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Donation after Circulatory Death in Lung Transplantation

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The shortage of donor lungs has become a serious obstacle to implementing lung transplantation (LTx). Donation after circulatory death (DCD) donors are among the several donor pools utilized to overcome the problem posed by the shortage of donation after brain death (DBD) donors. The active use of DCD donors is expected to significantly reduce mortality on the waiting list for LTx, as LTx from DCD donors has comparable outcomes to LTx from DBD donors. Further studies on efforts to shorten the warm ischemic time and use uncontrolled DCD are required.

Keywords: Lung transplantation, Donation after circulatory death, Donation after brain death

Introduction

The largest obstacle in lung transplantations (LTx) is the shortage of donor lungs. Despite recent improvements in the detection of potential donors and donor management, this issue persists. Studies on the use of lungs that fail to meet standard donor criteria in LTx and other alternatives are actively being conducted to solve the donor shortage problem. Out of these alternatives, several institutions have focused on donation after circulatory death (DCD) donors. Historically, the first LTx, which was performed by Hardy et al. [1] in 1963, was a transplant using a DCD donor's lung. Until 1980, the outcomes of all organ transplants were unsatisfactory. Therefore, DCD donors were often used, because the usage of organs of beating-heart donors had several ethical issues. Since then, advances in preservation techniques, the development of immunosuppressive drugs, and the improvement of transplant outcomes have made it possible to use brain-dead donors with beating hearts for transplantation. However, as the number of transplants increased, brain-dead donors alone became insufficient to cover all recipients, so DCD donors were again considered as an alternative option. LTx using DCD lungs is now actively implemented in Europe and North America, and the use of DCD donors has been reported to increase the current donor pool by up to 50% [2].

Terminology

In medical terms, death is primarily classified into circulatory death and brain death. Initially, the term "non-heart-beating donor" was used to describe organ donation after cardio-respiratory arrest. This term was adopted at the first International Workshop on Non-Heart-Beating Donors and used in the Maastricht classification. Since then, "non-heart-beating" and "cardiac death" have been used interchangeably in cases of circulatory death, while "heart-beating" has been used to refer to cases of brain death [3]. However, referring to specific organs, such as the brain or heart, as "dead" could lead to the misunderstanding that only a certain organ has ceased its functions and not the whole human body. The classification was thus modified to "circulatory death" versus "neurologic death," and donors in whom circulatory death has taken place began to be called "donation after circulatory death" donors [4]. Some argued that a more accurate term would be "donation after circulatory determination of death" (DCDD), but DCD remained the preferred term over DCDD because DCD was already in common use [3].

Theoretical background of donation after circulatory death lung use

Unlike other organs that receive oxygenated blood di-

rectly from blood vessels, the lung can transfer oxygen by passive diffusion through the alveolar wall. Therefore, mechanical ventilation without blood flow can maintain a certain level of cellular viability. Although experiments have shown that the lung can tolerate warm ischemia for approximately 60–90 minutes [5,6], the agonal phase is non-existent in experiments; hence, the conditions are different from actual clinical situations. In other words, since the cause of death in experiments is ventricular fibrillation or bleeding, the agonal phase usually does not exist.

However, in the clinical setting, pulmonary edema develops primarily as a result of hypoxic hypotension occurring in the agonal phase, and the sympathetic activation that also occurs in the agonal phase worsens pulmonary edema. Therefore, it is a principle that the agonal phase should be limited to within 1 hour in clinical practice. Multiple studies on the advantages of DCD lungs compared to donation after brain death (DBD) lungs have been reported. Catecholamine surges occur in DBD donors during the brain death process, triggering neurogenic pulmonary edema. In addition, the tissue levels of proinflammatory cytokines, which activate inflammatory pathways, are higher in DBD lungs than in DCD lungs [7].

Classification of donation after circulatory death donors

In the first International Workshop on Non-Heart-Beating Donors held in Maastricht, Netherlands, in 1995, DCD donors were principally classified into 2 categories and then 4 subsequent subcategories. Category I referred to patients who arrived at the hospital after death or were "dead on arrival." Category II referred to patients who could not be revived by resuscitation. Both categories I and II were defined as uncontrolled DCD (uDCD), as it was difficult to determine the exact warm ischemic time or evaluate the correct status of the donor lung graft. Category III referred to patients whose life support would be removed for them to await death according to plan, and category IV encompassed cases where unexpected cardiac arrest occurred in patients diagnosed with brain death. Categories III and IV were defined as controlled DCD (cDCD) (Table 1). More recently, euthanasia was defined as category V and included in cDCD [8].

Eligibility of donation after circulatory death donors

The selection process for candidate DCD donors must be carefully considered, as several legal and ethical issues may be involved. In 2006, the United Network for Organ Sharing (UNOS) defined potential DCD donors as patients who would die within 60 minutes after removal of life support while also experiencing irreversible cerebral injuries, high spinal cord injuries, or end-stage muscular skeletal disorder [9]. However, because it is very difficult to predict whether a patient will die within 60 minutes, evaluation tools that predict the time of death to identify potential DCD donors have been studied. In 2003, a research group from the University of Wisconsin group predicted the likelihood of death within 1 hour based on a score that took into account the respiratory rate, vasopressor use, age, intubation status, and oxygenation [10]. The UNOS also presented cardiopulmonary criteria in an attempt to predict the likelihood of death [11]. The Pittsburgh group conducted validation studies by including the Glasgow Coma Scale, O_2 ratio, and peak airway pressure along with the original UNOS criteria [12]. Thereafter, several models have been proposed, and these predictive tools provide significant assistance in identifying appropriate DCD donors.

Selection criteria for donation after circulatory death lungs

The selection criteria for DCD lungs are identical to the DBD criteria at most institutions. The acceptable lung donor criteria include age <55 years, a smoking history of below 20 pack-years, normal chest radiography and broncho-

Table 1. Maastricht classification of donation after circulatory death donors

Category	Circumstances	Controlled/uncontrolled	Description
Category I	- Dead on arrival	- Uncontrolled	- Impractical evaluation of graft function - Imprecise warm ischemic time
Category II	- Unsuccessful resuscitation	- Uncontrolled	- Impractical evaluation of graft function - Imprecise warm ischemic time
Category III	- Awaiting cardiac arrest - After the planned withdrawal of life support	- Controlled	
Category IV	- Unexpected cardiac arrest in a brain death donor	- Controlled	

scopic findings, and a partial pressure of oxygen to fraction of inspired oxygen ratio >400 mm Hg [13]. Some institutions utilize more extensive criteria.

Management of donation after circulatory death lungs

The clinical courses and procedures from the selection of DCD patients to lung procurement vary depending on national ordinances and institutional circumstances. Typically, when a potential candidate DCD donor is reported, recipient matching is performed after the medical team obtains consent through family interviews and institutional approval. The LTx physician examines the lung condition to determine whether it conforms to the acceptance criteria. When everything is ready, mechanical ventilation is halted, and extubation is conducted. If the patient does not recover within 5 minutes after cardiac arrest, he or she is declared dead. The patient is immediately transferred to the operating room for reintubation and mechanical ventilation while being cautious of aspiration. Thereafter, heparin is administered, followed by cardiac compression to circulate the heparin into the pulmonary vessels. Bronchoscopy is used to check for aspirations, and the secretions in the bronchus are completely removed. The following procurement process is identical to that for DBD lungs [14].

Reducing the warm ischemic time in DCD is critical. Although 30–90 minutes would usually be considered tolerable, most institutions consider below 60 minutes to be acceptable [14]. Organ preservation must be initiated as soon as possible after the declaration of death to reduce the warm ischemic time. Organ preservation is carried out with a hypothermia-based protocol in DCD, similar to DBD. The cooling process is primarily divided into topical cooling and antegrade perfusion, with the former involving administration of the preservation solution, Perfadex, into the thoracic cavity and the latter involving administration through the pulmonary artery (PA). Topical cooling sometimes involves infusion of cold Perfadex by inserting the chest tube into the thoracic cavities on both sides. This is performed when extra time is required for patient family interviews or organ allocation in uDCD [15]. Direct insertion of ice slush into the pleural cavity after sternotomy in the operating room is also a form of topical cooling. Infusion of Perfadex through PA is the gold-standard cooling method, and this moment is defined as the end of warm ischemia. After antegrade perfusion through the PA is completed, a retrograde flush is performed through the pulmonary vein to remove thrombi from inside the pulmonary vessels and enable the Perfadex to be transmitted to the parenchyma, which could not be reached by previous antegrade measures.

The agonal phase is defined as the time from life support withdrawal to circulatory arrest or the declaration of death. This time varies depending on the type of donor, as hypoxemia and hypoperfusion gradually progress until full cardiac arrest occurs, affecting ischemic organ injury. The definition of death is also inconsistent, as mechanical systole without peripheral pulsation is sometimes defined as death, while electrical asystole with a flat electrocardiogram (EKG) is also classified as death. However, several institutions regard the absence of peripheral beating as death, even if the EKG is not flat from the literal circulatory arrest perspective, to reduce the agonal phase; therefore, it may be necessary to evaluate the donor using arterial and venous pressure monitoring, echocardiography, and Doppler ultrasonography. After cardiac arrest occurs, the situation needs to be monitored for at least 2–5 minutes without conducting any particular action. This period is called the "no-touch" period; it also varies among institutions and can be as long as 20 minutes.

Another crucial issue regarding DCD donors is heparinization, and the time of injection is a matter of debate. If heparin administration is conducted before cardiac arrest, the ethical issue of cerebral hemorrhage being induced in patients with cerebral injuries exists. However, there is still an argument to support early heparinization, as thromboembolisms are found in 38% of donors and are directly related to transplantation outcomes [16]. Contrarily, experiments proved that thrombus formation could be prevented by administering heparin within 30 minutes of cardiac arrest; therefore, some have argued that it is not entirely necessary to administer heparin before cardiac arrest [17]. In some cases, heparin administration before cardiac arrest is legally prohibited. When heparin is administered after cardiac arrest, cardiac compression should be performed to circulate heparin to the lungs. In conclusion, heparin does not need to be administered before cardiac arrest, but it must be administered to prevent thromboembolism.

The necessity of withdrawal of the endotracheal tube is also debatable. The tracheal tube prevents aspiration into the airway, but it has the disadvantage of prolonging the agonal phase by preventing the collapse of the upper airway.

The evaluation of DCD lungs must be exceptionally critical because every donor has a different warm ischemic time. Similar to DBD, it is possible to perform bronchosco-

py, chest radiography, and arterial blood gas analysis for cDCD cases before cardiac arrest, enabling an accurate evaluation of the lung status, which is impossible for most uDCD cases. Some institutions infuse approximately 300 mL of donor blood to the PA after Perfadex infusion to conduct arterial blood gas analysis on the blood flowing out to the left atrium [18]. *Ex vivo* lung perfusion has also recently been conducted to evaluate the lung status.

Outcomes of donation after circulatory death

DCD LTx is usually implemented with lungs of Maastricht category III. According to the International Society of Heart and Lung Transplantation DCD Registry report, there is no significant difference in 5-year survival between cDCD LTx and DBD LTx [19], and cDCD LTx has shown better outcomes in 10-year survival [20]. Similar results have been observed in other studies, including the UNOS registry [21,22]. Primary graft dysfunction (PGD) occurred slightly more severely in cDCD 1 hour after transplantation than in DBD, but it recovered shortly thereafter, and no further difference was observed between the 2 groups. Several studies have reported that the incidence of chronic lung allograft dysfunction (CLAD) was not substantially different between the 2 groups [23]. In addition, the incidence of acute cellular rejection or airway complications showed no significant difference. LTx using uDCD, particularly category II lungs, has gradually increased in recent years; however, the survival, PGD, and CLAD incidence rates vary among institutions.

Conclusion

DCD lungs are pragmatic assets in overcoming the current shortage of donor lungs. In particular, the LTx outcomes of cDCD are not inferior to those of DBD donor lungs, so the active utilization of cDCD is expected to significantly reduce the waiting list mortality. However, legal and ethical issues surrounding DCD still exist, and resolving these problems seems critical for the vitalization of DCD. Furthermore, research on uDCD, including category II and euthanasia donors, needs to be actively conducted.

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Conflict of interest

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