Selection, preservation and evaluation of lungs from donors after circulatory death

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Introduction and aim of the thesis

In 1963, James Hardy performed the first human lung transplantation with a lung graft from donation after circulatory death (DCD) donor [1]. Since the introduction and the acceptance of brain death criteria in 1968, lung transplantation from donation after brain death (DBD), also referred to as heart-beating donor (HBD), became the main stay therapy for selected patients with end-stage lung failure refractory to medical therapy. Better understanding of the pathophysiology during the ischemic insult, refinements in lung preservation techniques and solutions, surgical technique, immunosuppression and postoperative care have all contributed to a better early and late survival [2]. As a result of its own success there is now an important discrepancy between the number of patients on the waiting list and the number of suitable donors. Only 15% to 30% of DBD donors have lungs that are suitable for transplantation [3]. The main reasons for non-use are lung contusion, aspiration, pulmonary infection, atelectasis and neurogenic pulmonary edema. Alternative strategies to increase the donor pool are living-donor lobar transplantation [4], downsized donor lungs, marginal donor lungs or extended criteria donor lungs, donation after circulatory death [5] and lungs conditioned with ex vivo lung perfusion [6].

Donation after circulatory death donors (DCD), or non-heart-beating donors (NHBD), are patients with an infaust prognosis but without fulfilling the neurological criteria of brain death. According to the Maastricht classification, DCD donors can be classified into four categories [7]. In category I (dead on arrival) and category II (unsuccessful resuscitation), cardiac death occurs unexpectedly outside the hospital and the situation for organ recovery is therefore uncontrolled. In category III (awaiting cardiac arrest) and category IV (cardiac arrest in a brain dead donor), circulatory arrest is anticipated and organs can be recovered under controlled circumstances. Nowadays the majority of DCD donors are category III DCD donors. The concept of lung transplantation from DCD donors was reintroduced by Egan in 1991 [8]. It was recognized that the lung is unique among other solid organs because pulmonary tissue remain viable by consuming the oxygen in the alveoli via diffusion, even after cessation of circulation [9-11]. Nevertheless, there are several concerns regarding the use of DCD lungs related to the warm ischemic period, the formation of micro thrombi, the injury inflicted by the agonal phase and the lung quality after resuscitation in the setting of DCD category I – II.

DCD is inevitable associated with a warm ischemic period. Warm ischemia is the ischemia of cells and tissues under normothermic conditions. It leads to endothelial cell and alveolar type II cell dysfunction resulting in pulmonary edema and graft dysfunction during reperfusion [12-14]. Nowadays there is experimental [8,15-17] and clinical evidence [18-20] that a limited period of warm ischemia does not compromise the pulmonary graft from the DCD donor. This period of 60 – 90 minutes can be safely extended if the lungs are ventilated, expanded after death or topically cooled via chest drains [16,21,22]. However, there is no uniform definition of warm ischemia. The start of the warm ischemia may include the moment of withdrawal, a systolic blood pressure below 50 mmHg or the circulatory arrest and ceases with cold flush preservation of the organ [23]. Another concern is the preservation of the lungs in the cadaver of an uncontrolled DCD donor. In the early days of lung transplantation prior to cold flush preservation, the lungs were cooled and stored by immersion in 4°C Collins solution as initiated by the Toronto Lung Transplant Group [24]. Topical cooling was reintroduced by Steen and colleagues [19]. A cold (4°C) preservation solution (Perfadex) was inserted via two intrapleural catheters resulting in collapse of the lungs by compression and a quicker surface cooling [25].

The formation of microthrombi after circulatory arrest and the subsequent development of primary graft dysfunction resulting from ischemia-reperfusion injury is a major concern. Flushing the lungs during procurement may be a strategy to remove the microthrombi, thereby improving graft performance. Numerous studies have been reported in the literature comparing the effect of different preservation routes in DBD. Anterograde flush is the technique most frequently applied clinically. It improves the pulmonary microcirculation and preserves the endothelial-epithelial barrier. Retrograde flush, via the left atrium into the pulmonary venous system using the pulmonary artery for outflow, is characterized by a low vascular resistance and high volume capacity resulting in a more uniform distribution of the preservation solution [26,27]. There is an advantage of flushing both the pulmonary and bronchial vessels and of limiting the effect on pulmonary artery hypothermic vasoconstriction. Furthermore, retrograde flush can washout residual blood, possible microthrombi and other tissue emboli that may obstruct the pulmonary vessels [28]. Experimental [29-33] and clinical [27,28,34] reports have shown that retrograde flush is not detrimental and improves graft performance with less edema and improved oxygenation. Ventilation during the perfusion of the preservation solution results in better distribution regardless of the route of delivery [26]. However, studies looking at the best route of pulmonary flush in the controlled and the uncontrolled donors are not available in the literature. Administration of agents like heparin or fibrinolytic agents may help to better preserve organ function [35,36]. However, this may raise ethical questions. Furthermore, permission to

intervene before or after death depends on the legislation for organ donation and harvesting (presumed consent versus explicit consent) and differs from country to country. In controlled DCD, pretreatment (i.e. heparin or phentolamine) can be given before death [37-39] or after the 5-minute no-touch interval [40]. In some centers donors are optimized but no heparin is given [18]. Microscopic evaluation of lungs harvested in a heparin-free donation scenario revealed no microvascular thrombi in the alveolar capillaries or in the pulmonary vasculature [41]. Although, these were controlled DCD lungs flushed retrograde and anterograde with Perfadex enriched with 50 000 IU heparin. Heparinization of the uncontrolled DCD followed by chest compression can potentially cause lung contusions and subsequent pulmonary hematomas. There is also concern of theoretically dispersing microthrombi through the lung.

Exsanguination and myocardial infarction or ventricular fibrillation are common causes of death in the uncontrolled DCD. This may lead to a period of hemodynamic instability prior to circulatory arrest and cardiac death. On the other hand, in patients not fulfilling the brain death criteria where ventilatory support is withdrawn (controlled DCD); a variable period of hypoxia will also result in hemodynamic instability and circulatory stop. Little is known about the impact of pre-mortem instability during this agonal phase or withdrawal phase on the quality of the graft prior to retrieval and on its performance after transplantation. Data investigating the impact of the agonal or withdrawal phase are limited. Experiments show that a period of hypotension followed by circulatory arrest impairs lung viability [42] and that pre-arrest hypoxic perfusion is less detrimental for the pulmonary allograft than for the cardiac allograft [43]. It is hypothesized that the injury to the graft in the pre-mortem agonal period could be more noxious than the injury that occurs during the warm ischemic interval prior to cold preservation.

Hypothermic static organ preservation is the golden standard to preserve donor lungs. However, it is often not possible to evaluate the organs inside the donor. In 2001, Stig Steen introduced the concept of ex vivo lung perfusion (EVLP) as a method to evaluate the lungs before implantation but also as a possible technique to condition the lungs [19,44]. This ex vivo perfusion is based on the circulation of Steen solution in a circuit outside the body. This technique is now used worldwide in many groups to evaluate donor lungs as part of a study protocol or in a clinical setting. Extended normothermic EVLP allows an assessment of DCD donor lungs and DBD donor lungs [45]. Transplantation of these lungs led to results comparable with conventionally selected lungs [46,47]. However, in DCD category I-II, lung function is often unknown at the time of recovery. These lungs were initially evaluated with a pulmonary flush technique [48]. After anterograde flush of the donor lungs with Perfadex, 300 mL of donor blood to which PGE_1 is added is flushed via the pulmonary artery with the lungs ventilated with 100 % oxygen. If the difference of the PaO_2 between the pulmonary artery and the left atrium is more than 300 mmHg lungs are accepted for transplantation. This taken into account the macroscopic aspect of the lungs. Recently, lungs were assessed using ex vivo lung perfusion before implantation [49].

The aim of this thesis is to address the above mentioned concerns in 7 chapters.
In **chapter 1**, we investigate the benefit and the most effective route (anterograde versus retrograde) of pulmonary flush following topical cooling after warm ischemia.

Studies looking at the best route of pulmonary flush in the controlled DCD immediately after the warm ischemic period prior to cold storage have not been performed thus far. In **chapter 2**, we compare the effect of anterograde pulmonary flush versus retrograde flush versus no flush followed by cold storage on graft function and on residual microthrombi.

Administration of heparin to the DCD donor remains controversial. The need for postmortem heparinization with additional chest compressions of the uncontrolled DCD is addressed in **chapter 3**.

No study so far has compared the different modes of cardiac death. The purpose of our study was to investigate pre-mortem hemodynamic disturbances during the agonal phase and we compare their influence on graft performance between animals succumbing from different modes of death (hypoxia versus hypovolemic shock versus cardiogenic shock). This is described in **chapter 4**.

Evaluation of lungs from uncontrolled DCD is thus far performed with a single flush technique or with ex vivo lung perfusion. In **chapter 5** we evaluate the feasibility of an evaluation of lungs from uncontrolled DCD donors with a lung perfusion system in the donor. In case of in situ lung perfusion, the lungs remain in the deceased body. The heart-lung block is connected to a reperfusion system and a bed site assessment is performed.

In 1995, Love et al. performed the first clinical successful lung transplantation with lungs from a DCD donor [50]. Since then the experience with use of controlled DCD donors is growing. It is a true alternative besides DBD lungs. In 2004 the first DCD lung program for the Netherlands was started in Groningen. In **chapter 6** we describe our initial experience with DCD lungs.

Normothermic ex vivo lung perfusion allows an extended assessment of unsuitable DCD category III donor lungs. In **chapter 7** we present a case report describing the conditioning of unacceptable DCD lungs during 4 hours of ex vivo lung perfusion followed by a successful transplantation.

Experiments reported in chapter 1 - 4 were realized at the KU Leuven under promotorship of Prof. dr. D. Van Raemdonck while chapter 5 - 7 were realized at the University of Groningen under promotorship of Prof. dr. M. Mariani and co-promotorship of Dr. M. Erasmus

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