



Brain death and management of the potential donor

Marcia Harumy Yoshikawa¹ · Nícollas Nunes Rabelo¹ · Leonardo Christiaan Welling² · João Paulo Mota Telles¹ · Eberval Gadelha Figueiredo¹

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Abstract

One of the first attempts to define brain death (BD) dates from 1963, and since then, the diagnosis criteria of that entity have evolved. In spite of the publication of practice parameters and evidence-based guidelines, BD is still causing concern and controversies in the society. The difficulties in determining brain death and making it understood by family members not only endorse futile therapies and increase health care costs, but also hinder the organ transplantation process. This review aims to give an overview about the definition of BD, causes, physiopathology, diagnosis criteria, and management of the potential brain-dead donor. It is important to note that the BD determination criteria detailed here follow the AAN's recommendations, but the standard practice for BD diagnosis varies from one country to another.

Keywords Brain death · Diagnosis · Management · Organ donation · Critical care

Introduction

The definition of death has changed over time from the irreversible loss of heart and lung functions to the irreversible loss of brain function. The transition of this concept began with the development of techniques that improved intensive care and resuscitation, including the first successful human cardiac defibrillation by Claude Beck in 1947 [1, 2] and the development of positive pressure ventilation by Bower and Bennett in 1950 [3, 4]. Since then, patients with cardiorespiratory arrest could recover from “death.” As cardiac and respiratory dysfunctions were no longer determinants of death, patients with severe brain injuries maintaining vegetative functions via vasoactive drug administration, metabolic corrections, and respirator utilization created complex prognosis and ethical dilemmas. Despite the presence of heart activity and circulation, is someone without breathing, reflexes, or cerebral electrical activity alive?

To deal with the uncertainty in the diagnosis of “death of nervous system,” a neurologist at Massachusetts General Hospital called Robert Schwab, in 1963, created clinical and electroencephalographic criteria to define death “in spite of cardiac action”: (1) fixed and dilated pupils, no elicitable reflexes, and no spontaneous movements, (2) apnea, and (3) isoelectric EEG [5]. Five years later, Schwab reported 90 patients that met that criteria: none of them survived and all had extensive brain necrosis [6].

The definition proposed by Schwab was improved by the Harvard Medical School ad hoc committee in 1968, which established brain death (BD) as (1) presence of clinical features (unresponsive coma, absence of reflexes, and any movements) after 1 h of observation; (2) absence of breath after 3 min without mechanical ventilation; and (3) isoelectric EEG. That definition also demanded the exclusion of hypothermia (below 32° C), suspension of central nervous system depressants (CNSd), and repetition of clinical tests within 24 h [7].

The definition is still evolving in the following years, but with little uniformity and creating legal challenges. For instance, the Minnesota Code of BD Criteria of 1971 limited the reflex evaluation to those that pass through the brainstem, allowing the injury in this region to determine the irreversible coma and the elimination of EEG silence as criteria of BD [8]. Five years later, brainstem death was adopted and emphasized in the UK by the Conference of the Medical Royal College and their faculties [9]. The brainstem death argument relied on the fact that both consciousness and respiratory control originated in that area, so the

✉ Marcia Harumy Yoshikawa
marcia.yoshikawa@fm.usp.br

¹ Department of Neurological Surgery, University of Sao Paulo, Rua Eneas Aguiar, 255, São Paulo 05403-010, Brazil

² Department of Neurological Surgery, State University of Ponta Grossa, Ponta Grossa, Brazil

loss of function could be considered death [10]. As a result, patients with cortical EEG activity could be considered dead in the UK and alive in the USA.

In 1995, the American Academy of Neurology (AAN) established practical parameters of BD that became the basis of many diagnosis protocols worldwide [11]. According to this document, which was revised in 2010 [12], the irreversible cessation of all brain and brainstem functions depends on 3 clinical findings: irreversible coma, absence of brain stem reflexes, and apnea [11]. In fact, there is no report of neurologic function recovery in adult patients who were diagnosed with BD with the AAN parameters. In 2014, the World Health Organization (WHO) established the definition of human death as “the permanent loss of capacity for consciousness and all brainstem functions, as a consequence of permanent cessation of circulation or catastrophic brain injury” [13].

The concept and the understanding of BD have evolved, and, although the medical definition has remained relatively consistent in its essence, the decision of a layperson to accept the medical determination of BD as death is frequently conflicting. People who disagree with BD argue that death is not only a biological event, but also a religious, philosophical, legal, and policy choice [14]. The uncertainty in the diagnosis of death is mainly related to the different understandings about the meaning of death, which must be chosen by societal consensus. Additionally, the difference between BD and other neurologic disorders is still unclear for the most part of the society [15].

This confusion of concept also hinders the organ transplantation process, since the “dead-donor rule” establishes that the removal of any life-sustaining organ must be performed only in patients declared dead [16, 17]. The organ transplantation has been bonded to BD in most part of its history: the invention of respiratory and cardiac support devices allowed not only the development of the BD concept, but also the organ preservation of potential donors by the perfusion maintained by a beating heart. Nowadays, organ donation of BD patients is impaired by three main reasons: (1) family refusal for organ donation, (2) hemodynamic collapse and cardiac arrest following BD diagnosis, and (3) the BD patient does not meet the acceptance criteria [18]. Therefore, considering that for many individuals with end-stage organ diseases the organ transplantation is the only feasible treatment, improving the BD understanding and the potential donor management are important steps to save many other lives [19, 20]. This review details BD determination according to AAN recommendations, but it is important to note that standard practice for the BD diagnosis varies between countries.

Materials and methods

Electronic searches were performed in PubMed and Google Scholar in June and July 2020. The keywords and MeSH

terms used were brain death diagnosis [Title/Abstract] OR brain death pathophysiology [Title/Abstract] OR brain death organ donor [Title/Abstract]. Additional studies were sought through snowballing. The studies found were analyzed by title and abstract, being those more appropriate and relevant to this review included.

Results

The initial search yielded 656 articles in PubMed and 381 in Google Scholar. We performed a pre-selection of articles, screening by titles and considering those more appropriate to the present review. Sixty-eight studies were included. The references of those articles were also analyzed, and 5 other relevant papers were identified and added.

Discussion

Pathophysiology of brain death

One of the most important mechanisms of BD involves increased intracranial pressure (ICP), which induces cerebral venous engorgement, brain swelling, brainstem compression and ischemia, and finally complete cessation of the intracranial blood flow. It progresses to aseptic necrosis and absence of blood uptake by the brain tissue [21–23]. Another mechanism of BD was reported by Palmer and Bader, in which the ICP does not exceed the mean arterial pressure, maintaining the normal intracranial blood flow. In this case, although the supply of oxygen, glucose, and other essential nutrients is preserved, the brain tissue oxygenation (PbtO₂) decreases to zero due to the collapse of the nervous system at the capillary and cellular levels [24, 25].

Regardless of the mechanism, the ischemia inherent to BD induces a number of hormonal, metabolic, and hemodynamic changes. The pontine ischemia causes vagal and sympathetic stimulation, which are manifested as bradycardia, hypertension, and an irregular breathing pattern (known as the “Cushing triad”) that evolves to apnea [26]. The ischemia affects the pituitary, hypothalamic, and medulla oblongata, resulting in failure of the central regulatory systems, unopposed sympathetic stimulation, loss of spinal sympathetic pathways, and following sympathetic denervation [21, 27]. This process causes a huge rise in the catecholamine release into the circulation (known as the “sympathetic storm”): the serum dopamine concentration increases in 800%; the epinephrine in 700%; and the norepinephrine in 100%. The sympathetic storm induces severe vasoconstriction, and consequent hypertension, tachycardia, and increased myocardial oxygen demand [26].

After BD, a range of dysfunctions and physiologic alterations in many systems occurs, including cardiovascular (hypotension, arrhythmias) [21], pulmonary (pulmonary edema, ventilator-induced lung injury) [21], thermoregulatory (hypothermia) [21], endocrine (diabetes insipidus, hypoglycemia) [28], renal (acute injury), and hematologic (disseminated intravascular coagulation) [21, 26]. Additionally, an important systemic inflammatory response occurs due to the upregulation of pro-inflammatory mediators, which may jeopardize the graft survival after transplantation [21, 29, 30].

Causes of BD

There are intracranial and extracranial brain injuries that can induce BD.

1. Intracranial causes of BD

The intracranial causes of BD can be classified as global (e.g., diffuse cerebral edema, generalized swelling) or localized (e.g., extensive right middle artery stroke) and as ischemic (e.g., extensive ischemia) or hemorrhagic (e.g., subarachnoid hemorrhage, intraventricular hemorrhage, subdural hematoma).

The most common causes in adults are traumatic brain injury and subarachnoid hemorrhage, while in children abuse is the most reported cause [31, 32].

2. Extracranial causes of BD

The most important extracranial cause of BD is cardiopulmonary arrest without appropriate resuscitation, resulting in decreased intracranial blood flow and ischemic brain damage. The ischemic tissue evolves with edema and brain swelling, increasing the ICP. The following steps of this process are described above [26, 33].

Diagnosis of BD in adults

Brain death is defined as the irreversible cessation of all brain functions. The AAN guideline states that BD diagnosis is clinical and made at the bedside, but subsidiary tests are required when the clinical examination is uncertain or the patient has any peculiarity. Some countries consider subsidiary tests mandatory by law. The following guidance for BD diagnosis is based on 2010 AAN recommendations [12] (Fig. 1).

1. Preconditions

(a) Identifying the cause of coma and its irreversibility

First of all, the cause of coma must be known and explained by neuroimaging. Spontaneous respirations must also be absent.

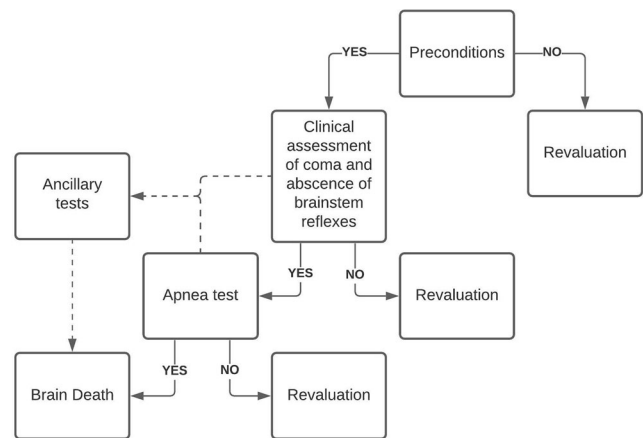


Fig. 1 Brain death (BD) diagnosis. Ancillary tests may be required when the clinical assessment or the apnea test cannot be performed properly (e.g., acute or pre-existing ophthalmologic conditions; facial and skull trauma; pre-existing cranial neuropathies; chronic respiratory acidosis). In some countries, the ancillary tests are mandatory for the diagnosis of BD. One clinical examination (coma, absence of brainstem reflexes, and apnea) positive to BD is sufficient to the diagnosis, but some centers require 2 positive assessments. “YES” meaning fulfilling criteria to BD diagnosis in the respective step; “NOT” meaning not fulfilling criteria to BD diagnosis in the respective step

Concerning coma irreversibility, there are a number of substances that can simulate BD (organophosphates, lidocaine, baclofen, vecuronium, and others), especially those classified as central nervous system depressant (CNSd) drugs (e.g., narcotics, benzodiazepines, tricyclic antidepressants, anticholinergics, barbiturates and their metabolites). The severe exogenous intoxication by these substances can cause partial loss of brain stem reflexes, although the pupillary response to light is preserved. Additionally, the “locked-in syndrome” caused by an infarction of the ventral pons (usually due to an acute occlusion of the basilar artery) or by Guillain-Barré syndrome (an acute and reversible polyneuropathy) may also mimic BD and should be excluded.

It is essential to assess the patient’s medical history, drug screen, drug clearance, and, if available, drug plasma level to exclude the presence of the substances aforementioned before starting the BD protocol. The plasma levels must be below the therapeutic range. If the present substance is known, but not the plasma level, it is necessary to observe the patient for a period of ≥ 4 times the elimination half-life of the substance. It is also important to consider the influence of other drugs, renal or hepatic dysfunction, and hypothermia when evaluating the drug clearance. Moreover, the presence of neuromuscular blocking agents and severe endocrine, electrolyte, or acid-base abnormality should be also excluded (an exception is severe refractory hypernatremia, which does not preclude BD diagnosis when it is not the only cause of coma) [15, 34].

The team involved in BD diagnosis has to determine whether the disturbances presented are secondary to the natural evolution of BD or a confounding variable.

(b) Core in normothermia or mild hypothermia

The brainstem reflexes might disappear in temperatures lower than 32 °C [35]. The precise temperature that allows BD diagnosis is unknown, but it is recommended to keep the core temperature normal or near to normal (above 36 °C). To achieve that, warming blankets should be provided to the patient.

(c) Normal systolic blood pressure

In order to perform a reliable neurologic examination, the systolic blood pressure should be kept at ≥ 100 mmHg. In case of hypotension, the use of vasopressor or vasopressin is required.

The patient in a coma state must also stay for at least 6 h under intensive care and observation in a hospital environment. When the primary cause is hypoxic-ischemic encephalopathy, it is necessary to expect a minimum period of 24 h after cardiac arrest or rewarming in therapeutic hypothermia before starting the protocol for brain death diagnosis [34–36].

2. Clinical examination

(a) Coma

Patients must lack all evidence of responsiveness.

Eye opening or eye movement to noxious stimuli is absent. Noxious stimuli should not produce a motor response other than spinally mediated reflexes. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise.

(b) Absence of brainstem reflexes

1. Absence of pupillary response to a bright light is documented in both eyes: usually, the pupils are fixed in a midsize or dilated position (4–9 mm). Constricted pupils suggest the possibility of drug intoxication. When uncertainty exists, a magnifying glass should be used.
2. Absence of ocular movements using oculocephalic testing and oculovestibular reflex testing: once the integrity of the cervical spine is ensured, the head is briskly rotated horizontally and vertically. There should be no movement of the eyes relative to head movement. The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the patency of the external auditory canal is confirmed. The head is elevated to 30°. Each external auditory canal is irrigated (1 ear at a time) with approximately 50 mL of ice water. Movement of the eyes should be absent during 1 min of observation. Both sides are tested, with an interval of several minutes.

3. Absence of corneal reflex: absent corneal reflex is demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen.
4. Absence of facial muscle movement to a noxious stimulus: deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supra-orbital ridge should produce no grimacing or facial muscle movement.
5. Absence of the pharyngeal and tracheal reflexes: the pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning. The catheter should be inserted into the trachea and advanced to the level of the carina followed by 1 or 2 suctioning passes.

(iii) Apnea

In the BD patient, the breathing drive must be absent. The irreversible apnea is tested with a CO₂ challenge. Documentation of an increase in PaCO₂ above normal levels is typical practice. The prerequisites are (1) normotension, (2) normothermia, (3) euvolemia, (4) eucapnia (PaCO₂ 35–45 mmHg), (5) absence of hypoxia, and (6) no prior evidence of CO₂ retention (i.e., chronic obstructive pulmonary disease, severe obesity). The procedure (Fig. 2) is as follows:

Adjust vasopressors to a systolic blood pressure > 100 mmHg.

Preoxygenate for at least 10 min with 100% oxygen to a PaO₂ > 200 mmHg.

Reduce ventilation frequency to 10 breaths/min to eucapnia.

Reduce positive end-expiratory pressure (PEEP) to 5 cm H₂O (oxygen desaturation with decreasing PEEP may suggest difficulty with apnea testing).

If pulse oximetry oxygen saturation remains > 95%, obtain a baseline blood gas (PaO₂, PaCO₂, pH, bicarbonate, base excess).

Disconnect the patient from the ventilator.

Preserve oxygenation (e.g., place an insufflation catheter through the endotracheal tube and close to the level of the carina and deliver 100% O₂ at 6 L/min).

Look closely for respiratory movements for 8–10 min. Respiration is defined as abdominal or chest excursions and may include a brief gasp.

Abort if systolic blood pressure decreases to < 90 mmHg.

Abort if oxygen saturation measured by pulse oximetry is < 85% for > 30 s. Retry procedure with T-piece, CPAP 10 cm H₂O, and 100% O₂ 12 L/min.

If no respiratory drive is observed, repeat blood gas (PaO₂, PaCO₂, pH, bicarbonate, base excess) after approximately 8 min.

If respiratory movements are absent and arterial PCO₂ is ≥ 60 mmHg (or 20 mmHg increase in arterial PCO₂ over a baseline normal arterial PCO₂), the apnea test result is positive (i.e., supports the clinical diagnosis of brain death).

If the test is inconclusive but the patient is hemodynamically stable during the procedure, it may be repeated for a longer period of time (10–15 min) after the patient is again adequately preoxygenated.

3. Ancillary tests

The clinical exam is enough for brain death diagnosis when the etiology of coma is known and the confounding factors

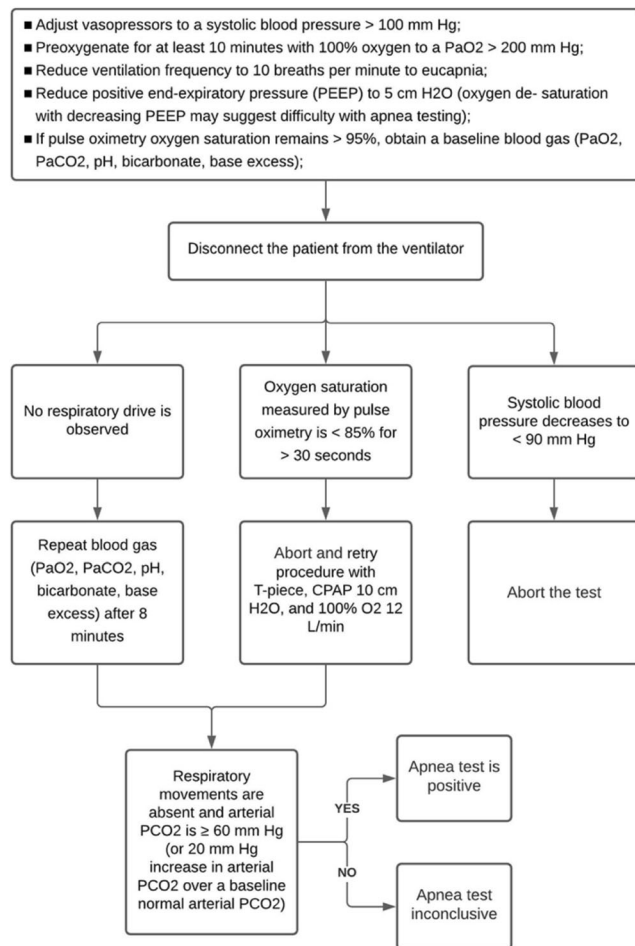


Fig. 2 Apnea test. To undergo the apnea test, the patient must be hemodynamically stable. A positive apnea test supports the clinical diagnosis of BD. When the patient is hemodynamically stable during the test, but the result is inconclusive, the patient must be preoxygenated again, and the test must be repeated for 10–15 min

were excluded [12]. However, the presence of some conditions might turn the clinical assessment unclear and demand ancillary tests.

Potential indications for ancillary tests include recent use of sedatives, opiates, or neuromuscular blockers; severe metabolic alterations; acute or pre-existing ophthalmologic conditions; facial and skull trauma; severe neuromuscular conditions; pre-existing cranial neuropathies; high spinal cord injuries; chronic respiratory acidosis; and abnormal movements making the diagnosis of BD unclear [37, 38].

The ancillary test aims to confirm the loss of bioelectrical activity of the brain or the cerebral circulatory arrest. As all tests have their limitations, the one that will be chosen depends on each case (Table 1). The selection must consider the patient’s clinical conditions, the test’s feasibility, and the expertise of the medical staff. Common confirmatory tests used today include electroencephalography (EEG), cerebral angiography, radionuclide imaging (RNI), transcranial Doppler (TCD), computed tomographic angiography (CTA), and magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) [12].

(a) Electroencephalography

EEG evaluates the synaptic potentials in the cerebral cortex, especially the region closest to the brain surface. Patients with BD have electrocerebral inactivity, which is defined as the absence of EEG ≥ 2 μV when recording from scalp electrode pairs ≥ 10 cm apart, with interelectrode impedance > 100 Ω and < 10,000 Ω, in at least 30 min of record time [39].

Although the EEG has some advantageous features (e.g., it can be performed at bedside, has low risk, and is noninvasive), it also has several limitations: reversible conditions (as drug effect, hypothermia, intoxications, metabolic alterations) [40, 41] can present flat EEG and induce false positives; typical electro-magnet fields in the intensive care unit (ICU) environment can be taken as a cortical activity, inducing false negatives [42–44].

(b) Four-vessel cerebral angiography

The absence of cerebral blood flow is the main evidence of BD. The four-vessel cerebral angiography is considered the gold standard method on BD diagnosis. When the patient is brain dead, no blood flow at the carotid bifurcation and circle of Willis is expected, although the external carotid flow is frequently present and some opacification in the proximal middle or anterior cerebral arteries may also appear [42, 43, 45]. The main limitations of the angiography are as follows: (1) the need of ionic contrast infusion and transportation to the hemodynamics suite can be problematic in unstable patients; (2) it is an invasive method; (3) it has limited availability. In

Table 1 Main advantages and disadvantages of each ancillary test

Ancillary test	Advantages	Disadvantages
EEG	<ul style="list-style-type: none"> • Can be performed at bedside • Low risk • Noninvasive 	<ul style="list-style-type: none"> • Vulnerable to confounders • Electro-magnet interference
Four-vessel cerebral angiography	<ul style="list-style-type: none"> • Gold standard for the evaluation of brain blood flow 	<ul style="list-style-type: none"> • Use of ionic contrast • Cannot be performed at bedside • Invasive • Limited availability
TCD	<ul style="list-style-type: none"> • Can be performed at bedside • Noninvasive • Low risk • Evaluates anterior and posterior circulation • Cheaper than angiography • Does not use contrast 	<ul style="list-style-type: none"> • Requires expertise of the medical staff • Limited bone window for assessment • Appropriate bone window is not present in all patients
RNI		<ul style="list-style-type: none"> • Limited availability • Time-consuming • Limited evaluation of posterior fossa and brainstem structures

hypotensive states, the blood flow may be not detected, resulting in a false-positive diagnosis, while in “open cranium” situations (such as traumatic skull fractures, ventricular drain, or decompressive craniotomy), false negatives may occur. An appropriate mean arterial pressure (> 100 mmHg) should be maintained during the exam [15].

(c) Transcranial Doppler

TCD evaluates the intracranial blood flow. In patients with BD, the TCD demonstrates reverberating flow patterns or small peaks without diastolic flow [44, 46]. It is a good option for an ancillary test, since it (1) can be performed at bedside, (2) is noninvasive, (3) does not need contrast administration, (4) can evaluate anterior and posterior circulation, and (5) is cheaper than angiography. Investigations have shown that the sensibility of TCD ranges between 86 and 99% and the specificity ranges between 98 and 99% [47]. However, it also presents some limitations, such as (1) the exam quality relies on the expertise of the medical staff; (2) limited bone window for TCD assessment (bitemporal, suboccipital, transorbital); (3) about 10% of the patients do not have an appropriate bone window [48, 49].

(d) Radionuclide imaging

RNI is a noninvasive method that uses radioisotopes (substances not nephrotoxic) to assess brain perfusion. Currently, the most used radioisotopes are the Tc 99m hexamethylpropyleneamine oxime (HMPAO) and the Tc 99m ethylenecysteinediethylester (ECD), which present good

lipophilicity and penetration into the brain parenchyma [50, 51]. The exam should be performed with anteroposterior and lateral projection, being the lack of radiotracer uptake by brain structures in the planar imaging, known as the “empty skull sign,” a finding compatible with BD. Previous studies indicate that RNI has high sensitivity (78–100%) and specificity (100%) [11].

The main limitations of this method (1) involve the limited availability, (2) is time-consuming, and (3) has limited evaluation of posterior fossa and brainstem structures. Nowadays, to enhance the assessment of the posterior fossa, the planar imaging has been associated with the single-photon emission computed tomography (SPECT). When those methods are combined, the results have an excellent agreement with the 4-vessel angiography [52].

(e) Other ancillary tests

Concerning other potential ancillary tests (including the somatosensory evoked potentials (SSEPs), computed tomographic angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and bispectral index), none of them is recommended by the AAN as an ancillary test for determining BD, since there is insufficient evidence to support their use [12].

Identifying the potential organ donor

When dealing with BD patients, recognizing eligible candidates to organ donation is an important step in the care and transplantation success. Previous investigations have

demonstrated that the use of standardizing organ donor protocols reduces the family refusal rate, decreases the loss of donors due to circulatory collapse, and transforms noneligible patients into actual donors [53]. International organ procurement and transplantation networks established as standard criteria for organ donation patients under 50 years of age who have suffered BD [54, 55]. Being a potential organ donor identified, the local organ network should be notified as soon as possible, and, after the family's consent for donation, further investigations should be performed to assess the viability and safety of the potential organ donation.

The assessment must exclude any risk of transmission of infectious or neoplastic diseases through organ or tissue transplantation and identify the functionality of organs that may be transplanted. The evaluation of the BD patient includes (1) clinical history; (2) physical examination; (3) auxiliary tests; and (4) inventory during the organ removal surgery [35]. The clinical history is assessed through analysis of medical records and interviews with family members. The physical examination, which must include the anthropometric measurements, is important to evaluate the compatibility between the size of the transplant and the biotype of the recipient, in addition to contributing to the investigation of conditions that contraindicate the transplant [35]. The auxiliary tests include two blood and urine cultures [56], biochemical testing every 24 h [57], and serologic tests. Other specific tests should be performed according to the organs that may be transplanted (e.g., creatine kinase MB isoenzyme (CK-MB) and/or troponin every 24 h, electrocardiogram and echocardiogram for heart donor) and the clinical suspicion of transmissible diseases [59]. The surgical inventory consists in the careful examination of organs during the removal, in order to detect potentially hidden tumors or pathological lymph nodes [56].

Management of the potential organ donor

BD induces significant metabolic, hormonal, and hemodynamic alterations, which must be properly treated in order to avoid cardiac and somatic death, as well as to improve the chances of success of a future transplantation. The appropriate care of a potential organ and tissue donor represents the chance of benefiting many other people (Table 2). The longer the delay until the organ removal, the worse is the inflammatory response and the outcomes of the transplantation. Thus, the recommended interval between the BD diagnosis and the organ removal is 12–24 h [35, 58, 59].

1. Monitoring

The patient should be maintained as close as possible to homeostasis. The measures should include admission in ICU, central vein access, invasive arterial pressure assessment, and

continuous monitoring of electrocardiogram, peripheral oxygen saturation (SpO₂), and urinary output. The care is similar to that offered for patients in critical clinical situations [35, 56, 58, 59].

2. Hemodynamic support

The “sympathetic storm” is a remarkable feature of the patient evolving to BD. This event occurs in two phases: (1) adrenergic hyperactivity—clinically manifested by tachycardia, hypertension, increased systemic vascular resistance, and increased myocardial oxygen consumption; (2) hypotension. The first phase lasts for approximately 30 min, and there is still no consensus about the need for treatment for the hypertensive crisis [60, 61]. As the pathophysiology involves increased systemic vascular resistance, the hypoperfusion of intra-abdominal organs may occur. Organ impairment is associated with systolic levels of 160 mmHg or higher for more than 30 min. If the temporary blood pressure control is necessary, it is recommended to use esmolol or nitroprusside [60, 62]. It is also essential to give appropriate attention to the hypotension that spontaneously happens after adrenergic discharge [61, 62].

The potential donor should have mean arterial pressure between 60 and 80 mmHg, or at least a systolic blood pressure of 100 mmHg. It is important to notice that patients with BD have depletion in circulating catecholamines which are associated with hyperglycemia or mannitol infusion that can promote osmotic diuresis and diabetes insipidus. These events disturb blood pressure control. The imaging often demonstrates left ventricular dysfunction due to hydro-electrolytic disorder, pulmonary hypertension, myocardial contusion, or neurogenic myocardial stunting [56, 60].

Fluid resuscitation is the initial hemodynamic support, but to define the volume needed is a challenge. An insufficient volume replacement increases the inflammatory response and organ dysfunction; besides, to start vasopressor drug administration without an appropriate volume replacement can induce arrhythmias or worsen vasoconstriction and organ ischemia [60]. On the other hand, excessive volume causes pulmonary edema and precludes the transplantation of this organ [59].

Monitoring central venous pressure (CVP) in all potential donors is the subject of debate. Values between 8 and 12 mmHg indicate neither responsiveness nor non-responsiveness to volume replacement; but CVP < 4 mmHg allows the increase of volume infusion. If the CVP increases more than 2 mmHg, the replacement should be stopped. One alternative for CVP measurement is the DeltaPp, a method with higher specificity and sensitivity. The initial infusion is 20–30 mL/kg of heated crystalloid solution (43 °C) for 30 min. After this volume expansion, if CVP and DeltaPp values

Table 2 Management of the potential organ donor

Parameter	Management and goals
Monitoring	<ul style="list-style-type: none"> • Admission in ICU • Central vein access • Invasive arterial pressure • Continuous monitoring of electrocardiogram, peripheral oxygen saturation (SpO₂), and urinary output
Hemodynamic support	<ul style="list-style-type: none"> • Maintain blood pressure between 60 and 80 mmHg, or at least a systolic blood pressure of 100 mmHg • Fluid resuscitation: initial infusion of 20–30 mL/kg of heated crystalloid solution (43 °C) for 30 min. If CVP < 4 mmHg, the volume infusion can be increased • Vasopressin in bolus, followed by dose of 0.5–2.4 U/h • Brady and tachyarrhythmia should be treated following the protocols of the American Heart Association. Do not use atropine for bradyarrhythmia treatment
Temperature control	<ul style="list-style-type: none"> • Maintain body temperature between 36 and 37.5 °C • Identify hypothermia as early as possible: central measurements in the tympanic membrane, nasopharynx, and esophagus • In hypothermia, warming blankets should be provided to the patient
Ventilation	<ul style="list-style-type: none"> • Tidal volume of 6 to 8 mL/kg of ideal body weight • FiO₂ adjusted to obtain PaO₂ ≥ 90 mmHg, PEEP 8–10, and Plato pressure < 30 cm H₂O
Nutritional support*	<ul style="list-style-type: none"> • Caloric intake equivalent to 70–85% of baseline energy expenditure • Contraindicated in conditions of severe hemodynamic instability
Hormone therapy	<ul style="list-style-type: none"> • Capillary blood glucose measured every 6 h • Persistent blood glucose levels above 180 mg/dL must be controlled following the institutional protocols. • pH should be kept between 7.35 and 7.45 • Serum sodium between 130 and 150 mEq/L and urine output between 0.5 and 4 mL/kg/h • In the presence of hypernatremia, it should be corrected with 0.45% saline solution or 5% glucose solution • Disturbances in other electrolytes (such as calcium, phosphorus, magnesium, and potassium) must also be monitored every 6 h • 15 mg/kg/day of methylprednisolone after the diagnosis • T3 replacement if the patient is unstable and under dopamine administration at doses higher than 10 µg/kg/min or with ejection fraction of less than 45%
Transfusion	<ul style="list-style-type: none"> • Blood transfusion if hemoglobin levels < 7 g/dL. When the hemoglobin level is between 7 and 10 g/dL, the blood transfusion should be performed exclusively if the resuscitation measures are not achieving the mean arterial pressure (MAP) goals • The hematocrit should be kept > 30% • Cryoprecipitate transfusion if the fibrinogen value is <100 mg/dL (even after administration of fresh plasma) and disseminated intravascular coagulation is suspected • The platelet transfusion is recommended when the platelet account is < 80,000/mm³

*There is no clear evidence that nutritional support implies higher rates of organ utilization

indicate the impossibility of any additional volume infusion, vasoactive drugs should be administered [56, 58–60].

The type of vasopressors and the dose limit are not standardized. There is concern about the cardiac viability after the use of high doses of beta-agonists (e.g., dopamine and dobutamine) especially when concomitant to low cardiac output and secondary hypoperfusion. Nonetheless, the use of those drugs is not formally contraindicated. The administration of vasopressin has been emphasized since this hormone helps in the management of diabetes insipidus and reduces the demand

for catecholamines. Vasopressin is used in bolus, followed by 0.5–2.4 U/h [35, 56]. Lactate levels and central venous saturation, although useful in cases of trauma and sepsis, are not appropriate to evaluate the response of potential donors to fluid resuscitation [56].

Another clinical feature common in patients undergoing brain death protocol is cardiac arrhythmia. This condition can promote a decrease in cardiac output and hypotension. Bradyarrhythmia and tachyarrhythmia should be treated following the protocols of the American Heart Association.

Patients with bradyarrhythmia should not receive atropine, and it may indicate the use of a temporary transcutaneous pacemaker followed by the transvenous pacemaker [40, 56, 63].

3. Temperature control

In order to maintain body homeostasis, it is fundamental to keep the temperature within physiological limits (36–37.5 °C). The temperature control depends primordially on the hypothalamus that integrates information from diverse areas of the body and manages the thermal physiology [34].

When the patient is evolving to brain death or is already brain-dead, the hypothalamus stops working, and the organism's temperature tends to equalize with the environment. In this context, it is important to identify hypothermia as early as possible, through central measurements in the tympanic membrane, nasopharynx, and esophagus. Measurements in the axilla, oral cavity, or rectum are not endorsed [34].

4. Ventilation

The lung parenchyma is affected by many inflammatory processes induced by brain death, and its function may become suddenly worse after the diagnosis. Some studies demonstrate that 30 to 40% of the potential donors develop lung injury, in which the most common conditions are acute lung injury (ALI) and respiratory distress syndrome (ARDS) [56, 64].

Inadequate ventilation, although mainly related to primary injury, is also a significant cause of lung damage. Thus, protective ventilation strategies in volume or controlled pressure mode should be performed, meaning the tidal volume of 6 to 8 mL/kg of ideal body weight, FiO_2 adjusted to obtain $PaO_2 \geq 90$ mmHg, PEEP 8–10, and Plato pressure < 30 cm H₂O [34].

Alveolar recruitment maneuvers (including the use of PEEP titrated according to hypoxemia and hemodynamic impairment) can also be useful, but there is insufficient evidence that supports their use. In summary, the primary goals of mechanical ventilation in the potential donor are arterial blood normalization, prevention of alveolar collapse, and maintenance of ventilatory parameters, avoiding hyperdistension and severe lung injury [34, 36, 56].

5. Nutritional support

The intense systemic inflammatory response induces metabolic stress. The following hypercatabolic state is responsible for an energy expenditure up to 2.5× higher than the basal rate [65]. The “sympathetic storm,” through the release of adrenaline, glucagon, and corticosteroids, is crucial in these metabolic changes [56]. After the “sympathetic storm,” the total energy expenditure reduces about 30% due to hypothermia, absence of muscle activity, and lower brain metabolism.

Currently, there is no clear evidence that nutritional intake implies higher rates of organ utilization. However, this support can influence the immune function, besides preventing loss of muscle mass. Dominquez-Roldan et al. recommend caloric intake equivalent to 70–85% of baseline energy expenditure [66]. Severe hemodynamic instability is one of the few contraindications [66].

6. Hormone therapy

Endocrine disorders are often observed in patients with brain death due to the decrease of insulin release by the pancreas and the higher peripheral tissue resistance, resulting in hyperglycemia. As the studies about glycemic control in potential donors did not achieve conclusive results, the current procedures follow the recommendations given by the American Association of Clinical Endocrinologists and the American Diabetes Association, which consists of capillary blood glucose measures every 6 h. This time interval should be shorter in patients under continuous infusion of insulin. Moreover, persistent blood glucose levels above 180 mg/dL must be controlled following the institutional protocols [58, 63].

Respiratory alkalosis (secondary to hyperventilation and diuretic treatment, which are used as strategies to lower intracranial pressure) and metabolic acidosis (secondary to hypoperfusion) are also common, being the last one responsible for the decreased response to catecholamines and consequent worsening of vasodilation and hypotension. Thus, the pH should be kept between 7.35 and 7.45, although values up to 7.2 are also tolerated [67].

Diabetes insipidus is the main urine output disturbance in patients with brain death. The consequent polyuria must be appropriately treated to avoid hemodynamic instability. The management includes maintaining serum sodium between 130 and 150 mEq/L and urine output between 0.5 and 4 mL/kg/h. In the presence of hypernatremia, it should be corrected with 0.45% saline solution or 5% glucose solution. As disturbances in other electrolytes, such as calcium, phosphorus, magnesium, and potassium, can predispose to cardiac arrhythmias. They must also be carefully monitored every 6 h [64].

Corticosteroids have anti-inflammatory properties that contribute to the effectiveness of lung transplantation and reduce post-transplant liver dysfunction, so the use of these substances is endorsed. Besides, adrenal insufficiency that follows BD worsens hemodynamic instability, being indicated by the replacement of 15 mg/kg/day of methylprednisolone after the diagnosis [68].

Regarding thyroid hormones, it is recommended to perform hormonal resuscitation, including T3 replacement, in BD patients unstable under dopamine administration at doses higher than 10 µg/kg/min or with ejection fraction of less than 45% [69].

7. Transfusion

The loss of peripheral vasomotor tone after BD causes an uneven blood flow distribution and poor perfusion of some organs may occur, despite systemic oxygen saturation and hemodynamic stability [6270]. Some authors use a theoretical basis to associate lower lactate levels of brain-dead patients with appropriate perfusion [70]. However, there are no studies that indicate better transplantation results in patients with lower lactate levels.

In order to provide adequate oxygen delivery, patients with hemoglobin levels lower than 7 g/dL should receive blood transfusion [62]. When hemoglobin is between 7 and 10 g/dL, the blood transfusion should be performed exclusively if the resuscitation measures are not achieving the mean arterial pressure (MAP) goals [62]. The hematocrit should be kept > 30% [69]. It is important to use cytomegalovirus-seronegative blood and leukocyte filters to minimize the potential for sensitization [69].

Regarding coagulation factors, up to 45% of the patients with head trauma evolve with some type of blood dyscrasia [34, 63]. At the same time, hypothermia, metabolic alterations, and acid-base disturbance worsen coagulation disorders. When the fibrinogen value is below 100 mg/dL (even after administration of fresh plasma) and disseminated intravascular coagulation is suspected, the patient should receive cryoprecipitate transfusion [34, 63]. The platelet transfusion is recommended when the platelet count is < 80,000/mm³ [69].

Conclusion

BD is a relatively recent diagnosis that still causes concern and controversies in the society, leading to legal challenges. To avoid legal conflicts, the use of a standardized protocol of BD is essential. The BD protocol must be performed in all patients with unresponsiveness, brainstem areflexia, and apnea. The exclusion of reversible causes of coma is fundamental and the investigation of BD must be carried out regardless of whether the patient is an organ donor or not.

Once BD is diagnosed, the identification of the potential donor can be performed. The physiological changes that come about during the brain death process make those patients unique. Informing family members properly, establishing a management plan, avoiding futile therapies, reducing health care costs, and optimizing intensive care occupancy are essential. Besides, this suffering moment can be transformed into an altruistic manifestation through organ donation.

Availability of data and material Not applicable

Code availability Not applicable

Author contribution Leonardo Christiaan Welling had the idea for the article. Material preparation, data collection, and analysis were performed by Marcia Harumy Yoshikawa. The first draft of the manuscript was written by Marcia Harumy Yoshikawa and critically revised by Nicollas Nunes Rabelo, João Paulo Mota Telles, and Eberval Gadelha Figueiredo. All the authors commented on previous versions of the manuscript.

Declarations

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