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Donation after circulatory death and lung transplantation

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ABSTRACT

Lung transplantation is the most effective modality for the treatment of patients with end-stage lung diseases. Unfortunately, many people cannot benefit from this therapy due to insufficient donor availability. In this review and update article, we discuss donation after circulatory death (DCD), which is undoubtedly essential among the strategies developed to increase the donor pool. However, there are ethical and legislative considerations in the DCD process that are different from those of donation after brain death (DBD). Among others, the critical aspects of DCD are the concept of the end of life, cessation of futile treatments, and withdrawal of life-sustaining therapy. In addition, this review describes a rationale for using lungs from DCD donors and provides some important definitions, highlighting the key differences between DCD and DBD, including physiological aspects pertinent to each category. The unique ability of lungs to maintain cell viability without circulation, assuming that oxygen is supplied to the alveoli—an essential aspect of DCD—is also discussed. Furthermore, an updated review of the clinical experience with DCD for lung transplantation across international centers, recent advances in DCD, and some ethical dilemmas that deserve attention are also reported.

Keywords: Tissue and organ procurement; Brain death; Lung transplantation; Respiratory insufficiency.

RATIONALE

Lung transplantation (LTx) is a life-saving therapy for managing patients with end-stage lung diseases such as COPD, cystic fibrosis, and pulmonary fibrosis. Unfortunately, this modality of treatment cannot be offered to more patients because of the lack of suitable donors, highlighting the disproportion of patients currently waiting for an organ transplant compared with the number of people on the waiting list.[1]

For example, although a significant number of liver and kidney transplants are performed every year in Brazil, cardiothoracic transplantation is still much lower than what is seen in other countries according to the Brazilian Association for Organ Transplantation.[2] In this context, given the number of active lung transplant centers in Brazil, an increment in the number of procedures performed every year is paramount.

The process of donation is always long and complex; it is necessary to deal with the emotions of the family of the donor, logistics, and expectations of the recipient, and constant attention needs to be paid to every single detail for this entire equation to move forward successfully. Regarding lungs, specifically, optimal donor management is so critical because a potential organ can be lost due to many factors. Less than ideal management leads to high numbers of potential donors becoming unsuitable for LTx.

In contrast to other organs, additional criteria need to be fulfilled for LTx to be considered[3,4] and are critical for the success of the process. The lungs are also susceptible to many insults, such as the intravascular volume status of the donor or the suboptimal management of secretions in the airways. Chart 1 highlights the criteria for lung acceptance for clinical LTx and the particular challenges that need to be considered. Thus, to avoid post-transplant complications, the acceptance rate of a donor for clinical LTx is low, making the relative scarcity of donors combined with low utilization a real challenge.

As the number of patients on the waiting list continues to rise, several strategies have been developed to increase the number of lung transplants. This includes the use of extended-criteria donors,[5] living-donor lobar LTx,[6] and ex vivo lung perfusion (EVLP) for organ rehabilitation.[7]

Another potential source to alleviate the shortage of donors is donation after circulatory death (DCD). This donation process has progressively gained acceptance, not only for LTx but also for kidney, liver, pancreas, and even heart transplantation.[8] This modality of donation has been shown to contribute to an increment in the number of transplants worldwide and represents a shift in a paradigm, given that the standard is donation after brain death (DBD). However, the number of DBD donors seems insufficient for the demand of patients in need of a life-saving transplant.[9,10] Advancements in the knowledge about DCD have bolstered the number of LTx, resulting in progressive increments in the number of DCD every year.[11,12] In the USA, DCD donors has incrementally been contributing to benefit more patients, and, specifically regarding the lungs, the number of DCD used for clinical

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Chart 1. Criteria for acceptance and challenges in donor management.

Standard Criteria for Lung Accepetance for Clinical Transplantation
Age < 55 years
Clear chest X-ray
Adequate gas exchange PAO_2 > 300 mmHg and FiO_2 100%
Smoking history < 20 pack-years
No evidence of aspiration/purulent secretions on bronchoscopy
No history of primary pulmonary disease or active pulmonary infection
Absence of organisms on gram-stained sputum smear
Absence of chest trauma

Challenges—Donor management—Lungs
Attention to the volume status
Mechanical ventilation management
Hygiene of the airways
Potential infectious sources
Careful assessment of medical history
Continuous discussions with the family

LTx has steadily increased (Figure 1), impacting the overall number of lung transplants.

DEFINITIONS

The conventional modality of donation accepted is DBD, and several tests are performed to diagnose and confirm this status, such as the absence of circulation and no brainstem reflexes.[13] On the other hand, DCD involves a patient who has a permanent absence of circulation (blood pressure and pulse activity) and respiration.[14] Although these concepts are broad, in order to clarify this issue, a classification stratified DCD into categories (designated the Maastricht criteria),[15] with sequential updates in this classification (Chart 2).[14] Understanding this classification is paramount, especially considering a critical subdivision between categories I and II (uncontrolled DCD) and types III and IV (controlled DCD). Of note, a modified Maastricht classification encompasses patients submitted to euthanasia as potential donors (classified as category V). Categories I and II are considered "uncontrolled" DCD, implying that death has occurred suddenly. Examples are patients whose death occurred in the ER of a hospital or even at a pre-hospital stage. On the other hand, DCD categories III and IV are considered "controlled" DCD, because death is anticipated but has not happened yet. It usually occurs in ICUs and encompasses patients with nonrecoverable injuries who depend on life-sustaining therapies, however without meeting the criteria for brain death. Young patients with devastating brain injuries and irreversible damage who have not evolved to a brain dead status yet are a typical example of DCD category III and are commonly found in clinical practice. These patients, unfortunately, are so sick that imminent death after withdrawal of life-sustaining therapy (WLST) is expected, and cessation of futile therapies that are prolonging the life of a critical patient is part of the process.[16]

Most importantly, from the categories highlighted above, Maastricht III is currently the most studied and preferred type of DCD in many centers around the world. That is why the focus of this review primarily resides on this category.

In Maastricht III, logistics are critical for success once a donor is identified and matched to a recipient. WLST happens in a controlled environment (typically in ICUs), where comfort and compassionate care of the patient are paramount. In addition, it is extremely important to provide support to the family of the donor. Heparin is administered, ventilatory support is discontinued, extubation is performed in most places, and cessation of medications used to maintain hemodynamic support is also part of this process.

After WLST is performed, there is a planned interval of time, usually ranging from 60-90 min (that can be extended even up to 180 min), during which vital signs of the donor are checked continuously. This period is called the "agonal phase" and lasts until there is termination of circulation and respiration. When the potential donor has cardiac arrest within the planned interval, there is a stand-off period, ranging from 2-5 min, during which the absence of circulation and respiration must be determined by two physicians, who should not be related to the transplant teams. Typically, once death is determined, the donor is then transferred to the operating room, where intubation and ventilation are restarted and lungs are procured. Figure 2 summarizes the complex process involved in controlled DCD.

There are several steps described within this process[17] that should strictly be followed:

- Comfort measures are provided for the donor during the process.
- The family of the patient is being supported.
- As mentioned above, determination of death is critical after WLST is performed, as is the stand-off period, during which the potential donor can be declared dead after cessation of circulation and ventilation for an interval of 2-5 min.
- There are no conflicts of interest.

The surgical technique for procurement of lungs from such donors is essentially the same as for DBD. Briefly, sternotomy is performed. Once the chest is open, the pericardium is incised, and the heart is exposed. The pulmonary artery trunk is identified and cannulated. The left atrial appendage is also open. The preservation solution is perfused in an antegrade fashion from the pulmonary artery, and the output is drained from the left atrium. Lungs are continuously ventilated during the entire process. The technique has been described in detail elsewhere.[18]

After the lungs are removed from the chest in a semi-inflated state, quality is assessed, and a decision is made about the their condition before proceeding

to transplantation.[19] Figure 3 highlights the critical differences between the DCD and DBD processes for the donation of lungs.

In order to establish criteria for eligibility regarding DCD, we must remember that this concept has an intimate relationship to the concept of "end-of-life" care. Although it can provide the opportunity of a life-saving transplant, it is essential to maintain critical aspects, such as preserving dignity and respect for the donor, fulfilling the wishes of the patient and his/her family, and respecting their values. Also, focusing on alleviating any distress or pain, providing support, and avoiding unnecessary prolongation of the death process is paramount.[20]

DCD is still not utilized in many places due to logistics, lack of expertise of the transplant center, and ethical considerations, such as the acceptance of the concept of WLST.[21,22] In addition, there is no legislation regarding DCD in some countries (e.g., Brazil), which makes this process even more challenging.

In summary, there are many challenges to overcome in the DCD implementation process, as described in Figure 4. Many potential DCD donors are missed every year, and these donors could certainly and positively impact on patients waiting for a life-saving transplant.[23]

DIFFERENCES BETWEEN DCD AND DBD

Some differences between DBD and DCD have been discussed above, but two are critical and deserve special attention:

The first situation is the agonal phase. There are many definitions for this phase; in general, the most accepted concept is the interval between WLST and cardiac arrest. Here, a certain amount of time is expected for cardiac arrest to happen, usually ranging from a few minutes to 120 min.[24] The impact of the amount of time that the agonal phase represents and its relation to prognosis is undoubtedly an issue for discussion, given that intervals beyond 120 min have also been reported to be feasible in clinical transplantation.[25] This period is critical, and different patterns of injuries can happen due to the effects that WLST can have on the donor, such as hypotension, hypoxia, and aspiration.

The second issue is the duration of the warm ischemic time (WIT). WIT is generally the interval between the donor's systolic blood pressure < 50 mmHg and lung perfusion with a cold preservation solution via pulmonary artery flush.[26] In comparison with DCD, DBD has the WIT minimized as much as possible. Although this interval is deemed safe when it lasts < 60 min, the fact that the duration of WIT can potentially impair a patient's prognosis is still a matter of discussion and becomes critical for DCD, considering the different pathways that this type of donor follows.[27] In the opposite direction, it is important to discuss the fact that the brain dead status is associated with a process that involves complex pathophysiology in which inflammatory, sympathetic, and hemodynamic mechanisms can ultimately lead to lung injury.[28] These injuries can lead to neurogenic lung edema that can negatively impact on the outcome of LTx, especially

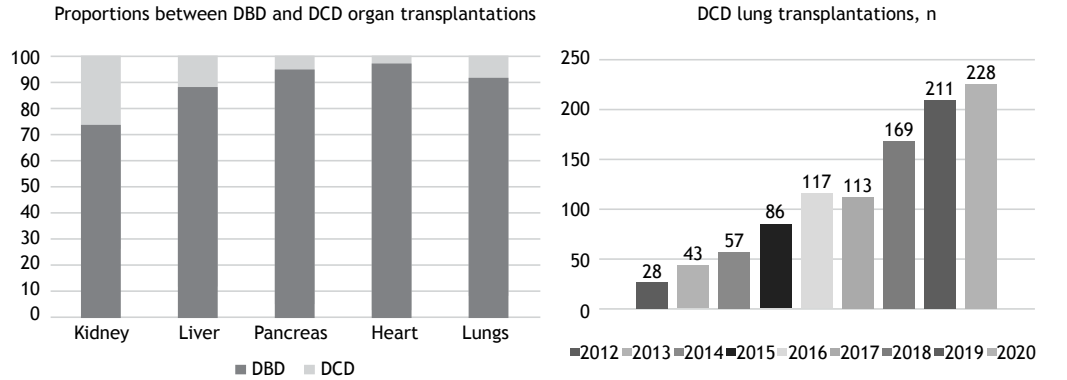

Figure 1. Proportions between donation after brain death (DBD) and donation after circulatory death (DCD) organ transplantations in 2020 and number of DCD lung transplantations between 2012 and 2020.*
*In accordance with data retrieved from the U.S. United Network for Organ Sharing website.

Chart 2. Donation after circulatory death classification.

Categories	Maastricht	Modified Maastricht
I	Dead on arrival at hospital	Found dead IA - Out of hospital IB - In-hospital
II	Death with unsuccessful resuscitation	Witnessed cardiac arrest IIA - Out of hospital IIB - In-hospital
III	Awaiting cardiac death	Withdrawal of life-sustaining therapy
IV	Cardiac arrest while brain dead	Cardiac arrest in a brain-dead patient prior to organ recovery
V		Euthanasia

Categories I and II - Uncontrolled donation after circulatory death
Categories III, IV and V - Controlled donation after circulatory death

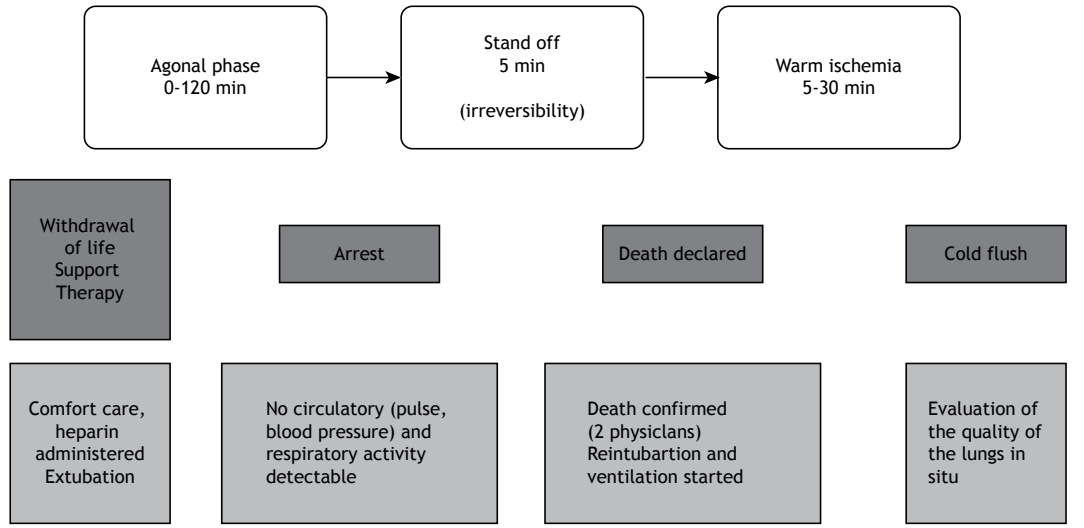

Figure 2. Process of donation after circulatory death.

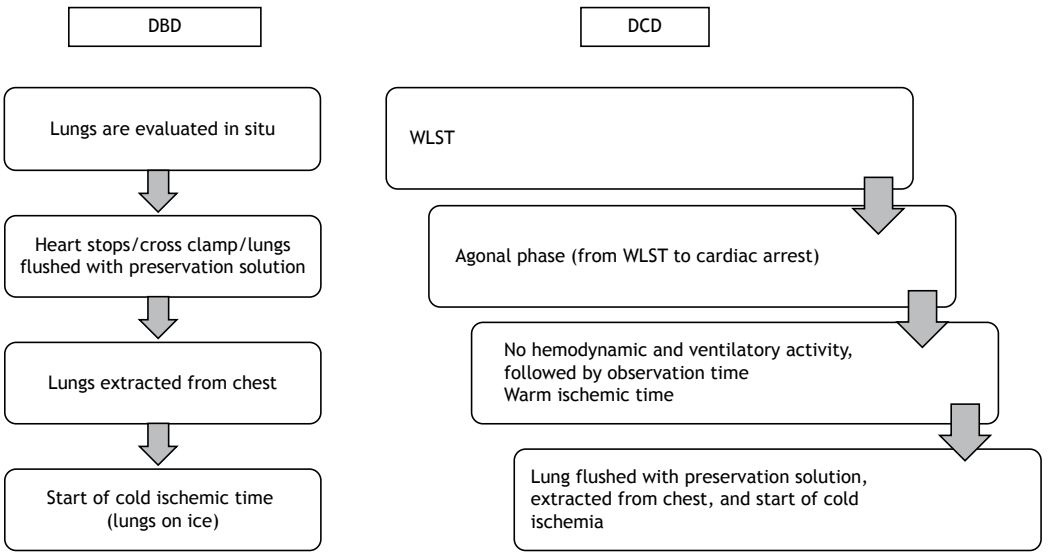

Figure 3. Donation process: donation after brain death (DBD) and donation after circulatory death (DCD). WLST: withdrawal of life-sustaining therapy.

in the early process of brain death.[29] Hence, DCD is potentially spared from this phenomenon since such donors are not exposed to the whole pathophysiological process involved in the brain death mechanism and its associated consequences.

More evidence has described the different pathways that DCD and DBD follow, which are also demonstrated in gene expression profiles. It appears that DBD has more commonly been associated with inflammatory profiles,[30] whereas DCD has shown donor-specific genetic signatures more associated with apoptosis and necrosis.[31]

HOW LONG CAN LUNG CELLS SURVIVE WITHOUT CIRCULATION?

Considering the DCD principles, a fundamental question related to this donation process is certainly for how long lung cells can survive so that the organ can be used for transplantation, since DCD implies a period during which lungs remain without circulation. To address this critical concept, an understanding of lung physiology is mandatory, and it is necessary to understand the lungs' particular capacity to maintain cell viability during WIT. Although this critical time can significantly impair the function of organs such as the liver, heart, kidney, and lungs, the latter can maintain cell viability when there is oxygen in the alveoli. Hence, even in the absence of circulation, ventilation of the lungs becomes paramount for the maintenance of cell viability. This concept is called aerobic lung preservation.[32]

After circulatory arrest, experimental data have shown that a state of atelectasis can be tolerated for 60 min at most without additional damage.[33] In this sense, it

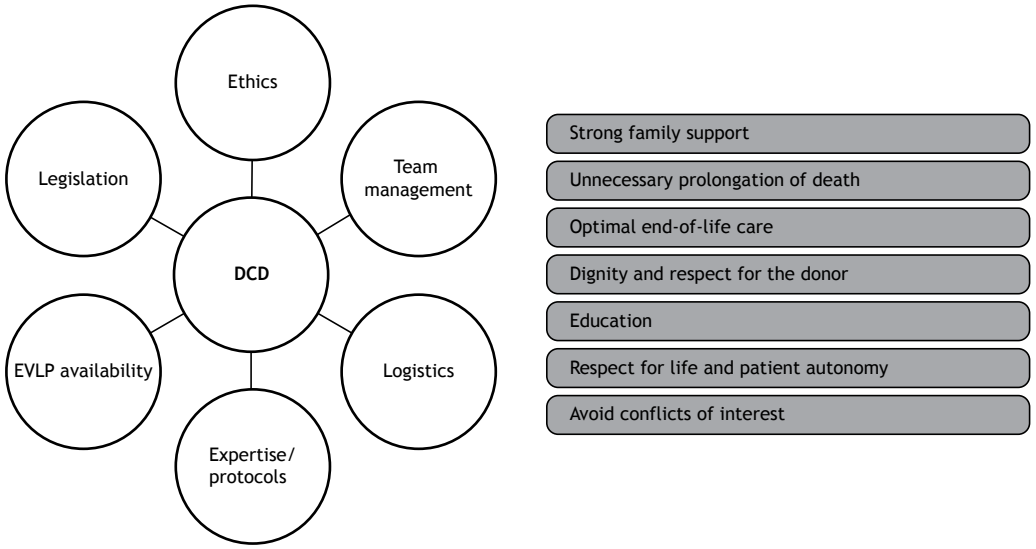

Figure 4. Potential barriers for donation after circulatory death (DCD) implementation and key principles. EVLP: ex vivo lung perfusion.

becomes critical to avoid collapse and atelectasis of the lungs, and its prevention appears to attenuate warm ischemic injury.[34,35] Also, the inflation of the lungs with oxygen seems to be a key component of preservation, because maintaining a reserve of oxygen in the alveoli can potentially minimize the effects of WIT.[36]

Having this in mind, a critical question is when lung cells start to die after cessation of circulation. In small animal models, the simple postmortem ventilation of lungs with oxygen seemed to attenuate ischemic injury to cells. In nonventilated rats, nonviable cells were 36%, 52%, and 77%, respectively, at 2, 4, and 12 h after death. Similar results were found in lungs ventilated with nitrogen. However, oxygen-ventilated cadaver rats had many less nonviable lung cells at the same time points: 13%, 10%, and 26%, respectively ($p < 0.01$), demonstrating that postmortem mechanical ventilation with oxygen can delay cell death.[37] The same research group also showed that, after 4-8 h from death, ultrastructural deterioration was significantly attenuated when oxygen ventilation was provided when compared with rats whose lungs were not ventilated.[38]

These data explain how lungs from DCD donors have the potential to maintain cell viability after cessation of circulation if ventilation/oxygen is provided, conferring a critical topic to be understood when we address this type of donation for clinical transplantation.

RESULTS OF CLINICAL EXPERIENCE WITH LTX USING DCD

A retrospective analysis carried out using the International Society for Heart and Lung Transplantation (ISHLT) circulatory death registry was published,[39] highlighting the experiences of many centers and their practices in the management of DCD, totalizing 306 LTx, between January of 2003 and June of 2013. The control group was constituted by DBD individuals available during the same period.

Most DCD donors were Maastricht category III, and several centers have reported their results with DCD LTx. When DCD and DBD were compared, there were no significant differences in 30-day mortality (96% vs. 97%), 1-year mortality (89% vs. 88%), or 5-year survival (61% vs. 61%).

A follow-up from the same ISHLT registry has been recently reported,[40] this time including more centers, involving patients submitted to LTx between 2003 and 2017 (1,090 DCD-related LTx), and equivalent long-term results were found between DCD and DBD.

These data show that DCD can be a safe resource to alleviate the waiting list of patients who desperately need a life-saving lung transplant. However, these reports addressed no critical perioperative data, such as incidence of primary graft dysfunction (PGD) and ICU length of stay (LOS). To address these issues, a review of retrospective single-center experiences focusing on these data is reported in Table 1.

These compiled data, in which DCD Maastricht category III was by far the most commonly used, also demonstrated no difference between medium- (1-year) or long-term survival, when DCD and DBD were compared regarding LTx.[25,41-45]

PGD is undoubtedly one of the critical factors that can influence the prognosis of patients submitted to LTx and is graded in accordance with the ISHLT classification.[46] Higher grades of PGD, especially at 72 h after LTx, are critical. However, DCD and DBD did not differ in the incidence of this complication at this time point. In addition, ICU LOS was equivalent, and hospital LOS also showed no differences, except for one report[45] that showed a longer hospital LOS in the DCD group.

Some of these studies also evaluated chronic lung allograft dysfunction (CLAD) or bronchiolitis obliterans syndrome (BOS). De Oliveira et al.[41] reported a 5-year

freedom-from-BOS rate of 72.3% for DCD and of 58.0% for DBD (p = 0.59). At one year after LTx, Van de Wauer et al.[42] described a significant advantage in the DCD group when compared with the DBD group. A favorable trend towards DCD was described by Ruttens et al.,[44] with a 5-year freedom from CLAD reported at 79.2% for DCD and 67.8% for DBD (p = 0.86). On the other hand, Sabashnikov et al.[43] reported a higher incidence of postoperative BOS in the DCD group (23.5%) than in the DBD group (11.7%; p = 0.049). Further analyses are necessary to clarify the relationship between DCD and CLAD.

Krutsinger et al.[47] reported his results using a systematic review and meta-analysis approach for comparison and found no differences in 1-year mortality, PGD, and acute rejection episodes when DCD and DBD groups were compared. More recently and using the same approach, Palleschi et al.[48] found no differences in 1-year survival, grade 2-3 PGD rates, or 1-year freedom from CLAD, but airway complications were more commonly found in the DCD group.

ETHICAL DILEMMAS

In some countries, the discussion about the use of controlled DCD is extremely complex because it involves WLST, end-of-life care, and cessation of futile therapies. In fact, in many instances, there is not even legislation that discusses DCD. This makes the dissemination of this process of donation even more challenging.

Although DCD Maastricht III is most commonly used for clinical transplantation, we need to understand that this type of DCD, together with Maastricht IV, comprises a situation in which the potential donor is so severely sick that death is anticipated, and this is not an easy issue to be accepted, understood, and respected in many places where there are different laws, ethical concerns, and religious beliefs. Unfortunately, the final product is that this potential pool of donors is restricted.

These "regulatory" boundaries potentially affect other DCD (uncontrolled Maastricht I and II categories). However, for other types of DCD to be used, other issues need to be tackled, such as the understanding of death and the irreversibility of situations. Taking this concept into consideration regarding uncontrolled DCD, when things can abruptly happen, such as a donor who dies at the arrival in the hospital or one who unfortunately dies after unsuccessful resuscitation efforts, may represent a different challenge for the families and the whole team involved in donation and transplantation. Education of the entire team involved in the donation process seems critical for developing a DCD program.[49] From a medical perspective, the challenge is undoubtedly a thorough understanding of the concept of death. The traditional standard of death remains the permanent cessation of circulation and respiration.[50]

Due to the nature of the events that can happen in these donation processes, it is paramount to educate the population and give support to the families when they are facing the most challenging times of their lives, dealing with the loss of a loved one. Hence, it is essential to understand the uncertainty about the timing of death and recognize efforts to optimize donation respecting the ethical boundaries.

Another critical point is that the introduction of DCD does not jeopardize the potential number of DBD donors. In fact, DCD seems to impact positively on the numbers of transplants and increase the number of DBD donors, potentially resulting from better donor referral policies, among others, which may play a role in this activity.[51]

Many people wish to donate their organs if, unfortunately, death happens; however, ultimately, the family will play a significant role in this critical decision, and the DCD process is different than that of conventional DBD.

DCD is, above all, an effort to save lives, and sometimes this type of donation can be unsuccessful for many reasons; for example, when the quality of the organ is not ideal or when the donor does not

Table 1. Perioperative data—donation after circulatory death vs. donation after brain death for lung transplantation.

Author	Year	DCD/DBD cases	DCD/DBD 1-year survival, %	DCD/DBD 5-year survival, %	DCD/DBD PGD, %[c]	ICU LOS	Hospital LOS
De Oliveira et al.[41]	2010	18/282	88/87	81.9/63.3	PGD Grade 2 or 3 within 72 h: 33.3/26.1	4/6	17/20
Van De Wauver et al.[42]	2011	35/77	91/91	73/66	PGD Grade 3 at 72 h: 6/11	4/5	32/33
Sabashnikov et al.[43]	2015	60/120	86.1/84.2	50.8/66.4	PGD Grade 3 at 72 h: 5/9	5/6	30/32
Ruttens et al.[44]	2017	59/331	87.3/90.9	70.9/78	Highest PGD < 72 h: 44.1/47.7	16.3/14.4	41.1/38.1
Costa et al.[45]	2018	46/237	91/92	78/75[a]	PGD Grade 3 at 72 h: 13/17	N/A	22/18*
Qaqish et al.[25]	2021	180/1088	N/A	8.0/6.9[b]	PGD Grade 2 and 3 at 72 h: 17.2 and 13.9/9, respectively	4.0	23/25

DCD: donation after circulatory death; DBD: donation after brain death; PGD: primary graft dysfunction; and LOS: length of stay. [a]Last follow-up three years after lung transplantation. [b]Values expressed as median of survival in years (p = 0.79). [c]In accordance with Snell et al.[46] *Statistically significant.

have cardiac arrest within a suitable time after WLST. However, even families of donors after circulatory death whose donation was unsuccessful appreciate the donation attempt. Families have reported that unsuccessful donation drawbacks are the waste of an organ highly needed, a lost opportunity to honor their loved one, and the loss of a way to ease their grief.[52]

A comprehensive education process for those involved in these types of donations is necessary to avoid potential conflicts in any possible step within the organ donation process. Education is vital to be tailored appropriately for each component of the decision making and management of DCD. Perceptions of the process can differ according to the family's perspective and the professionals involved in the transplant process.[53]

ADVANCES IN THE DCD—UNCONTROLLED DCD

The progressive acceptance of DCD has been important in order to increment the number of transplants and, as a result, save more lives. To move this discussion to the next phase, uncontrolled DCD is undoubtedly an area that needs to be addressed, considering the significant pool of donors in these categories.

Although uncontrolled DCD was not associated with the expected outcomes in the past,[54] recent data have shown promising results[55] and demonstrated some exciting concepts that potentially contributed to the reported outcomes and can undoubtedly benefit and help disseminate uncontrolled DCD.

Regarding lung preservation, a simple maneuver such as in situ lung inflation using a CPAP of 20 cmH_2O could protect an extended WIT (which, in the authors' experience,[55] was reported to be 2.8 h), creating critical time for the whole process of donation to happen. This period of time is significant for the lungs to be deprived of blood nourishment and to depend on aerobic lung preservation for maintenance of cell viability. In addition, the importance of EVLP was critical. During uncontrolled donation, many injuries can occur to the lungs, and EVLP would work to stratify better lungs that can maintain adequate function. With the anticipated expanded WIT intervals for uncontrolled DCD, the use of EVLP becomes an essential tool for organ usage.[56]

Despite the conflicting results presented with uncontrolled DCD, the development of standard protocols for donor management is critical to a better determination of outcomes, eventually disseminating this pool of donors.[57]

Ethical concerns such as the determination of irreversibility of cardiac arrest, the extension of resuscitation beyond futility, and the determination of death, as well as how to approach family members about uncontrolled DCD, are all areas that need to be taken into consideration to promote this mode of donation further.[58] However, it is undeniable that this modality can be a valuable resource for patients on the waiting list for a life-saving transplant.[59]

In summary, DCD does have the potential to impact significantly on the number of transplants. Clinical results to date have demonstrated excellent outcomes, at least equivalent to those of DBD. Ethical, cultural, and legislative barriers need to be further addressed in countries such as Brazil, so that this valuable source of organ donors can be fully utilized.

AUTHOR CONTRIBUTIONS

PARS: article design; drafting and review of the manuscript; final approval of the manuscript. DMMN, PJZT, and MC: review and final approval of the manuscript.

CONFLICT OF INTEREST

None declared.

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