An analysis of heart donation after circulatory determination of death

Anne Laure Dalle Ave,1,2 David Shaw,3 James L Bernat4

ABSTRACT
Background Heart donation after circulatory determination of death (DCDD) has provoked ethical debate focused primarily on whether heart DCDD donors are dead when death is declared and when organs are procured.

Objective and design We rigorously analyse whether four heart DCDD programmes (Cape Town, Denver, Australia, Cambridge) respect the dead donor rule (DDR), according to six criteria of death: irreversible cessation of all bodily cells function (or organs), irreversible cessation of heart function, irreversible cessation of circulation, permanent cessation of circulation, irreversible cessation of brain function and permanent cessation of brain function.

Conclusions Only death criteria based on permanency are compatible with the DDR under two conditions: (1) a minimum stand-off period of 5 min to ensure that autoresuscitation is impossible and that all brain functions have been lost and (2) no medical intervention is undertaken that might resume bodily or brain circulation. By our analysis, only the Australia heart DCDD programme using a stand-off period of 5 min respects the DDR when the criteria of death are based on permanency.

INTRODUCTION
Organ donation after circulatory determination of death (DCDD), also termed donation after circulatory death, donation after cardiac death and non-heart beating donation, has become increasingly common in the USA and in Europe. DCDD programmes most frequently provide kidneys for transplantation and, less frequently, lungs and livers. To date, only four centres have been reported doing heart DCDD: Cape Town in 1967,1 Denver in 2008,2 Sydney in 20153 and Cambridge in 2015.4

The 2008 report by Boucek et al2 of heart DCDD in three newborns provoked a firestorm of ethical controversy, principally around the question of how donors who were declared dead by cardiocirculatory criteria could actually be dead if their hearts regained normal function in recipients. Because of this unresolved ethical issue and the technical problem of heart susceptibility to warm ischaemia time (WIT), heart DCDD was not reported again until recently.3 4 Although technical difficulties apparently have been resolved by centres in the UK and Australia, the ethical debate over heart DCDD continues. In this article, we provide a rigorous analysis of the acceptability of heart DCDD to address the question of whether heart DCDD donors are dead at the moment that death is declared and when organs are procured.

MEDICAL CONSIDERATIONS—DESCRIPTION OF HEART DCDD PROTOCOLS
In table 1, we compare the heart DCDD protocols of Cape Town,1 Denver,2 Cambridge4 and Sydney.3 Because there have been no publications of the cases of heart DCDD in Cambridge, we based our analysis on a 2009 article by Ali et al,7 in which they described the use of a heart DCDD protocol until heart explantation, but without heart transplantation, which appears similar to the description found in the press.8

Because the heart is particularly susceptible to WIT, heart DCDD protocols aim to minimise it. Studying published heart DCDD protocols,1–3 4 7 we identified three principal means to decrease the ischaemic insult to the heart:

1. The use of organ preservation techniques after the declaration of death:
   A. Cardiopulmonary bypass,1 also termed in situ normothermic regional perfusion,7 extracorporeal membrane oxygenation (ECMO) or extracorporeal support.7
   B. Cold fluid infusion through a femoral cannula.9
2. A reduced stand-off period, defined as the time between circulatory arrest and the declaration of death, to 75 s,2 2 min3 or 3 min.2
3. The use of ex vivo perfusion.2 3 4

The use of ECMO in DCDD
Although ECMO has been used in some DCDD centres to decrease WIT,7 9 10 it is not the norm. Because cardiac and brain circulation resumes with the use of ECMO, DCDD protocols employing this technique use either an inflated thoracic aortic balloon9 or a clamp on the ascending aorta10 to exclude simultaneous cardiac and brain perfusion, and to avoid brain resuscitation. The two heart DCDD protocols reporting the use of ECMO were those of Cape Town1 and of Cambridge.4 7 Brain and cardiac perfusion were not prevented in the first heart DCDD reported by Barnard.1 In the Cambridge heart DCDD protocol, a cross-clamp was positioned on the aortic arch vessels to permit bodily and cardiac recirculation, while still excluding brain circulation.4 7 This is an unusual protocol because it ‘revives’ the heart inside the donor’s body by using ECMO. As the heart recovered normal function, ECMO was weaned. The team waited 50 min before the heart was procured, in order to confirm good heart function for transplantation.

Cold fluid infusion
Cold fluid infusion is widely used in DCDD protocols.11 Because blood is replaced by cold fluid

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infusion, there is no possibility of restoring cardiac or cerebral function with this method. This method was chosen by the team in Denver.2

A reduced stand-off period

In a majority of DCDD protocols, a stand-off period of 5 min is used, but the stand-off period varies between 2 and 20 min depending on the DCDD protocol.12 Because the heart is sensitive to WIT, a reduced stand-off period was used in the heart DCDD protocols of Denver (75 s and 3 min)2 and Sydney (2 min for two donors).3

Ex vivo perfusion

To decrease the cold ischaemia time, that is, the time from heart explantation to heart transplantation, the Australian team has used the ‘normothermic ex vivo cardiac perfusion device’,3 also used by the Cambridge team.4

ANALYSIS OF THE DEAD DONOR RULE IN HEART DCDD

The dead donor rule (DDR) states that vital organ procurement must not kill the donor and therefore the donor must be dead before organ procurement begins. Several scholars have raised concerns that the DDR is violated in DCDD programmes because the donor is not dead at the moment of donation.13 14 This issue continues to stir controversy. Obviously, whether heart DCDD protocols respect the DDR depends on the choice of the criterion of death. In our analysis, we analyse each heart DCDD protocol according to six plausible criteria of death (see table 2):

1. Irreversible cessation of all bodily cells function (or organs)
2. Irreversible cessation of heart function
3. Irreversible cessation of circulation
4. Permanent cessation of circulation
5. Irreversible cessation of brain function
6. Permanent cessation of brain function.

This analysis is necessary because, as Veatch stated, ‘virtually all observers have assumed that DCDDD could, in principle, provide any vital organs except hearts’5 and because several scholars questioned the validity of the diagnosis of death in heart DCDD.

Irreversible cessation of all bodily cells function (or organs)

Death can be defined as an irreversible event, or as a gradual process8 ‘that occurs over a continuum of time’,15 beginning with organs sensitive to ischaemia, such as the brain and the heart, and finishing with the very last cells of the body, such as the skin.

If death were determined using the criterion of irreversible cessation of all bodily cells function (or organs), neither donation after the brain determination of death (DBDD) nor DCDD would respect the DDR. In DBDD although the functions of the whole brain have been irreversibly lost,16 some brain cells remain alive.17 Furthermore, in the context of DBDD, all other organs are functional because circulatory and respiratory functions are sustained by life-sustaining therapy. In DCDD, the functions of organs have not been lost irreversibly because organs regain function once transplanted. In practice, death is not determined by the criterion of irreversible cessation of all bodily cells function (or organs). Typically in the intensive care unit (ICU) setting, ICU physicians declare death after 2–10 min of cessation of cardiocirculatory functions,12 and thus long before the point at which the function of all bodily cells has ceased. This criterion of death is unnecessarily conservative, is incompatible with usual medical practice and eliminates all organ transplantation.13

Irreversible cessation of heart function

Death is often declared using the criterion of irreversible cessation of heart function. Because the heart is the organ that produces circulation, once the heart stops and circulation ceases (assuming no medical intervention), the function of all the other organs ceases progressively, commencing with the brain. The term irreversible implies that no technology (such as defibrillation or the use of ECMO) or action (such as cardiopulmonary resuscitation (CPR)) can restore heart function, which is thus irretrievably lost. Using this criterion, a deceased organ donor who has been previously determined dead by irreversible cessation of heart function cannot donate her/his heart for transplantation because the heart will have lost any possibility of functional restoration, and thus cannot be used for successful transplantation. If heart transplantation were to succeed in such

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**Table 1** Comparison between the four heart DCDD protocols

<table>
<thead>
<tr>
<th>Criteria used to diagnose death</th>
<th>W-LST:</th>
<th>Premortem intervention</th>
<th>Organ preservation after death</th>
<th>Brain circulation prevented</th>
<th>Restart of heart function</th>
<th>Press 2015, Cambridge4</th>
<th>Dhital, 2015, Australia3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where</td>
<td>By whom</td>
<td>How</td>
<td>Stand-off period</td>
<td>Criteria used to diagnose death</td>
<td>In recipient</td>
<td>In recipients</td>
<td>In the donor for 50 min</td>
</tr>
<tr>
<td>Extubation</td>
<td>By the ICU team</td>
<td>In situ cooling cannula</td>
<td>5 min (2 min for two donors)</td>
<td>5 p, ≥16 y.o., no intracranial bleeding</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Extubation and W-LST</td>
<td>By the ICU team</td>
<td>ECMO cannula</td>
<td>5 min (2 min for two donors)</td>
<td>5 p, ≥16 y.o., no intracranial bleeding</td>
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DCDD, donation after circulatory determination of death; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NA, not available; OR, operating room; p, patient; W-LST, withdrawal of life-sustaining treatment; y.o, years old.

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possible, but while the heart remains amenable to resuscitation that will not be attempted. A systematic review showed no reported cases of autoresuscitation after withdrawal of life-sustaining treatment (when CPR was not performed), and no reported cases of autoresuscitation beyond 7 min after failed CPR. In a review, an expert consensus panel stated that no cases of autoresuscitation had been reported after 65 seconds to 2 minutes of cardiac arrest. Thus, in the context of controlled DCDD after withdrawal of life-sustaining treatment, death can confidently be determined after 5 minutes of asystole, because the cessation of circulation is permanent and will inevitably become irreversible.

Although this purported change in death criteria has been criticized, it conforms to the usual practice of death determination using the circulatory criterion in non-donation circumstances. This criterion remains valid only if no attempts to restore circulation, such as ECMO or CPR, are performed after the declaration of death, to avoid negating the previous declaration of death. DCDD programmes that resume circulation after death declaration using ECMO, such as in the heart DCDD protocols of Cape Town and Cambridge, are incompatible with death determination using the criterion of permanent cessation of circulation.

The Denver heart DCDD protocol raised the concern that ‘circulation was not permanently lost after 75 s before pronouncing death’, because autoresuscitation might have been possible after such a short stand-off period. The Australian heart DCDD protocol, which reported a stand-off period of 2 min for two patients, raised similar concerns that autoresuscitation might have been possible. The Society of Critical Care Medicine stated that 2 min was sufficient and more than 5 min was unnecessary. Although we agree that a 2-min stand-off period is probably sufficient to prove the impossibility of autoresuscitation in controlled DCDD, we continue to recommend a 5-min stand-off period for heart DCDD to be absolutely certain that the cessation of circulation is permanent. This prudent recommendation acknowledges that the autoresuscitation database remains small and incomplete, and therefore lacks a high confidence limit. It also takes into account that physicians continue to report cases of autoresuscitation, including following withdrawal of life-sustaining therapy (W-LST).

Thus, if permanent cessation is used as a criterion to determine death in DCDD programmes, there is an urgent need for studies analysing after how many minutes following W-LST the possibility of autoresuscitation vanishes. Such studies will permit the determination of a less arbitrary stand-off period for DCDD programmes, which may be particularly relevant for heart DCDD programmes that depend on a short stand-off period for organ preservation.

By this analysis, heart DCDD protocols that violate a stand-off period of at least 2–5 min, such as Denver and perhaps as Australia (for two patients), or who start ECMO after death declaration, such as Cape Town and Cambridge, may violate the DDR (but further studies are needed to confirm the stand-off period necessary to preclude the possibility of autoresuscitation). The only heart DCDD protocol that fully respects the DDR is that of Australia.

Irreversible cessation of brain functions

Another possibility is to use brain death criteria in DCDD programmes instead of cardiac or circulatory death criteria. When cardiocirculatory function ceases and persists long enough, all brain functions cease. But diagnosing death in DCDD using the criterion of irreversible cessation of brain functions raises two questions: (1) which diagnostic tests should be used to determine death? and (2) how long is it necessary to wait to achieve irreversible cessation of brain function?

Are brain death tests valid in the context of DCDD? Brain death tests were not developed for the circumstance of profound and global brain damage in which circulatory and respiratory functions are sustained medically. In Switzerland for instance, brain death tests are used to determine death in the context of DCDD. However, we believe that, although the use of brain death tests in the context of DCDD might prove the cessation of brain function, they cannot prove that the cessation of brain function is irreversible. Before performing brain death tests, reversible metabolic or toxic disorders that might induce a transitory cessation of brain functions, and thus that might mimic brain death must be excluded but this is impossible in DCDD.

Further, the stand-off period necessary to achieve irreversible cessation of all brain functions is unknown, but stand-off periods of 5 or even 10 min are insufficient to achieve the irreversible cessation of brain function. Evidence from patients suggests that neurons can survive for up to 20 min after circulation has ceased, and animal results suggest that brain function can return after as much as an hour without circulation. Thus, heart DCDD protocols using a stand-off period of 5 min or less do not respect the DDR according to the criterion of irreversible cessation of brain functions.

Permanent cessation of brain functions

As we showed in the debate over whether cessation of circulation must be irreversible or permanent, some scholars have argued that, in the setting of systemic circulatory arrest, death could be determined using the permanent cessation of brain functions. The issue would then be ‘not whether the body or brain circulation and function can be resumed (because it can), but rather, whether it will be’. Using a permanency criterion for brain death would mean that no actions (such as the use of ECMO) will be implemented to restore brain circulation, even if brain function is not irreversibly lost, because resuscitation manoeuvres might restore some brain function.

If we accept a determination of brain death based on permanent cessation, how long a stand-off period is sufficient to ensure permanency? It must be sufficiently long to ensure that the period during which autoresuscitation can occur has elapsed (as it is the case for the criterion of permanent cessation of circulation) and that all brain functions have been lost, to exclude the possibility that a donor could feel pain or have awareness. A stand-off period of 5 min would be of sufficient duration to exclude the possibility of autoresuscitation but the minimum duration is unknown. Within seconds of circulatory arrest, electroencephalographic activity becomes flat, and all brain functions cease within minutes. To ensure that the possibility of awareness or the feeling of pain has been lost, we propose a stand-off period of 5 min, despite the fact that it is an arbitrary limit. DCDD programmes need studies to demonstrate with confidence after how many minutes of brain circulatory cessation all brain functions cease. If this time is situated between 2 and 5 min, a 5 min stand-off period is a more confident limit.

Furthermore, because the brain may be responsive to restoration of its blood supply after a 5 min stand-off period, the use of ECMO or any technology that might resume brain circulation must be prohibited.

Using the criterion of permanent cessation of brain functions, heart DCDD protocols that permit a stand-off period shorter than 2–5 min may violate the DDR (in Denver, and perhaps in
Australia for two patients); heart DCDD protocols that used ECMO without proving that brain circulation was excluded may have violated the DDR (Cape Town). The Cambridge protocol used an aortic arch clamp that probably excluded brain circulation. If this exclusion can be demonstrated, it probably respected the DDR. But although an aortic arch clamp blocks blood flow through both carotid and vertebral arteries, it may spare small collateral arteries from the segmental spinal arteries that arise from the thoracic aorta and anastomose with branches of the vertebral arteries. These collaterals conceivably could provide a little perfusion to the brainstem. To ensure that the aortic arch clamp completely blocks brain perfusion, brain circulation should be tested and proven absent. In particular, brain stem perfusion should be proven to have stopped because its function can continue with a smaller blood flow than the cerebral hemispheres.

Based on a criterion of permanent cessation of brain functions, only the heart DCDD protocol from Australia respected the DDR because it used a stand-off period of 5 min for one patient and did not employ ECMO. Table 3 compares the four described heart DCDD protocols in relation to six described criteria of death. Only the criteria of death based on the notion of permanency allow some heart DCDD protocols to respect the DDR.

**CONCLUSION**

Our analysis suggests that some heart DCDD protocols likely violate the DDR because they use a shortened stand-off period or ECMO. In DCDD, only the criterion of death based on permanency (either the permanent cessation of circulation or the permanent cessation of brain functions) respects the DDR. If health professionals who practice heart DCDD protocols wish to comply with the DDR, they should determine death either based on the criterion of permanent cessation of circulation or permanent cessation of brain functions. But certain conditions must be respected. If the criterion of permanent cessation of circulation is used, heart DCDD protocols must follow two conditions: (1) use a minimum stand-off period of 5 min to ensure that the possibility of autoresuscitation has elapsed (unless future studies prove otherwise); (2) strictly avoid the use of any actions or technology that may resume bodily circulation.

If the criterion of permanent brain death is used, heart DCDD protocols must respect a minimum stand-off period of 5 min (unless future studies prove otherwise) to exclude the possibility of autoresuscitation, and to ensure that all brain functions have been lost. The use of any technology that might preserve brain circulation, even partially, is forbidden. Thus, the use of ECMO would be permissible only if it confidently excluded brain circulation, including the brainstem. This condition would be achieved only if the use of ECMO were accompanied by a mechanism to prove that there was absent brain circulation. Until this is achieved, it is not defensible to merely ‘assume’ that brain circulation has ceased, and thus ECMO should be avoided.

According to our analysis, of the four heart DCDD programmes, only Australia using a stand-off period of 5 min respects the DDR when death is based on a criterion of permanent cessation of circulation. It remains unclear if heart DCDD programmes that use a stand-off period of 2 min, such as Australia’s for two patients, respect the DDR.

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**REFERENCES**

