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Using the brain criterion in organ donation after the circulatory determination of death☆,☆☆,★,★★

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ABSTRACT

The UK, France, and Switzerland determine death using the brain criterion even in organ donation after the circulatory determination of death (DCDD), in which the United States and Canada use the circulatory-respiratory criterion. In our analysis of the scientific validity of the brain criterion in DCDD, we concluded that although it may be attractive in theory because it conceptualizes death as a unitary phenomenon, its use in practice is invalid. The preconditions (ie, the absence of reversible causes, such as toxic or metabolic disorders) for determining brain death cannot be met in DCDD. Thus, although brain death tests prove the cessation of tested brain functions, they do not prove that their cessation is irreversible. A stand-off period of 5 to 10 minutes is insufficient to achieve the irreversibility requirement of brain death. Because circulatory cessation inevitably leads to cessation of brain functions, first permanently and then irreversibly, the use of brain criterion is unnecessary to determine death in DCDD. Expanding brain death to permit it to be satisfied by permanent cessation of brain functions is controversial but has been considered as a possible means to declare death in uncontrolled DCDD.

1. International DCDD Death Determination Practices

Prior to the development of tracheal positive-pressure ventilators in the 1940s and 1950s [1], physicians determined death by showing the prolonged absence of respiratory and cardiocirculatory functions because the functions of the brain and all other organs also ceased at this time [2]. However, once mechanical ventilation could sustain respiratory (and thereby cardiocirculatory) functions, it became possible for a patient with a completely destroyed brain to have respiration and ventilation supported mechanically.

To recognize the essential role of brain function in human life, to allow lawful withdrawal of life-sustaining therapy in cases of profound brain damage, and to address the growing needs of organ transplantation, a new test for death determination was proposed based on the cessation of brain function. In 1968, the Ad Hoc Committee of the Harvard Medical School defined “irreversible coma” or “brain death” as a “new criterion for death” and proposed tests to determine it [3]. In 1981, the medical consultants on the diagnosis of death to the US President's Commission added specificity and consensus to the tests for brain death [4]. In the United States, the most widely accepted brain death test battery for adults is that published in the Report of the Quality Standards Subcommittee of the American Academy of Neurology [5]. The brain criterion of death is now widely accepted around the world [6]. The US President's Commission [4] also discussed the circulatory-respiratory determination of death, which, for simplicity, we shorten to “circulatory death determination.” However, this issue did not become controversial until programs of organ donation after the circulatory determination of death (DCDD) in the 1980s forced physicians to pay greater attention to the exact moment of death [7] because of the time pressures of organ donation [8].

In the United States and many other countries, physicians determine death using 1 of 2 criteria: (1) the irreversible cessation of circulatory and respiratory functions or (2) the irreversible cessation of all functions of the entire brain, including the brain stem [9]. There remains a debate over whether the 2 criteria are independent or whether the circulatory criterion is valid because once satisfied, the brain criterion

Abbreviations: DCDD, donation after the circulatory determination of death; DBDD, donation after the brain determination of death; SAMS, the Swiss Academy of Medical Science; EEG, electroencephalogram; CPR, cardiopulmonary resuscitation.

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inevitably becomes satisfied because the brain is destroyed by ischemia from absent circulation.

In Canada, the diagnosis of death is based on the single brain criterion (brain death): "a person is dead when an irreversible cessation of all that person's brain functions has occurred" and is determined either by (1) "the prolonged absence of spontaneous circulatory and respiratory functions" or (2) "when the determination of the prolonged absence of spontaneous circulatory and respiratory functions is made impossible by the use of artificial means of support, the irreversible cessation of brain functions can be determined by any means recognized by the ordinary standards of current medical practice" [10].

In France, the law on Public Health also bases the diagnosis of death on the single brain criterion. Article R 1231-2 refers specifically to cessation of brain functions, while cardiorespiratory functions are artificially sustained [11]. Article R 1231-1 refers to the cessation of brain functions, secondary to the persistent cessation of respiratory and cardiac functions, and states that death can be determined only if 3 criteria are simultaneously met: absence of consciousness and spontaneous motor activity, absence of brain stem reflexes, absence of spontaneous ventilation [11].

In the United Kingdom, there is no legal definition of death and "professional guidance provides the legal standard" [12]. The "Code of practice for the diagnosis and confirmation of death," enacted by the Academy of Medical Royal Colleges, defined death based on the single brain criterion, stating that "the definition of death should be regarded as the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe" [13]. In the context of the cessation of cardiorespiratory function, this code of practice recommends to confirm death by identifying the following: (1) "the simultaneous and irreversible onset of apnea and unconsciousness in the absence of the circulation," (2) mechanical asystole for at least 5 minutes, and (3) "the absence of pupillary responses to light, of the corneal reflexes, and of any motor response to supra-orbital pressure" [13]. The British Transplantation Society stated that "death is in essence a neurological event and occurs when there is a permanent loss of the capacity of consciousness and all brain stem function," where death is confirmed by the absence of consciousness, respiration, and other brain stem functions, whereas asystole is identified by a flat arterial line or echocardiography [14].

In Switzerland, the diagnosis of death is also based on the single brain criterion. The Swiss Federal Act on Transplantation of Organs, Tissues and Cells, active since 2007, states that "a person is dead when all cerebral functions, including the brain stem, have irreversibly ceased" [15]. In the context of DCDD, the diagnosis of death relies on the determination of the irreversible cessation of cerebral functions, if the absence of cardiac activity has been observed for at least 10 minutes by means of echocardiography, and if the following clinical signs, determined by the Swiss Academy of Medical Sciences (SAMS), have been identified [16]: (1) coma; (2) bilaterally dilated pupils, unresponsive to light; (3) absent oculocephalic and vestibulo-ocular reflexes; (4) absent corneal reflexes; (5) no cerebral response to painful stimuli; (6) absent cough and gag reflexes; and (7) absent spontaneous respiration.

Thus, in some countries, death determination, even in a DCDD donor, is based on the brain criterion rather than on the circulatory criterion. In this article, we analyze the scientific validity and implications of the use of the brain criterion for the determination of death in DCDD.

2. Should there be 1 or 2 criteria to determine death?

Determining death based on the single brain criterion is attractive, because it conceptualizes death as a unified phenomenon as one of us stated: the event that separates "the biological processes of dying and bodily disintegration" [17,18]. Death has been defined as "the cessation of functioning of the organism as a whole," whose critical functions include consciousness, control of circulation, respiration and temperature, and control of homeostasis (fluid, electrolytes, neuroendocrine) [17,19].

In practice, physicians determine death in 2 general clinical situations. The first is in the presence of profound global brain damage in which respiratory and circulatory functions are maintained by life-sustaining therapy, particularly mechanical ventilation, and tests for death show the irreversible absence of the clinical functions of the brain. "Brain death" tests have been developed and validated to determine death in this small minority of patients dying in intensive care units [5,20]. The whole-brain criterion is the irreversible cessation of all clinical brain functions, including those of the brain stem. In the UK, the irreversible cessation of brain stem functions is deemed sufficient for death determination. In practice, brain stem death tests are usually equivalent to whole brain death tests.

In the much more common second clinical situation, respiration and circulation have ceased in the absence of cardiopulmonary resuscitation (CPR) or after failed CPR. Physicians diagnose death using the circulatory-respiratory criterion. Using the brain criterion of death in such cases—as practiced in Switzerland and in the UK—is conceptually sound because in the absence of resuscitative efforts, cessation of systemic circulation inevitably produces an irreversible cessation of brain functions. But are brain death tests applicable, feasible, and necessary in the context of DCDD?

3. Brain death tests in donation after the brain determination of death

Brain death tests are used to diagnose death in a patient with irreversible loss of all brain clinical functions whose respiratory and circulatory functions are maintained by life-sustaining therapy including mechanical ventilation with endotracheal intubation. Prior to testing for brain death, clinicians must assure 2 essential preconditions that prove irreversibility: (1) the presence of a structural brain lesion that is sufficient to produce the clinical findings (eg, anoxia, major brain trauma, and cerebral hemorrhage) by history, examination, and neuroimaging, and (2) the exclusion of potentially reversible metabolic or toxic effects (eg, electrolyte, temperature, hemodynamic, or endocrine disorders) that might provoke a global but potentially reversible central nervous system depression mimicking brain death [5].

Once these preconditions have been met, brain death tests must show 3 principal findings: unresponsiveness, brain stem areflexia, and apnea. The tests document utter unresponsiveness to noxious stimuli, absence of pupillary response to light and dark, absence of eye movements to vestibuloocular reflex testing, absence of corneal reflexes, absence of facial muscle movement to noxious stimuli, absence of pharyngeal and tracheal reflexes, and true apnea [5]. The apnea test is usually performed last and must show no respiratory effort in the face of hypercapnia maximally stimulating the medullary respiratory centers. The apnea test has similar prerequisites: normotension, normothermia, euvolemia, eucapnia, absence of hypoxemia, and no prior evidence of carbon dioxide retention [5].

Ancillary tests may be performed to confirm the cessation of brain electrical output (electroencephalogram [EEG] and evoked potentials) or to prove the absence of intracranial circulation (cerebral angiography, radionuclide angiography, or transcranial Doppler ultrasound) [5]. Emerging confirmatory tests using computed tomography angiography, magnetic resonance angiography, magnetic resonance perfusion, and single-photon emission computed tomography are promising but not have been sufficiently validated.

4. Brain death tests in DCDD

4.1. Are brain death tests applicable in DCDD?

Brain death tests can be applied only if preconditions have been met that identify a structural cause and exclude potentially reversible metabolic or toxic factors. In DCDD, the first condition is met, because complete circulatory cessation inevitably progresses to brain death but the second condition cannot be met. Circulatory arrest violates the precondition excluding hemodynamic disorders. Circulatory arrest causes an

increase of blood carbon dioxide levels. Hypercapnia stimulates the sympathetic nervous system, which induces pupillary dilatation, interfering with the test of pupillary responsiveness to light. In uncontrolled DCDD, epinephrine and atropine may have been used during advanced cardiac life support interfering with the test of pupillary reaction to light. In controlled DCDD, norepinephrine or other vasopressors may have been used prior to withdrawal of life-sustaining therapy, also interfering with the test of pupillary responsiveness to light. In controlled DCDD, sedatives and analgesics usually used during the process of withdrawal of life-sustaining therapy suppress brain functions and may interfere with the tests that evaluate brain death.

Because preconditions to determine brain death cannot be met in the DCDD patient, accepted brain death tests cannot be applied. If the preconditions are not met, although brain death tests may prove the cessation of the tested brain functions, they cannot prove that the cessation is irreversible. Because irreversibility of brain functions is required for brain death, the SAMS tests cannot determine brain death. Ancillary brain death tests are not feasible in DCDD. They are time-consuming and, if performed, would result in a marked increase in organ warm ischemia time that would render the organs unusable.

Brain death testing is a retrospective determination showing that global irreversible brain damage had occurred previously that obliterated all brain functions. Brain death tests were not intended to be used prospectively which would be required if they were used in DCDD. The tests proposed by the SAMS in Switzerland or by the Academy of Medical Royal Colleges in the UK are only a selection of some of the tests of ceased brain function without the preconditions, exclusions, apnea test, and more detailed and time-consuming testing that is necessary for a complete brain death determination.

We presume that the SAMS instituted the brain tests for 2 reasons: (1) to maintain consistency in death determination by using the single brain criterion required in Swiss law and (2) to show that circulatory cessation was sufficiently prolonged to abolish testable brain functions. However, claiming patients are brain dead using these tests is invalid because the tests as described cannot prove irreversibility. However, in the context of circulatory arrest, the tests do show the *permanent* cessation of brain functions; that is, that brain functions have ceased and will not restart in the absence of resuscitative efforts to restore circulation.

4.2. Is a stand-off period of 5 to 10 minutes long enough to achieve brain death?

The development of DCDD programs in the 1990s prompted the need to expedite death determination to decrease warm ischemia time and optimize graft outcome. However, an overly rapid death determination can interfere with the deceased organ donation requirement to respect the dead donor rule: the "ethical and legal requirement that the multi-organ donor must first be dead and that donors should not be killed in order to obtain their organs" [21]. The tension between the twin goals of a timely death determination performed expeditiously after circulatory cessation to optimize transplanted organ health and a death determination performed long enough after circulatory cessation to respect the dead donor rule has raised considerable debate among scholars over "the exact moment of death" [8].

The stand-off (or "hands-off") period—the time between circulatory arrest and death determination—varies among DCDD protocols from 75 seconds to 20 minutes [22]. Given the most commonly used stand-off period of 5 minutes [22], several authors argued that DCDD protocols violate the dead donor rule because circulatory cessation is not yet irreversible [23–28], a claim that led some of them to advocate discontinuing DCDD programs [25,27]. Other authors proposed replacing the dead donor rule with a secured informed consent [28,29], but some advocates of the dead donor rule countered that the rule represents a fundamental right that cannot be waived by informed consent [30].

The most serious problem in using brain death for DCDD is that more than 10 minutes of circulatory cessation is required to develop brain death [31]. Several studies on the outcome of out-of-hospital cardiac arrest showed that even with a no-flow period of 20 to 30 minutes—ie, the time from collapse to CPR—some patients survived with good neurologic outcomes [32–35]. In 2015, a study reported patients who survived a no-flow as long as 30 minutes with good neurologic outcomes, when the initial rhythm was a ventricular fibrillation [32]. In a 1997 study, survivors were reported after a no-flow period of 15 and 20 minutes [33]. In a retrospective cohort study from 1992 to 2010, which studied "the interaction of no-flow time on the association between post arrest mild therapeutic hypothermia and good neurological outcome," the "maximum benefit" was observed at 180 days in patients "with no-flow times beyond 8 minutes" [35]. In a personal communication, the authors reported survivors with good neurologic outcome after a no-flow period for as long as 19 minutes, but there may have been a protective effective on the brain of the mild therapeutic hypothermia.

These studies suggest that some brain neurons may survive a circulatory deprivation of 20 minutes. However, these results should be interpreted with caution, because no monitoring was used between the collapse and the initiation of CPR. Therefore, the alleged no-flow state may have been low-flow with residual circulation permitting a degree of cerebral perfusion.

Animal studies provide evidence that some brain functions can be restored after circulatory cessation for as long as 1 hour [36,37]. Hossmann et al [36,37] reported the restoration of some cerebral activity in cats and monkeys, after the exclusion of the cerebral circulation for an hour. When pigs sustained a cardiac arrest induced for 15 minutes, some had a good neurologic outcome [38], particularly with the use of extracorporeal support when resuscitation failed [39]; other demonstrated survival but with severe brain lesion [40], even with the use of extracorporeal support [41]. In a study in which cardiac arrest was induced in pigs, the authors concluded that 10 minutes was sufficient to achieve brain death, based on the performance of brain death tests at 30 minutes after return of spontaneous circulation [42]. We question the validity of this study because of methodological flaws. Indeed, other animal studies have demonstrated that after the cerebral circulation resumes, it takes longer than 30 minutes for the cerebral functions to reappear. The study of Hossmann et al [36] showed that "EEG and evoked potentials began to recover after 3 hours following ischemia," "spontaneous respiration returned on the 2nd day," and neurologic outcome improved between the first and fourth weeks of evaluation. In another study, after 60 minutes of ischemia, it took 30 minutes in monkeys and 45 minutes in cats for the EEG to recover, and full recovery required 24 hours [43].

Even if animal studies are not applicable to humans, they suggest that some mammalian brain neurons may survive after a no-flow of at least 20 minutes and that a stand-off period of 10 minutes is probably insufficient to achieve brain death.

4.3. Using irreversible versus permanent cessation to determine brain death

There is an important distinction between a permanent and irreversible cessation of function that becomes relevant in death determination in DCDD. Cessation of a function is irreversible if no known or available technology can restore it, and it cannot restore itself. Permanent cessation of that function means that the function in question will not restart because it will not return spontaneously and no medical intervention will be conducted to restore it. In short, irreversible cessation means that the lost function cannot return, whereas permanent cessation means that it will not return [44].

Physicians often declare death before the precise moment of biological death which requires irreversible cessation of vital functions. In intensive care units and emergency departments, physicians often declare death once respiratory, circulatory, and brain functions all have ceased permanently but before they have ceased irreversibly [45]. Physicians declare death at the point of permanent cessation of circulation for social and practical reasons. They know that the circulation will not restart by itself, and that no resuscitative attempts will be made. Irreversible

cessation of circulation is the inevitable consequence of permanent cessation if no intervention interrupts this progression [44,45].

No one knows exactly how long it takes for a permanent cessation of circulation to produce an irreversible cessation of all brain functions [45], but it may take as long as 1 hour [46]. However, circulatory cessation leads to a rapid cessation of all brain functions within only a few minutes. If circulation is not restored, because the possibility of autoresuscitation has elapsed and because there will be no resuscitation attempt, all brain functions will have ceased permanently [45]. Thus, it might be argued that even if the state of irreversible cessation of brain functions has not yet been reached, death could be declared because the cessation of circulatory and brain functions is permanent [45].

Whether autoresuscitation is possible depends on the context. After the withdrawal of life-sustaining therapy (as in controlled DCDD), 2 minutes probably is sufficient to exclude the possibility of autoresuscitation [47]. However, after a failure of CPR efforts in the context of a refractory cardiac arrest (as in uncontrolled DCDD), autoresuscitation may occur up to 7 minutes after the cessation of unsuccessful CPR [48]. To be certain that autoresuscitation will not occur in controlled DCDD, we recommend respecting a stand-off period of at least 5 minutes.

It is unknown exactly how long it takes for all brain functions to cease after the cessation of systemic circulation. Safar [49] stated that "in sudden normothermic cardiac arrest, brain oxygen stores and consciousness are lost within 20 seconds, and glucose and adenosine triphosphate stores are lost within 5 minutes." In 2 case reports, the EEG was suppressed after, respectively, 10 and 15 seconds of asystole [50,51]. Hossmann et al [37] showed that in cats and monkeys, electrocortical activity, measured by EEG, stopped within 12 seconds after of the cessation of brain circulation. In a study published in 1973, Hossmann and Kleihues [43] showed that after the exclusion of brain circulation, the EEG became flat within 20 seconds and the evoked potentials "disappeared after two to four minutes." However, such studies of the 1970s may not have confidently excluded the cerebral circulation as the later ones. In a more recent study, an isoelectric EEG was reached after 22 to 74 seconds of cardiac arrest in pigs [42]. These studies show that brain functions almost certainly cease after 2 to 5 minutes of cardiac arrest causing a complete absence of circulation.

However, these results should be interpreted with caution because (1) animal studies cannot be directly applied to humans, (2) ordinary EEG measures only thalamocortical functions and does not directly measure brain stem function, and (3) the available data for human beings are few, consisting of 2 case reports. To avoid the unacceptable risk of procuring organs while some brain functions persist, it is necessary to ensure that all brain functions are lost before organ procurement is begun. Most neurologists agree that pain sensation and awareness are abolished once the EEG becomes completely flat, so there is consensus that pain and awareness are not possible within several minutes of complete circulatory cessation to the brain at normothermia. Additional research is necessary to determine with more confidence exactly how many minutes it takes for all brain functions to cease after cardiac arrest. A stand-off time of at least 5 minutes after complete circulatory arrest (as is common in DCDD protocols) ensures the cessation of all brain functions.

4.4. Are brain death tests necessary in DCDD?

When respiration and circulation have permanently ceased, death can be determined without assessing brain functions directly [4]. Brain death tests ordinarily are used to determine death only in those cases in which a patient's ventilation is being supported [19]. In cases of circulatory arrest, the traditional tests confirming the permanent absence of circulatory function are sufficient to predict that the brain will be rapidly and inevitably destroyed by lack of blood flow and oxygen to neurons [19]. Thus, the only requirement to prove death based on permanent cessation of circulation should be the confirmation of ongoing complete circulatory arrest by appropriate means (arterial line, echocardiography, electrocardiogram). Specific brain death tests are unnecessary.

5. Conclusion

The application of the brain criterion to DCDD, although theoretically coherent, is impractical because the validated brain death tests cannot be performed properly. Brain death tests require that potentially reversible disorders that may suppress brain functions have been excluded and all tests, including that for apnea, be performed. In the context of DCDD, circulatory arrest, hypercapnia, and the later use of vasopressors, sedatives, and analgesics all may interfere with the standardized evaluation of brain death.

Brain death tests are difficult or impossible to perform thoroughly before organ donation in DCDD because of the time pressure of organ donation. If brain death tests are used to determine death after circulatory arrest, they can confirm that the cessation of brain functions is permanent but they cannot prove that the cessation is irreversible at the time they are used.

A stand-off period of 5 to 10 minutes is insufficient to achieve the irreversible cessation of all brain functions that is necessary to determine brain death. Studies on the outcomes of out-of-hospital cardiac arrest patients suggest that some neurons in the human brain may survive a deprivation of circulation of at least 20 minutes and animal studies suggest that some brain functions may be restored after a deprivation of circulation of 30 to 60 minutes. Therefore, DCDD donors at the time they are declared dead do not satisfy the irreversibility requirement of brain death.

In the setting of circulatory cessation, physicians declare death by showing the permanent cessation of respiratory and circulatory functions but are not required to prove that the cessation of these functions is irreversible [45]. In DCDD, physicians can determine death on the grounds of permanent cessation of circulatory functions by showing that (1) no intervention will be performed to restore circulation that could reestablish brain circulation and (2) the possibility of autoresuscitation to restored circulation has elapsed. The stand-off period must be sufficient length to exclude possible autoresuscitation.

Altering brain death determination procedures to require only that brain functions have ceased permanently rather than irreversibly would be a departure from accepted medical practice. It remains unclear whether physicians or society would accept brain death as a prospective determination using the permanent cessation of brain functions rather than its current status as a retrospective determination to document irreversible brain damage that occurred previously. Also unclear is the duration of circulatory cessation necessary to achieve the permanent loss of all brain functions. Assuming no attempts will be made to restore circulation, some might argue that the donor is dead after a stand-off period of 5 minutes, because the donor has sustained a permanent cessation of both circulatory and brain functions. The expansion of brain death determination to being prospective using permanent cessation of brain functions is controversial but has been discussed as one possible basis for death determination is uncontrolled DCDD [52].

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