of observation were proposed by the Cuban Commission.<sup>1,49-52</sup>

Six hours at least, if a structural and irre-

versible CNS insult can be demonstrated by clinical and neuroimaging evidences.

In cases of acute hypoxic-ischemic brain injury, clinical evaluation should be delayed for 24 hours subsequent to the cardio-respiratory arrest, or an ancillary test could be performed.

Periods of observation can be shortened according to medical criteria by the application of confirmatory tests, to demonstrate a complete cessation of brain circulation, or to demonstrate loss of bioelectrical activity.

## Confirmatory tests

It is widely accepted that BD is a clinical diagnosis, and currently it is defined as a complete and irreversible loss of brain function. Confirmatory laboratory tests are recommended when specific components of the clinical testing cannot be evaluated reliably.<sup>50,51,106</sup> Sometimes the apnea test cannot be performed or it must be interrupted by the examiner. Eye injuries may impede an appropriate assessment of pupillary, corneal, or vestibulo-reflex testing. In those patients with perforated tympanic membranes iced water caloric irrigation for exploring the vestibulo-ocular reflexes is proscribed. Furthermore, the diagnosis of BD in children and neonates is more complicated and usually ancillary tests are advocated.<sup>57,58,107-111</sup>

Confirmatory tests are recommended to shorten periods of observation according to physicians' criteria and in those conditions interfering with the clinical BD diagnosis. The Cuban Commission proposed that confirmatory tests should be mandatory in cases of patients with primary brainstem lesions undergoing BD diagnosis.<sup>1,49-51</sup>

Confirmatory tests in BD can be divided into those proving absent CBF and those that demonstrate loss of bioelectrical activity.

## Tests to demonstrate absent cerebral blood flow

Bernat recently emphasized that "the most confident way to demonstrate that the global loss of clinical brain functions is irreversible is to show the complete absence of intracranial blood flow."<sup>112</sup> Ingvar and colleagues defended this, concluding that the permanent cessation of CBF produces total brain infarction.<sup>113,114</sup>

Several tests that can measure CBF accurately and validly in suspected brain-dead patients have been developed in the last decades. The first technique used to demonstrate absence of intracranial circulation in BD distal to the intracranial portions of the internal carotid and vertebral arteries was cerebral angiography.<sup>115-117</sup> Other techniques used to

determine absent CBF have been: cerebral intravenous digital subtraction angiography, intravenous radionuclide angiography, single photon emission tomography (SPECT), echoencephalography, measurement of arm-to-retina circulation time, ophthalmic artery pressure measurement, xenon-enhanced computed tomography, MRI angiography, CT angiography and CT perfusion, and transcranial Doppler ultrasonography (TCD).

Although it has not been widely used as an ancillary test in BD, the 18F-FDG PET scan has been used by some authors to study brain-dead patients, and confirmed no intracerebral uptake or retention of tracer, consistent with a diffuse absence of brain metabolism.<sup>118,119</sup>

Another technique that could be useful in monitoring biochemical changes *in vivo*, from coma to BD, is proton magnetic resonance spectroscopy (1H-MRS). N-acetyl aspartate (NAA) content is a measure of neuronal integrity, choline (Cho) content mirrors membrane turnover, and creatine (Cre) relates to energy dependent systems. Falini *et al.* serially studied a patient with severe global hypoxic-ischemic brain injury using 1H-MRS. Particularly notable was a quick decline of NAA in the acute phase, suggesting the severity of the neuronal insult, and after seven weeks of evolution the irreversible death of the major part of the neuronal population was confirmed.<sup>120</sup> We have also applied this technique to monitor metabolic changes in the evolution from a persistent vegetative state to a minimally conscious state.<sup>121</sup>

TCD has been recommended for assessing CBF in suspected brain-dead patients.<sup>122-128</sup> TCD is a noninvasive technique that measures local blood flow velocity and direction in the proximal portions of large intracranial arteries. TCD requires training and experience to perform it and interpret results; hence, it is typified as operator-dependent.<sup>129,130</sup> In the ICU setting, intensivists or neurologists usually receive training to apply this technique using portable Doppler devices in suspected brain-dead cases. Oscillating flow, systolic spikes, or no flow patterns are typical Doppler-sonographic flow signals found in the presence of cerebral circulatory arrest, which if irreversible, results in BD.<sup>1,131,132</sup>

Nonetheless, recent reports affirmed that multi-slice CT angiography (CTA) is a robust tool to demonstrate the lack of intracranial blood flow, showing a high sensitivity and a wide safety margin for diagnosing BD. In the near future it might be the preferred test for proving CBF.<sup>29,124,133</sup>

## Tests to demonstrate loss of bioelectrical activity

The EEG has been closely linked to BD since the pioneering descriptions of the death of the nervous system and coma dépassé.<sup>134,135</sup> The set

of criteria based on a brainstem standard, like those from the Commonwealth countries, does not include EEG.<sup>3,5,136-140</sup> On the contrary, EEG is recommended by most countries adopting the "whole brain death" definition.<sup>141-145</sup>

Although EEG is sensitive to hypothermia, drugs, or extreme hypotension,<sup>146</sup> and several artifacts can appear in the ICU environment, this technique is still extensively used as an ancillary test in BD diagnosis. Buchner *et al.* proposed that its sensitivity as well as specificity can reach up to 90%.<sup>147</sup> On the other hand, multimodality evoked potentials (MEP) and electroretinography (ERG) are highly resistant to drug intoxication and hypothermia, and have been shown to be reliable in the ICU environment.<sup>148-154</sup> Owing to these features, a substantial interest in multimodality evoked potentials (MEPs) in BD has grown over the past two decades, and a wealth of data are now available in the literature.<sup>151,152,155-159</sup> However, considered as single tests, they have their limitations and they are not included routinely as confirmatory tests for BD diagnosis.<sup>1,160</sup> Hence, we have proposed to combine EEG, MEP, and ERG in a test battery to study brain-dead patients in order to increase diagnostic reliability.<sup>49,152,158,161-168</sup>

Therefore, an adequate medical practice would be to assess comatose patients by monitoring CBF by TCD, and neuronal function by the above mentioned neurophysiologic test battery. If TCD fails to validate the absence of CBF, CTA can be used to confirm BD diagnosis.<sup>1</sup>

## Brain death and organ transplants

Although it is commonly believed that the concept of BD was developed to benefit organ transplants, it evolved independently. Transplantation owed its development to advances in surgery and immunosuppressive treatment; BD owed its origin to the development of intensive care. A historical review demonstrates that the BD concept and organ transplantation arose separately and advanced in parallel, and only began to progress together in the late 1960s.<sup>5-8,11,12,169,170</sup> Of course, organ procurement programs have induced a tie relationship between organ transplants and BD diagnosis in most countries and, hence, it is extremely important to educate the public to understand that BD means death of the individual, and of the importance of organ donation for transplants.

## Conclusions

BD should be understood as the ultimate clinical expression of a brain catastrophe leading to a complete and irreversible neurological stoppage, characterized by irreversible coma, absent brainstem reflexes, and apnea. We have enumerated three possible situations for diagnosing death based on the "signs of death". This methodology of diagnosing death does not mean that there are different types of death. The irreversible loss of cardio-circulatory and respiratory functions can cause death only when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain.

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