

Applied Cardiopulmonary Pathophysiology 15: 38-48, 2011

## Initial experience with transplantation of lungs recovered from donors after euthanasia

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### Abstract

**Objectives:** Donors after cardiac death (DCD) have increasingly provided organs for lung transplantation (LTx). The use of lungs from donors after euthanasia has not yet been reported.

**Methods:** Between 01/2007-12/2009, 17/145 (11.7%) isolated LTx were performed from controlled DCD, including 4 (2.8%) after euthanasia. All donors expressed their wish for organ donation once their request for euthanasia was granted according to Belgian legislation. All donors suffered from an unbearable non-malignant disorder.

**Results:** The warm ischemic time between circulatory arrest and cold flush of donor lungs was 14 [10-16] min. Total ischemic time until reperfusion of the graft was 329 [225-414] min for the first lung and 517 [346-547] min for the second lung. No severe graft dysfunction was observed beyond 24 hours. One recipient died in the ICU from a problem unrelated to the graft. The remaining patients were extubated after 2 [2-3] days and discharged from ICU after 7 [4-7] days and from hospital after 33 [23-36] days. FEV<sub>1</sub> and FVC increased from 16 [15-21]% and 52 [51-59]% pre-transplant to 85 [61-94]% and 79 [63-84]% at the time of hospital discharge, respectively; (p<0.01). Actuarial 1-year and 3-year survival was 75%.

**Conclusion:** Euthanasia donors accounted for 23.5% of all DCD lung donors with excellent post-transplant graft function and good early recipient outcome.

**Key words:** lung transplantation, donation after cardiac death, donation after brain death, non-heart-beating donors, euthanasia, end-of-life

### Abbreviations

BOS bronchiolitis obliterans syndrome  
DBD donor after brain death  
DCD donor after cardiac death  
FEV<sub>1</sub> forced expiratory volume in one second

FVC forced vital capacity  
LTx lung transplantation  
PGD primary graft dysfunction

## Introduction

Lung transplantation (LTx) is a life-saving therapeutic option for well selected patients suffering from any form of end-stage pulmonary disease. Early and late survival rates have improved in recent years [1]. As in other types of solid organ transplantation, the application of this treatment modality to all patients in need is hampered by current organ shortage. Transplant teams around the world are exploring new sources to enlarge the donor pool with the aim to shorten the waiting time for a suitable organ and to decrease waiting list mortality [2]. Alternatives to diminish lung donor shortage are the use of living donors, extended criteria donors, and donors after cardiac death (DCD). Our group has recently reported equal short-term outcome with lungs recovered from these last two categories when compared to standard, brain-dead donors (DBD) [3, 4].

In 2002, Belgium was the second country in the world following the Netherlands to adopt a law legalizing physician-assisted death and euthanasia under very restricted conditions [5]: Euthanasia has to be requested in writing by a conscious patient (or his/her representative with no interest in the patient's death) suffering from an intractable medical disorder causing continuous and unbearable physical and/or mental suffering, with no hope for improvement, or facing imminent death. Patient's general and psychiatric health status has to be assessed and confirmed by an external medical expert. The euthanasia procedure can not take place within 30 days after the request. In the past 5 years, several Belgian transplant teams have been contacted by the treating physician after a patient expressed a voluntary and explicit wish for organ donation at the time of euthanasia [6, 7]. In July 2007, our lung transplant team for the first time was contacted by another transplant coordination team to explore whether we were willing to recover and transplant lungs from a donor after euthanasia. After a first successful procedure, three

more patients have been transplanted with lungs from such an euthanasia donor.

The aim of this paper is to report our experience with LTx after euthanasia, to present outcome in recipients, and to discuss practical and ethical considerations.

## Patients and methods

### *Study design*

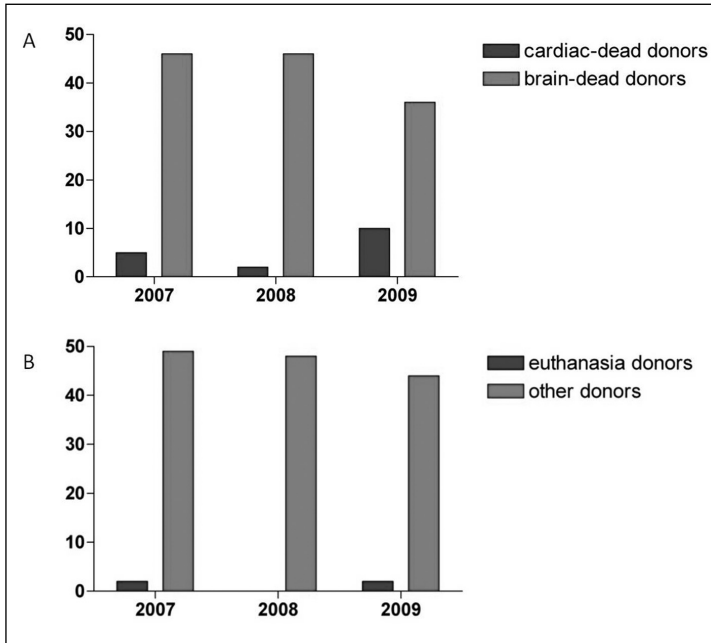
All consecutive LTx procedures done at the University Hospitals Leuven between January 2007 and December 2009 were reviewed using a prospectively gathered database. A total of 145 LTx (125 double and 20 single) were performed, 128 with lungs from DBD and 17 (11.7%) with pulmonary grafts recovered from DCD. The annual number of LTx during the study period is shown in figure 1.

During this 3-year period, four transplant procedures were carried out with lungs recovered from donors after euthanasia, two in 2007 and two more in 2009. The numbers of euthanasia donors comprise 23.5% of all (4/17) DCD and 2.8% of all (4/145) donors in the study period. Follow up after the transplant until the end of the study (31/08/2010) ranged from 8 months to 37 months.

Informed consent for data analysis was obtained from the recipients according to the Belgian law on patients' rights regarding data registration. Approval for analyzing recorded data was waived by the institutional ethics committee on human research given the retrospective nature of the study.

### *Donors*

Three donors were offered by the transplant coordination team of the University Hospital Antwerp and one donor by our local donor office. Euthanasia request was granted by an independent team of physicians not taking care of the transplant recipients. The donors suffered from an unbearable physical (n=3) or



*Figure 1: Annual number of lung transplantations performed at the University Hospitals Leuven between 2007 and 2009 **A)** with grafts from donors after cardiac death versus donors after brain death; **B)** with grafts from euthanasia donors versus other donors.*

mental (n=1) disorder. All donors explicitly and voluntarily expressed their wish to become an organ donor once their request for euthanasia was granted. All consecutive cases were discussed and individual approval for organ retrieval was given by the ethics committee of the donor hospital involved in the euthanasia procedure. All donors were visited by a senior transplant coordinator who

discussed the whole procedure and answered all questions of the donor and family.

Donor characteristics are listed in table 1. A brief medical history was available from all donors. A chest X-ray was taken in the days before the procedure. No information on lung function, gas exchange, or sputum gram stain was available.

*Table 1: Donor characteristics*

N°	Donor Center*	Age (yrs)	Gender	Blood Group	Height (cm)	Weight (kg)	CMV	Disorder	WIT (min)
1	UZA	48	M	B	183	65	neg	MUSC	14
2	UZA	50	F	O	161	65	neg	MUSC	10
3	UZA	62	M	B	184	101	neg	NEURO	13
4	UZL	52	F	O	166	65	pos	MENT	16

N°: number

\*Coordinating donor center

UZA: University Hospital Antwerp; UZL University Hospitals Leuven

CMV: cytomegalovirus; neg: negative; pos: positive

MUSC: muscular disorder (multiple sclerosis); NEURO: neurological disorder (pontocerebellar atrophia); MENT: mental disorder (automutilation)

WIT: warm ischemic time between circulatory arrest and cold pulmonary flush

yrs: years; cm: centimeter; kg: kilogram; min: minutes

## Recipients

Permission to accept and transplant these lungs was previously obtained from our institutional ethics committee in case such organs would be offered. Informed consent on the possibility of receiving an organ from a DCD is obtained from all recipients when entering the waiting list. So far we have not experienced any objection by the candidates to this type of donor. Information on the specific cause and mode of death is never discussed with the individual recipient at the time of organ offer as Belgian law prohibits to reveal any donor information.

Organs were allocated in accordance with the rules set by Eurotransplant International Foundation (Leiden, the Netherlands). Lungs from DCD are offered firstly to centers in the donor's nation that have previously agreed to transplant DCD organs. Transplant teams then have the freedom to choose a suitable recipient from their own waiting list who matches best with the organ offered.

Recipient characteristics are listed in table 2. Four patients (2 males – 2 females) with a median age of 54 [31-39] years underwent bilateral lung transplantation for emphysema (n=2), pulmonary fibrosis (n=1), and obliterative bronchiolitis following a first transplant (n=1). The median time on the waiting list was 240 [195-499] days.

## Organ retrieval

Donors were admitted to the hospital a few hours before the planned euthanasia procedure. A central venous line was placed in a room adjacent to the operating room. Donors were heparinized immediately before a cocktail of drugs was given by the treating physician who agreed to perform the euthanasia. The patient was announced dead on cardiorespiratory criteria by 3 independent physicians as required by Belgian legislation for every organ donor. The deceased was then rapidly transferred, installed on the operating table, and intubated. The thorax and abdomen were shaved, disinfected and draped. A rapid sterno-laparotomy was performed. The abdominal team took care of liver and kidney preservation with a rapid flush cooling technique via a cannula inserted into the abdominal aorta. The thoracic team then opened pleural cavities and quickly inspected both lungs before topical cooling with ice-cold saline was started. The pericardium was opened, the main pulmonary artery was encircled and a 24 Fr pulmoplegia catheter was inserted through the right ventricular outflow tract. The heart was decompressed and vented by cutting left and right atrial appendages. Antegrade pulmoplegia was started with 2.8L Perfadex® solution while the lungs were ventilated with 50% inspired oxygen followed by

Table 2: Recipient characteristics

N°	Year LTx	Age (yrs)	Gender	Blood Group	Height (cm)	Weight (kg)	CMV	Indication	W L (ds)	FU (ms)
1	2007	30	M	B	167	55	pos	OB	195	37
2	2007	49	F	O	162	73	pos	PF	240	34
3	2009	59	M	B	184	84	pos	EMP	499	11
4	2009	54	F	O	166	60	pos	EMP	211	8

N°: number

LTx: lung transplantation

CMV: cytomegalovirus; pos: positive

OB: obliterative bronchiolitis; PF: pulmonary fibrosis; EMP: emphysema

WL: waiting list time

FU: follow up

Yrs: years; cm: centimeter; kg: kilogram; ds: days; ms: months

retrograde flush with one additional liter of the same perfusion solution after the heart was extracted. Lungs were then explanted, packed and transported to the recipient hospital in the standard way.

The anesthesia in the recipient was not started until both lungs had been inspected in situ and found suitable for LTx by the donor team.

## Results

### Donor operation

The warm ischemic time defined as the period between circulatory arrest and cold flush of the lungs in the donor, was 14 [10-16] min (table 1). No technical difficulties were experienced with this preservation technique. No thrombi or debris were seen in the pulmonary artery in any case upon retrograde flush.

### Recipient operation

Operative details are listed in table 3. Both lungs were implanted sequentially in all recipients through an anterior thoracotomy in 2 patients with emphysema, a lateral thoracotomy in 1 patient with obliterative bronchiolitis

after a first transplant, and an anterior thoraco-sternotomy (clam-shell) in 1 patient with pulmonary fibrosis. Cardiopulmonary support during implantation was not necessary in any recipient.

The warm ischemic time to implant the pulmonary graft was 54 [53-58] min for the left side and 59 [49-76] min for the right side. The total ischemic time until reperfusion of the graft was 329 [225-414] min for the first lung and 517 [346-547] min for the second lung. The total operative time was 382 [300-411] min.

### Oxygenation and primary graft dysfunction

The evolution in oxygenation in the first 48 hours after LTx is shown in figure 2. Primary graft dysfunction (PGD) as defined by the International Society for Heart and Lung Transplantation [8], resolved within the first 24 hours. None of the recipients developed PGD grade III necessitating extracorporeal oxygenation support. The radiographic appearance of the lungs in the first 48 hours in a patient is shown in figure 3.

Table 3: Operative details

N°	type	incision	bypass	WIT-L (min)	WIT-R (min)	ischemia 1 <sup>st</sup> (min)	ischemia 2 <sup>nd</sup> (min)	operation (min)
1	SSL*	LT	no	58	49	329	547	411
2	SSL	CS	no	53	58	414	517	315
3	SSL	AT	no	51	76	302	434	382
4	SSL	AT	no	54	59	225	346	300

N°: number

SSL: sequential, single lung transplantation

LT: lateral thoracotomy; CS: clam-shell; AT: anterior thoracotomy

WIT: warm ischemia time during implantation; L: left lung; R: right lung

1<sup>st</sup>: first lung implanted; 2<sup>nd</sup>: second lung implanted

\* redo transplantation after first double lung transplant

min: minutes

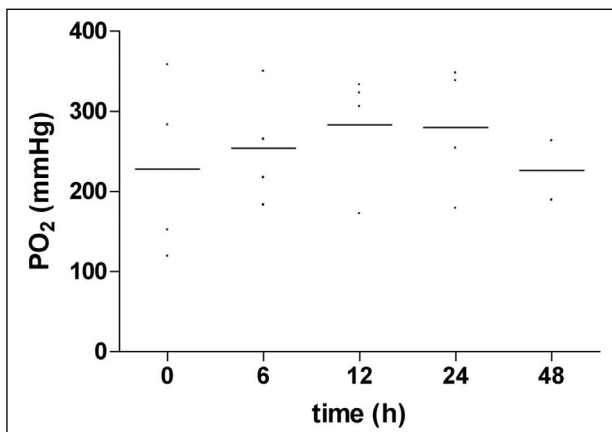


Figure 2: Mean oxygenation index ( $n=4$ ), defined as partial arterial oxygen pressure in radial artery ( $PaO_2$ ) over delivered fraction of inspired oxygen ( $FiO_2$ ), in the first 48 hours (h) after lung transplantation from euthanasia donors.

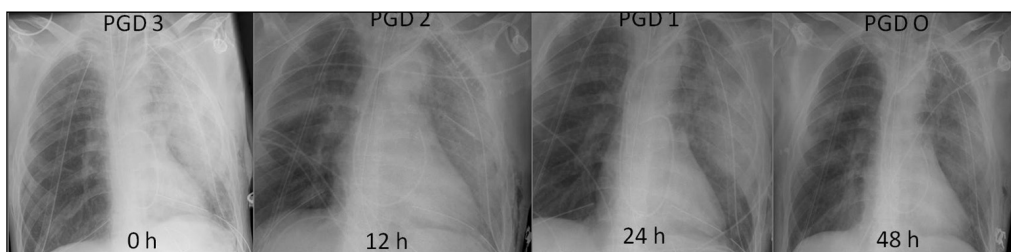


Figure 3: Consecutive chest X-rays over the first 48 hours (h) in patient  $n^{\circ}1$  after lung transplantation from a euthanasia donor. The images show a progressive resolution of the dense infiltrate in the left lung. This was believed to result from ischemia-reperfusion injury in the left lung that was firstly implanted and reperfused off bypass. The oxygenation index ( $PaO_2/FiO_2$  expressed in mm Hg) improved from 152 on arrival in the ICU to 265 at 12 h, and 306 at 24 h. Patient was extubated at 48 h. PGD: primary graft dysfunction (as defined by ISHLT [8]).

### Hospital outcome

The patient with pulmonary fibrosis, who deteriorated rapidly on the waiting list, died in the intensive care unit from a previously unknown cardiac valve problem 3 months after LTx. The pulmonary grafts have functioned well ever since the transplant. The 3 remaining patients were extubated after 2 [2-3] days. Median stay in the intensive care unit was 7 [4-7] days. Three patients (75%) left the hospital alive after 33 [23-36] days.

### Late outcome

All 3 patients are alive and doing well. The actuarial 1-year and 3-year survival in this small series is 75%.

### Pulmonary function

Pulmonary function in the three surviving patients is shown in figure 4. FEV1 and FVC increased from 16 [15-21]% and 52 [51-59]% pre-transplant to 85 [61-94]% and 79 [63-84]% at the time of hospital discharge, respectively; ( $p<0.01$ ).

Two patients have retained an excellent pulmonary function (BOS 0) while FEV1 dropped in 1 patient who remains in a stable situation with mild obstructive lung disease (BOS 1) not responsive to azithromycin therapy [9].

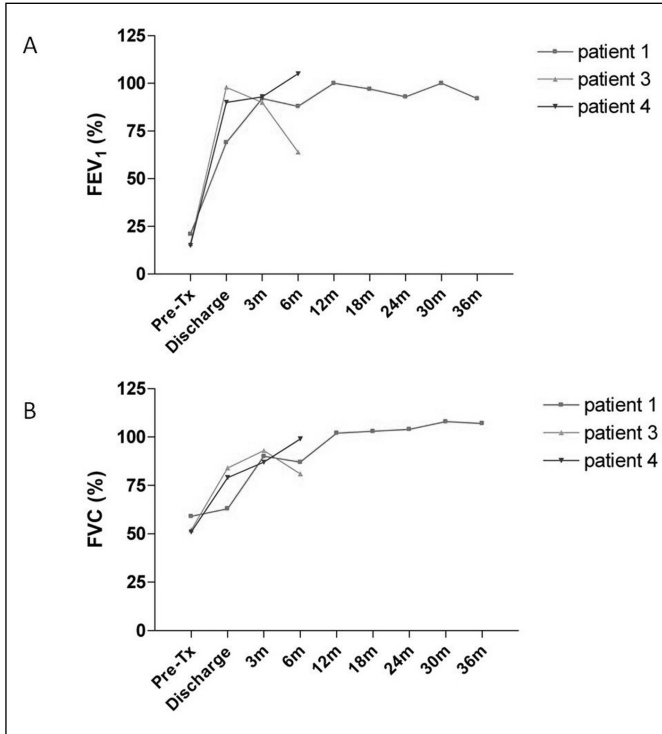


Figure 4: (A) Forced expiratory volume in 1 second (FEV<sub>1</sub>) and (B) Forced vital capacity (FVC) in 3 hospital survivors up to 36 months (m) after lung transplantation from euthanasia donors.

## Discussion

We reported our experience in 4 recipients transplanted with lungs recovered from euthanasia donors. Immediate graft function was excellent in all recipients and pulmonary function improved significantly early after the transplant in 3 surviving patients. Survival one and three years after LTx is comparable to our lung recipients from DCD donors [3].

From this small series it is not possible to study the prevalence of bronchiolitis obliterans syndrome (BOS) and to compare the impact of euthanasia on long-term survival with other donors. A larger series and longer follow up is needed before any firm statement can be made. Nevertheless, a difference may be expected as the quality of the pulmonary graft from a euthanasia donor may be superior compared to any other brain-dead and cardiac-dead donor. In contrast to these donors, euthanasia donors do not experience an agonal phase before circulatory arrest as seen in donors dying from hypoxemia or from cardio-

genic or hypovolemic shock [10]. There is also no catecholamine storm as observed in brain-dead donors [11]. It is well known that these acute events in organ donors result in increased serum levels of inflammatory cytokines triggering lung inflammation [12-14]. This may result in so called neurogenic edema prior to retrieval and reperfusion edema after transplantation. Ischemia-reperfusion injury is a known risk factor for later development of BOS identified in larger series [15, 16] although not always confirmed by other authors [17]. On the other hand, a possible toxic effect on human lung tissue of a lethal dose of barbiturates given at the time of euthanasia, is not yet known [18].

Total ischemic times in the present study (5.5 hours for the first lung and 8.5 hours for the second lung) seem somewhat longer than usually observed in our lung transplant population with an average of 4 - 4.5 hours for the first implanted lung and 6 - 6.5 hours for the second lung. We believe that this was influenced by logistical reasons. According to a

specific Eurotransplant policy, organs from a controlled DCD can not be allocated earlier than 4 hours prior to the scheduled retrieval in the donor hospital. This may result in recipients not arriving in the hospital on time to be fully prepared. On one occasion our operating room dedicated to lung transplant procedures was still occupied because another transplant had just started at the time of second organ offer. Lung implantation times (usually less than 1 hour) as well as total operative time (around 6 hours for double lung) did not differ much compared to LTx from other donors. This observation confirms that the transplant procedure itself does not differ much according to the type of donor.

Belgium was the second country in the world following the Netherlands to adopt a law legalizing euthanasia under very restricted conditions [5]. A nationwide survey on end-of-life decisions in medical practice in Flanders in 1998 estimated that 1.3% [95% CI 1.0-1.6] of all deaths resulted from euthanasia and physician-assisted suicide [19]. This study was conducted 4 years before the practice of euthanasia was legalized in 2002. Since the law has been adopted, biannual reports are being published by the Federal Control and Evaluation Commission, the body which monitors the application of the law [20]. A constant increase in registered cases has been observed, predominantly in the Flemish part of the country. Noteworthy, the World Medical Association considers both euthanasia and physician-assisted suicide to be in conflict with basic ethical principles of medical practice. It has adapted strong resolutions condemning both practices, urging all national medical associations and physicians to refrain from participating in them even if national law allows or decriminalizes the practice [21]. The question remains whether the explicit will of an individual to donate organs after death can be denied irrespective of the cause.

In 2005, transplant teams in Belgium for the first time have been confronted with a request by some euthanasia patients for organ donation after death. The first 4 cases in Bel-

gium (3 from Antwerp and 1 from Liege) have been reported previously [7]. Since then, two more cases have been performed (1 in Antwerp and 1 in Leuven). To the best of our knowledge, the present paper is the first in the literature that reports on the outcome after LTx from euthanasia donors.

It is important to stress that organ donation can not be discussed with the treating physician until after request for euthanasia is granted according to the law. It is also important to understand that the majority of patients requesting euthanasia do not fulfill the criteria for organ donation because of terminal cancer. Only patients suffering from a debilitating benign disease such as a neurological or muscular disorder are considered suitable for organ donation. Finally, a clear separation between the request for euthanasia, the euthanasia procedure, and the organ procurement is of utmost importance to exclude any conflict of interest between the donor and the recipient and between the teams involved. The Ethics Committee of Eurotransplant has formulated six distinct recommendations on organ donation and transplantation after euthanasia [22]: 1. euthanasia has to be an accepted procedure in the legal framework of the donor country; 2. the euthanasia procedure and the determination of death after the euthanasia procedure have to be in line with national law and national practices; 3. the euthanasia procedure itself and the explantation should follow a clear protocol; 4. the euthanasia procedure and the organ retrieval as well as the organ allocation should be kept as separate as possible; 5. all donors have to be reported to Eurotransplant, the allocation should follow the NHBD allocation rules in the donor resp. recipient country; 6. organs from donors after a euthanasia procedure shall only be allocated to patients registered on the waiting list for organ transplantation in Eurotransplant, and within Eurotransplant, in countries that accept the transplantation of this type of donor organ.

In the last decade, much research has been conducted on the use of DCD lungs [23]. A number of teams worldwide have



now reported successful outcomes mainly from controlled DCD [3, 24-30]. Lungs from uncontrolled donors after unexpected cardiac death can also be successfully transplanted [31, 32] although the incidence of PGD seems to be somewhat higher. At the First International Workshop on non-heart-beating donors organized by G. Kootstra in Maastricht, the Netherlands, March 30-31, 1995, four types of donors were identified, so called "Maastricht Categories" [33]. Categories I (dead on arrival) and II (unsuccessful resuscitation) comprise the *uncontrolled* donors. Categories III (awaiting cardiac arrest) and IV (cardiac arrest in brain-dead donor) include the *controlled* donors. Donors after euthanasia resemble the Maastricht Category III donor (awaiting cardiac arrest in a non-brain-dead patient) and their organs suffer a period of inevitable warm ischemia. Euthanasia donors, however, are usually not supported on a ventilator in an intensive care unit. The mode of death is completely different compared to ventilatory switch-off awaiting hypoxic cardiac arrest. It has therefore been suggested to classify euthanasia donors separately as DCD Category V.

The present study suffers from some limitations. First of all, this is a retrospective analysis of a small series of patients. We did not attempt to compare the outcome with a matched group of patients transplanted with lungs from other DCD. Secondly, the follow up in this study is still very limited and we do not know what the results will be on the long term. Thirdly, the three patients that survived had a diagnosis of obstructive lung disease (emphysema: 2; obliterative bronchiolitis: 1). It is well known that this category of recipients is the easiest to transplant with low post-operative mortality when compared to patients with severe pulmonary hypertension at risk to develop PGD. The outcome after transplantation with lungs from euthanasia donors in these higher risk patients should therefore be further awaited.

In conclusion, euthanasia donors accounted for 2.8 % of all donors and 23.5% of all DCD donors. LTx from these donors result-

ed in excellent immediate graft function and good early outcome comparable to other DCD. Larger experience and longer follow-up are needed to study the prevalence of BOS and its impact on long-term survival.

## Acknowledgements

The authors acknowledge the help from the transplant coordinators at the University Hospital Antwerp (Gerda Beeumen, Walter Van Donink) and the University Hospitals Leuven (Dirk Claes, Stijn Dirix, Joachim de Roey, Bruno Desschans, Glen Van Helleputte) in caring for donors and recipients.

We would like to thank Stéphanie De Vleeschauwer and Jef Geens, MD for collecting and analyzing data presented in this study.

We are grateful to Paul Schotsmans, STD, co-president of the Belgian Advisory Committee on Bioethics and Martin Hiele, MD, PhD, chair of the Institutional Ethics Committee for critically reviewing the manuscript.

## Funding

Dirk Van Raemdonck is a senior clinical investigator supported by the Fund for Research-Flanders (G.3C04.99)

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