Understanding the Brain-based Determination of Death When Organ Recovery Is Performed With DCDD In Situ Normothermic Regional Perfusion

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The brain-based determination of death ("brain death") is now widely accepted throughout the world. It states that the irreversible cessation of brain functions is the fundamental criterion for human death. The recent World Brain Death Project provided a comprehensive cataloguing of all aspects of brain death including its medical and legal acceptance throughout the world.[1] Organ donation after the brain-based determination of death (DBDD) currently accounts for the majority of multiorgan donations internationally.

Organ donation after the circulatory determination of death (DCDD) has grown worldwide since the Institute of Medicine of the United States endorsed the practice of controlled DCDD in 2000[2] and a US national conference on DCDD in 2005 standardized its practice.[3] DCDD donations are expanding but remain fewer than the number of DBDD donations. DCDD donor death determination requires the permanent absence of systemic circulation. When systemic circulation is absent, brain circulation ceases. The essential feature of the unified brain-based concept of death is that permanent cessation of systemic circulation produces permanent cessation of brain circulation and neuronal perfusion resulting in permanent cessation of brain functions. Thus, the determination of death by circulatory criteria is consistent with the determination of death by neurologic criteria.

In situ normothermic regional perfusion (NRP) is emerging as a component of organ recovery procedures in controlled DCDD. Controlled DCDD is practiced in hospitalized patients after the planned withdrawal of life-sustaining therapy (WLST). NRP uses extracorporeal membrane oxygenation to reestablish circulation to specific regions

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of the body following death determination. The circulation reestablished may be restricted to the abdominal cavity (A-NRP) or may also include the thoracic cavity (TA-NRP). NRP reportedly improves organ utilization and recipient outcomes comparable with those of organs from DBDD donors,[4,5] but it also raises complex medical, ethical, and legal questions that must be resolved.[6-8] DCDD donor death determination requires the permanent absence of systemic circulation but NRP protocols reestablish systemic circulation. This situation raises the principal question in NRP: if resumption of circulation by NRP contradicts the conditions of the death declaration, how can a donor be declared dead by permanent cessation of circulation?

The use of the unified brain-based concept of death resolves the dilemma by clarifying that the relevant circulation that must cease is circulation to the brain.[9,10] If NRP is effectively restricted to ensure no circulation to the brain, thereby preventing brain perfusion and function, NRP fulfills the requirements of donor death determination and respects the dead donor rule. Ensuring that circulation to the brain has ceased permanently and will not be restarted allows donors to be declared dead based on the permanent cessation of brain functions despite the restoration of regional circulation to the abdomen or thorax.

DEATH DETERMINATION IN DONATION AFTER CIRCULATORY DETERMINATION OF DEATH

Under current DCDD protocols, a declaration of death requires determining that the potential organ donor's circulation has ceased permanently. Three conditions establish permanent cessation of systemic circulation: (1) circulation has ceased completely, as evidenced by intra-arterial pressure monitoring, electrocardiography, or echocardiography; (2) no circulation persists beyond the time interval during which autoresuscitation has been reported to occur; and (3) no intervention is made to restore circulation after death has been declared.[11]

If these conditions are met, the permanence criterion is fulfilled, the donor is validly declared dead, and the subsequent recovery of donated organs does not violate the dead donor rule.[11] Although legal standards differ among jurisdictions, physicians who follow DCDD protocols can be confident that they are acting in accordance with standards accepted around the world that have long equated death with permanent cessation of systemic circulation.[8]

In controlled DCDD protocols, a minimum of 5 min of absent circulation establishes that the heart will not restart spontaneously and that circulatory cessation is permanent. This controlled DCDD death standard was recommended by the Institute of Medicine[2] and is in common use in the United States and in most European countries.[12] The 5-min standard has been confirmed by a large prospective observational study of autoresuscitation, in which death was determined by circulatory criteria following WLST, in which the longest interval reported between asystole and autoresuscitation was 4 min and 24 s.[13]

THE UNIFIED BRAIN-BASED DEATH DETERMINATION IN DCDD

There is a widespread medical acceptance that human death can be declared on the basis of the permanent cessation of brain functions, defined as the permanent loss of the capacity for consciousness, of the capacity to breathe, and of all brain stem reflexes.[1,14] The permanent cessation of brain functions can be caused by primary brain pathology, such as traumatic head injury, stroke, or meningitis, or by hypoxic–ischemic brain damage secondary to the loss of brain perfusion during circulatory arrest. The unified brain-based concept of death provides that when the cessation of brain function results from circulatory arrest, the relevant circulation which has ceased is that of the brain.[9,10]

In applying the unified brain-based concept of death to the determination of death in DCDD, permanent cessation of systemic circulation initially causes brain circulation to cease. Permanent cessation of brain circulation results in the permanent absence of neuronal perfusion, which results in the permanent cessation of brain functions. Thus, the unified brain-based concept of death provides that, in DCDD, the permanent cessation of systemic circulation leads to the permanent cessation of brain functions.[9,10]

Physiologic studies of patients dying following WLST show that cessation of brain activity closely correlates with cessation of systemic circulation. The electroencephalogram becomes isoelectric within 30 s of cardiac arrest resulting in absent circulation to the brain[15] and can occur even sooner when WLST is followed by severe hypotension and hypoxemia before cardiac arrest.[16,17] Cessation of brain circulation triggers a physiologic cascade: cessation of brain perfusion leading to cessation of brain neuronal activity leading to cessation of brain function. After 5 min of complete cessation of brain circulation, death can be declared on the grounds that brain circulatory cessation is permanent and, therefore, the cessation of brain functions is permanent. Permanence is established when the interval during which autoresuscitation can occur has elapsed and no resuscitative intervention will be attempted.

A physiologic function that ceases *irreversibly* means that the function *cannot* be restored. A physiologic function that ceases *permanently* means that the function *will not* be restored.[18] From its inception, the determination of brain death has confirmed the irreversible cessation of brain functions. The testing that enables a formal brain death determination is a retrospective assessment of brain functions that had ceased previously (they cannot be restored).

The determination of death by circulatory criteria is a prospective (real time) assessment that requires only the permanent absence of circulation to the brain to ensure the permanent absence of brain functions. According to the unifying brain-based concept of death, the permanent cessation of circulation to the brain enables a valid determination of death because it results in the permanent cessation of brain functions (see Figure 1). Cessation of brain functions is the true endpoint of the brain-based concept of death, which is the consequence of the permanent cessation of circulation to the brain.

After circulation has ceased permanently, direct testing of brain functions would be the ideal method to prove its absence. But for technical reasons, electrophysiological assessment of brain function is not feasible in the DCDD donor, particularly the assessment of brain stem functions. Therefore, in DCDD protocols, the cessation of circulation to the brain is used as a surrogate for the cessation of brain functions.

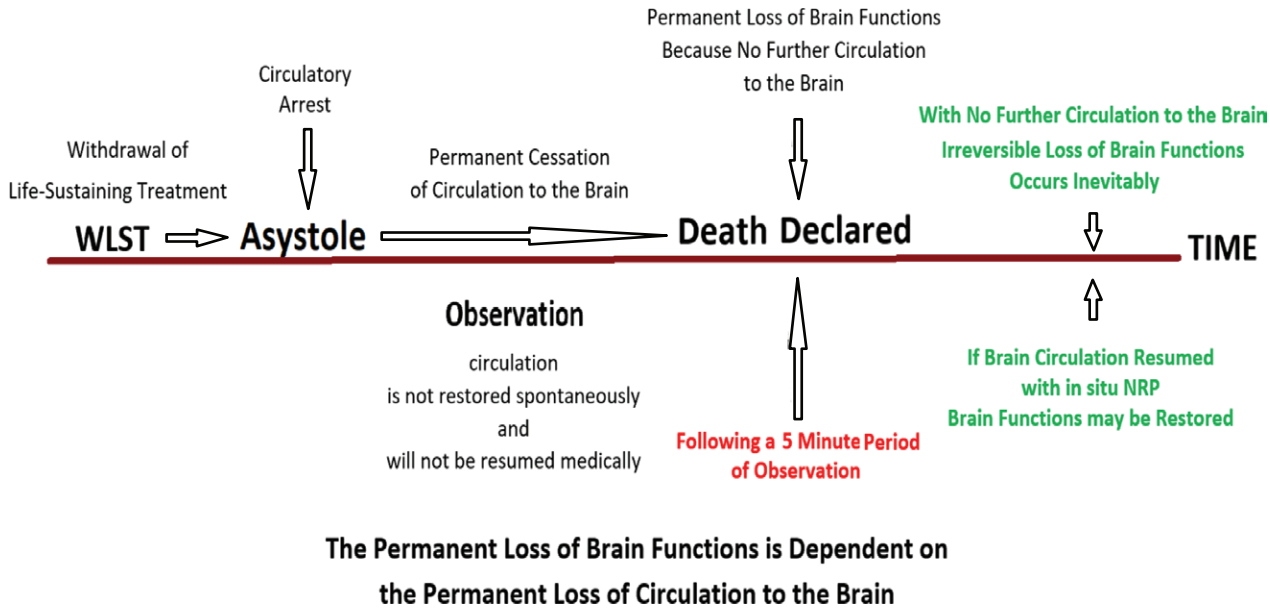

FIGURE 1. Brain functions are time dependent on circulation to the brain.

This practice is justified by the strict causal relationship between brain function and circulation that exists when brain circulation ceases: brain function cannot continue in the absence of brain circulation. However, the mere presence of measurable brain circulation does not necessarily imply the presence of brain functions because detected blood flow may not achieve the necessary perfusion threshold to allow brain functions. Yet, the presence of brain blood flow indicates that brain functions remain possible. These precise thresholds are currently unknown.

THE GOAL OF TA-NRP IS TO RESTORE CIRCULATION TO THORACIC AND ABDOMINAL ORGANS

NRP has been added to DCDD protocols after the declaration of death as an in situ preservation strategy to reperfuse organs, reduce warm ischemic damage, and allow organs to be better assessed before being recovered for transplantation. In A-NRP, the aorta is clamped or blocked to restrict circulation to the abdominal organs, whereas TA-NRP requires stapling of the aortic arch vessels. The purpose of the arch vessel or abdominal aortic clamping is to exclude blood flow to the brain and restrict blood flow to only those organs being recovered for transplantation. When TA-NRP is initiated, mechanical ventilation is also restarted. The donor's heart is assessed for transplantation suitability after the resumption of sinus rhythm and cardiac contractions. The restarted donor heart provides circulation to perfuse thoracic and abdominal organs and also provides an opportunity to assess the heart's functional suitability for transplantation. But do these techniques succeed in totally excluding brain circulation?

POTENTIAL INADEQUACIES OF CLAMPING THE AORTIC ARCH VESSELS TA-NRP

Brain circulation may not be completely excluded by arch vessel clamping because of potential collateral arterial circulation to the brain and the dynamics of brain circulatory autoregulation. Brain circulation is a robust system of direct and collateral arteries distributed by the aorta. Blood flow proceeds from the arch to the brain through the carotid and vertebral arteries that ultimately form the Circle of Willis. At the level of the medulla, the vertebral arteries give off branches that merge to form the anterior spinal artery. The anterior spinal artery distributes blood flow to the spinal cord and brain from collateral supply derived from branches from the aorta in cervical (C1–T3), thoracic (T4–T8), and lumbar regions (T9 to the conus medullaris) via the spinal artery of Adamkiewicz. That artery can direct blood flow cephalad toward the collateral branches along the spinal cord if the circulation to the brain is impaired through the major arch routes of blood flow. Clamping of the brain's main arteries may stimulate collateral circulation to the brain by cerebral autoregulation in the presence of the cephalad arterial blood flow generated by NRP.[19]

Current human data are insufficient to assure zero brain blood flow during in situ NRP, although animal models are reassuring.[20] A recent TA-NRP experiment in a small sample of pigs found that clamping of the arch vessels prevented brain activity as assessed by electroencephalogram, evoked potentials, cerebral blood flow, and oxygen uptake.[21]

But because of the uncertainty that complete cessation of blood flow to the brain results by only clamping the arch vessels, current protocols in the United Kingdom and Spain have added the step of severing the arch vessels distal to the clamps and draining or aspirating blood from the cephalad ends of the severed vessels while exposed to atmospheric pressure.[22] This technical maneuver is intended to divert any possible collateral blood flow away from the brain. For a unified brain-based circulatory determination of death to be valid in NRP, it is essential that all brain circulation has ceased completely and is not restored by NRP or any other means. Animal and human studies must be performed to reassure that brain circulation

is eliminated completely when TA-NRP is incorporated into controlled DCDD protocols. These studies could also inform the best methods of clinical direct brain monitoring during TA-NRP.

To resolve the clinical uncertainty over restoring circulation to the brain, studies, such as those planned in the United Kingdom and Spain, should be conducted to assess brain blood flow during TA-NRP, for example, by contrast angiography. Given that brain monitoring is not sufficiently sensitive to detect functioning, particularly in areas difficult to examine, like the brain stem, one must assume that the presence of brain perfusion indicates the potential for brain functioning.

RECOMMENDATIONS TO DEVELOP AN INTERNATIONAL CONSENSUS ON A UNIFIED BRAIN-BASED CONCEPT OF DEATH WHEN NRP IS IMPLEMENTED

International Professional Societies That Develop Medical Standards Should Work to Achieve a Consensus on the Unified Brain-based Concept of Death

The unified brain-based concept of death is applicable to both DBDD and DCDD although the clinical criteria for death determination are distinct. The brain-based concept of death provides that the permanent absence of brain functions is achieved by the permanent absence of circulation to the brain.[23] Determining death by the permanent cessation of brain functions is consistent with the medical standards for determining death outside the context of organ donation.[1] If circulation to the brain ceases completely and permanently, no brain function can continue.

Establishing international professional consensus on the unified brain-based concept of death will provide a framework for TA-NRP DCDD policy and practice, thereby promoting public trust and addressing potential barriers to opportunities for donation and transplantation. Such a consensus has been accomplished previously by international expert collaboratives on death determination based on solid scientific evidence.[1,14,24] Future clinical and laboratory research should determine if any residual brain circulation exceeds the threshold for neuronal perfusion necessary for brain functions, even when the most restrictive vascular blocking techniques of NRP protocols are implemented.

Protocols of DCDD Organ Recovery, Especially With In Situ Organ Preservation Using TA-NRP, Must Ensure the Permanent Absence of Circulation to the Brain

Current protocols in TA-NRP must be validated to provide assurance that the techniques to stop or divert collateral blood flow to the brain are experimentally proven and clinically effective. Programs using TA-NRP before such validation is available should consider implementing a system of brain monitoring using sensitive techniques to provide reassurance in the complete and continued absence of brain functions during TA-NRP–assisted organ recovery.[25]

The Surgical Recovery Maneuvers Used to Prevent Circulation to the Brain During NRP Must Be Legally, Ethically, and Socially Acceptable

Discussions between qualified organ donation professionals and potential donor families should include information about the aims, methods, and technical maneuvers of NRP protocols that are sufficient to allow family members and surrogates to make informed decisions about authorizing organ donation. Transparency in these conversations ensures public trust in the system of organ donation.

Some commentators have emphasized the desirability of pursuing ex situ normothermic perfusion because it avoids the ethical and legal issues of in situ NRP while providing many of its benefits.[26] However, this alternative is associated with substantially higher costs and has its own limits in countries where legislation requires an observation period longer than the 5-min standard for the declaration of death.

To support the development of best practices for communicating with potential donors and families, studies of donor families and hospital personnel should be conducted to explore their attitudes and understanding of TA-NRP. Transparency in these conversations ensures public trust in the system of organ donation.

We are encouraged by the efforts of the Canadian panel that has adopted the unified brain-based concept of death into a national clinical practice guideline for death determination after the arrest of circulation and brain functions.[27] Their rationale and recommendations can serve as a model worldwide, particularly where TA-NRP is implemented. Alignment between NRP protocols and prevailing clinical, ethical, and legal standards remains necessary.[7,8]

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