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Commentary: Stay calm amid the agonal storm in controlled lung donation after circulatory determination of death

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Breathe deeply and step back is common advice to keep calm in stressful circumstances. This might be especially true in controlled lung donors after circulatory determination of death (cDCDDs) where warm ischemic time (WIT) dictates outcome. The variable period of progressive hypoxia and hypotension between withdrawal of life-sustaining therapy (WLST), asystole and death determination may result in abandoning organ procurement when prolonged cardiopulmonary instability occurs because the risk of serious graft injury jeopardizing recipient outcome.¹ Different time intervals from WLST to asystole (agonal phase) and to flush-cooling of lungs (asystolic phase) were defined by the International Society for Heart and Lung Transplantation² and the European Society for Organ Transplantation³ (Table 1).

Compared with other solid organs, cDCDD lungs tolerate WIT well. In a multivariable analysis of International Society for Heart and Lung Transplantation DCD Registry data, no association of agonal time (T0-T3) and functional WIT (T2-T5) on 1-year recipient mortality after lung transplantation (LTx) was found.⁴ In their report, Qaqish and colleagues⁵ from the University of Toronto demonstrate that lungs with an agonal phase >60 minutes can be safely

Keep calm during the agonal storm in controlled lung donation after circulatory death.

CENTRAL MESSAGE

Transplant lungs from circulatory-dead donors can be safely recovered at long intervals after withdrawal from life-sustaining therapy if functional warm ischemic time before cold flush remains short.

used in their hands. They assessed whether the duration of documented agonal phase in 180 cDCDDs (rapid: 0-19 minutes [n = 90], intermediate: 20-59 minutes [n = 38], or long: >60 minutes [n = 20]) influenced post-LTx outcome compared with 1088 donors after neurologic determination of death (DNDD). No significant differences were found in short- and long-term recipient survival, primary graft dysfunction, intensive care unit stay, mechanical ventilation days, or total hospital stay.

Two intriguing findings are important to consider for other teams to feel comfortable with increasing their agonal phase cutoffs. First, the hypotensive period starting with systolic blood pressure <50 to 60 mm Hg (T2) until asystole (T3) was intriguingly short in the Toronto experience and did not differ between the 3 cDCDD groups (rapid: 3.7 ± 3.8 minutes, intermediate: 7.5 ± 7.7 minutes, and long: 8.1 ± 11.8 minutes; $P = .06$). The period T2 to T3 is generally considered the most important trigger inducing lung injury as blood flow cessation induces an endothelial response by change in shear stress rather than by hypoxia.⁶ This might explain the excellent outcomes of cDCDD lungs exposed to a prolonged agonal phase. Furthermore, the time between asystole and cold flush (T3-T5), as well as functional WIT (T2-T5) might be important determinants of outcome and have not been investigated. Indeed, for kidneys the asystolic time determines primary nonfunction⁷

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TABLE 1. Specific time points in the setting of a controlled donation after circulatory death donor from withdrawal from life-sustaining therapy until lung preservation by cold flush

Controlled donation after circulatory death			ISHLT*	ESOT†	
Event	Agonal phase	Asystolic phase‡	Time point	Total WIT	Functional WIT
Withdrawal of life-sustaining therapies	—		T0	—	
Oxygen saturation <80%	—		T1	—	
Systolic blood pressure <50 mm Hg	—		T2	—	—
Cessation of cardiac output/asystole		—	T3	—	—
Resumed lung inflation/ventilation		—	T4	—	—
Start of pulmonary flush		—	T5	—	—

ISHLT, International Society for Heart and Lung Transplantation; ESOT, European Society for Organ Transplantation; WIT, warm ischemic time. *Defined by the DCD Registry Steering Committee of the ISHLT. Cypel M, Levvey B, Van Raemdonck D, Erasmus M, Dark J, Love R, et al. International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report. *J Heart Lung Transplant*. 2015;34:1278-82. †Defined by the European Working Group of the ESOT.‡Including the no-touch period.

and for liver evidence suggests functional WIT to be a more important risk factor for posttransplant cholangiopathy.⁸ Certain events can lengthen these times; for example, transporting the donor when WLST does not take place in the operating room (Figure 1). In addition, cDCDD lung retrieval is often part of a multiorgan retrieval. Because abdominal organs are more vulnerable to WIT, priority may be given to rapid recovery of liver and kidneys while

lungs remain in the chest after cold flush and topical cooling. This will increase pneumonectomy time that might influence outcomes, similar to those in kidney⁹ and liver.¹⁰ Second, it is important to realize that Qaqish and colleagues⁵ frequently and selectively uses pretransplant evaluation by ex vivo lung perfusion (EVLP). Although good outcomes without EVLP have been reported in cDCDD LTx,² in the current study, pre-LTx EVLP was used in

FIGURE 1. Multiorgan recovery team at the University Hospitals Leuven, Leuven, Belgium. While the lead anesthesiologist ensures that the consented donor receives comfort therapy during the agonal phase, the scrubbed team is waiting outside the operating room for circulatory arrest following withdrawal from life-sustaining therapy. A 5-minute no-touch period is respected. Surgery is not started until death has been certified by 3 independent physicians.

65.6% of cDCDDs and 13.7% of DNDD. All 20 lungs in donors with an agonal phase >60 minutes underwent EVLP despite short T2 to T3 times comparable to donors with short and intermediate agonal phases. Although recipient survival rates were similar between EVLP and non-EVLP LTx, the exact role of EVLP remains unclear.

During the same time period as the Toronto study,⁵ 664 isolated LTx were performed at the University Hospitals Leuven, Belgium, including 125 (18.8%) with cDCDD lungs. The mean agonal and asystolic phase (including 5 minutes no touch) were 11.6 minutes (range, 0-49 minutes) and 9.9 minutes (range, 2-24 minutes), respectively. As such, total WIT was only 21.6 minutes (range, 2-71 minutes). Except for 5 cases enrolled in the Expand study, all cDCDD lungs were transplanted without prior EVLP. Short and long-term post-LTx recipient outcome was similar between cDCDDs versus DNDDs.¹¹

An important reason for success for any cDCDD program is the selection of potential donors based on objective criteria. It would have been interesting if the authors provided more details on patient's medical status, their selection process, any pre-mortem intervention focusing on donor comfort, and the number of aborted procedures to gain more insight in how to optimize cDCDD organ donation worldwide.

Organ retrieval practice in cDCDDs is likely to change considerably as an increasing number of centers are introducing abdominal normothermic regional perfusion to preserve abdominal organs in situ. The optimal preservation strategy is still not clear and the role of thoraco-abdominal normothermic regional perfusion is currently unknown.¹²⁻¹⁴

Qaqish and colleagues⁵ add to the evidence not to panic if the agonal phase in cDCDDs is prolonged. Further research is needed to clarify which parameters during the different phases of total WIT ultimately influence organ quality. Meanwhile, keep calm amid the agonal storm!

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