38.1 History

When analyzing the history of medicine and its technological development, as well as in anthropology and philosophy, two subjects have always generated apprehension in the general population. How can the heart beat in a dead person and how to use organs from people who already died to bring life to others waiting for a transplant?

Cardiorespiratory arrest invariably follows brain death (BD). Victor Horsley, in 1894, described cases of cerebral hemorrhages, tumors, and traumatic brain injuries in which there was death due to respiratory failure before the cardio-circulatory arrest [1]. The development of the iron lung in the 1930s, in Boston, and its application in the 1950s, during the polio epidemic, allowed artificial delay of the dynamic process that involves the brainstem dysfunction, respiratory arrest, and subsequent cardiac arrest [2]. In other words, the installation of positive pressure mechanical ventilation prevents respiratory arrest and delays cardiorespiratory death. In addition, vasoactive drugs and metabolic corrections replace vegetative functions of the brain. These measures complete the support of some vital functions of the body in BD [3, 4].

Two French neurologists, Mollaret and Goulon, published in 1959 an article entitled *Le Coma Dépassé*, which defined some aspects of what is evolution to BD at the initial phase. The *coma dépassé*, which can be translated as a state of impaired consciousness “beyond” the coma, was described through the presentation of 23
patients with severe neurological conditions ventilated artificially. It was characterized by the immobility of the eyeball in the neutral position, mydriasis not reactive to light, absence of a blinking reflex, absence of a swallowing reflex, chin drop, absence of motor response to any stimulus, muscle hypotonia, tendon areflexia, plantar reflexes mistaken, sphincter incontinence, absence of spinal automatism, absence of spontaneous breathing after discontinuation of artificial ventilation, immediate cardiovascular collapse after discontinuation of noradrenaline infusion, disturbance of thermoregulation, and electroencephalographic silence [5].

If from a neurophysiological perspective, the recognition of brainstem function arrest can be understood, the clinical evaluation and the possibility of having some residual neurological function have improved the clinical criteria for defining BD in the last 50 years [6].

After the description by Mollaret and Goulon, the first set of criteria for BD was published by Hockaday et al. in 1965, including the absence of spontaneous breathing for 30 minutes, absence of tendon reflexes of any kind, absence of pupillary reflexes, absence of oculocardiac reflex, and isoelectric electroencephalogram (EEG) for at least 30 minutes [7].

In 1968, an ad hoc Harvard Medical School committee proposed the first definition of BD. It has included clinical features (irresponsive coma, absence of reflexes, and any movements) after 1 hour of observation, absence of breath after 3 minutes of disconnection of the respirator. Isoelectric EEG, exclusion of hypothermia (below 32° C), and suspension of central nervous system depressants (CNSD) were also necessary. Complementarily, the aforementioned clinical tests were repeated within 24 hours [8, 9].

In 1971 the Minnesota Code of Brain Death Criteria included the need for diagnosis of irreparable intracranial injury and the exclusion of metabolic causes. The authors reduced the observation time to 12 hours, established 4 minutes of disconnection of the mechanical ventilation without breathing movements for apnea. They also restricted the need for evaluating only the reflexes that pass through the brainstem, featuring, for the first time, that the injury to this region would be the moment of irreversibility [10].

The next step in the evolution of the BD concept was a document that would have significant international influence. The Uniform Determination of Death Act (UDDA), approved in Hawaii in 1980 by the National Conference of Commissioners on Uniform State Laws, has been the recommendation for use in all US states [11] as it affirms that:

An individual who has maintained an irreversible arrest of circulatory and respiratory functions or maintained an irreversible arrest of all functions of the entire brain, including the brainstem, is dead. The determination of death must be made according to accepted medical standards.

Irreversibility was established by diagnosing the cause of the coma, which was irrecoverable and sufficient to justify the dysfunction. Regarding observation time, 6 hours was considered enough. For cases of exogenous intoxication, hypothermia, shock, and children, more time was necessary. In 1995, the American Academy of Neurology reaffirmed these criteria, specifying how to perform the apnea test and a series of possible clinical observations which do not invalidate the BD diagnosis,
like Babinski’s sign, normal blood pressure, and absence of diabetes insipidus, among others [12].

Although not universally accepted, the equivalence of BD and death is a legal standard throughout most of the Western countries, and even the undeveloped countries are following. There is an increasing prevalence of its legal standard in practice [6, 11, 13].

Despite most countries have a legal provision for BD, institutional protocols for diagnosis are not universal and are often absent, particularly in lower-income countries and in those without an organized transplant network. Even among countries with an organized diagnostic protocol, there is substantial variation in the criteria that are used [3, 4, 6, 11–13]. The most significant differences between the criteria adopted in each country are the number of clinical examinations (ranging from one to three different examiners); intervals between exams (1–24 hours, for adults); mandatory complementary examination (being optional in several countries); preferential type of complementary test to be performed; and qualification of the doctor who performs the examinations (requirements in several countries are previous experience with the clinical tests, minimum time since graduation, and having some medical specialization) [3, 14–16].

38.2 Diagnosis

BD is defined as the determination of human death after irreversible cessation of all clinical brain functions. Its diagnosis is clinical, made at the bedside. When the clinical examination is inconclusive, or the patient has any peculiarity, ancillary tests are required. In some countries, like Brazil, ancillary tests are mandatory by law [3, 4, 14].

Practice parameters of BD have been established in 1995 and revised in 2010 by the American Academy of Neurology. These parameters are the basis of diagnosis protocols worldwide. Some differences exist between countries and even between US states. In adults, there are no published reports of neurologic recovery after a diagnosis of BD, using the criteria published in 1995. In the 2010 revision, the authors observed that confirmatory tests were less reliable and useful than has been suggested in 1995 [6, 11, 12]. According to Shewmon et al., BD diagnosis depends on this triad: the presence of pre-conditions excluding reversible causes of neurological impairment (e.g., traumatic brain injury, subarachnoid hemorrhage, extensive ischemic stroke), clinical examination, and ancillary tests (when necessary) [13].

38.3 Pre-conditions

The diagnosis of coma etiology must be established in clinical evaluation and confirmed by neuroimaging or other diagnostic tools (Fig. 38.1). The uncertainty of the presence of an irreversible lesion, or its cause, makes it impossible to determine
BD. A minimum period of observation and intensive care treatment in a hospital environment for at least 6 hours in a coma state must be respected. When hypoxic-ischemic encephalopathy is the primary cause enrolled, a minimum period of 24 hours after cardiac arrest or rewarming in therapeutic hypothermia should be expected before starting the BD diagnosis protocol. The cause of the coma must be known and registered [3, 16–18].

38.4 Excluding Confounding Factors

Some clinical conditions can simulate BD or worsen a critical neurological state, confusing the clinical exam. One example is hydroelectrolytic disorders. It is the responsibility of the team involved in BD diagnosis to determine whether these abnormalities are secondary to the natural evolution to BD or a confounding variable that impairs the neurological examination. Severe hypernatremia refractory to treatment does not preclude BD determination, except when it is the only cause of the coma [3, 4, 14–16].

Also, hypothermia can confound the clinical exam. Normothermia must be a goal and sometimes needs external warming. The exact temperature that is appropriate to BD diagnosis is not known, but a minimum core temperature of
Severe exogenous intoxication, including those by CNSd (e.g., opioid analgesics and other sedatives) commonly used in the ICUs, needs to be ruled out. When CNSd are used in continuous infusion and habitual dosages, it will be necessary to wait for a minimum interval of four to five half-lives after the drug suspension before starting procedures for determining BD (Table 38.1) [14, 16].

If CNSd are used in the presence of liver failure or renal failure, after therapeutic hypothermia, or when intoxication is suspected due to higher than the usual doses, more time is necessary to start the protocol of BD diagnosis. The exact time should be individualized. It takes into consideration the severity of liver and kidney dysfunctions, the doses, and for how long it has been used [14, 16].

### 38.5 Clinical Evaluation (Neurologic Assessment)

The three cardinal findings in BD diagnosis are coma or unresponsiveness, absence of brainstem reflexes, and apnea [3, 4, 14].

**A. Coma**
Patients must lack all evidence of responsiveness with no motor response to pain. It should be tested in all extremities and cranial segments (usually nail-bed pressure on the four limbs and supra-orbital pressure). The latter is essential in situations of spinal cord injury, in which the synaptic reflex may be absent if spinal shock is suspected.

B. Absence of brainstem reflexes

Absent pupillary light reflex: Pupils should be fixed and unresponsive to intense light stimulation (flashlight) and may have an irregular contour and variable or asymmetric diameters.

Absent corneal reflexes: The absence of a blinking response to direct stimulation of the lower lateral corner of the cornea with a drip of cold saline or cotton wool soaked in saline or distilled water.

Absent oculocephalic reflexes: The absence of deviation of the eye(s) during rapid movement of the head in the lateral and vertical direction. Do not perform on patients with suspected or confirmed cervical spine injury.

Absent oculovestibular reflexes (caloric responses): No deviation of the eye(s) during 1 minute of observation, after irrigation of the external auditory canal with 50–100 ml of cold water (±5 °C), with the head placed in a supine position and at 30°. The minimum examination interval between both sides should be 3 minutes. Perform otoscopy before verifying the absence of tympanic perforation or occlusion of the external auditory canal.

Absent gag reflex: Should be absent on stimulation of the posterior pharynx.

Absent cough: With tracheal suctioning (cannot be evaluated only with the manipulation of the orotracheal tube).

C. Apnea

This test is the last one to be performed since the apnea test can per se harm the patient [3, 4, 18]. The three steps are described in Fig. 38.2.

Plum and Posner, two of the leading researchers in the comatose patient investigation, suggested the use of blood gas analysis during the apnea test. They established that if PaCO₂ were in the normal range 1–2 minutes without artificial ventilation, then it would be enough to produce CO₂ tension elevation to stimulate the respiratory center. Speeds of PaCO₂ increase in apnea patients were estimated at 4.1 mmHg/min in the first 4 minutes and 2.7 mmHg/min in the subsequent 6 minutes. Therefore, a patient who starts the test with PaCO₂ of 30 mmHg will need 8 minutes of apnea to overcome 55 mmHg; if started with PaCO₂ of 35 mmHg, he will need 6 minutes, and if started with PaCO₂ of 40 mmHg, he will need 4 minutes of observation [19].

In some patients, ventilatory conditions do not allow a persistent increase in PaCO₂ to be achieved without concomitant hypoxia. In these situations, apnea testing can be performed using the connection of a “T-piece” to the orotracheal tube coupled to a continuous positive airway pressure (CPAP) valve with 10 cm H₂O and oxygen flow at 12 L/minute. The apnea test should not be performed on ventilators
that do not guarantee oxygen flow in CPAP mode, which results in hypoxemia [3, 4, 11, 14, 16, 18].

### 38.6 Pitfalls and Special Situations

Some conditions can make clinical BD’s diagnosis a difficult task. In cases of severe facial trauma, preexisting pupillary abnormalities, and high-level spinal cord injuries, it is sometimes impossible to assess brainstem reflexes. Exogenous intoxication, especially in the presence of renal or hepatic insufficiency, makes the diagnosis a challenge. In patients with chronic dioxide carbon retention (e.g., COPD and other pulmonary pathologies), the trigger for respiratory incursion can be higher than standardized in several protocols. Some authors recommend that 20 mmHg raise above the baseline PaCO₂ value is necessary for situations of chronic carbon dioxide retention. Spinal cord reflexes, including complex-spontaneous motor movements, can be present in BD patients, and it can be clinically difficult to differentiate them from cerebral motor-induced movements. Besides, false triggering of the ventilator can commonly happen and compromise apnea diagnosis [4, 14–16].

One of the most frightening movements for family members and health professionals that does not exclude the diagnosis of BD is Lazarus sign. It is a sequence of movements that lasts a few seconds and can occur spontaneously, during the apnea test, by the passive movement of the head or right after the disconnection of the mechanical ventilation device. It begins with the extension of the arms, followed by crossing or touching them in the chest and finally resting next to the trunk, and flexion of the trunk may also occur. However, not just this movement pattern may occur
Saposnik et al. describe innumerable movement patterns, including plantar flexor or extensor responses, cremasteric reflex, myoclonus, abdominal cutaneous reflex, and facial myokymia, among others [20].

### 38.7 Ancillary Tests

Usually, with a known cause of coma and excluding the confounding factors, the clinical exam is sufficient for BD diagnosis. However, some situations can bring doubts, as explained above. In some countries, these tests are mandatory by law as a complement of the clinical diagnosis [3, 4, 14].

The choice of test must be individualized. All tests have their own limitations, and the selection depends on the patient’s clinical conditions, transport availability, feasibility of the test in the institution, and expertise of the medical staff. Confirmatory tests are divided in two essential types: brain blood flow and electrophysiological exams [14, 21, 22].

Essentially, if brain blood flow is absent, the brain is considered dead. It occurs when intracranial pressure, due to tissue edema or mass effect, raises and exceeds systemic arterial pressure obstructing blood flow completely.

BD extinguishes all cerebral electric activity also, and this is the basis of electrophysiologic assessment.

Both methods have limitations. Brain blood flow can be nonexistent in hypotensive states leading to a “false positive” diagnosis. “False negatives” also can occur in “open cranium” situations like traumatic skull fractures, decompressive craniectomy, or ventricular drains. Electrophysiologic tests are probably a best option in these situations. On the other hand, blood flow tests are not affected by hypothermia, exogenous intoxication, or metabolic disorders, which can mimic the absence of cerebral electric activity, being a false positive isoelectric electroencephalogram [14, 16, 21].

Brain blood flow tests include cerebral angiography, transcranial Doppler, magnetic resonance angiography, computed tomographic angiography, and nuclear medicine radionuclide scanning. Electrophysiological tests include electroencephalography and somatosensory evoked potentials [4, 16, 21].

### 38.8 Brain Blood Flow Tests

Four-vessel cerebral angiography is considered the “gold standard” method on BD diagnosis. It is expected no blood flow at carotid bifurcation and beyond at the circle of Willis. External carotid flow is normally present. A minority of BD patients can still have minimal arterial flow (especially in “open skull situations”), delaying the diagnosis and the needs of repeated exams for confirmation. Other disadvantages include the ionic contrast infusion and transportation until the hemodynamics suite.
These aforementioned disadvantages can be a problem in unstable patients. Mean arterial pressure should be monitored strictly during the cerebral angiography [14–16].

In contrast, transcranial Doppler (TCD) is non-invasive and safe and has lower cost than angiography. It can be performed at bedside but demands expertise. Approximately 9% of patients do not have an adequate bone window for Doppler insonation, so the confirmatory test needs to be changed. Small systolic peaks without diastolic flow or a reverberating flow pattern are suggestive findings of BD. The exam sensibility is 70% and specificity is near 100% [3, 4, 6, 9, 16, 23].

There are other possible brain blood flow confirmatory tests not usually standardized in most protocols. Magnetic resonance angiography (MRA) is one of the alternatives. Absence of brain blood flow supports the diagnosis. Small studies suggest good sensitivity, but specificity is still uncertain. Computed tomographic angiography (CTA) is also an alternative, and its sensitivity seems to be similar to other ancillary tests. However, there are many doubts regarding test specificity. Other disadvantages include use of contrast and the needs for transportation [6, 11]. Nuclear medicine seems to be a good alternative for diagnosis, but it is not widely available. Studies using 99mtc-labeled hexamethylpropyleneamine oxime (HMPAO) and subsequent imaging with single-photon emission computed tomographic (SPECT) brain scintigraphy show excellent specificity (no false positives) and sensitivity that are similar to transcranial Doppler [11, 21].

38.9 Electrophysiologic Tests

Electrocerebral silence or a flat electroencephalogram (EEG) has been included in the first guidelines for BD diagnosis. It is still recommended as an ancillary test in most countries, especially in the USA. This silence is defined as the absence of any electrical potential >2 microvolts, non-artifactual, in a 30-minute minimum record time. Nonetheless, it has several limitations. As exposed before, a flat EEG may be present in severe intoxications, hypothermia, and metabolic disorders, what does not imply in an irreversible brain injury, with some studies showing the presence of false positives in these situations. In the ICU environment, the presence of electrical artifacts is common, which can be interpreted as cortical activity leading to false negative results [6, 11, 17, 21].

Evoked potential tests also have limited use in BD diagnosis. Somatosensory evoked potentials (SSEP) and brainstem auditory evoked potentials (BAEP) are the two available modalities for this purpose. Anatomically, these tests show brainstem integrity but cannot test the functional integrity of other CNS structures, which can be a dilemma in brainstem lesions. There are descriptions of patients with evoked potential tests supporting BD diagnosis with preserved EEG. Some authors postulate the combination of evoked potential tests and EEG to BD diagnosis accuracy [22, 24].
38.10 Ethical Aspects

Cerebral death (brain death) is a popular term for the neurological cause of death. Nevertheless, it is doubly mistaken: first for inducing the false interpretation that the brain and not the individual is dead and second for the anatomical mistake, since conceptually in the vast majority of other countries, the loss of function is necessary for the whole brain (from the Greek word enkephalos) and not exclusively cerebral (from the Latin word cerebrum). The use of the term brain death partially corrects this problem. However, the introduction of the etymological debate on this topic is unnecessary [25, 26].

In the medical literature, there is no conceptual difference between the words cerebral death and encephalic death, since both comprise irreversible dysfunction of the brain, brainstem, and cerebellum. However, there are significant differences with two other anatomically restrictive concepts: brainstem death, used in the UK, which does not require brain damage, and neocortical death, which does not require cerebral and brainstem injury. As already noted, extensive injury to the brainstem compromises both breathing and awakening, involving Christian-Jewish fundamentals of life. However, the most striking criticism of the brainstem death criterion is the possibility of diagnostic confusion with locked-in syndrome [27]. Although in locked-in syndrome, tetraparesis and cranial palsy due to pontine lesion coexist with preserved awakening, coma is common in the early stages, making the diagnosis difficult. Also, even though the brainstem lesion is rationally compatible with philosophical-ontological, religious, pathophysiological, and clinical-prognostic concepts of death, the uncomfortable possibility of cortical preservation and consequent maintenance of the content of consciousness, even if inaccessible due to the inability to awakening, makes it a stressful situation [27].

If the acceptance of death criteria anatomically restricted to the brainstem is complex, the criteria for neocortical death are more complicated. This model requires only damage to the brain areas involved in the content of consciousness, affecting what is considered the essence of the human being. The loss of reason and consequent depersonalization would be equivalent to death, implying that patients in a persistent vegetative state are dead, since they maintain breathing and the sleep-wake cycle only.

Although valid, more in-depth discussions on the subject are not the scope of this chapter.

In countries where the legislation is not strict regarding post-BD management, three situations of cardiorespiratory support may occur after BD. The first is the organ preparation for removal and subsequent transplantation. The second, very sad, is a pregnant woman in BD with a viable fetus when life and death cohabit the same body. The third and controversial situation is the maintenance of cardiorespiratory function at the request of family members or the patient himself, given several bioethical arguments in favor of redefining death, as well as its legal repercussions [25].
In the religious sphere, Judaism, Catholicism, and Islamism do not create restrictions to the concept of BD or organ removal [26, 27]. However, Tibetan Buddhism correlates death with decomposition. Gypsies require to keep the body intact for a year after death so the soul can reconstruct its steps. The Shintoism believes that the dead body is impure and dangerous, a fact that contributed to the difficulty in accepting BD and transplants in Japan [17, 28–30].

Despite the robust scientific and philosophical knowledge on the subject, there are indications that its diffusion, both between doctors, other health professionals, and among general population, is unequal. The decision between bioethical duties of non-maleficence and justice, respect for patient’s autonomy, and minimization of family suffering belongs to the medical staff. Safety, consistency, clarity, and transparency in information transmission are an essential part.

38.11 Management of the Potential Organ Donor

38.11.1 Monitoring

The monitoring of the potential donor should be as complete as possible. What is observed is often less proactive management, given the severity of the brain injury, in addition to the lack of knowledge about the multiple organ donation processes. The care of a potential organ and tissue donor represents the prospect of, at least, obtaining benefits for many other people. Keeping the donor as close as possible to their homeostasis will enable donation and, probably, good organ preservation in the short, medium, and long terms. These patients should, therefore, receive individualized care, always thinking in the possible beneficiaries. All should be admitted to the intensive care unit, monitored with continuous electrocardiography, peripheral oxygen saturation (SpO₂), necessary vital data, urinary output control, central vein access, and invasive pressure monitoring. The objectives do not differ from those recommended for other critical clinical conditions [17, 29, 31].

38.11.2 Hemodynamic Support

After the establishment of BD, the removal of viable organs for transplantation should occur as soon as possible. Bureaucratic obstacles often delay the entire process. In this context, it is essential to guarantee the supply of oxygen to the tissues, maintaining the physiological functions and eventual dysfunctions that may occur. The longer delay worsens in the inflammatory response and impairs the use of tissues for transplantation. It is recommended that the interval between the diagnosis of BD and the removal of organs should occur 12 to 24 hours [32].
In the hemodynamic management scenario, blood pressure measurement in a non-invasive manner is imprecise in shock situations, usually observed in BD patients. Despite low evidence to support the use of invasive methods to monitor hemodynamic support, the recommendations for this are strong within specialty societies [33, 34].

A striking feature of the patient who is evolving to BD is the occurrence of the so-called sympathetic storm. This disturbance occurs in two phases; the first is related to adrenergic hyperactivity and is clinically recognized by tachycardia, hypertension, increased systemic vascular resistance, and increased oxygen consumption by the myocardium. There is characteristically a considerable increase in systolic pressure than in diastolic pressure. This phase lasts approximately 30 minutes, and subsequently, hypotension occurs. In the acute phase, when blood pressure levels are elevated, there is no consensus in the literature as to whether treatment of this hypertensive crisis is necessary or not. As its pathophysiology is related to the increase in systemic vascular resistance, there may be intra-abdominal organ hypoperfusion. This visceral involvement occurs mainly when systolic levels of 160 mmHg or higher occur for more than 30 minutes. If necessary, the use of esmolol or nitroprusside is recommended for blood pressure control temporarily. Attention should be done to the hypotension that spontaneously occurs after adrenergic discharge of the sympathetic storm [32, 35].

The mean arterial pressure target of potential donor patients is between 60–80 mmHg and at least 100 mmHg systolic blood pressure. The exposed values are not a guarantee of tissue perfusion, and the analysis of tissue perfusion markers should be used. It should be noted that in patients already in BD, there is depletion of circulating catecholamines, which is associated with eventual osmotic diuresis due to hyperglycemia or mannitol infusion, as well as diabetes insipidus. These previous factors hinder the blood pressure control. Left ventricular dysfunction often occurs, due to myocardial contusion, hydroelectrolytic disorders, pulmonary hypertension, or neurogenic myocardial stunting [32].

Hemodynamic support is initially performed with volume replacement, but defining how much volume is needed is a greatest task. Insufficient replacement increases the inflammatory response and worsens organ dysfunction. The initiation of vasopressor drugs without adequate volume replacement can lead to arrhythmias or overact vasoconstriction and organ ischemia [36]. In contrast, excess volume leads to acute pulmonary edema and makes this organ unfeasible for transplantation [29, 31, 32, 35].

The central venous pressure monitored in every potential donor is subject to criticism. Values of 8–12 mmHg are not able to define the responsiveness or non-responsiveness to volume replacement. However, CVP <4 mmHg allows more volume infusion. The infusion volume is stopped if the CVP rises more than 2 mmHg. The use of DeltaPp has higher sensitivity and specificity than the CVP measurement and is a good alternative. In a practical way, 20–30 ml/kg of heated crystalloid solution at 43 degrees for 30 minutes is initially infused. If, after volume expansion, and CVP and DeltaPp values define that there is no possibility of more volume infusion, the vasoactive drug infusion is indicated [14, 17, 30, 35].
There is no consensus on which drugs to choose, and there is no dose limit. There are concerns about cardiac viability after using high doses of beta-agonists (dopamine and dobutamine), mainly when used in the context of low cardiac output and secondary hypoperfusion. Despite this, there is no formal contraindication for its utilization. Vasopressin selection is emphasized since it is a hormone with a vasopressor activity that helps in the management of diabetes insipidus. It reduces the need for catecholamines and, consequently, their complications. One unit is used in bolus, followed by 0.5–2.4 U/hour [14, 30].

Lactate levels, as well as central venous saturation, despite useful in situations of trauma and sepsis, are not adequate to assess the response to fluid resuscitation in potential donor patients [17, 35, 37].

Cardiac arrhythmias are also common in patients undergoing BD protocol. They can lead to reduced cardiac output and hypotension. Its etiology is multifactorial, and among the most frequent causes are hypovolemia, hypotension, hypothermia, catecholamine administration, myocardial contusion, acid-base equilibrium, and hydroelectrolytic disturbances. All types of arrhythmias are found, from supraventricular and ventricular tachyarrhythmias to conduction disorders with bradyarrhythmias. Tachyarrhythmias and bradyarrhythmias should be treated according to American Heart Association protocols. Atropine should not be used in bradyarrhythmias, and the temporary transcutaneous pacemaker followed by the transvenous pacemaker may even be indicated [14, 16].

### 38.12 Temperature Control

Keeping body temperature within physiological limits (36–37.5°C) is essential for maintaining the homeostasis. The primordial function on temperature control belongs to the hypothalamus, which integrates information through the skin, organs, spinal cord, and brain and, through its efferences, controls thermal physiology [16].

After BD, or in its evolutionary process, the hypothalamus ceases its functions. In this context, there is a tendency for the organism temperature to equalize with the environment. The early identification of hypothermia is essential and preferably through central temperature measurement obtained in the esophagus, tympanic membrane, or nasopharynx. Measurements in the oral cavity, axilla, or rectum are not recommended [28, 36].

### 38.12.1 Ventilation

BD induces many inflammatory changes that compromise the lung parenchyma. Lung function can worsen suddenly in patients after BD diagnosis. About 30–45% of potential BD donors develop lung injury, most often acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [14, 16].
Despite being related to primary injury, inadequate ventilation strategies are also responsible for tissue damage. Protective ventilation strategies in volume or controlled pressure mode, tidal volume 6–8 ml/kg of ideal bodyweight, and FiO₂ adjusted to obtain PaO₂ ≥ 90 mmHg, PEEP 8–10, plateau pressure < 30 cm H₂O are widely recommended [4, 16, 18, 35, 36, 38].

Alveolar recruiting maneuvers can be useful, but there is no strong evidence to justify their use. Among these, the application of PEEP is recommended, but it should be titrated according to hypoxemia and hemodynamic impairment. The ultimate objectives of mechanical ventilation in the potential BD donor are arterial blood gas normalization, alveolar collapse avoidance, and maintenance of ventilatory mechanical parameters that protect from hyperdistention and potentization of lung injury [35].

### 38.12.2 Nutritional Support

The exacerbated systemic inflammatory response is correlated to metabolic stress. The hypercatabolic state, very common after severe head trauma, can lead to an energy expenditure up to 2.5× higher than the basal metabolic rate. The massive release of adrenaline, glucagon, and corticosteroids during the “sympathetic storm” is a significant contributor to these metabolic changes [39].

After the sympathetic storm, there is a decrease in baseline energy expenditure due to hypothermia, reduced brain metabolism, and absence of muscle activity. It is estimated a 30% reduction in total energy expenditure.

There are no studies that demonstrate a higher rate of organ utilization in patients submitted to nutritional intake. However, the caloric intake aims not only to prevent the loss of muscle mass but also to influence immune function. One of the few contraindications for nutritional support are those patients with severe hemodynamic instability. According to Domínguez-Roldan et al., nutritional support equivalent to 70–85% of baseline energy expenditure should be offered [29, 37].

### 38.12.3 Endocrine-Hormonal Therapy

Endocrinological and hormonal disorders are very common in patients with BD diagnosis. There is a decrease in insulin release by the pancreas as well as higher resistance in peripheral tissues. This condition leads to hyperglycemia. Studies on glycemic control in potential BD donors have not yielded conclusive results, and current procedures follow established protocols of American Association of Clinical Endocrinologists and American Diabetes Association in which the measurement of capillary blood glucose should be done every 6 hours. Shorter intervals are necessary if insulin is in continuous infusion. It is observed that persistent blood glucose levels above 180 mg/dl must be corrected according to institutional protocols [40].
Both respiratory alkalosis and metabolic acidosis are frequently observed. The first is consequent to hyperventilation and diuretic treatment in an attempt to reduce intracranial pressure. When increasing the affinity of hemoglobin for oxygen, there is a microcirculation impairment. Metabolic acidosis, often secondary to tissue hypoperfusion, reduces the response to catecholamines and generates more vasodilation and hypotension. The ideal is to maintain the pH between 7.35 and 7.45, but values up to 7.2 are tolerated [28].

Changes in urine output are frequent in the BD donor. The main disturbance is diabetes insipidus. The polyuria occurrence can lead to hemodynamic instability if not properly treated. The main recommendations are to keep serum sodium between 130 and 150 mEq/L and urine output between 0.5 and 4 ml/kg/h. In the case of hypernatremia, its correction should be made with 5% glucose solution or 0.45% saline solution. Other electrolytes such as magnesium, phosphorus, calcium, and potassium must be monitored every 6 hours, and their changes must be corrected since they predispose to the occurrence of cardiac arrhythmias [38, 41].

Regarding the use of corticosteroids, there is evidence that their use contributes to the effectiveness of lung transplantation. Due to its anti-inflammatory properties, some studies demonstrate a reduction in post-transplant liver dysfunction. Besides, adrenal insufficiency that occurs after BD worsens hemodynamic instability, and in this context, the replacement of 15 mg/kg/day of methylprednisolone after confirmation of BD is indicated [29, 37].

Clinical evidence demonstrates that the replacement of thyroid hormones results in better hemodynamic stability and higher uptake of hearts for transplantation. As there are no studies on absorption via the gastrointestinal tract in situations of BD, the preferred route is intravenous. However, some countries do not have an intravenous presentation, and in these cases, 1–2 mcg/kg is recommended soon after BD diagnosis [42].

### 38.12.4 Antibiotics

One of the emerging concepts is the so-called borderline donors. Until recently, potential donors were excluded due to the presence of an identified infection, whether bacterial, fungal, viral, or parasitic. In these situations, many organs are no longer used, and a review of transplant contraindications has been prepared. Antibiotic indications and which organs may be used differ between protocols in each country. Eventually, even in the same nation, there are differences between states [43].

One of the most emblematic examples of transplantation in infected patients are the hepatitis B or C donors. They have their livers transplanted in patients who have the same virus [44].

Despite this, some systemic viral infections like HTLV I, HTLV II, rabies, adenovirus, enterovirus, measles, West Nile, and parvovirus; herpetic
meningoencephalitis parasitic infections such as leishmaniasis, trypanosomiasis, and malaria; and prionic diseases are contraindications to transplantation. HIV-positive patients, on the other hand, do not have a contraindication for transplantation as long as the recipient is also seropositive. There are even organ donation programs among HIV-positive patients [34].

38.12.5 Transfusions

Oxygen consumption is reduced in the BD donor, but it is not yet known the metabolic needs and oxygen supply to organ demands. In parallel, due to the loss of peripheral vasomotor tone, there is an uneven blood flow distribution, and some organs may be poorly perfused despite hemodynamic stability and systemic oxygen saturation.

Some authors try to correlate BD patients with lower lactate levels as donors with “theoretically” appropriate perfusion. Despite this theoretical basis, there are no studies that demonstrate better results in patients with lower lactate levels. The indication to evaluate lactate is based on critically ill patients’ studies, which such a marker helps to orient therapy.

As with critically ill patients, the best strategy for transfusing patients is controversial. Effectively, hemoglobin levels below 7 g/dl are avoided, and patients should receive blood transfusion. In situations where hemoglobin is between 7 and 10 g/dl, blood transfusion is recommended only in order to help hemodynamic stability if the MAP goals are not achieved with resuscitation measures [17, 37].

Concerning coagulation factors, it is known that patients with head trauma develop some type of coagulation disorders in up to 45% of cases. Concomitantly, hypothermia, metabolic, and acid-base balance disorders that occur in the BD patient further worsen the coagulation disorders installed. There is no consensus when to indicate clotting factors or platelet transfusion, and some protocols aim to maintain platelet count above 50,000/mm³. If disseminated intravascular coagulation is suspected and the fibrinogen value is below 100 mg/dl even after fresh plasma, the cryoprecipitate transfusion is indicated [17, 37].

38.13 Conclusions

BD diagnosis should be performed in all unresponsiveness, absence of brainstem reflexes, and apnea patients. The exclusion of reversible causes for the neurological condition is essential. Such measures must be carried out regardless of the condition of a donor for organ transplantation.

The observed physiological disarrangements turn the BD patient as unique, with many peculiarities. Establishing a management plan in order to avoid futile therapies, providing safe information to family members, reducing costs, and
optimizing the intensive care occupancy are essential. Furthermore, the option for organ donation transforms the intense suffering moment into an altruistic manifestation.

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