Prioritizing Direct Heart Procurement in Organ Donors after Circulatory Death does not Jeopardize Lung Transplant Outcomes

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Retrospective analysis: January 2012 – February 2022

**DCD Heart + Lung**

- N=7
- Increased warm ischemic time: 24 min
- p=0.002

**DCD Lung**

- N=49
- Similar PGD at 72 hours

**Similar 1-year graft survival**

- Similar percent survival (CI = 95%)
- p=0.378

<table>
<thead>
<tr>
<th>Subjects at risk</th>
<th>Months</th>
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<tbody>
<tr>
<td>7</td>
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<tr>
<td>49</td>
<td>98%</td>
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Prioritizing Direct Heart Procurement in Organ Donors after Circulatory Death does not Jeopardize Lung Transplant Outcomes

Stefan Schwarz¹, MD, PhD, Johannes Gökler², MD, Roxana Moayedifar², MD, Clemens Atteneder², MD, Giovanni Bocchialini³, MD, Alberto Benazzo¹, MD, PhD, Thomas Schweiger¹, MD, PhD, Peter Jaksch¹, MD, Andreas O Zuckermann², MD, Arezu Z Aliabadi-Zuckermann², MD, Konrad Hoetzenecker¹, MD, PhD

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Central message: Prioritizing direct heart procurement has no detrimental effect on early post-lung transplant outcomes despite significantly prolonged warm ischemic time and delayed ventilation for the lungs.

Perspective statement: This study provides a first analysis of lung transplant outcomes using DCD donors where the heart was also explanted using a direct procurement technique. As DCD hearts are increasingly being utilized, the question arises if the heart's warm ischemic time can be safely minimized while accepting prolonged warm ischemia and delayed ventilation for the lungs.

Central picture: Perfusion of the lung after explantation of the heart
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CA</td>
<td>Circulatory arrest</td>
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<tr>
<td>cDCD</td>
<td>Controlled donation after circulatory death</td>
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<tr>
<td>CIT</td>
<td>Cold ischemic time</td>
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<td>DCD</td>
<td>Donation after circulatory death</td>
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<td>DP</td>
<td>Direct procurement</td>
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<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
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<td>EVLP</td>
<td>Ex-vivo lung perfusion</td>
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<td>International Society for Heart and Lung Transplantation</td>
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<td>LTx</td>
<td>Lung transplantation</td>
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<td>NRP</td>
<td>Normothermic regional perfusion</td>
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<td>PGD</td>
<td>Primary graft dysfunction</td>
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<tr>
<td>PHP</td>
<td>Prioritized heart procurement</td>
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<tr>
<td>SWIT</td>
<td>Surgical warm ischemic time</td>
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<tr>
<td>WIT</td>
<td>Warm ischemic time</td>
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<tr>
<td>WLST</td>
<td>Withdrawal of life support therapy</td>
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Abstract

Objectives
Organ donation after circulatory death (DCD) has become a standard in liver, kidney and lung transplantation (LTx). Based on recent innovations in ex-vivo heart preservation, heart transplant centers have started to accept DCD heart allografts. As the heart has very limited tolerance to warm ischemia, changes to the DCD organ procurement procedures are necessary. These changes entail delayed ventilation and prolonged warm ischemia for the lungs. It is unclear if this negatively impacts lung allograft function.

Methods
A retrospective analysis of DCD lungs transplanted between 2012 and February 2022 at the Medical University of Vienna was performed. Group ‘heart+lung’ consisted of cases where the heart was procured by a cardiac team for subsequent normothermic ex-vivo perfusion (EVP). A control group (‘lung’) was formed by cases where only the lungs were explanted. In ‘heart+lung’ group cases, the heart procurement team placed their cannulas after circulatory death and a hands-off time, collected donor blood for EVP and performed rapid organ perfusion with Custodiol solution. Subsequently the heart was explanted. Up to this point, the lung procurement team did not interfere. No concurrent ventilation of the lungs or perfusion of the pulmonary artery was performed. After the cardiac procurement team had left the table, ventilation was initiated and lung perfusion was performed directly through both stumps of the pulmonary arteries using two large bore foley catheters. This study analysed procedural explant times, postoperative outcomes, PGD, length of mechanical ventilation and ICU stay as well as early survival after LTx.

Results
A total of 56 DCD lungs were transplanted during the study period. In 7 cases (12.5%), the heart was also procured (‘heart+lung’). In 49 cases (87.5%), only the lungs were explanted (‘lung’). Basic donor parameters were comparable between groups. Median time from circulatory arrest to lung perfusion (24min vs 13.5min; p=0.002) and skin incision to lung perfusion (14min vs 5min; p=0.005) were significantly longer for ‘heart+lung’ procedures. However, this did not affect post-transplant PGD scores at 0 h (p=0.851), 24 h (p=0.856), 48 h (p=0.929) and 72 h (0.874). At 72 h after transplantation, none of the lungs in the ‘heart+lung’
but 1 (2.2%) in ‘lung’ group were in PGD3. Median length of mechanical ventilation (50 h vs 41 h; p=0.801), ICU stay (8 d vs 6 d; p=0.951) and total hospital stay (27 d vs 25 d; p=0.814) were also comparable. In-hospital mortality was only recorded in one patient of the ‘lung’ group (2.2%).

**Conclusion**

Although prioritized DCD heart explantation is associated with delayed ventilation and significantly longer warm ischemic time to the lungs, post lung-transplant outcomes within the first year are unchanged. Prioritizing heart perfusion and explantation in the setting of DCD procurement can be considered acceptable.

**Introduction**

While organ donation after brain death (DBD) continues to represent the majority of procured organs, controlled donation after circulatory death (cDCD) has successfully expanded the donor pool. In recent years and has become a standard in liver, kidney and lung transplantation (LTx). According to the International Society for Heart and Lung Transplantation (ISHLT), cDCD donor lungs are utilized in 10% of transplants overall. They account for up to a third of all LTx in Australia, Canada and some European countries, while it is still less common in the United States with around 2% of LTx.1-3 Recent innovations have renewed the interest in cDCD heart allografts and some heart transplant centers have started to utilize organs from cDCD donors.4-6 Currently, two basic techniques to retrieve cDCD hearts exist. Direct procurement (DP) and *ex situ* perfusion involves rapid cold perfusion and explantation of the heart, followed by evaluation on a normothermic *ex-situ* machine perfusion device. Thoracic normothermic regional perfusion (NRP) on the other hand requires the introduction of extracorporeal circulatory support after declaration of death. Once cardiac action has re-established and stabilized, the heart can be procured in a similar way to the DBD setting.4 Currently, DP is the more common method, owing to logistical issues and ethical as well as legal hurdles for NRP in many countries. The addition of another stakeholder (heart) to the often hectic setting of cDCD procurements has a potential impact for the other organs (lung, liver, kidney). Current consensus recommends simultaneous procedures for all organs in cDCD.7 Given the heart’s very limited tolerance to warm ischemia, changes to established cDCD organ procurement may
be desirable to optimize outcomes. Prioritizing heart perfusion and explantation, while delaying lung perfusion provides full access to the thorax for the cardiac team. Delaying ventilation provides an undisturbed surgical field, which is crucial for fast and safe heart dissection in this setting. Recruitment or ventilation of the lungs during this phase causes motion and can obstruct surgical exposure, potentially prolonging warm ischemic time for the heart. The downside of a prioritized heart procurement (PHP) strategy is delayed alveolar aeration and prolonged warm ischemia for the lungs. Currently, there is no data on the consequences of such a practice and if it negatively impacts lung allograft function. Therefore, we aimed to analyze our early experience with PHP in cDCD lungs.

Patients and Methods
Ethics approval was granted by the institutional review board of the Medical University of Vienna (EK-Nr 1951/2020, November 23, 2021). We retrospectively analyzed cDCD (i.e. Maastricht category III) lungs transplanted between January 2012 and May 2021 at the Medical University of Vienna. A total of 56 cDCD lungs were accepted during this time, representing 5.7% of the total center volume. General criteria for organ offer acceptance did not differ between DCD and DBD donors. Seven donors where the heart was also procured were assigned to group ‘heart+lung’. In the remaining 49 donors, the lung was the only thoracic organ procured. These cases formed group ‘lung’ and served as controls. One donor with abdominal normothermic regional perfusion was excluded from this analysis. (Figure 1)

Definitions
Agonal phase was defined as withdrawal of life support therapy (WLST) to circulatory arrest (CA). Acceptable agonal phase duration for the lungs was limited to 120 minutes. CA was defined as zero systolic arterial blood pressure flatline. Warm ischemic time (WIT) was defined as time between circulatory arrest and begin of cold lung perfusion. Surgical warm ischemic time (SWIT) was defined as time between skin incision and start of cold lung perfusion.

Surgical procedures
If allowed, heparin (400 units/kg bodyweight) was given before WLST. In all ‘heart+lung’ cases, heparin was administered prior to WLST. Bronchoscopy was performed in all cases,
either before WLST if allowed by local rules or immediately after declaration of death in parallel to sternotomy and preparation for perfusion.

In ‘lung’ group cases, the pericardium was opened after rapid sternotomy and a 22 French curved-tip cannula placed in the main pulmonary artery. Cold perfusion was performed with 6 liters of Perfadex (*XVIVO Perfusion; Göteborg, Sweden*) supplemented by a total of 1mg prostaglandin E1. If the administration of heparin before WLST was prohibited by local jurisdiction, 10,000 units were added to the perfusion solution.

In all ‘heart+lung’ cases, the heart procurement was prioritized. After sternotomy, donor blood was collected for EVP followed by rapid heart perfusion with 1 liter Custodiol® HTK solution. The explantation of the heart was performed in a standard manner. The lung procurement team was standing by during this first part of the procedure. No concurrent ventilation of the lungs was performed. After the cardiac procurement team had left the table, ventilation was initiated. Lung perfusion using the solution and additives described above was performed by inserting two cuffed large bore (18-20 French) foley catheters directly into the left and right pulmonary artery via the opened arterial bifurcation. *(Suppl.Figure 1)*

Following cold lung perfusion, standard procurement was performed as described elsewhere.™

After explantation, retrograde flushing was performed with 1 liter of Perfadex through the left atrial cuff. For the implantation, we followed our institutional standard procedure with the use of central veno-arterial extracorporeal membrane oxygenation (ECMO) in all cases. If defined criteria for early organ function were not met at the end of the procedure, the ECMO was switched to a femoro-femoral veno-arterial configuration and prophylactically prolonged into the postoperative period.

**Recipient data**

Recipient data as well as perioperative and follow-up data were retrieved from our institutional databases. Radiological assessment for PGD grading was provided by trained chest radiologists.

**Outcome parameters**

Early recipient outcome analysis included results within the first year post-transplant. Primary graft dysfunction (PGD) grades at T24, T48 and T72 hours were assessed according to current ISLHT guidelines. Patients with postoperatively prolonged ECMO support were graded as PGD 3 or PGD ‘ungradable’ depending on the chest x-ray. Total length of mechanical ventilation was defined as the time to successful extubation without early reintubation (<3
days). In case of tracheostomy, length of mechanical ventilation was defined as the time when the patient tolerated mere oxygen insufflation without any mechanical breathing assistance for more than six continuous hours. Furthermore, length of ICU and total hospital stay, postoperative complications, in-hospital mortality, airway complications and one-year survival were determined. Histologically verified acute rejections of both perivascular (“A-grading”) and airway (“B-grading”) form were evaluated and reported in case of grade 2 or greater. The value of best forced expiratory volume at 1 second (FEV1) reached during follow-up was calculated as the percentage of the predicted value for each respective recipient.

DBD cohort
Donor and recipient demographics were further compared between DCD transplants (n=56) (combining ‘heart+lung’ and ‘lung’ groups) and a matched, contemporary cohort of DBD transplants (n=165).

Statistical analysis
Statistical analysis was performed in IBM SPSS 26 (IBM Analytics, Armonk, NY). P-values below 0.05 were considered statistically significant. Missing data were appropriately coded and cases were excluded from the respective analysis. Continuous variables were compared using t-tests or Mann-Whitney U-Test according to data distribution. Chi-squared test or Fisher’s exact test were used for categorical variables as applicable. Figures were created using GraphPad Prism 8 (GraphPad Software, La Jolla, CA). Propensity score matching was performed using R software (R Core Team: R: A language and environment for statistical computing, Vienna, Austria, R Foundation for Statistical Computing, 2019) employing the package "MatchIt". Matching of all DCD cases (groups ‘heart+lung’ and ‘lung’ combined) cases to a contemporary control group of DBD cases (1:3) was performed using recipient age, BMI, underlying diagnosis and weight list urgency as covariates. Greedy matching with caliper set at 0.3 was performed.

Results
Donor demographics
Basic donor characteristics are detailed in Table 1. The majority of donors in the ‘heart+lung’ group suffered from isolated head trauma (58%), 1 (14%) from a cerebrovascular incident and 1 (14%) of prolonged status asthmaticus. In 1 case (14%) where the donor had suffered a circulatory arrest before regaining spontaneous circulation, the donor heart was eventually rejected after evaluation on EVP. ‘Heart+lung’ donors had received cardio-pulmonary resuscitation more often (n=6; 86%) compared to the ‘lung’ donors (n=20; 42%). Median Oto scores were similar with 4 (IQR 2 – 6) in the ‘heart+lung’ group vs 5 (IQR 3 – 6) in the ‘lung’ group. Most donor parameters were comparable between the combined DCD group and the matched DBD control group. Cerebrovascular incidents were found significantly more often in the control group (69%), while isolated head trauma was more common in the DCD group (18%)(p<0.001). Mean last donor paO2 was higher in the control group (428±104 mmHg vs 391±94 mmHg; p=0.017)

**Organ procurement**

Time sequences of organ procurement for both groups are depicted in Figure 2. Median length of the agonal phase was similar in both groups (12 min vs 11 min; p=0.937). Time between circulatory arrest and cold lung perfusion (i.e. WIT) included different hands-off periods ranging from 3 to 10 minutes. Median WIT was 24 minutes (IQR: 20 – 26) in ‘heart+lung’ donors compared to 13.5 minutes (IQR: 9 – 18) in ‘lung’ donors (p=0.002). In order to correct for varying hands-off times between donor site jurisdictions, we also calculated SWIT as defined above. In ‘heart+lung’ donors, median SWIT was 14 minutes (IQR: 9 – 17) compared to 5 minutes (IQR: 4 – 8) in donors with lung procurement only (p=0.005).

**Recipient demographics**

Recipient data are summarized in Table 2. Both patient groups were similar in age (p=0.511), sex distribution (p=0.700) and primary diagnosis (p=0.552). Median lung allocation scores were similar in ‘heart+lung’ and ‘lung’ groups with 32.6 (IQR 32 – 34) and 37.4 (IQR 33 – 63), respectively. A comparable proportion of patients were ventilator dependent immediately before transplantation (p=0.999) or required pre-transplant extra-corporeal bridging therapy (p=0.999). One patient (‘lung’ group) was transplanted on cardio-pulmonary bypass in order to correct a giant pulmonary artery aneurysm as described elsewhere11, all other patients received routine intraoperative central veno-arterial ECMO as described above. Patients in the ‘heart+lung’ group required a median of 2.5 units (IQR 2 – 4.5) of packed red blood cells and
a median of 5.5 units (IQR 4 – 8) of fresh frozen plasma. In the ‘lung’ group, a median of 5 units (IQR 2 – 8) of packed red blood cells and 10 units (IQR: 8 – 13) of plasma concentrates were used (p=0.012 and p=0.049, respectively). This difference may be explained by the higher proportion of patients with cystic fibrosis and primary pulmonary hypertension in the ‘lung’ group. Six ‘lung’ group patients (12%) but none in the ‘heart+lung’ group required postoperative veno-arterial ECMO due to impaired early organ function according to our above-described protocol (p=0.999).

Most recipient demographic parameters were similar in the combined DBD group and the matched DBD control group. Mean graft ischemic time was significantly shorter for DBD controls with 365±65 minutes (p=0.002). This can be most likely explained by the travel distance between Vienna and centers in Belgium and the Netherlands with the highest frequency of DCD donation.

Outcomes

Rates of PGD were similar at all time points in both groups (Figure 3). At 72 hours, all 7 patients in the ‘heart+lung’ group were classified as PGD 0. In the ‘lung’ group, the majority was graded as PGD 0 (n=39; 84.8%), 3 (6.5%) as PGD 1, 2 (4.3%) as PGD 2 and 1 (2.2%) as PGD 3. One patient (2.2%) was ungradable with a clear chest X-ray while still on veno-arterial ECMO (p=0.874). Patients required mechanical ventilation for a median of 50 hours (IQR 30 – 68) in the ‘heart+lung’ group vs 41 hours (25 – 76) in the ‘lung’ group (p=0.801). Postoperative stay on the ICU was similar with a median of 8 days (IQR: 4 – 11) vs 6 days (IQR: 4 – 20) days (p=0.951). Median length of hospital stay (27 vs 25 days) was also comparable (p=0.814). Median length of mechanical ventilation, post-operative ICU stay and hospital stay were similar between the combined DCD group and the DBD control group (p=0.870, p=0.580 and p=0.415, respectively). No significant difference in 5-year survival was found between the DCD and DBD group. (Suppl.Figure 2)

Only one patient (‘lung’ group) died in the early postoperative course, resulting in an in-hospital mortality rate of 2.0% compared to 0% in the ‘heart+lung’ group (p=0.999). One-year survival was comparable (‘heart+lung’: 100%; ‘lung’: 90.3%; p=0.378) (Figure 4). One patient (2%) in the ‘lung’ group developed an airway complication. This case of bronchial dehiscence of the right main bronchus was found 3 months post-transplant and healed without need for intervention. Rates of acute perivascular rejection ≥A2 (‘heart+lung’: 0%; ‘lung’: 4.1%; p>0.999) and acute airway rejection ≥B2 (‘heart+lung’: 14.3%; ‘lung’: 0%; p=0.125) did not
differ between groups. Best FEV1 values reached during follow-up were 85.6% vs 82.9% of the predicted value in the ‘heart+lung’ vs ‘lung’ group, respectively \( (p=0.911) \). This peak value was reached after a median of 114 days in the ‘heart+lung’ group and 166.5 days in the ‘lung’ group \( (p=0.443) \). The study rationale and important outcomes are also summarized in Figure 5 and Video 1.

Discussion

DCD heart transplantation is an emerging practice with excellent results and has the potential to significantly increase heart transplant activity.\(^{12}\) However, data on the functional outcome of the lungs from cDCD heart donors is lacking. To the best of our knowledge, this study represents the first analysis of outcome in this group of cDCD donors. Moreover, it is the first to examine the practice of prioritizing heart procurement while delaying both lung perfusion and ventilation. These results of our early experience suggest that 1) the delay of lung inflation and cold perfusion by PHP is typically limited to 10-15 minutes and 2) the use of this protocol has no effect on early lung performance.

Messer et al. were the first to mention potential advantages of PHP strategy in cDCD heart procurement.\(^{6}\) In the UK, the most recent national protocol for cDCD procurement of heart and lungs now recommends PHP with early lung reinflation and delayed cold perfusion. This decision was made despite concerns from some lung transplant representatives.\(^{13, 14}\) The major advantages of a PHP strategy for the heart are obvious: i) reduced WIT ii) better surgical exposure and iii) reduced cold ischemic time (CIT) as there is no need to wait for completion of the pulmonary perfusion. Donor management and multi-organ procurement have always been areas which require balancing of contrary interests to ensure success for many stakeholders. In case of cDCD, where aspects contributing to WIT are not modifiable, steps of the surgical procurement procedure become even more important. This is illustrated by ongoing discussions about potential delays of 90-120 seconds in initiating cold perfusion in combined cDCD liver and heart explantation.\(^{15, 16}\) When sharing the even smaller operating field of the chest, it is clear that procedural aspects are even more important. Establishing evidence-based guidelines is essential in order to safely expand the use of cDCD hearts.

There is a profound body of evidence showing that outcomes of cDCD lung transplantation are equal to DBD donors.\(^{2, 17-21}\) Importantly, none of the available reports on cDCD lungs describe if other organs were procured. It can be assumed based on the only recent start of cDCD heart
transplant programs, that these reports did not include any donors where the hearts were used. While data on combined heart and lung cDCD procurement is thus lacking, several studies have previously aimed to identify limits for acceptable cDCD lungs. These studies can also be used to discuss the impact of prioritizing heart explantation on cDCD lung donation.

The agonal phase is usually defined as the time from WLST to CA. In our study, this interval was significantly shorter in the ‘heart+lung’ group than in the ‘lung’ group. The difference is most likely explained by the restrictive time limit of 15 minutes of agonal phase for cDCD heart procurement in order to prevent potentially irreversible damage to the heart. The Vienna Heart Transplant Program currently accepts a maximum agonal phase of 15 before abstaining from heart procurement. For the lungs, an agonal time of up to 120 minutes is considered acceptable by our center. Based on a registry report published by Cypel et al., internationally this center-specific time frame ranges from 30 to 180 minutes. Single-center studies as well as a multi-center study have shown no impact of agonal phase duration on lung transplant outcomes within these limits. This wide range LTx centers are willing to accept while reporting excellent outcomes shows the confidence in lung tolerance to warm ischemia.

As our results show, WIT of the lungs is significantly prolonged by the addition of PHP. A working group by the International Society for Heart and Lung Transplantation has recommended standardized time points and intervals for cDCD reporting. However, definitions for the start of WIT still vary in the literature between WLST, hemodynamic instability or CA. Currently, ISHLT-interval 4 (SPB<50mmHg to cold perfusion) is usually seen as most relevant and sometimes also termed ‘functional warm ischemia’. The extent to which warm ischemic time impacts cDCD lung outcomes remains controversial. Impaired early oxygenation capacity of transplanted cDCD lungs with prolonged time between low blood pressure (<50mmHg) and CA has been reported. On the other hand, Levvy et al. found no impact of functional warm ischemia defined as donor systolic blood pressure <50mmHg to initiation of cold perfusion on early survival in a multi-center registry study. A higher risk of airway complications has sometimes been postulated for cDCD lungs due to hypoperfusion of the main bronchi during functional WIT. Extending WIT by PHP could therefore further increase the risk for anastomotic problems based on this consideration. In our cohort, only 1 bronchial complication was recorded in the ‘lung’ group and none in the ‘heart+lung’ group. This however could also be due to the generally low complication rate with a single running suture technique.
An important contributor to warm ischemia is the so-called hands-off time. This period is highly variable between jurisdictions, ranging from 2 minutes in Australia to 10 minutes in most parts of Europe and even 20 minutes in Italy. Hands-off times in the cohort of this analysis ranged from 3-10 minutes. As this interval is unmodifiable, we instead focused on time from skin incision to cold perfusion in our analyses. While skin to perfusion time in the ‘lung’ group was comparable with published data, it was significantly longer in the ‘heart+lung’ group. Heart procurements in our series were performed by different cardiac teams from more than one institution. However, all were highly experienced in the explant procedure. Topical cooling would be a strategy to potentially reduce some effects of warm lung ischemia while the heart is being procured. We aimed to provide the cardiac teams with optimal procurement conditions and therefore abstained from any measures impairing surgical exposure and delaying the procedure in any way.

The lungs are known to have the unique property to maintain oxygen supply to the parenchyma through passive diffusion from the alveoli even in absence of perfusion. The protective effect of inflation during normothermic lung ischemia on ATP stores and lactate generation has been previously shown by De Leyn et al. This factor has been utilized by Italian centers, in light of a mandatory 20 minutes stand-off period. They have instead focused on in situ preservation by alveolar recruitment while facilitating abdominal normothermic regional perfusion. According to a case series by Palleschi et al., the Milan group incurred warm ischemic times of 80 - 250 minutes from asystole to pulmonary flush. Four lungs were procured and underwent EVLP, 3 of these lungs were found to be suitable, while the organ with the longest WIT was rejected after EVLP. Of note, no topical cooling was performed with this technique, in contrast to the in situ preservation protocols other groups have proposed. Animal models have shown that the prevention of alveolar collapse, rather than ventilation or fraction of inspired oxygen may protect the lungs during warm ischemia. In a series of uncontrolled DCD lung transplants, the Toronto group used mere inflation with continuous positive airway pressure of 20 cmH2O to protect the organ during a WIT of 106 to 199 minutes, yielding excellent results. They explained the utilization rate of only 15% with negative effects of warm ischemia without concurrent lung inflation in the time necessary to obtain family consent. In order to provide the cardiac team with optimal, undisturbed surgical exposure, we accepted delayed initiation of lung inflation and ventilation during warm ischemia for PHP of 10-15 minutes until the heart was explanted. We did not find any detrimental impact on post-transplant outcomes with this approach. While medium continuous pressures or ventilation with regular tidal volumes could
impair surgical conditions for heart procurement, early alveolar recruitment, continuous low volume inflation or very low tidal volume ventilation may be feasible lung protective strategies to overcome concerns regarding PHP. In case of doubts over the organ quality of cDCD lungs, ex-vivo lung perfusion (EVLP) is an excellent method to assess the lungs and potentially repair a primarily unacceptable organ in the future. In our current cDCD protocol, EVLP is not mandatory but only used in selected cases to evaluate grafts of questionable quality. In this series, none of the lungs in group ‘heart+lung’ but 2 (4.0%) in the group ‘lung’ required EVLP evaluation.

Our study has several limitations. It is a retrospective analysis, which comes with the possibility of miscoded data and missing parameters. Consensus on the systolic blood pressure threshold that defines insufficient organ perfusion and represents the start of functional warm ischemia is still lacking.\textsuperscript{34, 35} Inconsistencies in the reporting of this parameter (40, 50 or 60 mmHg) prevented us from meaningfully calculating comparable functional warm ischemic times for our cohort. Since our study covers a practice that only recently transitioned from experimental to routine, the cohort size for PHP is limited and it is too early to report on long-term outcomes. The sample size also limits the possibilities to statistically adjust for differences between the groups. In addition, the risk for a type II error may be increased. As a single-center analysis, our study provides a homogenous cohort of a high-volume program and offers good data granularity. However, multi-center or registry studies examining this topic would be beneficial. Furthermore, as our study covers an extended time frame and increased heart cDCD is a recent development, era effects cannot be ruled out.

In conclusion, this study of our early experience shows that PHP in cDCD is associated with delayed ventilation and prolonged warm ischemic time for the lungs. However, prioritizing heart perfusion and explantation in the setting of cDCD procurement did not affect early post lung-transplant outcomes.

Author Contributions
SS and KH conceived and designed the study; JG, RM, CA, GB and PJ collected donor data; SS, AB, TS and PJ collected recipient data; SS performed the statistical analysis and interpreted the data; SS and KH wrote the manuscript draft; AOZ and AZAZ contributed important
conceptual content; All authors revised the manuscript with significant intellectual contributions.

Tables and Figures

Figure 1: Patient inclusion

Abbreviations: cDCD - controlled donation after circulatory death; NRP - normothermic regional perfusion;

Figure 2: Procurement procedure

Abbreviations: CA - circulatory arrest; CLP - cold lung perfusion; H-O - hands-off time; min - minutes; SI – skin incision; SWIT – surgical warm ischemic time; WLST – withdrawal of life-sustaining therapy;

Figure 3: Primary graft dysfunction score

Abbreviations: PGD – primary graft dysfunction;

Figure 4: One-year survival

Shaded areas equal 95% confidence intervals.

Figure 5: Overview of study rationale and outcomes

Supplementary Figure 1: Perfusion set with foley catheters

Supplementary Figure 2: Five-year survival compared to matched controls

Shaded areas equal 95% confidence intervals.

Abbreviations: DBD - donation after brain death; DCD - donation after circulatory death;

Video 1: Description of the study rationale and basic results
Table 1: Donor parameters

Abbreviations: BMI – body mass index; cm – centimeters; CPR – cardio-pulmonary resuscitation; f – female; IQR – inter-quartile range; kg – kilograms; m – male; paO2 – partial pressure of arterial oxygen; paCO2 – partial pressure of arterial carbon dioxide; SD – standard deviation;

Table 2: Recipient parameters

Abbreviations: A1AD – alpha-1 antitrypsin deficiency; BMI – body mass index; COPD – chronic obstructive pulmonary disease; CPB – cardio-pulmonary bypass; d – day; ECLS – extra-corporeal circulatory support; ECMO – extra-corporeal membrane oxygenation; f – female; FFP – fresh frozen plasma; h - hours; ICU – intensive care unit; IQR – inter-quartile range; kg – kilograms; m – male; MV – mechanical ventilation; paO2 – partial pressure of arterial oxygen; paCO2 – partial pressure of arterial carbon dioxide; postOP – postoperative; pRBC – packed red blood cells; SD – standard deviation; VA – veno-arterial;

References


<table>
<thead>
<tr>
<th></th>
<th>heart+lung n=7</th>
<th>lung n=49</th>
<th>p-value</th>
<th>matched DBD controls n=165</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (median; IQR)</td>
<td>42 (28 - 48)</td>
<td>53 (42 - 58)</td>
<td>0.342</td>
<td>48 (36 - 56)</td>
<td>0.770</td>
</tr>
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<td>Sex (m%/f%)</td>
<td>42.9%/57.1%</td>
<td>59.2%/40.8%</td>
<td>0.447</td>
<td>41.2%/58.8%</td>
<td>0.044*</td>
</tr>
<tr>
<td>Height (cm) (median; IQR)</td>
<td>175 (165-180)</td>
<td>175 (168-180)</td>
<td>0.771</td>
<td>170 (165-180)</td>
<td>0.982</td>
</tr>
<tr>
<td>Weight (kg) (median; IQR)</td>
<td>76 (70-90)</td>
<td>74.5 (70-85)</td>
<td>0.436</td>
<td>74 (65-83)</td>
<td>0.185</td>
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<tr>
<td>BMI (median; IQR)</td>
<td>26 (21-29)</td>
<td>25 (23-27)</td>
<td>0.562</td>
<td>25 (22-27)</td>
<td>0.969</td>
</tr>
<tr>
<td>Blood group (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A</td>
<td>1 (14.5%)</td>
<td>22 (45%)</td>
<td>0.237</td>
<td>61 (37%)</td>
<td>0.535</td>
</tr>
<tr>
<td>- B</td>
<td>1 (14.5%)</td>
<td>2 (4%)</td>
<td></td>
<td>19 (11%)</td>
<td></td>
</tr>
<tr>
<td>- 0</td>
<td>5 (71%)</td>
<td>21 (43%)</td>
<td></td>
<td>77 (47%)</td>
<td></td>
</tr>
<tr>
<td>- AB</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
<td></td>
<td>8 (5%)</td>
<td></td>
</tr>
<tr>
<td>Cause of condition (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Cardiac incident</td>
<td>1 (14%)</td>
<td>8 (16%)</td>
<td>0.089</td>
<td>7 (4%)</td>
<td>&lt;0.001*</td>
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<tr>
<td>- Cerebrovascular incident</td>
<td>1 (14%)</td>
<td>23 (48%)</td>
<td></td>
<td>114 (69%)</td>
<td></td>
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<tr>
<td>- Isolated head trauma</td>
<td>4 (58%)</td>
<td>6 (12%)</td>
<td></td>
<td>13 (8%)</td>
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<tr>
<td>- Polytrauma</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td></td>
<td>10 (6%)</td>
<td></td>
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<tr>
<td>- Other</td>
<td>1 (14%)</td>
<td>9 (18%)</td>
<td></td>
<td>21 (13%)</td>
<td></td>
</tr>
<tr>
<td>CPR (n; %)</td>
<td>6 (86%)</td>
<td>20 (42%)</td>
<td>*0.044</td>
<td>43 (26%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Oto score &gt;7 (n; %)</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
<td>0.999</td>
<td>22 (14%)</td>
<td>0.217</td>
</tr>
<tr>
<td>Intubation days (median; IQR)</td>
<td>7 (3 - 8)</td>
<td>4 (2 - 8)</td>
<td>0.463</td>
<td>4 (2 - 6)</td>
<td>0.232</td>
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<tr>
<td>Last paO2 (mmHg) (mean±SD)</td>
<td>409±82</td>
<td>387±97</td>
<td>0.687</td>
<td>428±104</td>
<td>0.017*</td>
</tr>
<tr>
<td>Last paCO2 (mmHg) (mean±SD)</td>
<td>38±7</td>
<td>40±8</td>
<td>0.705</td>
<td>39±8</td>
<td>0.486</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
<td>n=49</td>
<td>p-value</td>
<td>n=165</td>
<td>p-value</td>
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<td>--------------------------</td>
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<td>---------</td>
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<tr>
<td>Age (median; IQR)</td>
<td>56 (38 - 61)</td>
<td>55 (36 - 61)</td>
<td>0.511</td>
<td>53 (36 - 61)</td>
<td>0.817</td>
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<tr>
<td>Sex (m%/f%)</td>
<td>43%/57%</td>
<td>53%/47%</td>
<td>0.700</td>
<td>51%/49%</td>
<td>0.910</td>
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<td>Diagnosis (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- COPD</td>
<td>5 (72%)</td>
<td>20 (42%)</td>
<td></td>
<td>73 (44%)</td>
<td></td>
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<tr>
<td>- Fibrosis</td>
<td>1 (14%)</td>
<td>7 (15%)</td>
<td></td>
<td>28 (17%)</td>
<td></td>
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<tr>
<td>- Cystic Fibrosis</td>
<td>0 (0%)</td>
<td>11 (24%)</td>
<td></td>
<td>35 (21%)</td>
<td>0.983</td>
</tr>
<tr>
<td>- Primary pulmonary hypertension</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td>0.552</td>
<td>0 (0%)</td>
<td>0.817</td>
</tr>
<tr>
<td>- A1AD</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0.525</td>
<td>0 (0%)</td>
<td>0.983</td>
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<tr>
<td>- Other</td>
<td>1 (14%)</td>
<td>5 (11%)</td>
<td></td>
<td>20 (12%)</td>
<td></td>
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<tr>
<td>Lung allocation score (median; IQR)</td>
<td>32.6 (32 - 34)</td>
<td>37.4 (33 - 63)</td>
<td>0.801</td>
<td>36.4 (33 - 49)</td>
<td>0.962</td>
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<tr>
<td>Transplant type (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- full</td>
<td>5 (71%)</td>
<td>24 (49%)</td>
<td></td>
<td>94 (57%)</td>
<td>0.661</td>
</tr>
<tr>
<td>- size reduced</td>
<td>2 (29%)</td>
<td>24 (49%)</td>
<td>0.525</td>
<td>64 (39%)</td>
<td></td>
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<td>- lobar</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0.525</td>
<td>7 (4%)</td>
<td></td>
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<tr>
<td>Mean ischemic time (min) (mean±SD)</td>
<td>458±239</td>
<td>414±98</td>
<td>0.748</td>
<td>365±65</td>
<td>0.002*</td>
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<tr>
<td>ECLS Bridging (n; %)</td>
<td>1 (14%)</td>
<td>9 (18%)</td>
<td>0.999</td>
<td>17 (10%)</td>
<td>0.136</td>
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<tr>
<td>Intubated pre-transplant (n; %)</td>
<td>1 (14%)</td>
<td>7 (15%)</td>
<td>0.999</td>
<td>11 (7%)</td>
<td>0.098</td>
</tr>
<tr>
<td>Type of intraoperative support (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no support</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td>3 (2%)</td>
<td></td>
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<tr>
<td>- intraOP ECMO</td>
<td>7 (100%)</td>
<td>48 (98%)</td>
<td></td>
<td>158 (95%)</td>
<td>0.629</td>
</tr>
<tr>
<td>- CPB</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td></td>
<td>4 (3%)</td>
<td></td>
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<tr>
<td>Intraoperative pRBC units (median; IQR)</td>
<td>2.5 (2 - 4.5)</td>
<td>5 (2 - 8)</td>
<td>*0.012</td>
<td>4 (3 - 8)</td>
<td>0.944</td>
</tr>
<tr>
<td>Intraoperative FFP units (median; IQR)</td>
<td>5.5 (4 - 8)</td>
<td>10 (8 - 13)</td>
<td>*0.049</td>
<td>10 (7 - 14)</td>
<td>0.963</td>
</tr>
<tr>
<td>Prolonged postOP VA ECMO (n; %)</td>
<td>0 (0%)</td>
<td>6 (12%)</td>
<td>0.999</td>
<td>21 (13%)</td>
<td>0.691</td>
</tr>
<tr>
<td>Length of MV (h) (median; IQR)</td>
<td>50 (30 - 68)</td>
<td>41 (25 - 76)</td>
<td>0.801</td>
<td>42 (21 - 96)</td>
<td>0.870</td>
</tr>
<tr>
<td>ICU stay (d) (median; IQR)</td>
<td>8 (4 - 11)</td>
<td>6 (4 - 20)</td>
<td>0.951</td>
<td>8 (5 - 15)</td>
<td>0.058</td>
</tr>
<tr>
<td>Hospitalization (d) (median; IQR)</td>
<td>27 (25 - 37)</td>
<td>25 (20 - 41)</td>
<td>0.814</td>
<td>30 (21 - 47)</td>
<td>0.415</td>
</tr>
</tbody>
</table>
Prioritizing Direct Heart Procurement in Organ Donors after Circulatory Death does not Jeopardize Lung Transplant Outcomes

S Schwarz, J Gökler, R Moayedifar, C Atteneder, G Bocchialini, A Benazzo, T Schweiger, P Jaksch, AO Zuckermann, AZ Alabadi-Zuckermann, K Hoetzenecker

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Director
K Hoetzenecer

Surgeons
W Klepetko
S Taghavi
G Lang
J Matilla
B Moser
MA Hoda
T Schweiger
S Schwarz

Pulmonologists
P Jaksch
G Muraközy
S Kovacs
cDCD procurements
N = 68

Excluded:
- No progression to arrest (N=4)
- Organ quality (N=7)

Excluded:
- Abdominal NRP (N=1)

heart+lung
N = 7

lung
N = 49
Prioritizing Direct Heart Procurement in Organ Donors after Circulatory Death does not Jeopardize Lung Transplant Outcomes

**Retrospective analysis:**
January 2012 – February 2022

<table>
<thead>
<tr>
<th>DCD Heart + Lung</th>
<th>vs</th>
<th>DCD Lung</th>
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<tbody>
<tr>
<td>N=7</td>
<td></td>
<td>N=49</td>
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</table>

**Increased warm ischemic time**

- 24 min
- 13 min
- p=0.002

**Similar PGD at 72 hours**

**Similar 1-year graft survival**
Prioritizing Direct Heart Procurement in Organ Donors after Circulatory Death does not Jeopardize Lung Transplant Outcomes

Presenter: Dr. Stefan Schwarz
Invited Discussant: Dr. Ashish Shah

Dr. Ashish Shah:

Well, thank you for the opportunity to review your manuscript and your paper and the opportunity by the society. So, the authors have reviewed a relevant, albeit small, experience in the world of DCD donation that addresses the question whether heart-recovering delays in lung ventilation, presumably prolonged warm ischemia, and potential injury to the lung is associated with worse lung outcomes. The authors conclude that a short delay is not associated with worse post-transplant outcome. It is important to note, as you have noted in your talk, this is really about direct procurement and not about normothermic regional perfusion, which will be a completely different [inaudible], I believe. In your manuscript, you actually mention that heparin is given when allowed. Have any of these cases involved donors that did not get heparin prior to withdrawal?

Dr. Stefan Schwarz:

So, since we procure lungs across the Eurotransplant region, this is different according to centers and jurisdictions. So, at some centers, it is allowed to give medication such as heparin before withdrawal, and this was the case in some of these cases. In donors where this was not allowed, we put 10,000 units of heparin in the first bag of prophylactic perfusion and performed explanation this way.

Dr. Shah:

Did you recover hearts when you were not allowed to give heparin?

Dr. Schwarz:

It's likely that this was only cases where the heart was procured.

Dr. Shah:

Okay. My second question is the actual warm ischemic times are really quite short in both groups. So, in your team's mind, what would be the limits to
where you wouldn't utilize the lung? How long would you wait for that heart
team to get their act together?

Dr. Schwarz:

So, what gave us the confidence to set aside and leave the thoracic cavity to the
cardiac colleagues was our confidence in the ability of the lung to accept
prolonged periods of warm ischemia. We would wait for up to two hours for
circulatory arrest to set in, so we're well within those limits. Of course,
ventilation is also a factor, and we know that the lung is more tolerant to
cessation of perfusion as long as ventilation is reinstituted early. I think, for
these reasons, it's not really up to us, or we won't come into the range where we
will have fears, probably, because the heart warm-ischemia time will be the
limit in this question.

Dr. Shah:

I'll just conclude with just a comment. I think we're at the very beginning of
really understanding the limits of warm ischemia and novel strategies to rescue
these organs. DCD for heart transplant is here to stay. And the challenges
associated with multi-organ recovery will grow unless we truly understand what
actually matters and what doesn't matter during these recoveries. So, I applaud
the authors' initial look at this issue and look forward to future work by your
very esteemed group to see what the true physiologic limits are and for other
groups to really understand, ultimately, where NRP fits in this. Because I have a
sneaking suspicion this will be very different. So, we look forward to I think
your presentation's a very nice presentation.

Dr. Schwarz:

Thank you.

Unidentified Speaker 1:

A very nice presentation, and congratulations with the excellent results. I have a
question regarding your heart and lung group, with regards to the numbers. So
were these hearts and lungs transplanted all in Vienna or were there cases that
the heart was taken by another group and only the lungs were transplanted in
Vienna and, vice versa, when lungs were taken by another group these were not
included in this series.

Dr. Schwarz:
So, this study was purely from the outlook of [inaudible] Lung Transplant Center. Some of these hearts were procured by the Vienna heart transplant team, some of those by other teams.

Unidentified Speaker 1:

But the results on the outcome of the lungs was-- it's only on the lungs that were transplanted in Vienna?

Dr. Schwarz:

Yes. Exactly.

Unidentified Speaker 2:

I'll ask one question, if I may. So, I apologize if I've missed it, but so you transplanted seven sets of lungs from situations where the heart was procured with DPP, correct?

Dr. Schwarz:

Yes.

Unidentified Speaker 2:

Were there any situations where you went out with the intent to procure lungs when a heart was being procured and ended up declining those lungs?

Dr. Schwarz:

There were instances where there was pneumonia, for example, but there was no exclusions based on the prioritized heart procurement.

Unidentified Speaker 2:

Okay. So, what criteria did you use when you went out to look at the lungs after you were there in the chest? Basically, I'm asking under these situations, what would make you decline a set of lungs where the heart was being procured? Do you look at compliance, the bronchi, other sorts of strategies like that, or did you have a defining time period for warm ischemia as well?
Dr. Schwarz:

Since we are confident that the lung will tolerate the warm ischemia, there was no fixed limit. But we looked, as you said, at the bronchoscopy, at the elastic recoil, and of course, at the parenchyma quality at the back table. But we always explanted the lungs and [inaudible] them on the back table before accepting or declining.

Unidentified Speaker 2:

Great. Anyone else? A very nice presentation. And I think as Dr. Shah alluded to, I mean, this is a very dynamic and changing field, and I think this adds significantly to the literature. But one of the real questions is what's going to be the impact of NRP. Does anyone in the audience have experience with transplanting lungs from a donor where NRP was used to procure the heart?

Unidentified Speaker 3:

Y, we did two cases in our center. And we had the medical student who did their survey, and she collected five cases. And I think your case is included in that as well.

Unidentified Speaker 2:

So, to be clear-- I'm sorry. You transplanted how many?

Unidentified Speaker 3:

Two.

Unidentified Speaker 2:

Two?

Unidentified Speaker 3:

Two out of eight NRP-- thoracoabdominal NRP procedures. We declined two other lungs because of bad quality.
Unidentified Speaker 2:

Because of back table assessments?

Unidentified Speaker 3:

Yeah.

Unidentified Speaker 2:

And you transplanted both of those directly, or with EVLP?

Unidentified Speaker 3:

Directly.

Unidentified Speaker 2:

Directly? Okay. Ashish?

Dr. Shah:

I'll say I think we-- I think there's probably five or six NRP cases we've gone out for. Two we utilized for lung transplant. The other four, I'd say, Matt Bacchetta, who runs our program, elected to send those to a lung bioengineering [inaudible]. They all failed. The last two-- so I'm going to add another two-- as soon as we reperfused on NRP, those lungs really failed badly. And we're in the midst of trying to understand if this is just couple case-- again, these are small cases, so it's really hard to know. But I suspect there may be another injury that's possible with reperfusion. It could be neurogenic, also. Even though we do interrupt the cerebral circulation, there may be some other element here we're missing. So, as you said, we're going to see how this shakes out in the future.

Unidentified Speaker 2:

Yeah. I think, really quickly, our experience in Cleveland has been, I think, we've done three. One set of lungs for NRP, we transplanted directly. Actually, Dr. Ahmad transplanted those. I think Vanderbilt took the heart. And the other two, we put both those on EVLP because we had concerns. And both of those sets of lungs ended up not being transplantable.
Dr. Shah:

Yeah. And I think one of the things that Matt is a little worried about is that maybe even that second EVLP run might-- there's some priming that may be going-- I mean, I don't want the audience to think that we have a total grasp of this. These are very potentially unique cases, but there's definitely a signal there that we need to look into this a little bit closer.

Unidentified Speaker 2:

Yes. Yeah, I completely agree. Okay. Thank you very much.