Donation after cardiac death for lung transplantation: a review of current clinical practice

Christopher Wigfield

Purpose of review
This review presents a concise update on clinical donation after cardiac death (DCD or DDCD) lung transplantation. Lung allografts have predominantly been procured from donors after determination of neurologic death but will not meet the existing demand. A steadily increasing need for lungs is evident worldwide, especially in an era of improved outcomes for recipients. Other solid organ utilization from donors after determination of cardiac death has markedly increased internationally, but the utilization rate of lungs from such donors is still considerably less. The multifaceted reasons for this discrepancy are considered, and the recent evidence available supporting DCD for lung transplantation in clinical practice is presented in context. The recent experimental research studies are not within the remit of this appraisal.

Recent findings
The more recent and markedly increased lung recipient cohorts showed very satisfactory survival outcomes for DCD transplantation in several programs. The overall utilization rate, however, remains low. The background and the rationale of lung donor allograft expansion to proactively include DCD allografts from controlled (Maastricht category III donors) is re-emphasized in this review. The feasibility of other DCD categories for lung transplantation is considered. This is particularly prudent with the advent of the ex-vivo lung perfusion modality in pulmonary procurement.

Summary
Despite evidence for adequate survival outcomes and reported favorable primary graft dysfunction rates, DCD lung transplantation remains underutilized in most countries. Waiting times could be notably reduced and mortality of lung candidates arguably decreased by a more decided and appropriate implementation of proven DCD lung transplant strategies.

Keywords
donation after cardiac death, lung donor, lung procurement, lung transplantation

INTRODUCTION

The persistent primary limitation to achieve transplantation for candidates waiting for lungs has been the allograft quality offered from brain death donors. Despite improvements in donor management, up to 80% of declared brain death organ donors do not have suitable lungs for transplantation [1,2]. Donation of lung allografts provided after cardiac death in a few innovative centers has generated considerable interest worldwide. Despite publications demonstrating very acceptable results, general application has been sluggish in most countries [3▪▪]. This review will reflect on several facets of this continued challenge.

The current evidence for donation after cardiac death (DCD) lung transplantation is summarized. The international experience with this approach is reviewed and the more recent developments are discussed in the context of the latest advances in the field. Specific emphasis is given to the possible utility of ex-vivo lung evaluation and procurement principles for particular DCD lung allografts. The background and current practice of clinical DCD lung transplantation are reviewed first.

University of Chicago Medical Center, Chicago, Illinois, USA

Correspondence to Christopher Wigfield, MD, MD FRCS (C/TH), University of Chicago Medical Center, Chicago, IL 60637, USA. Tel: +1 773 702-3551; e-mail: cwigfield@surgery.bsd.uchicago.edu

Curr Opin Organ Transplant 2014, 19:455–459

DOI:10.1097/MOT.0000000000000115

KEY POINTS

- This update on clinical DCD lung transplantation reviews utilization rates and multifaceted reasons for internationally variable adaptation of this valid option to increase lung donor procurements. More recent evidence supporting DCD for lung transplantation in clinical practice is presented in context.
- The feasibility of various DCD category lung allografts for lung transplantation is appraised with consideration of the EVLP modality in pulmonary procurement.
- A more proactive application with appropriate implementation of proven DCD lung transplant strategies is advocated.

BACKGROUND FOR DONATION AFTER CARDIAC DEATH LUNG TRANSPLANTATION

The introduction of brain death as a legal definition changed the approach to organ donation in the late 1960s [4,5]. However, procuring solid organs from donors after complete cardiac and circulatory cessation preceded the brain death legislation, valid today in most transplant communities. DCD lung transplantation constitutes the first source in lung transplantation and the feasibility is well established [6–10].

The practical advantages of declared brain death to facilitate organ procurement are widely recognized but must be balanced by its limitations. These are at least, in part, due to the latent neuroendocrine and cytokine-induced sequelae eventually damaging lungs [11]. This often occurs in addition to multiple often clinically manifest causes of acute donor lung injury resulting in an unacceptable reduction of allografts available for recipients. We have not met the demand for lungs from brain death donors alone for decades. United Network for Organ Sharing data show that the organ donation rate for lungs has increased from 0.24 in 1998 to 0.41 in 2011 in the USA. This has been achieved with increasing use of extended criteria-deceased donors (ECD). The limitations of ECD lungs with troublesome impact on early outcomes were noted in some reports [12,13].

Meanwhile, the search for meaningful alternatives prompted a few innovative surgeons and their programs to successfully reconsider DCD lung transplantation [14–16]. Initially, small case series provided restrained endorsements, with few exceptions [17–20]. Since this early resurgence of DCD lung transplantation, several larger cohorts have more enthusiastically documented their reassuring outcomes for both early graft function and survival [21–23,18]. Some longer term follow-up has since indicated that no significant disparity was noticed for 3-year and 5-year survival or DCD chronic graft dysfunction rates when compared with recipients of donors after determination of neurologic death (DDND) lungs [24▪,25▪]. More recently, the International Society for Heart and Lung Transplantation (ISHLT) has implemented a registry for DCD lung transplantation [26▪▪]. In summary, a group of early DCD lung transplant adaptors may have now shown an utilization rate yet to be emulated by late converters [27] (Table 1).

REVIEW OF DONATION AFTER CARDIAC DEATH DEFINITION

Categorization of potential DCD donors has been provided elsewhere [28,29]. The Maastricht criteria for DCD donors have been clinically useful and are summarized in Table 1. Because of the legislative requirements for presumed consent, few nations are currently in a position to take advantage of the dramatic donor pool expansion potentially possible with Maastricht criteria I and II category donors [30,31]. The ethical propriety of category III and IV DCD lung transplantation has been affirmed by several regulatory institutions, and a joint statement of several professional societies has established a framework for the practice and provision of donors after determination of cardiac death (DDCD) lung transplantation [32–34,35▪]. DCD lung transplant protocols for consideration and adaptation to specific Organ Procurement Organization environments have been published and are not reconsidered in this review [36,37].

CURRENT EVIDENCE FOR DONATION AFTER CARDIAC DEATH LUNG TRANSPLANTATION

Several programs published cohorts with 1-year survival rates compatible with outcomes from conventional brain death donor allografts. Retrospective data have now also suggested a lower-than-expected primary graft dysfunction (PGD) rate. This has been confirmed in the analysis of the ISHLT registry data. The most encouraging data have been made available by a national DDCD collaborative in Australia. Reported in 2012, 72 DCD lung transplants were performed between 2006 and 2011 from 210 recognized category III donors (37 potentially suitable donors did not arrest within the stipulated postwithdrawal window). Exceptionally, this effectively increased the donor lungs available in 2010 by 28% in that procurement

Table 1. Maastricht criteria for donation after cardiac death lung transplantation

Maastricht DCD donor group	Clinical circumstances	Likely allograft availability	Specific consideration for lung transplantation
Category I	Donor declared dead on arrival of Hospital (DoA)	Potentially vast numbers	Poor donor risk profile assessment
Category II	Declared donor after unsuccessful resuscitation	Large increase in donor pool	Very limited donor status assessment, but better than Cat I
Category III	Awaiting cardiac death, after withdrawal of treatment	Estimated up to 30% donor expansion	Good risk assessment, logistic concerns, time/donor progression issues
Category IV	Cardiorespiratory arrest after previous diagnosis of brain death	Infrequent occurrence	Additive BD and DCD procurement factors present

DCD, donation after cardiac death.
Modified for context from [28].

system. The reported grade 3 PGD was 8.5%, confirming previous reports of lower-than-expected PGD in DCD lung allografts and 'chronic rejection' was noted in 5% of recipients. Documenting excellent 1-year and 3-year outcomes of DCD lung transplantation as well as an approximately 50% reduction of expected PGD in that cohort, the collaborative concluded that 'category III DDCD lung transplantation, therefore, provides a significant, practical, additional quality source of transplantable lungs [38].' This has to be seen in the setting of the significant geographic challenges and relatively longer ischemic times encountered with no detrimental effect on allograft function. Such clinical evidence and previous experimental research data have experts in this field, considering the lungs to be somewhat 'ischemically privileged' in the right circumstances [39]. These circumstances may well include the absence of prolonged effects of brain death induced detriments of pulmonary vasculature stress and aggravated alveolar permeability changes [40,41].

In the light of the documented clinical experience, it remains surprising that implementation of DCD lung allografts as a truly alternative source has not found more widespread application [42]. The multiple aspects to be considered include regulatory issues, societal acceptance, lack of integration in end of life decision process, poor application of exiting DCD protocols to lung procurement and occasional lack of the required surgical expertise and preparedness for some specific logistic challenges.

As previously reported, the proportion of DCD donors providing lung transplants is lamentable in most regions and remains at less than 5% in the USA, for example [43,44▪]. Concerted efforts in other countries have resulted in marked improvement of utilization rates of controlled DCD lung allografts, particularly Australia and the United Kingdom and some countries without brain death legislation.

The experience observed in cohorts with presumed consent for uncontrolled DCD lung transplantation is noteworthy. Although the early reported experience with this approach resulted in unacceptably increased PGD rates, the utility of ex-vivo lung perfusion (EVLP) may be of particular interest in this setting as both optimization of lungs and minimization of risks are feasible [45,46]. The legislative prerequisites and clinical complexity documented with the Spanish experience with uncontrolled DCD lung transplantation have to be considered the future challenge [47]. In most nations, organ donation is viewed as the ultimate altruistic gift and significant progress is needed to achieve public awareness of the potential benefits for the recipients currently not surviving the waiting time for lungs.

To maximize 'the gift' from identified DCD donors, however, should be our primary task. A much more proactive approach is advocated, and although only a small proportion of DCD lungs should require EVLP, this may augment the interest and utilization in this valid donor source in lung transplantation [48]. The clear advantage in extra-corporeal perfusion and ventilation will be the organ-specific and individualized therapeutic strategy applied to optimize each set of lungs en bloc prior to transplant [49▪]. Multiple options have been discussed and experimental results are increasingly reported. Ultimately, this approach should also result in a clinical risk reduction, as likely nonviable lung grafts are ruled out without exposing the recipients.

CLINICAL OUTCOMES OBSERVED

Reviewing the more recent available evidence, most publications are retrospective reports and observational studies. No randomized controlled trials are feasible in this context. The comparison of contemporaneous observed survival rates in the largest series of DDND versus DDCD should allow for

confidence to implement more DCD lung transplant programs.

The data provided this year from the ISHLT DCD registry demonstrate the utility of DCD lung transplantation, bearing in mind somewhat varying protocols. The initial registry report includes 224 DCD lung transplants compared with 2744 contemporaneous DDND lung transplants from multiple centers in the same time span. Greater than 95% of the DCDs preformed were Maastricht category III, and less than 4% were category IV, DCDs. A small European reported from a single center reported utilization of 'category V' (<2% legal euthanasia DCD donor cases). Heparin was reportedly given in less than half of all DCD donors prior to procurement. Extubation of donors was performed in compliance of protocols at the time of withdrawal and occurred in 87% of DCD lung procurements. The median time from withdrawal of life support to cardiac arrest was 15 min (5–46 min) in this pooled cohort. The average time required to administer antegrade pulmoplegia was cited as 32 min (20–77 min) and clearly within previously reported ranges. No significant differences were noted for demographic factors for recipients and the length of stay after transplantation. Remarkably, the 30-day mortality observed was 3% in both groups and the 1-year survival was 89% in the DCD and statistically not different.

The mode of death and its potential impact on DCD lung transplant recipients was assessed retrospectively and appears to influence early recipient survival. Mortalities observed within 30 days were from donors with severe head trauma (reported $P = 0.002$), further underscoring the recognized adverse effect of CNS-associated pulmonary damage.

Notably, EVLP was not used in the vast majority of these DCD lung transplants performed. A particularly low incidence of severe PGD was recorded in contributing programs [26▪▪]. The combination approach may well allow additional ECD DCD lungs to be optimized, but currently available evidence does not suggest that this may be a routine application for category III and IV DCD lungs [50,51].

The ISHLT DCD Registry publication coincided with the United Kingdom Steering Group DCD lung transplant activity report. A renaissance of DCD is evident accounting for 14% of lung transplants performed with equivalent 1-year survival outcomes (79.5% DDCD vs. 79.2% DDND cohort; $P = 0.9$) [52▪]. Again, it was noted by the authors that this was achieved despite the occurrence of significantly longer ischemic times for DCD lung allografts.

As further clinical experience will be published, the quality of evidence will need to be assessed in relation to other specific outcomes to be considered. In particular, the freedom from bronchiolitis obliterans syndrome or evolving chronic lung allograft dysfunction phenotypes requires careful evaluation of all cohorts. Early indications are that comparable bronchiolitis obliterans syndrome rates may be expected and some prospectively collected data would be desirable to assess this.

Ultimately, moving forward and to understand the potential and limitations for all categories of DCD lung procurement we will require more detailed analyses such as planned by the Scientific Registry of Transplant Recipients in the USA and envisaged elsewhere [53].

CONCLUSION

The globally increasing demand for lungs for transplantation is driving the process of utilization of various donor resources. It has long been apparent that ECD lungs alone from DDND will not suffice. DDCD lungs remain underutilized, despite very favorable results reported internationally. Contribution of outcomes observed to the international registry is advocated to allow for better understanding of perceived advantages and potential limitations.

Acknowledgements

The author would like to acknowledge the visionary leadership in DCD lung transplantation provided by Dr Robert Love MD.

Conflicts of interest

The author declares his service at ISHLT as Educational Affairs Director.
The author declares his service on the NOVEL EVPL trial as Safety Commission Officer.
The author has a nonrelevant Speaker Bureau affiliation with BARD and Cormatrix.
No other potential conflicts of interest to be declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2011 data report. Am J Transplant 2013; 13 (Suppl s1):1–234.
2. OPTN/SRTR Annual Data Report: lung http://srtr.transplant.hrsa.gov/annual_reports/2012/flash/06_lung_13/v2index.html.
3. ▪▪ Levvey BJ, Harkess M, Hopkins P, *et al.* Excellent clinical outcomes from a national donation-after-determination-of- cardiac-death lung transplant collaborative. Am J Transplant 2012; 12:2406–2413.
Most relevant article providing evidence for the safe implementation of DCD lung transplantation with outstanding outcomes and provides testament to the fact that DCD may provide a significant proportion of additional lung allografts when an adequate strategy is employed.

4. Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. A definition of irreversible coma. Report of the Ad Hoc Committee of the DCD lung transplantation – a review 12 of 16 Harvard Medical School to examine the definition of brain death. JAMA 1968; 205:85–88.
5. Wijdicks EF. The diagnosis of brain death. N Engl J Med 2001; 344:1215–1221.
6. Hardy JD, Webb WR, Dalton ML, *et al.* Homotransplantation in man. JAMA 1963; 186:1065–1074.
7. Love RB, Stringham JC, Chomiak PN, *et al.* Successful lung transplantation using a nonheart-beating donor. J Heart Lung Transplant 1995; 14:S88.
8. D'Alessandro AM, Love RB, Hoffman RM, *et al.* Controlled nonheart beating donors: a potential source of extrarenal organs. Transplant Proc 1995; 27: 707–709.
9. Steen S. Transplantation of lungs from a nonheart-beating donor. Lancet 2001; 357:825–829.
10. Oto T, Levvey B, McEgan R, *et al.* A practical approach to clinical lung transplantation from a Maastricht category III donor with cardiac death. J Heart Lung Transplant 2006; 26:2196–2199.
11. Avlonitis VS, Wigfield CH, Kirby JA, Dark JH. The hemodynamic mechanisms of lung injury and systemic inflammatory response following brain death in the transplant donor. Am J Transplant 2005; 5:684–693.
12. Aigner C, Winkler G, Jaksch P, *et al.* Extended donor criteria for lung transplantation–a clinical reality. Eur J Cardiothorac Surg 2005; 27:757–761.
13. Botha P, Fisher AJ, Dark JH. Marginal lung donors: a diminishing margin of safety? Transplantation 2006; 82:1273–1279.
14. Love RB, D'Allesandro AM, Cornwell RA, Meyer KM. Ten year experience with human lung transplantation from nonheart beating lung donors. J Heart Lung Transplant 2003; 22:S87.
15. Erasmus ME, Van der Bij W, Verschuuren EAM. Nonheart beating lung transplantation in the Netherlands: the first experience. J Heart Lung Transplant 2006; 25:S63.
16. Mason DP, Murthy SC, Gonzalez-Stawinski GV, *et al.* Early experience DCD lung transplantation – a review 13 of 16 with lung transplantation using donors after cardiac death. J Heart Lung Transplant 2008; 27:561–563.
17. Snell GI, Levvey BJ, Oto T, *et al.* Early lung transplantation success utilizing controlled donation after cardiac death donors. Am J Transplant 2008; 8:1282–1289.
18. Cypel M, Sato M, Yildirim E, *et al.* Initial experience with lung donation after cardiocirculatory death in Canada. J Heart Lung Transplant 2009; 28:753–758.
19. Puri V, Scavuzzo M, Guthrie T, *et al.* Lung transplantation and donation after cardiac death: a single center experience. Ann Thorac Surg 2009; 88:1609–1614.
20. Egan TM. Nonheart-beating donors in thoracic transplantation. J Heart Lung Transplant 2004; 23:3–10.
21. Levvey BJ, Harkess M, Hopkins P, *et al.* Excellent Clinical Outcomes From a National Donation-After-Determination-of-Cardiac-Death Lung Transplant Collaborative. American Journal of Transplantation 2012; 12:2406–2413.
22. Erasmus ME, Verschuuren EA, Nijkamp DM, *et al.* Lung transplantation from nonheparinized category III non-heart-beating donors. A single-centre report. Transplantation 2010; 89:452–457.
23. De Vleeschauwer SI, Wauters S, Dupont LJ, *et al.* Medium-term outcome after lung transplantation is comparable between brain-dead and cardiac-dead donors. J Heart Lung Transplant 2011; 30:975–981.
24. ■ De Oliveira NC, Osaki S, Maloney JD, *et al.* Lung transplantation with donation after cardiac death donors: long-term follow-up in a single center. J Thorac Cardiovasc Surg 2010; 139:1306–1315.

One of the few articles to date considering the mid-term and long-term outcomes in this setting in with retrospective analysis.

25. ■ De Vleeschauwer SI, Wauters S, Dupont LJ. Medium-term outcome after lung transplantation is comparable between brain-dead and cardiac-dead donors. J Heart Lung Transplant 2011; 30:975–981.

European data describing the mid-term outcomes in this setting with retrospective analysis.

26. ■■ Cypel M, Levvey B, Van Raemdonck D, *et al.* Favorable outcomes of donation after cardiac death in lung transplantation: a multicenter study. J Heart Lung Transplant 2013; 32:S15.

Highly relevant and integrative look at the DCD lung transplant outcomes noted from an international multicenter analysis.

27. Rogers EM. Diffusion if innovations. 5th ed New York: Free Press; 2003.
28. Kootstra G, Daemen JH, Oomen AP. Categories of nonheart-beating donors. Transplant Proc 1995; 27:2893–2894.
29. Kootstra G, Kievit JK, Heineman E. The non heart-beating donor. Br Med J 1997; 53:844–853.
30. Steinbrook R. Perspective: organ donation after cardiac death. N Engl J Med 2007; 357:209–213.
31. Nijkamp DM, van der Bij W, Verschuuren EA, *et al.* Nonheart-beating lung donation: how big is the pool? J Heart Lung Transplant 2008; 27:1040–1042.
32. Institute of Medicine, National Academy of Sciences. Nonheartbeating organ transplantation: practice and protocols.. Washington, DC: National Academy Press; 2000.
33. Bernat JL, D'Alessandro AM. Report of a national conference on donation after cardiac death. The organ procurement and transplantation network and the united network for organ sharing. Am J Transplant 2006; 6:281–291.
34. United Network for Organ Sharing Scientific Registry Data: www.unos.org. [Accessed June 2014]
35. ■ Gries CJ, White DB, Truog RD, *et al.* 'An Official American Thoracic Society/ International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: ethical and policy considerations in organ donation after circulatory determination of death'. Am J Respir Crit Care Med 2013; 188:103–109.

Recent concerted effort to provide awareness and conceptual framework for the practice and acceptance of DCD lung transplantation.

36. Wigfield CH, Love R, Dark J. Lung transplantation from non-heart-beating donors – donation after cardiac death (DCD). In: Talbot D, D'Alessandro A, editors. Organ donation after cardiac death. New York: Oxford University Press Inc; 2009; Chapter 14.
37. Marcelo Cypel, Jonathan C. Yeung, Shaf Keshavjee. Novel approaches to expanding the lung donor pool: donation after cardiac death and ex vivo conditioning. Clin Chest Med 2011; 32:233–244.
38. Levvey BJ, Harkess M, Hopkins P, *et al.* Excellent clinical outcomes from a national donation-after-determination-of- cardiac-death lung transplant collaborative. Am J Transplant 2012; 12:2406–2413.
39. Van Raemdonck D, Rega FR, Neyrinck AP, *et al.* Non heart-beating donors. Semin Thorac Cardiovasc Surg 2004; 16:309–321.
40. Avlonitis VS, Fisher AJ, Kirby JA, Dark JH. Pulmonary transplantation: the role of brain death in the donor lung injury. Transplantation 2003; 75:1928–1933.
41. Avlonitis VS, Wigfield CH, Golledge HDR, *et al.* Early hemodynamic injury during donor brain death determines the severity of primary graft dysfunction after lung transplantation. Am J Transplant 2007; 7:83–90.
42. Van De Wauwer C, Verschuuren EA, van der Bij W, *et al.* The use of nonheart-beating lung donors category III can increase the donor pool. Eur J Cardiothorac Surg 2011; 39:e175–e180.
43. Steinbrook R. Perspective; organ donation after cardiac death. N Engl J Med 2007; 357:209–213.
44. ■ Wigfield CH, Love RB. Donation after cardiac death lung transplantation outcomes. Curr Opin Organ Transplant 2011; 16:462–468.

Previous review in Current Opinion on this topic providing detailed background information, definitions, and clinical protocol information not elaborated in this update.

45. Varela A, Nuñez JR, Gamez AP, *et al.* Are out hospital nonheartbeating donors (NHBD) better than brain death lung donors? J Heart Lung Transplant 2004; 23:S87.
46. Nuñez JR. Bipulmonary transplants with lungs obtained from two non-heart-beating donors who died out of hospital. J Thorac Cardiovasc Surg 2004; 127:297–299.
47. Suzuki Y, Tiwari JL, Lee J, *et al.* Should we reconsider lung transplantation through uncontrolled donation after circulatory death? Am J Transplant 2014; 14:966–971.
48. Cypel M, Yeung JC, Liu M, *et al.* Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011; 364:1431–1440.
49. ■ Cypel M, Keshavjee S. Strategies for safe donor expansion: donor management, donations after cardiac death, ex-vivo lung perfusion. Curr Opin Organ Transplant 2013; 18:513–517.

Useful synopsis of the options to tackle the donor scarcity issue in lung transplantation.

50. Egan TM, Haitchcock JA, Nicotra WA, *et al.* Ex vivo evaluation of human lungs for transplant suitability. Ann Thorac Surg 2006; 81:1205–1213.
51. Erasmus ME, Fernhout MH, Elstrodt JM, Rakhorst G. Normothermic ex vivo lung perfusion of nonheart-beating donor lungs in pigs: from pretransplant function analysis towards a 6-h machine preservation. Transplant Int 2006; 19:589–593.
52. ■ Thomas HL, Taylor R, Simon AR, *et al.* On behalf of the Steering Group, UK Cardiothoracic Transplant Audit. Donation after circulatory death lung activity in the UK – 100 transplants and counting. J Heart Lung Transplant 2013; 32:S15.

Retrospective documentation of a national effort to increase DCD lung transplantation providing a governance example of such process.

53. Leppke S, Leighton T, Zaun D, *et al.* Scientific Registry of Transplant Recipients: collecting, analyzing, and reporting data on transplantation in the United States. Transplant Rev 2013; 27:50–56.