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Abstract

Background: Donation after circulatory death (DCD) is becoming increasingly common, yet little is known about the way potential donors receive end-of-life care.

Purpose: The aims of this systematic review are to describe the current practice in end-of-life care for potential donors and identify metrics that are being used to assess discomfort among these patients.

Research design and Study Sample: This review encompasses published literature between June 1, 2000 and June 31, 2020 of end-of-life care received by potential DCD patients. The population of interest was defined as patients eligible for Maastricht classification III donation after circulatory death for a solid organ transplantation. Outcomes examined included: analgesic or palliative protocols, and surrogates of discomfort (eg dyspnea, agitation).

Results: Among 141 unique articles, 27 studies were included for full review. The primary reason for exclusion was lack of protocol description, or lack of reporting on analgesic medications. No primary research studies specifically examined distress in the DCD eligible population. Numerous professional guidelines were identified. Surveys of critical care practitioners identified concerns regarding the impact of symptom management on hastening the dying process in the DCD population as a potential barrier to end-of-life palliative treatment.

Conclusions: There is a paucity of empirical evidence for end-of-life symptom assessment and management for DCD patients. Key evidence gaps identified for DCD include the need for: i) a multidisciplinary structure of treatment teams and preferred environment for DCD, ii) objective tools for monitoring of distress in this patient population, and iii) evidence guiding the administration of analgesic medications following withdrawal of life sustaining therapy.

Keywords

donation after circulatory death, palliative care, organ donation, neurocritical care

In the last 2 decades, there has been a revival of donation after circulatory death, particularly arising from the limits of the existing donor pool from donation after brain death.^{1,2} Solid organ transplants, as of 2017, only met about 10% of the total donor need according to World Health Organization estimates.³ Donation after circulatory death (DCD) generally occurs in patients with severe and irreversible brain injury in whom the decision has been made to withdraw life sustaining treatments. Patients are declared dead based on cardiopulmonary criteria as opposed to donation after brain death, which is defined as the irreversible loss of all functions of the entire brain determined by complete loss of consciousness, brainstem reflexes, ventilatory drive and absence of reversible features.⁴

Despite unanimous support from the United Network for Organ Sharing, the Joint Commission on Accreditation of

Healthcare organizations, and the Institute of Medicine³ mandate that hospitals have comprehensive DCD protocols

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in place, wide and persistent variation in the final phase just prior to withdrawal of life sustaining treatments and before cardiopulmonary arrest persists.^{1,2} Largely driven by concerns regarding ethical ambiguity many experts in the field, as well as professional societies, have since ventured to address these issues by drafting guidelines.⁵

In developing guidelines for DCD, it is essential that the decision to withdraw life sustaining therapy is decoupled from organ donation, and as such the procuring transplant team is never to be involved in conversations regarding prognosis or ventilator withdrawal.^{2,6} As a prerequisite, all eligible DCD cases comprise patients in whom the decision to transition to comfort care has been decided. If these patients expire quickly during this phase, organs may be recovered for transplant depending on organ viability.

Typical DCD subjects are from a heterogeneous population often with numerous medical comorbidities, including those that have catastrophic brain injury, terminal neuromuscular disorders such as amyotrophic lateral sclerosis (ALS), and high spinal cord injuries. Generally, these are patients whose death would be considered imminent once life sustaining treatment is withdrawn. Since these patients do not meet brain death criteria, it is critically important that best practices are utilized when it comes to amelioration of discomfort at end-of-life.

There remain numerous situations in which patients are minimally conscious⁷ following withdrawal of life support measures, further emphasizing a need for appropriate comfort-based therapy. In this way, neurologists are uniquely poised to assess and identify responsiveness, and discomfort, in these individuals. As it stands a broad group of non-neurologists are more often involved in the end-of-life care of these neurologically complex patients. Given the heterogeneity in this population, neurohospitalists are positioned to identify patients at higher risk for retained awareness, and thus discomfort, during the withdrawal-of-life sustaining therapy (WLST), that may not be captured by imperfect measures of distress such as vital sign variation. Neurologists are often consulting on the care of these patients prior to WLST, or managing them as neurointensivists, thus there exists an opportunity for care of neurologically vulnerable patients to continue until death and potential organ procurement.”

The primary objective of this review is to describe variation in palliative and comfort focused care provided for the potential DCD donor prior to death, and to examine the metrics currently being utilized to assess discomfort during the final phase prior to donation.

Methods

An initial search strategy was modeled after recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement⁸ and the Assessment of Multiple Systematic Reviews (AMSTAR) tool.⁹ The population of interest was defined as patients eligible for Maastricht classification III donation after circulatory death

for a solid organ transplantation. Outcomes examined included the inclusion of analgesic or palliative protocols, as well as the recording of surrogates of discomfort such as pain, anxiety, tachycardia, dyspnea, or agitation.

An initial search strategy involved searching multiple databases including PubMed, Embase, the Cochrane Database and Web of Science between June 21, 2000 and July 1, 2020 for original English-language research published in peer-reviewed journals, which included reviews, editorials, cross sectional surveys, and professional society guidelines, between June 1, 2000 and June 31, 2020. Search terms were devised and included terms such as “palliative”, “comfort”, “pain”, “analgesia”, “sedation”, “opioids”, “dyspnea”, “symptoms”, “ethics”, “end-of-life care”, “NHBD”, “DCD”, and “organ donation”. Terms such as “Autism”, “developmental coordination disorder,” “dynamic cooling device” were excluded to avoid search terms with similar acronyms utilized in other clinical contexts.

We reviewed titles and abstracts from the initial database searches to identify articles eligible for full text review. Prior to selecting an article for full review, text search functions were utilized to identify if end-of-life care was discussed in the body of the work. This search was supplemented by hand-searching the reference lists of the full-text articles to identify potentially relevant studies.

Studies that met the following criteria were included for full text review: reported the use of analgesic or sedative medications either in methods or as covariates/outcome, included patients eligible or undergoing Maastricht III organ transplants after cardiopulmonary arrest or represented institutional/societal guidelines and detailed recommendations for end-of-life care.

Results

The search strategy (Figure 1) yielded 141 unique articles; after excluding studies from the database search that did not include the population of interest, 71 studies underwent brief review, and additional studies were further excluded if they did not discuss end-of-life care of potential donor patients in the body of the work. After including manually reviewed studies, 27 studies were selected for full text review. Of these, 2 articles were retrospective cohort studies,^{10,11} 3 were cross sectional surveys of intensive care unit (ICU) practitioners,¹²⁻¹⁴ 5 were case studies,¹⁵⁻¹⁹ 6 were professional society or institutional guidelines,^{5,20-23} and the remainder (n = 11) were reviews or position papers. Primary sources of bias originate from the lack of primary research identified, with the only original empirical evidence stemming from retrospective or cross-sectional survey data.

Comfort Focused Medications and Time to Death

Among these articles, 2 retrospective cohort studies examined the role of sedative analgesics in the potential DCD

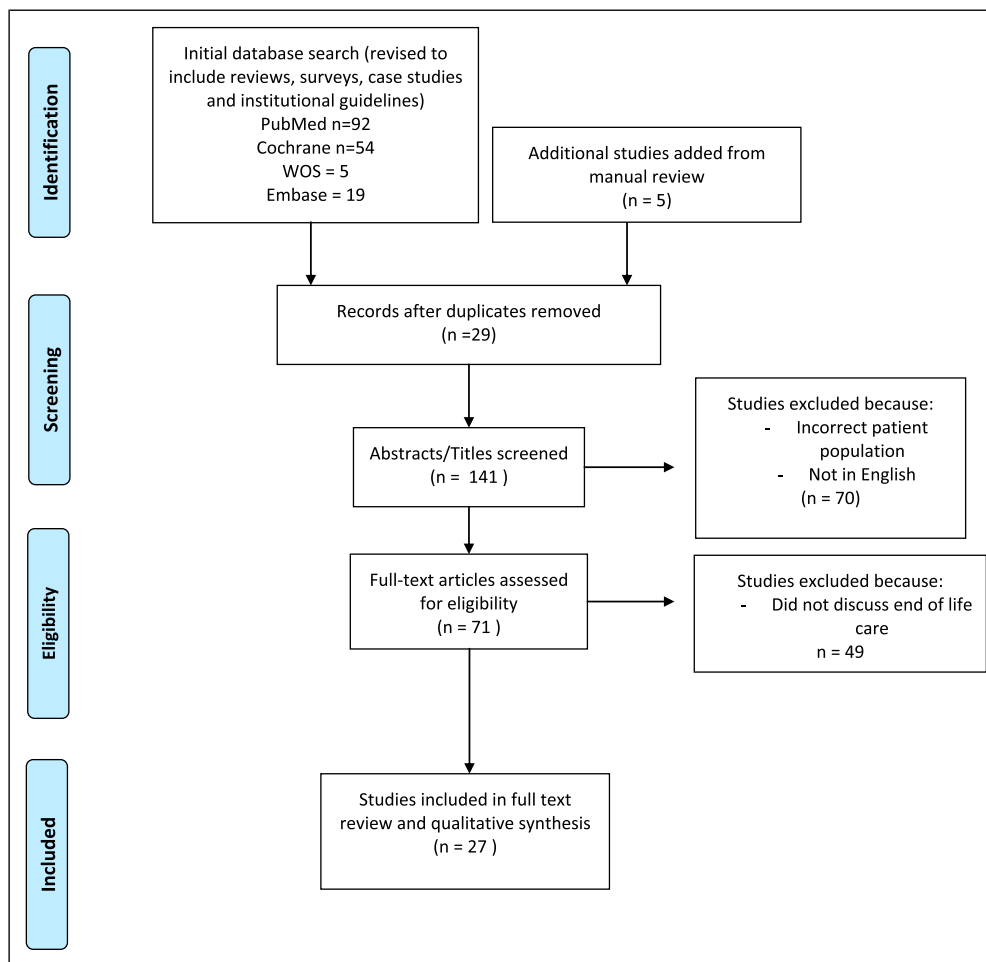


Figure 1. Search strategy and study screening protocol.

population, both examining the question of comfort-focused care expediting time to death in this population. Among 128 patients being considered for controlled DCD, LeDoux et al compared time to death after withdrawal of life sustaining therapy between DCD and non-DCD patients.¹⁰ They found that a DCD protocol with comfort focused measures did not reduce time to cardiopulmonary arrest compared to non-DCD patients receiving standard comfort focused care. The study was limited by a lack of reporting for validated measures of discomfort, or surrogate markers, such as vital sign abnormalities, secretions, facial grimacing or perceived discomfort by bedside clinicians. Further, specific medications and treatment protocols utilized during withdrawal of life sustaining therapy were not described.

A separate retrospective study of 505 DCD patients examined the association of the use of comfort focused medications (opiates, benzodiazepines) at end-of-life and time to death.¹¹ Among 72% of patients receiving at least 1 comfort medication, there was a lower risk of death in the first 60 minutes after withdrawal of life sustaining therapy (aOR .35

CI [.21-.59]) in those treated with comfort focused medications.

Evaluation of Discomfort and Distress

No studies specifically examined discomfort or distress, or reported a specific protocol for use of comfort focused medications during DCD. The use of sedatives and analgesics,⁵ and importance of involving trained palliative care practitioners²⁴ are mentioned, but protocols for evaluating DCD patients, including indications for palliative care specialist involvement are not suggested.

A survey of pediatric critical care nurses (n= 93) involved in DCD cases found 95% of respondents felt analgesics should be used for discomfort, and 11% expressed concern for undertreating pain.¹² In a cross sectional survey of critical care practitioners across Australia and New Zealand, the vast majority (92%) of physician respondents either agreed or strongly agreed with prescribing palliative medications during palliative ventilatory withdrawal, though 1 in 4 respondents reported they avoid higher doses given concern for

perceived hastening of death. A similar percentage (23%) of physicians reported altering their end-of-life care in DCD eligible patients, with 60% of physicians reporting they were concerned that DCD eligible patients would receive inappropriate doses of palliative medication (either excess or inadequate).¹³ In a large cross sectional survey in the United States (n = 3204), the majority of intensive care physicians and nurses felt they should “help manage potential donors”, but differences in end of life care among DCD were not reported.¹⁴

The most specific model for caring for DCD patients was described by Kelso et al, who described co-management of DCD patients with palliative care providers alongside the intensive care team, and suggested monitoring for signs of discomfort, while treating episodes of tachypnea, moaning, grimacing, restlessness or myoclonus with opioids or sedatives accordingly. In this paradigm, the intensive care nurse administered medications prescribed by a palliative care provider at bedside, and the intensive care team pronounced death and facilitated transfer to the organ-recovery team.²⁵ Others suggest establishing vital sign parameters by which to administer medications such as titration of benzodiazepines and opiates to heart rate less than 100 beats per minute or respiratory rate less than 20.^{26,27} While oral secretions are unlikely to be distressing to the patient themselves,²⁸ anticholinergic medications such as scopolamine (ie 0.4mg IV or IM) or glycopyrrolate have been proposed for secretion management,^{25,28} especially if a patient’s family is at bedside.

Sedative and Analgesic Regimens

While there is emerging consensus emphasizing DCD patient’s equal right to comfort-focused care^{1,2,6,26,27} prior to circulatory arrest, there are few specific protocols or rigorous evaluations of sedative and analgesic regimens utilized during DCD. Many institutions may view DCD as the same as WLST, however different care processes and physical location within the hospital where DCD unfolds (ie operating room vs intensive care unit) warrants rigorous appraisal. While 1 study examined variation among adult donation center protocols (serviced by the New England Organ Bank), investigators found that 60% (54/90) of the participating hospitals specifically indicated that analgesics were accepted in the DCD protocol.²⁹

Many suggest that DCD organ donors prior to donation should be treated in concordance with institution specific standard of care in regard to end of life care.^{2,3,30–32} As such, assuming a protocol similar to that of the palliative ventilatory withdrawal of any other critically or neurologically ill patient could be proposed,^{26,33} the mainstay of which involves treatment with benzodiazepines and opioid pain medications.³⁴ Frontera^{26,30} suggests titration of benzodiazepines and opiate boluses to vital sign parameters, such as heart rate less than 100 beats per minute or respiratory rate less than 20. While Kelso et al²⁵ utilize a regimen by which 5-10mg IV

morphine or 2-4mg IV midazolam are used for respiratory distress every 5 minutes titrated to distress, is cited as the standard of care at their institution.

Mounting evidence suggests palliative benefit in the administration of anticipatory doses of opioids prior to WLST to avoid respiratory distress,³⁵ and avoidance of sedative monotherapy given concerns around paradoxically worsening dyspnea. There were no publications recommending premedication prior to palliative ventilatory withdrawal (anticipatory dosing) among DCD patients. However premedication with analgesic medications for dyspnea was mentioned in several case reports.^{17,36,37}

Outcome data measuring donor patient comfort, and specific types of sedative analgesics utilized are extremely limited. The largest published single center cohort found 382 DCD cases between 1984 and 2000,³⁸ but there was no mention of sedative and analgesic regimens used among DCD patients prior to death. Only 1 study of pediatric DCD patients mentioned specific sedatives and analgesics used (fentanyl mean dose of 4 µg per kilogram and lorazepam mean dose of .1 mg per kilogram).³⁹ Many articles made no mention of palliative analgesics,^{38,40–43} while others described adhering to “institutional care and comfort measures”^{44,45}

Consciousness and DCD

Undetected or covert consciousness is a major concern among DCD patients as places them at risk for distress,⁴⁶ yet few studies evaluated potential DCD patients for covert consciousness. A small case series of DCD eligible patients (n=3) demonstrated changes to bispectral index on processed electroencephalogram (EEG) during the period following withdrawal of life sustaining treatment (WLST).¹⁵ Only 1 other small case series attempted to replicate these results,¹⁶ however, given very few patients were included in these studies, no conclusions can be drawn. Task-based EEG monitoring⁴⁷ has not been evaluated in this population.

Patients known to have preserved awareness and arousal such as in amyotrophic lateral sclerosis (ALS), or high spinal cord injury, highlights the need for well-developed protocolization of treatment of peri-mortem distress in the DCD population. These patients are distinct from other DCD donors who often have devastating brain injury but fail to meet brain death criteria. While uncommon, multiple cases of DCD after progressive respiratory failure secondary to ALS have been reported.^{17,18} In all cases, organ donation per DCD protocol was desired by the donor and discussed in anticipation of an inevitable progression of their neuromuscular disease. As an example, one such patient was admitted electively in the setting of progressive disease; after a period of opioid dose titration, pre-medication with fentanyl and midazolam were utilized prior to withdrawal of ventilator support, and DCD.¹⁷ Similarly, patients with high spinal cord injury, or brain stem injury that spare the cortical arousal networks, as in the locked-in patient,¹⁹ emphasize the need

for detailed multidisciplinary planning for DCD in this heterogeneous population.

Institutional and Professional Society Guidelines

Many professional societies have published guidelines, with the goal of standardizing the DCD process and supporting best practices. The guidelines are comprehensive, offering frequent and broad assurances that the comfort of the donor is fundamental and not to be violated. The report from the national conference on donation after cardiac death, for example, states that “quality end of life care...is the absolute priority” and “sedatives and opioids should be administered in the customary manner”.⁴⁸ Similarly the Society of Critical Care Medicine asserts that the donor has “equivalent right”⁵ to comfort care as other patients and, in concert with the American Thoracic Society and the United Network of Organ Sharing, released a statement that includes the mandate to “manage symptoms of pain, anxiety, and breathlessness”.²¹ The American Society of Transplant Surgeons,²⁰ American Thoracic Society,²¹ and the Canadian²² position statements have similar declarations, mentioning specifically that procurement team members are not to be involved in managing potential discomfort of the patient. A review of 72 unique institutional DCD protocols across children’s hospitals found that 89% [CI 80-95%] of protocols highlighted the importance of palliative care, while only 7% [CI 2-15%] recommended or required palliative care specialist involvement. Specific palliative medications or measures of peri-mortem discomfort were not discussed.²³

Discussion

The DCD process is a unique clinical situation requiring specific evidence to reduce the potential for distress and discomfort. While there is consensus that comfort focused sedatives and analgesics have a role in end-of-life care for DCD patients, standards for monitoring and treating these patients are not clear. There is very little systematic empirical research examining palliative care during DCD. Professional society guidelines and position statements assert the importance of comfort-focused therapy without proposing a standard of care for such regimens. The evidence gap may be due to an assumption that existing end of life care practices are generalizable to DCD patients. The atypical setting, neurophysiological state, and heightened potential for clinician moral distress⁴⁹ are unique to DCD, and call for specific evidence to support best practices in the care of DCD patients.

The principle of double effect supports the use of sedative analgesics with the intent of alleviating distress even if there is a risk of hastening death.⁵⁰ Moreover, analgesic medications and benzodiazepines seem to prolong the time before cardiopulmonary arrest in DCD eligible populations,^{10,11} and previous experiences in critically ill patients suggest that

sedatives do not hasten death.^{51,52} The DCD population includes patients with severe neuromuscular disease with preserved awareness, as well as those with brain injury that still maintain some cortical function, such as in patients with malignant middle cerebral artery infarctions or large brain-stem hemorrhages. These patients may not be able to communicate discomfort but neurologically have intact pain and arousal networks, leaving them at risk for limited recognition and undertreatment of distress.

Most of the hallmark studies in the DCD literature make no mention of the use of sedation or analgesia in the donor prior to transplantation. This is likely due to the requirements of the donation process, which necessitates separation of the transplant recovery team and the treating physicians of the donor prior to death. Thus, by design, the transplant teams rarely have access to the data regarding how the donor patient was treated prior to arrest. However, minimal data suggest significant variation in donor environment, as preferred by organ procurement organizations.⁵³ There is likely additional variation as it relates to background or level of training (intern to attending staff or advanced practice providers), and area of specialization (anesthesiology, critical care, and palliative care), but this has not been extensively studied.²⁹

Potential DCD donors represent a heterogeneous population of critically ill patients, with similarly varied degrees of awareness. Both the bedside evaluation and noninvasive neuromonitoring of consciousness among these patients are imperfect.^{7,46,47,54} This population of patients is at high risk for under-treatment of end-of-life distress and discomfort due to concerns surrounding expediting patient death, and uncertainty regarding the ability of patients with severe neurologic injury to experience distress. As such, neurologists and neurointensivists caring for these patients are uniquely positioned to develop evidence based guidelines for the DCD process in collaboration with other specialties providing end of life care. At present no major neurological professional society has developed or endorsed specific guidelines for the care of DCD patients.

There are multiple limitations to this review that are worth highlighting. Most strikingly, the lack of empirical evidence studying end-of-life care in the DCD population creates a space for conjecture in the synthesis of lower quality research. The authors attempted to mitigate this by using a systematic approach and openly calling attention to times when conclusions or future avenues of research were not supported by high quality empirical evidence. Additionally, while the search strategy followed PRISMA guidelines, the transplantation research is multi-disciplinary, and it is possible our search strategy may have missed small empiric studies of end-of-life care among the broad array of sub-categories of patients.

Overall improved systems of support for clinicians caring for these patients may be beneficial, and foster an appreciation for unrecognized symptoms at end-of-life among DCD patients. Some institutions identified in this review designate

specific palliative care providers to be responsible for administration of sedation and analgesia during the DCD process, while the critical care team is responsible for pronouncing death of the patient and facilitating transition to the transplant recovery team.^{25,31} Future research could support an empirical approach to optimal team composition and dynamics for reducing potential for distress, and to better characterize the experiences of those involved with potential DCD patients. Some evidence suggests that concerns regarding sedative and analgesia dosing decisions persist.¹³ One potential strategy to address this gap could be a mixed methods study of neurologist and non-neurologists, to gain a detailed understanding of approaches to analgesic and sedative regimens. To extend the ongoing work of researchers in palliative and end-of-life care,⁵⁵ there is a role for neurologists to refine and validate objective measures of distress among patients with severe brain injury.

This review has identified significant evidence gaps in the practice of comfort focused care among patients at end-of-life who are being considered for DCD. Specifically, there is a need for the development of evidence-based interdisciplinary guidelines detailing: i) the multidisciplinary structure of treatment teams and the preferred environment for DCD, ii) objective tools for monitoring of distress, and iii) the administration of sedative and analgesic medications following withdrawal of life sustaining therapy among the DCD population.

Appendix

Abbreviations

ALS (amyotrophic lateral sclerosis)
 DCD (donation after circulatory death)
 EEG (electroencephalogram)
 ICU (intensive care unit)

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SPC has nothing to disclose, WSS reports Ownership interest in MindRhythm, Inc, RS has nothing to disclose, DBW reports grants as below during the conduct of the study; personal fees from American Thoracic Society, personal fees from UpToDate, outside the submitted work; SLM has nothing to disclose, CRF has nothing to disclose.

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