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Pedro Augusto Reck dos Santos

Doação Após Morte Circulatória e Transplante de Pulmão

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Pedro Augusto Reck dos Santos

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Orientador(a): Prof. Dr. Paulo J Z Teixeira
Coorientador(a): Prof. Marcelo Cypel

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Formato da Tese:

A presente tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências da Saúde, sendo apresentada através de dois artigos científicos originais, aprovados para publicação, sobre o tema estudado:

1- Artigo Original Referente a revisão sobre o conceito de doadores pós-parada cardíaca no Brasil. Publicado no Jornal Brasileiro de Pneumologia (ISSN 1806-3756 online); Qualis B2 ainda na classificação da Plataforma Sucupira 2013-2016. No entanto, o atual fator de impacto do Jornal Brasileiro de Pneumologia é 2,624 – tal impacto no contexto atual equivale a Qualis A2; cujas normas de publicação podem ser consultadas no Anexo 6.1.1.

2- Artigo Original Referente ao uso de doação após morte circulatória para recipientes de alto-risco. Publicado no Journal of Heart and Lung Transplantation (ISSN 1557-3117 online); Fator de Impacto 10,247; Qualis A1, cujas normas de publicação podem ser consultadas no Anexo 6.1.2.

Epígrafe:

For everything there is a season, and a time for every purpose under heaven.

Ecclesiastes 3:1.

Lista de Abreviaturas e Siglas:

Termos em Português:

TxP: Transplante Pulmonar

DMC: Doação após Morte Circulatória

DME: doação após morte encefálica

AR: alto risco

Termos em Inglês:

DCD: Donation after Circulatory Death

DBD: Donation after Brain Death

HR: High-Risk

LTx: Lung Transplantation

IPAH: Idiopathic Pulmonary Arterial Hypertension

ISHLT: International Society for Heart and Lung Transplantation

ECMO: Extra-corporeal Membrane Oxygenation

DLTx: Double Lung Transplants

CI: Confidence Intervals

NE: Not-estimable

FEV1: Forced Expiratory Volume in 1 Second

BDD: brain dead donor

EVLP: Ex Vivo Lung Perfusion

WLST: Withdrawal of Life Support Therapies

ICU: Intensive Care Unit

PA: Pulmonary Artery

LA: Left Atrium

WIT: Warm Ischemic Time

PGD: Primary Graft dysfunction

LOS: Lenght of Stay

CLAD: Chronic Lung Allograft Dysfunction

BOS: Bronchiolitis Obliterans Syndrome

CPAP: Continuous Positive Airway Pressure

Resumo:

Introdução: O Transplante Pulmonar (TxP) é a modalidade mais eficaz para o tratamento de pacientes com doenças pulmonares em estágio terminal. Infelizmente, muitas pessoas não podem se beneficiar dessa terapia devido à disponibilidade insuficiente de doadores. Em nosso primeiro artigo, discutimos a Doação após Morte Circulatória (DMC), que sem dúvida é essencial entre as estratégias desenvolvidas para aumentar o pool de doadores. No entanto, existem considerações éticas e legislativas no processo de doação da DMC que são diferentes da Doação após Morte Encefálica (DME). Entre outros, os aspectos críticos do DMC são o conceito de terminalidade, a cessação de tratamentos fúteis e retirada de terapia de suporte de vida. Além disso, descrevemos uma justificativa para o uso de pulmões provenientes de DMC e fornecemos algumas definições importantes, destacando as principais diferenças entre DMC e DME, incluindo aspectos fisiológicos pertinentes a cada categoria. A capacidade única dos pulmões de manter a viabilidade celular sem circulação, supondo que o oxigênio seja fornecido aos alvéolos – um aspecto essencial da DMC – também é discutida. É feito uma revisão atualizada da experiência clínica da DMC para TxP em centros internacionais, avanços recentes na DMC e alguns dilemas éticos que merecem atenção a esse respeito. Em nosso segundo artigo, baseado no fato de que o TxP com DMC demonstrou resultados equivalentes em comparação à DME, quisemos avaliar a segurança da DMC, em comparação com o DME. Os dados do uso de DMC para receptores de alto risco (AR) são limitados, e é por isso que fizemos essas comparações entre DMC e DME. **Métodos:** Realizamos um estudo de “propensity score matching” para avaliar o impacto do transplante com DMC em receptores de AR. Além disso, avaliamos o efeito do perfil do receptor (AR vs. não AR) em DMCs e DMEs

no TxP. **Resultados:** Entre 2009 e 2018, foram identificados 1.829 transplantes pulmonares duplos (TxPD) para receptores de AR. Destes, 131 foram realizados com doadores DMC. Não houve diferença na sobrevida entre doadores DMCs e DMEs entre os receptores de AR-TxPD (p=0,16). No entanto, os receptores AR tiveram pior sobrevida em comparação com os não AR na DMEs (p<0,001), mas não no transplante usando DMC (p=0,95). **Conclusões:** Nossos achados sustentam que os pulmões provenientes de DMC são apropriados para receptores de AR e não devem ser considerados doadores inferiores ou de alto risco. Seu uso deve, acima de tudo, ser mais estimulado e não restringido.

Abstract:

Introduction: Lung Transplantation (LTx) is the most effective modality for the treatment of patients with end-stage lung diseases. Unfortunately, many people cannot benefit from this therapy due to insufficient donor availability. In our first article, we discuss Donation after Circulatory Death (DCD), which is undoubtedly essential among the strategies developed to increase the donor pool. However, there are ethical and legislative considerations in the DCD donation process that are different from the brain dead donor (BDD). Among others, DCD critical aspects are the concept of the end of life, cessation of futile treatments, and withdrawal of life support therapy. In addition, we describe a rationale for using DCD lungs and provide some important definitions, highlighting the key differences between DCD and BDD, including physiological aspects pertinent to each category. The lungs' unique ability to maintain cell viability without circulation assuming oxygen is supplied to the alveoli – an essential aspect of DCD lung donation – is also discussed. Furthermore, an updated review of the clinical experience with DCD for LTx across international centers, recent advances in DCD donation and some ethical dilemmas that deserve attention in this regard are also reported. In our second article, based on the fact that LTx using donation after circulatory death (DCD) donors has demonstrated equivalent outcomes compared to donation after brain dead (DBD) donors, we wanted to evaluate the safety of DCD donation, in comparison to BDD. Data from the use of DCDs for high-risk (HR) recipients is limited, and that is why we did these comparisons between DCDs and BDDs. **Methods:** We performed a propensity match study to evaluate the impact of DCD transplantation on HR recipients. In addition, we assessed the effect of recipient profile (HR vs. non-HR) in DCDs and DBDs LTx.

Results: From 2009-2018, 1829 double lung transplants (DLTx) for HR recipients were identified. Of these, 131 were performed using DCD donors. There was no difference in survival between DCDs and DBDs among HR-DLTx recipients (p=0.16). However, HR recipients had worse survival compared to non-HR recipients in DBD (p<0.001) but not in DCD transplantation (p=0.95). **Conclusions:** Our findings support that DCD lungs are appropriate for HR recipients and should not be considered inferior or higher-risk donors. Its use should be further stimulated rather than restricted

Palavras-Chave:

Obtenção de Tecidos e Órgãos

Morte Encefálica

Transplante de Pulmão

Insuficiência Respiratória

Keywords:

Tissue and Organ Procurement

Brain Death

Respiratory Insufficiency

Donation After Circulatory Death

Lung Transplantation

Brain Dead Donation

End-Stage Lung Diseases

Lista de Ilustrações:

Todas as figuras descritas nesta tese estão colocadas já no local dos dois artigos submetidos e aceitos para publicação.

Artigo 1 – Jornal Brasileiro de Pneumologia

Artigo 2 – Journal of Heart and Lung Transplantation

Lista de Tabelas:

Todas as Tabelas descritas nesta tese estão colocadas já no local dos dois artigos submetidos e aceitos para publicação.

Artigo 1 – Jornal Brasileiro de Pneumologia

Artigo 2 – Journal of Heart and Lung Transplantation

Sumário

1. Revisão de Literatura

Esta tese apresenta e é baseada em dois artigos já submetidos e aceitos para publicação que versam sobre a doação após morte circulatória. O primeiro dos artigos é uma revisão sobre o tema, onde múltiplos aspectos são discutidos. Neste sentido, esta revisão de literatura é uma busca a dois pontos importantes a que o leitor se faz necessário ter uma idéia. O primeiro são aspectos históricos relacionados ao Transplante Pulmonar, e o segundo diz respeito a estratégias que têm sido empregadas com o intuito de se aumentar o número de doações em todo mundo. Aqui, faz-se importante mencionar a DMC. Conforme relatado, a revisão abrangente recai sobre o artigo escrito com este propósito, publicado em Jornal Brasileiro, tratando-se, “to the best of our knowledge”, como o primeiro artigo a ter este foco no nosso País.

1.1 Transplante Pulmonar – aspectos históricos

O transplante de pulmão é uma terapia que visa oferecer ao paciente em falência pulmonar uma alternativa de tratamento eficaz. Ainda que hoje seja uma realidade, a jornada do transplante pulmonar reside em raízes históricas cujos princípios iniciais estão intrinsecamente relacionados ao trabalho pioneiro de Alexis Carrel, onde a técnica de anastomoses vasculares foi definida(1).

Modelos animais de transplantes pulmonares foram descritos no passado (2) até o momento em que a equipe liderada por Hardy (3) descreveu os primeiros resultados com essa terapia. Ainda que a indicação naquela época hoje em dia seja questionada, pois o paciente apresentava enfisema pulmonar e uma neoplasia primária de pulmão, a sobrevida limitada após o transplante mostrou que esta terapia seria potencialmente realizável em humanos.

O que se seguiu foram inúmeras tentativas de se realizar o transplante pulmonar com sucesso em muitos outros centros no mundo inteiro, sem os resultados almejados. De uma forma geral, o transplante de órgãos encontra seus desafios em complicações infecciosas, rejeições do órgão e disfunção do mesmo. Neste sentido, o advento da Ciclosporina foi importante pois mudou este panorama(4). Aqui, o transplante de pulmão revelou umas das diferenças fundamentais quando comparado aos outros órgãos – é o único órgão que mantém contato com o meio-ambiente - vias aéreas. As complicações brônquicas revelaram-se como o “calcanhar de Aquiles” desta modalidade.

O grupo de Toronto foi o primeiro que descreveu resultados animadores do transplante pulmonar, inicialmente com o transplante unilateral(5). Este resultado foi construído baseado em muitos insucessos (6), e o posterior sucesso alcançado através de amplas pesquisas onde se aprendeu o manejo das complicações da anastomose brônquica, sejam eles decorrentes de isquemia e/ou de cicatrização insuficiente decorrente de drogas imunossupressoras. Em modelos experimentais de transplante, o manejo dos imunossupressores foi essencial para que a viabilidade da anastomose brônquica se mantivesse (7), o uso do omento como cobertura a vitalizar a anastomose

(8) (9) e em especial o uso da Ciclosporina foi comprovado num cenário experimental como peça importante desta equação (10).

O transplante inicialmente unilateral, evolui para posterior uso de ambos os órgãos, baseado em modelos experimentais (11) e também no sucesso descrito com o uso do transplante cardiopulmonar em bloco (12,13). No entanto, o uso do bloco cardiopulmonar parecia excessivo pois muitos pacientes que necessitavam de transplante tinham função cardíaca normal. O grupo de Toronto novamente é responsável por este passo importante, ao descrever o transplante pulmonar bilateral realizado com sucesso (14) (15).

Com a transplante pulmonar bilateral, muitos pacientes puderam vislumbrar uma chance real de cura. Aqui, um marco importante foi uma modificação na técnica empregada que permitiu simplificar o processo de implante sequencial (16), evitando em muitos casos o uso de suporte circulatório, facilitando o processo.

Com a técnica progressivamente sendo mais utilizada, os resultados começaram a ser descritos na literatura para diferentes populações de pacientes (seja para transplante uni ou bilateral), como fibrose pulmonar (17), enfisema (18), fibrose cística (19), doenças vasculares (20).

Aliado a isso, melhoras no manejo do doador (21), na preservação dos enxertos pulmonares (22) , no reconhecimento e manejo da disfunção primária do enxerto (23) e da rejeição (24), bem como da lesão de isquemia e reperfusão (25), na identificação da disfunção crônica do enxerto (26), bem como na seleção dos recipientes (27), tornaram o transplante de pulmão uma modalidade de tratamento segura e que provou, ao longo

dos anos, sua eficácia. O atual limite reside no fato de que há muito mais pacientes que necessitam de transplante pulmonar do que de doadores viáveis, e esforços que possibilitem o aumento do número de doações são vitais para minimizar o número de pacientes que, ainda nos dias atuais, morre esperando por um órgão.

1.2 Transplante Pulmonar – estratégias para aumentar o número de doações

Há sem dúvida uma grande necessidade de se aumentar o número de doações para todo o tipo de transplantes. No que tange ao transplante de pulmão, existem no contexto atual algumas alternativas sendo empregadas com esta finalidade.

- Recondicionamento pulmonar “ex-vivo”: esta técnica consiste na identificação de pulmões que outrora não seriam potencialmente usados para o transplante pulmonar e submeter tais órgãos a um período em que seriam perfundidos e ventilados fora do corpo, para avaliação de sua real qualidade(28). Com esta abordagem, os pulmões são ventilados com um regime que minimiza injúria e são perfundidos com uma solução de preservação que possibilita uma redução do edema e minimiza lesões adicionais. Um conhecimento da fisiologia pulmonar é crítico, pois os pulmões são avaliados ao longo do tempo, onde parâmetros como a complacência pulmonar, pressões em vias aéreas, resistência vascular pulmonar, oxigenação, dentre outros, tornam-se vitais para que se determine se este órgão é passível e/ou apresenta condições para ser usado para transplante (29).

Com o passar do tempo, as evidências se acumulam sobre os resultados desta modalidade de “reparo pulmonar”, hoje já de reconhecida importância em nosso meio (30) (31). No cenário atual, a perfusão ex-vivo passou a ser não somente uma ferramenta para reavaliar pulmões a serem posteriormente usados para transplante, mas também considerada como potencial plataforma terapêutica seja para o manejo de infecções (32) (33), manejo de lesões provenientes de aspiração (34), bem como de alternativas que forneçam novas perspectivas como o uso de células-tronco para reparo pulmonar (35) ou até mesmo como um meio de se criar compatibilidade sanguínea para que órgãos possam ser mais facilmente alocados (36). Tais perspectivas são animadoras com essa terapêutica a ser cada mais incorporada ao Transplante Pulmonar.

- Transplante Pulmonar Lobar: O transplante pulmonar, especialmente para crianças e adultos com baixa estatura, trata-se de uma situação desafiadora, pois há uma raridade e uma dificuldade em fazer o *matching* entre a maioria dos doadores disponíveis, que frequentemente tem dimensões de caixa torácica maior do que estes recipientes precisam. Neste sentido, alternativas técnicas como a redução pulmonar, ou o transplante de somente lobos, ao invés do pulmão inteiro, faz-se necessário. Os resultados obtidos até o momento são bastante satisfatórios com esta técnica (37). Nesta área, além do próprio transplante, existem outras técnicas para “redução” das dimensões de um órgão a ser transplantado, como a realização de ressecção de zonas periféricas, ou até mesmo a bipartição pulmonar, onde um pulmão é dividido em dois, e usado para um transplante bilateral (38).

Existem situações em que, seja pela dificuldade de se encontrar doadores ou seja por características culturais, o transplante de lobos é realizado com doadores vivos. Em

tal modalidade, frequentemente dois adultos doam lobos para o transplante em uma criança. Esta iniciativa foi inicialmente descrita pelo grupo de Starnes (39), e posteriormente empregada em muitos outros centros, especialmente no Japão(40). Importante nesta modalidade de transplante é notar os riscos que o doador pode correr durante as lobectomias que são realizadas, via de regra, em dois pacientes diferentes quase que de maneira simultânea. (41)

- Doadores Marginais: Sabe-se que a procura pelo doador ideal é tarefa árdua, pois as características do mesmo são raramente encontradas – vide Figura 1, Artigo 1. Diante disso, as equipes de transplante pulmonar encontram-se com o dilema de aceitar doadores que, muitas vezes, não se encontram dentro dos parâmetros ideais.

Aqui, critérios como por exemplo, a idade do doador é avaliada. De Perrot analisou se doadores com > 60 anos poderiam impactar o resultado do transplante, e, nesta casuística, idade não pareceu ser fator a ser considerado (42). Outro fator importante quando considerado se o doador é marginal diz respeito ao tabagismo prévio. Aqui, importante considerar a quantidade de tabagismo do doador, conforme descrito por Bonser (43) que demonstrou que determinadas quantidades tinham um risco associado maior de algum desfecho negativo. Há, sem dúvida, outros critérios a serem considerados, como valores subótimos de gasometria, Raio-X com infiltrados pulmonares, broncoscopia suspeita. No entanto, apesar de estudos terem demonstrado que no passado o transplante com doadores marginais carecia de grande cuidado pois poderia estar associado a maior risco de mortalidade após o transplante (44), no contexto atual, o uso destes doadores deve ser considerado especialmente tendo em vista o prognóstico do paciente em lista de espera (45) (46).

Todas estas estratégias têm como objetivo o aumento do número de doações e a doação após a morte cardíaca também se consolida como uma modalidade que irá possibilitar um maior número de transplantes. Esta modalidade ainda carece de ampla discussão sobre os aspectos técnicos e éticos, bem como uma análise maior dos resultados após o transplante, especialmente em receptores de alto risco.

2. Justificativa e Objetivos

Há uma necessidade de se buscar novas alternativas para aumentar o número de transplantes em todo o mundo. A doação após morte circulatória tem sido uma maneira de se aumentar o número de transplantes, porém ainda não empregada no Brasil. Além disso, no contexto do transplante pulmonar em nível internacional, estes doadores ainda são vistos como se fossem de alto-risco ou mesmo considerados de inferior qualidade quando comparados ao doador em morte cerebral.

Esta tese tem como objetivos:

- Introduzir e discutir este assunto no Brasil através da revisão da literatura internacional sobre o tema.

- Avaliar se doadores após morte circulatória são seguros até mesmo para receptores de mais alto risco quando comparados com doadores em morte cerebral.

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4. Artigos Científicos

4.1 Artigo Científico – Jornal Brasileiro de Pneumologia

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Donation after Circulatory Death and Lung Transplantation

Pedro Augusto Reck dos Santos[a,e], Paulo José Zimermann Teixeira[b,e], Daniel de Messias Moraes Neto[c], Marcelo Cypel[d]

[a] Assistant Professor - Department of Cardiothoracic Surgery, Mayo Clinic, AZ, USA.

[b] Prof. Associado de Pneumologia - Departamento de Clínica Médica. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brasil.

[c] Clinical Assistant Professor – Department of Cardiothoracic Surgery, Stanford, CA, USA.

[d] Professor of Surgery, Division of Thoracic Surgery. University of Toronto, University Health Network, Toronto, ON, Canada.

[e] Programa de Pós-Graduação em Ciências da Saúde – Universidade Federal de Ciências da Saúde de Porto Alegre. Porto Alegre, RS, Brasil.

Orcid:

Pedro A Reck dos Santos 0000-0002-5497-3188

Paulo J Z Teixeira 0000-0002-4906-6970

Daniel MM Neto 0000-0003-3721-2675

Marcelo Cypel 0000-0001-5652-1938

Corresponding Author:

Pedro Augusto Reck dos Santos MD MSc

Department of Cardiothoracic Surgery

Mayo Clinic Arizona

5777 E Mayo Blvd

Phoenix, AZ 85054

Tel: (412)3989072

email: Reckdossantos.pedro@mayo.edu

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Abstract:

Lung Transplantation (LTx) is the most effective modality for the treatment of patients with end-stage lung diseases. Unfortunately, many people cannot benefit from this therapy due to insufficient donor availability. In this review, we discuss Donation after Circulatory Death (DCD), which is undoubtedly essential among the strategies developed to increase the donor pool. However, there are ethical and legislative considerations in the DCD donation process that are different from the brain dead donor (BDD). Among others, DCD critical aspects are the concept of the end of life, cessation of futile treatments, and withdrawal of life support therapy. In addition, this review describes a rationale for using DCD lungs and provides some important definitions, highlighting the key differences between DCD and BDD, including physiological aspects pertinent to each category. The lungs' unique ability to maintain cell viability without circulation assuming oxygen is supplied to the alveoli – an essential aspect of DCD lung donation – is also discussed. Furthermore, an updated review of the clinical experience with DCD for LTx across international centers, recent advances in DCD donation and some ethical dilemmas that deserve attention in this regard are also reported.

Rationale:

Lung Transplantation (LTx) is a life-saving therapy for managing patients with end-stage lung diseases such as COPD, cystic fibrosis, and pulmonary fibrosis. Unfortunately, this modality of treatment cannot be offered to more patients because of the lack of suitable donors, highlighting the disproportion of patients currently waiting for an organ compared to the number of people on the waiting list(1).

For example, in Brazil where a significant number of liver and kidney transplants are performed every year, cardiothoracic transplantation is still much below what is seen in other countries according to the Brazilian Association for Organ Transplantation (2). In this context, considering the number of active Lung Transplant centers in Brazil, an increment in the number of procedures performed every year would be paramount.

The process of donation is always a long and complex process, where it is necessary to deal with the emotions of the family of the donor, logistics, the expectations of the recipient, and the constant attention that needs to be paid to every single detail for this entire equation to move forward with success. For lungs, specifically, optimal donor management is so critical that a potential organ can be missed due to many factors. Less than ideal management leads to high numbers of potential donors becoming unsuitable for LTx.

In contrast to other organs, additional criteria need to be fulfilled for the lungs to be considered for transplantation (3) (4) and are critical for the success of the process. The lungs are also susceptible to many insults such as the intravascular volume status of the donor or the suboptimal management of secretions in the airways. Table 1 highlights the

criteria for lung acceptance for clinical LTx and particular challenges that need to be considered. Thus, to avoid post transplant complications, the acceptance rate of a donor for clinical LTx is low, making the relative scarcity of donors combined with low utilization a real challenge.

As the number of patients on the waiting list continues to rise, several strategies have been developed to increase the number of transplants. This includes the use of extended criteria donors (5), living lobar lung transplantation (6), and Ex Vivo Lung Perfusion (EVLP) for the rehabilitation of organs(7).

Another potential source to alleviate the shortage of donors is donation after circulatory death (DCD). This donation process has progressively gained acceptance, and not only for lungs but also kidneys, livers, pancreas, and even heart transplantation(8). This modality of donation has been shown to contribute to an increment in the number of transplants worldwide and represents a shift in a paradigm, considering that the standard donors accepted are brain dead donors (BDD). However, the number of BDD seems insufficient for the demand of patients in need of a life-saving transplant(9,10). Advancements in the knowledge about DCD donation have bolstered the number of LTx, resulting in progressive increments in the number of DCDs every year(11,12). In the USA, DCD has been contributing incrementally to benefit more patients, and specifically to the lungs, the number of DCD donors used for clinical LTx has increased steadily (Figure 1) impacting the overall number of lung transplants.

Definitions:

The conventional modality of donation accepted is the brain dead, and several tests are performed to diagnose and confirm this status, like the absence of circulation and no brain stem reflexes(13). On the other side, DCD consists of a donation in a patient who has a permanent absence of circulation (blood pressure, pulse activity) and respiration (14). However these concepts are broad, and to clarify it, a classification stratified DCD into categories – called the Maastricht criteria(15), with sequential updates in this classification(14) (Table 2). Understanding this classification is paramount, especially considering a critical subdivision between categories I and II (uncontrolled DCD donation) and types III and IV (controlled). Of note, a Modified Maastricht classification encompasses patients with Euthanasia as potential donors, classified as Category V.

Categories I and II are considered "uncontrolled" DCD donors, implying that death has occurred suddenly. Examples are patients whose death occurred in the Emergency of a Hospital or even at a Pre-Hospital stage.

On the other side, DCD categories III and IV are considered "controlled" DCD donors because death is anticipated but did not happen yet. It usually occurs in ICUs and encompasses patients with non-recoverable injuries and depend on life-sustaining therapies, however without meeting criteria for brain death. Young patients with devastating brain injuries and irreversible damage that did not evolve to a brain dead status yet are a typical example of a DCD category III and commonly found in clinical practice. These patients, unfortunately, are so sick that anticipation of imminent death

after withdrawal of life support therapy (WLST) is expected, and cessation of futile therapies that are prolonging the life of a critical patient is part of the process(16).

Most importantly, from the categories highlighted above, Maastricht Type III is currently the most studied and the preferred type of DCD being done in many centers around the world. That is why the focus of this review will primarily reside on this category.

In Maastricht III, logistics are critical for success once a donor is identified and matched to a recipient. WLST therapy happens in a controlled environment (typically in ICU), where comfort and compassionate care of the patient are paramount. In addition, it is extremely important to provide support to the family of the donor. Heparin is administered, ventilatory support is discontinued, extubation is performed in most places, and cessation of medications used to maintain hemodynamic support is also part of this process.

After WLST is performed, there is a planned interval of time, usually ranging from 60-90 minutes (can be extended to even up to 180 minutes), where vital signs of the donor are checked continuously. This period is called the "agonal phase" and lasts until the termination of circulation and respiration. When the potential donor has cardiac arrest within the planned interval, there is a stand-off period, ranging from 2-5 minutes, where the absence of circulation and respiration must be determined by two physicians, who should not be related to the transplant teams. Once death is determined, typically, the donor is then transferred to the operative room, where intubation and ventilation are restarted and lungs are procured. Figure 2 summarize the complex process involved in controlled DCD donation.

There are several steps described within this process (17) that should be strictly followed:

- Comfort measures are provided for the donor during the process.
- The family of the patient is being supported
- Determination of death is critical after WLST is performed. As mentioned above, the importance of the stand-off period, where the potential DCD donor can be declared dead after cessation of circulation and ventilation for an interval of 2 to 5 minutes
- No conflicts of interest.

The surgical technique for procurement of lungs from DCD donors is essentially the same as for a BDD donor. Briefly, sternotomy is performed, and once the chest is open, the pericardium is incised, and the heart is exposed. The pulmonary artery (PA) trunk is identified and cannulated. The left atrium (LA) appendage is also open. The preservation solution is perfused in an antegrade way from the PA, and the output is drained from the LA. Lungs are continuously ventilated during this entire process. The technique is described in detail elsewhere(18).

After the lungs are removed from the chest in a semi-inflated state, quality is assessed, and a decision is made about the lungs' condition before proceeding to transplantation(19). Figure 3 highlights the critical differences between the DCD and BDD process for the donation of lungs.

In order to establish criteria for eligibility regarding DCD, we must remember that this concept has an intimate relationship to the concept of "end of life" care. While it can provide the opportunity of a life-saving transplant, it is essential to maintain critical aspects

like preserving dignity and respect for the donor, exploring the patient's wishes and the family, and respecting values. Also, providing family support, focusing on alleviating any distress or pain, and providing support and avoiding unnecessary prolongation of the death process is paramount (20).

DCD donation is still not utilized in many places due to logistics, lack of expertise of the transplant center, and ethical considerations such as the acceptance of the concept of WLST (21,22). In addition, there is no legislation towards using DCD donors in some places like Brazil, which makes this process even more challenging to start.

In summary, there are many challenges to overcome in this DCD implementation process, as described in Figure 4. Many potential DCD donors are missed every year, and these donors could certainly positively impact patients waiting for a life-saving transplant (23).

Differences between DCD and DBD:

Some differences between BDD and DCD donors were discussed above, but two are critical and deserve special attention.

The first situation is the Agonal Phase. There are many definitions for this phase, but in general, the most accepted concept is the interval between WLST and cardiac arrest. Here, a certain amount of time is expected for the cardiac arrest to happen, and usually, it ranges from few minutes to 120 minutes(24). The impact of the amount of time that the agonal phase represents and its relation to prognosis is undoubtedly an issue for discussion, considering that intervals beyond 120 minutes were also reported to be

feasible in clinical transplantation(25). This period is critical and different patterns of injuries can happen due to the effects that WLST can have on the donor, like hypotension, hypoxia, aspiration.

The second issue is the duration of the Warm ischemic time (WIT). WIT is generally the interval between donor systolic blood pressure < 50 mmHg until the lungs are perfused with a cold preservation solution via pulmonary artery flush(26). In comparison to DCD donors, BDD has the WIT minimized as much as possible. While this interval is deemed safe when it lasts < 60 minutes, the fact that the duration of WIT can potentially impair a patient's prognosis is still a matter of discussion and becomes critical for DCD donors, considering the different pathways that this type of donor follows (27).

In the opposite direction, it is important to bring for discussion the fact that the brain dead status is associated with a process that involves complex pathophysiology where inflammatory, sympathetic, and hemodynamic mechanisms can ultimately lead to lung injury (28). These injuries can lead to neurogenic lung edema that can negatively impact the outcome of LTx, especially early in the process of brain dead (29). Hence, DCDs are potentially spared from this phenomenon since they are not exposed to the whole pathophysiologic process involves in the brain dead mechanism and its associated consequences.

More evidence has been describing the different pathways that DCD and BDD donors follow, which are also demonstrated in gene expression profiles. To that end, it appears that BDD donors were associated more commonly with inflammatory profiles (30) whereas

DCD donors showed genetic signatures more associated with apoptosis and necrosis (31).

How long can the lung cells survive without circulation:

Considering the DCD principles, a fundamental question related to this donation process is certainly for how long the lung cells can survive so the organ can be used for transplantation since DCD donation implies a period where lungs remain without circulation. To address this critical concept, an understanding of lung physiology is mandatory, and it is necessary to understand the lungs' particular capacity to maintain the viability of the cells during WIT. While this critical time can significantly impair the function of organs like the liver, hearts, kidneys, and lungs, the latter can maintain the viability of the cells when there is oxygen in the alveoli. Hence, even in the absence of circulation, the ventilation of the lungs becomes paramount for the maintenance of cell viability. This concept is called aerobic lung preservation (32).

After circulatory arrest, experimental data showed that an atelectatic state tolerated 60 minutes as the maximal time without additional damage (33). In this sense, it becomes critical to avoid collapse and atelectasis of the lungs, and its prevention appears to "attenuate" from warm ischemic injury (34,35). Also, the inflation of the lungs with oxygen seems to be a key component of preservation because maintaining a reserve of oxygen in the alveoli can potentially minimize the effects of WIT. (36).

Having this in mind, a critical question is when lung cells start to die after cessation of circulation. In small animal models, the simply post mortem ventilation of lungs with oxygen seemed to attenuate the ischemic injury to cells. In nonventilated rats, nonviable cells were 36%, 52%, and 77% of cells at 2, 4, and 12 hours after death. Similar results were found in lungs ventilated with nitrogen. However, oxygen-ventilated cadaver rats had much less nonviable lung cells at the same time points: 13%, 10%, and 26% ($p < 0.01$), demonstrating that postmortem mechanical ventilation with oxygen can delay cell death (37). The same group also showed that for 4 and 8 hours after death, ultrastructural deterioration was significantly attenuated when oxygen ventilation was provided compared to rats whose lungs were not ventilated. (38)

These data explain how lungs from DCD donors have the potential to maintain cell viability after cessation of circulation if ventilation/oxygen is provided, conferring a critical topic to be understood when we address this type of donation for clinical transplantation.

Results of Clinical Experience with Lung Transplantation Using DCDs:

A retrospective analysis from the International Society for Heart and Lung Transplantation (ISHLT) DCD Registry was published(39), highlighting the experiences of many centers, with their practices in the DCD management, totalizing 306 LTx, from January 2003 to June 2013. The control group was constituted by BDD that occurred in the same period.

Most DCD donors were Maastricht Category III, and several centers have reported their results with DCD LTx. When comparing DCD and BDD donors, there were no significant

differences in mortality at 30 days (96% vs. 97%), one year (89 vs. 88%), and five-year survival (61% on both groups), respectively

A follow-up from the same ISHLT DCD Registry was recently reported (40), this time including more centers, from patients submitted to LTx from 2003 to 2017, with 1090 DCD included, with equivalent long-term results when DCDs and BDD donors were compared.

These data show that DCD donors can be a safe resource to alleviate the waiting list of patients who desperately need a life-saving lung transplant. However, these reports did not address critical perioperative data, such as the incidence of primary graft dysfunction (PGD) and ICU length of stay (LOS). To address these issues, a review of retrospective single-center experiences focusing on these data is reported in Table 3.

These compiled data, where DCD Maastricht Category III was by far the most common used, also demonstrated no difference between medium (1 year) or long -term survival, when a comparison between DCD and BDD were used for LTx (25) (41-43) (44) (45).

PGD is undoubtedly one of the critical factors that can influence the prognosis of patients submitted to LTx and is graded according to the ISHLT classification(46). In this regard, higher grades of PGD, especially at 72 h after LTx, are critical. Hence, DCD and BDD did not differ in the incidence of this complication at this time point. In addition, ICU LOS was equivalent, and Hospital LOS also showed no differences, except for one report (45) that pointed toward a longer Hospital LOS in the DCD group.

Some of these studies also evaluated the Chronic Lung Allograft Dysfunction (CLAD) or Bronchiolitis Obliterans Syndrome (BOS). De Oliveira reported a 5 Year Freedom-from-

BOS rate of 72.3% for DCD and 58% for BDD (p=0.59) (41). At one year after LTx, Van de Wauer described a significant advantage in the DCD group compared to BDD(42). A favorable trend towards DCD was described by Ruttens et al. (44) with five-year Freedom-from-CLAD reported at 79.2% for DCD and 67.8% for BDD (p=0.86). On the other side, Sabashnikov et al. reported a higher incidence of postoperative BOS in the DCD group (23.5%) than BDD (11.7%), p=0.049. Further analysis is necessary to clarify the relationship between DCD and its relationship with CLAD.

Krutsinger et al. reported his results using a systematic review and meta-analysis approach for a comparison and found no difference in 1-year mortality, PGD, and acute rejection episodes when compared DCD and BDD donors(47). More recently and using the same approach, Palleschi et al. also did not find differences in 1-year survival, grades 2-3 PGD rates, and 1-year freedom from CLAD, but airway complications were more commonly found in the DCD groups(48).

Ethical Dilemmas:

In some countries, the discussion about controlled DCD organ donation use is extremely complex because it involves WLST, end-of-life care, cessation of futile therapies. In fact, in many instances, there is not even legislation that discusses DCD. This makes the dissemination of this process of donation even more challenging.

While DCD Maastricht Type III is the most commonly used for clinical transplantation, we need to understand that this type of DCD donation, together with Type IV, comprises a

situation where the potential donor is so severely sick, and death is anticipated, and this is not an easy issue to be accepted, understood and respected in many places where there are different laws, ethical concerns, and religious beliefs. Unfortunately, the final product is that this potential pool of donors is restricted.

These "regulatory" boundaries potentially affect other DCD donors (uncontrolled - Maastricht I and II categories). However, for other types of DCDs to be used, other issues need to be tackled, like the understanding of death and the irreversibility of situations. Taking this concept into consideration regarding uncontrolled DCD donation, where things can happen abruptly like a donor who dies at the arrival in the Hospital or another one who unfortunately dies after unsuccessful resuscitation efforts, may represent a different challenge for the families and the whole team involved in donation and transplantation. Education of the entire team involved in the donation process seems critical for developing a DCD program(49).

From a medical perspective, the challenge is undoubtedly a thorough understanding of the concept of death. The traditional standard of death remains the permanent cessation of circulation and respiration (50).

Due to the nature that events can happen in these donation processes, it is paramount to educate the population and give support to the families when they are facing the most challenging times of their lives, dealing with the loss of a loved one. Hence, it is essential to understand the uncertainty about the timing of death and recognize efforts to optimize donation respecting the ethical boundaries.

Another critical point is that the introduction of DCD donation does not jeopardize the potential number of BDD donors. In fact, DCD seems to positively impact the numbers of transplants and increase the number of BDD, potentially resulting from better donor referral policies, among others, which may play a role in this activity. (51)

Many people wish to donate their organs if, unfortunately, death happens; however, ultimately, the family will play a significant role in this critical decision, and the DCD donation process is different than conventional BDD.

DCD donation is, above all, an effort to save lives, and sometimes this donation can be unsuccessful for many reasons, like if the quality of the organ is not ideal or if the donor does not have a cardiac arrest in suitable time after WLST. But even families from DCD donors whose donation was unsuccessful appreciated the donation attempt. Unsuccessful donation harms reported by the families were waste of an organ for a much in need, a lost opportunity to honor their loved one, and a way to ease their grief (52)

A comprehensive education process for those involved in these types of donations is necessary to avoid potential conflicts in any possible step within organ donation. Education is vital to be tailored appropriately for each component of the decision-making and management of the DCD donor. Perceptions of the process can differ according to the family's perspective and the professionals involved in the transplant process (53).

Advances in the DCD donation – Uncontrolled DCD

The progressive acceptance of DCD donors has been important in order to increment the number of transplants and, as a result, save more lives. To move this discussion to the next phase, uncontrolled DCD donation is undoubtedly an area that needs to be addressed, considering the significant pool of donors that these categories represent.

While uncontrolled DCD donation was not associated with the expected outcomes in the past(54), recent data has been showing promising results(55). This group demonstrated some exciting concepts that potentially contributed to their reported outcomes and can undoubtedly benefit and help disseminate these types of DCD donations.

First, regarding lung preservation, a simple maneuver like in situ lung inflation of the lungs using a continuous positive airway pressure (CPAP) of 20 cmH_2O could protect an extended WIT (which, in their experience, was reported to be 2.8 hours), creating critical time for the whole process of donation to happen. Their reported time is significant for the lungs to be deprived of blood nourishment and depending on aerobic lung preservation for maintenance of cell viability.

Second, the importance of EVLP was critical. During the uncontrolled donation, many injuries can occur to the lungs, and EVLP would work to stratify better lungs that can maintain adequate function. With the anticipated expanded WIT intervals for uncontrolled DCD donors, the use of EVLP will become an essential tool for organ usage (56).

Despite the conflicting results presented with uncontrolled DCD donation, the development of standard protocols for donor management will be critical to better determine the outcomes, eventually disseminating this pool of donors(57).

Ethical concerns like the determination of the irreversibility of a cardiac arrest, the extension of resuscitation beyond futility, the determination of death, and also how to approach family members about uncontrolled DCD donation are all areas that will need to be taken in consideration to further promote this mode of donation (58). But it is undeniable that this modality can be a valuable resource for patients on the waiting list for a life-saving transplant, (59).

In summary, DCD donation does have the potential to significantly impact the number of transplants significantly. Clinical results to date have demonstrated excellent outcomes, at least equivalent to BDD. Ethical, cultural and legislation barriers need to be further addressed in countries like Brazil in order to be able to fully utilize this valuable source of organ donors.

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Tables and Figures Legends:

Table 1 - Criteria for Acceptance and Challenges in Donor Management

Standard Criteria for Lung Acceptance for Clinical Transplantation
Age < 55 years
Clear chest X-ray
Adequate gas exchange PaO2 > 300 mmHg with FiO_2 100%
Smoking history < 20 pack years
No evidence of aspiration / purulent secretions at bronchoscopy
No history of primary pulmonary disease or active pulmonary infection
Absence of organisms on sputum Gram's stain
Absence of chest trauma

Challenges – Donor Management - Lungs
Attention to the volume status
Mechanical ventilation management
Hygiene of the airways
Potential infectious sources
Careful assessment of the Medical History
Continuous discussions with the family

Table 2 - DCD classification

DCD Categories	Maastricht	Modified Maastricht
I	Dead on arrival at Hospital	Found dead IA – Out of Hospital IB – In - Hospital
II	Death with Unsuccessful Resuscitation	Witnessed Cardiac Arrest IIA Out of Hospital IIB In-Hospital
III	Awaiting Cardiac Death	Withdrawal of life-sustaining therapy
IV	Cardiac arrest while brain dead	Cardiac arrest on a patient brain dead, prior to organ recovery
V		Euthanasia

Categories I and II – Uncontrolled DCD donor
Categories III, IV and V – Controlled DCD donor

Table 3 - Perioperative Data – DCD vs DBB Lung Transplantation

Author	Year	DCD / BDD cases	Survival 1 y	Survival 5 y	PGD [c]	ICU LOS	Hospital LOS
De Oliveira	2010	18 / 282	88 / 87	81.9 / 63.3	PGD Grade 2 or 3 within 72 h: 33.3 / 26.1	4 / 6	17 / 20
Van De Wauver	2011	35 / 77	91 / 91	73 / 66	PGD Grade 3 at 72h: 6 / 11	4 / 5	32 / 33
Sabashnikov	2015	60 / 120	86.1 / 84.2	50.8 / 66.4	PGD Grade 3 at 72h: 5 / 9	5 / 6	30 / 32
Ruttens	2017	59 / 331	87.3 / 90.9	70.9 / 78	Highest PGD < 72h: 44.1 / 47.7	16.3 / 14.4	41.1 / 38.1
Costa	2018	46 / 237	91 / 92	78 / 75 [a]	PGD Grade 3 at 72h: 13 / 17	N/A	22 / 18 *
Qaqish	2021	180/1088	N/A	8.0 / 6.9 [b]	PGD Grade 2 and 3 at 72h: 15 / 17.2 and 13.9 / 9, respectively	4.5 / 4	23 / 25

1 year and 5 year Survival are represented as DCD / BDD (%)
Primary Graft Dysfunction (PGD) represented as DCD/BDD (%)
ICU LOS (Length of Stay) and Hospital LOS are represented in DCD / DBD (days)

a) last follow up reported was at 3 years post Lung Transplantation
b) Median survival DCD / BDD (years; p=0.79)
c) PGD graded according to the ISHLT classification

* - Data that reached statistical significance

Figure 1 – DCD / BDD Organ Transplantation and DCD Lung Transplantation – United Network for Organ Sharing (UNOS)

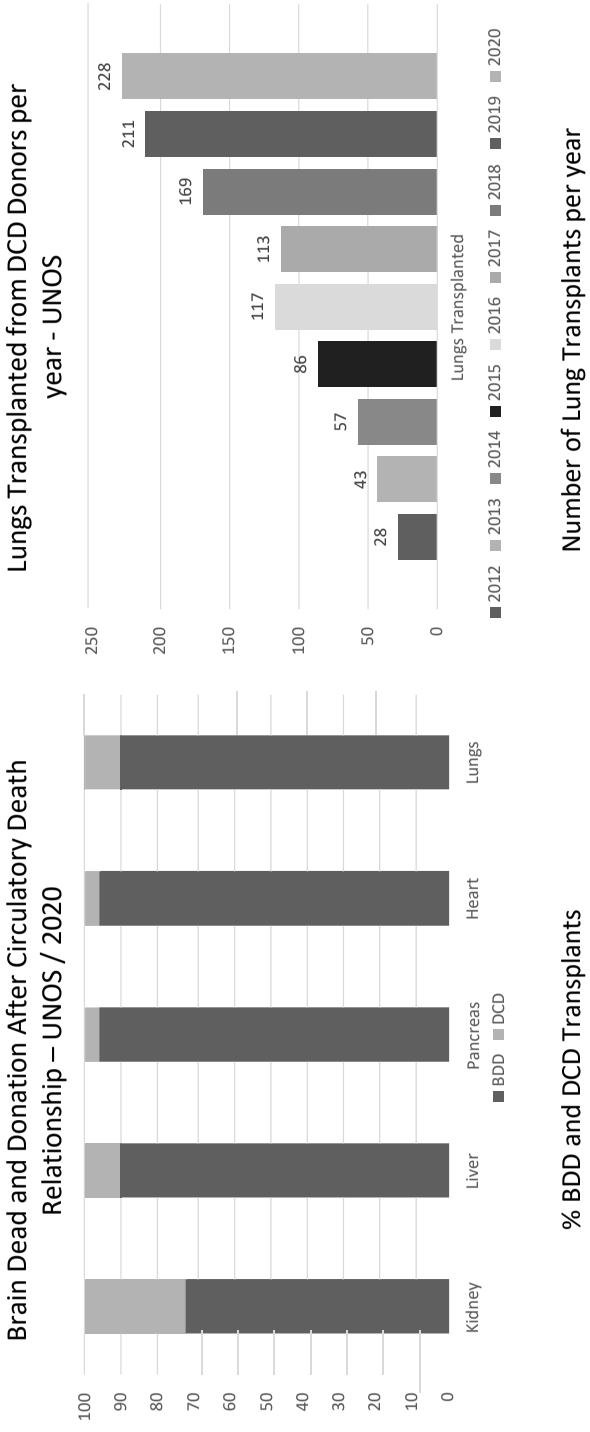


Figure 2 – DCD Donation Process

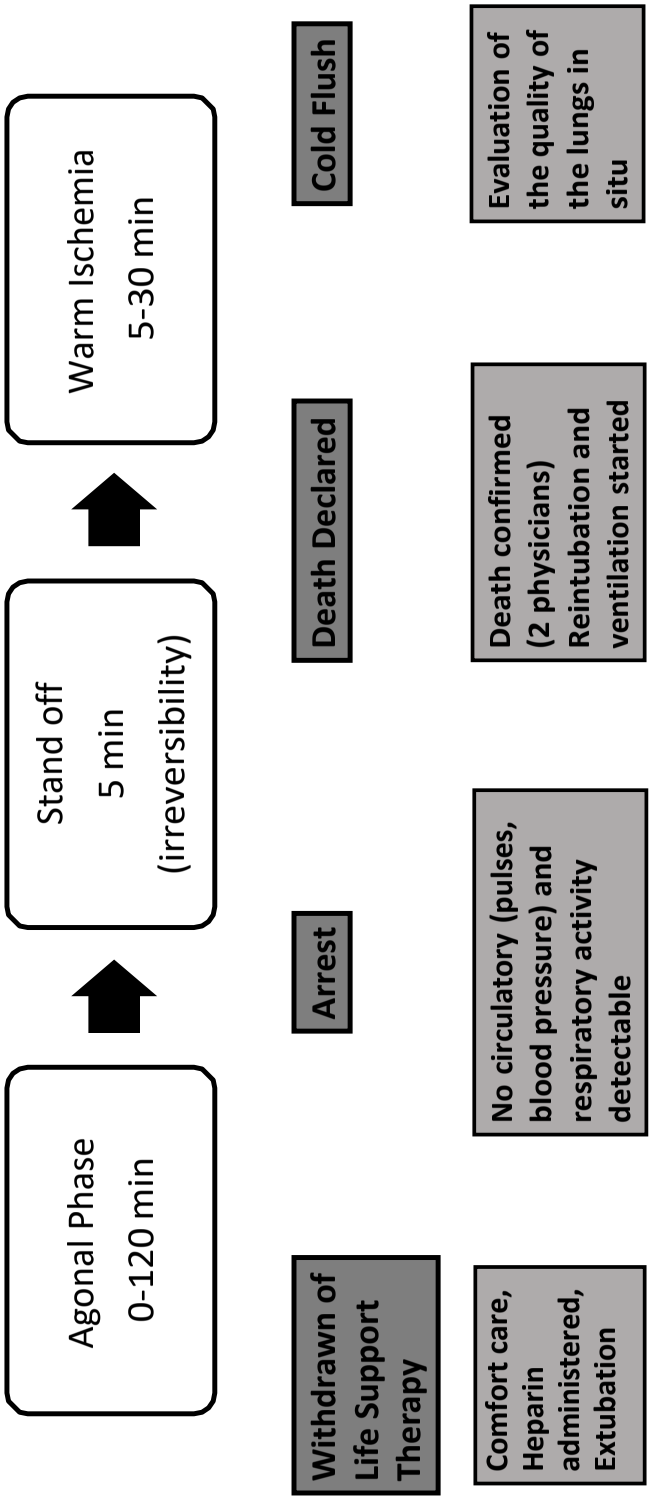


Figure 3 - Process of Donation – Brain Dead and Donation after Circulatory Death

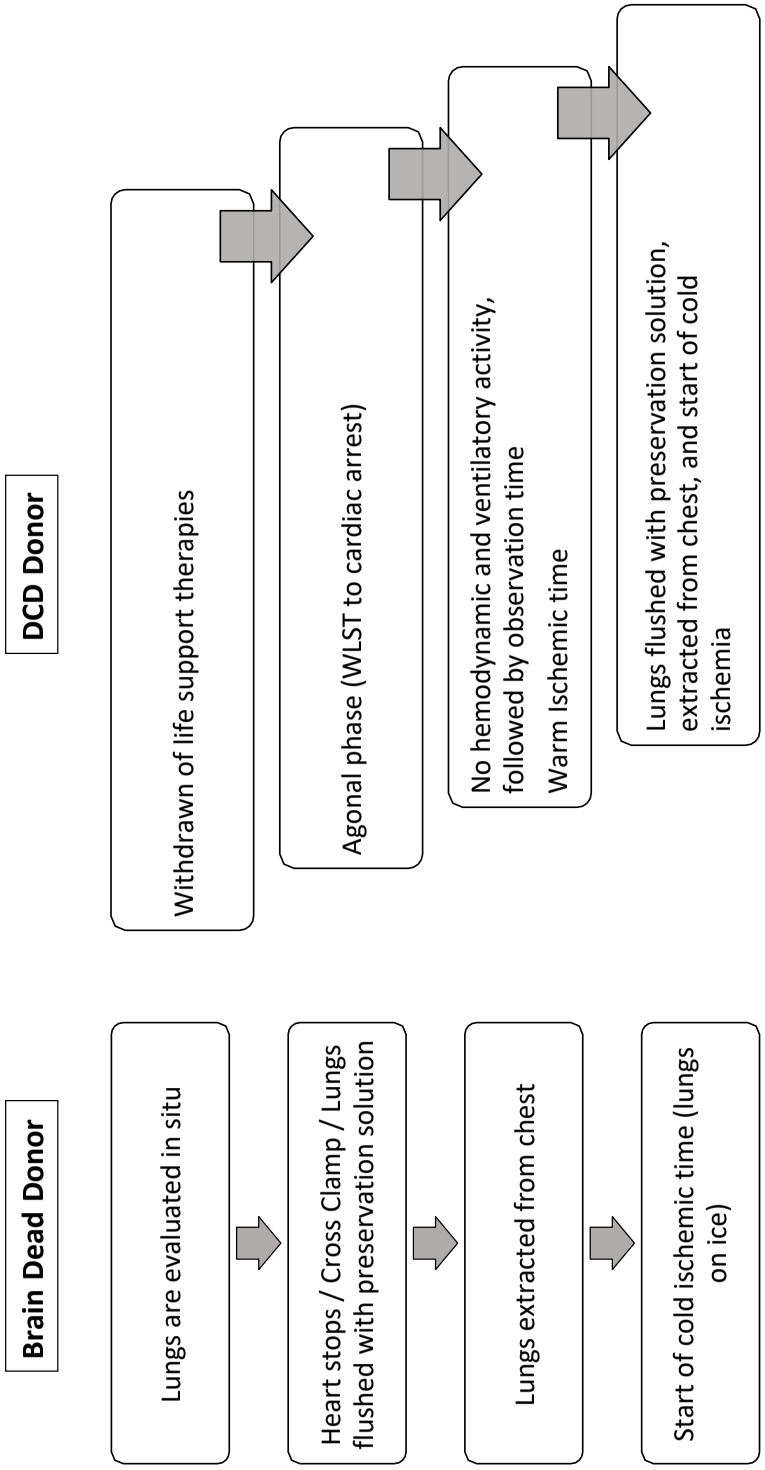
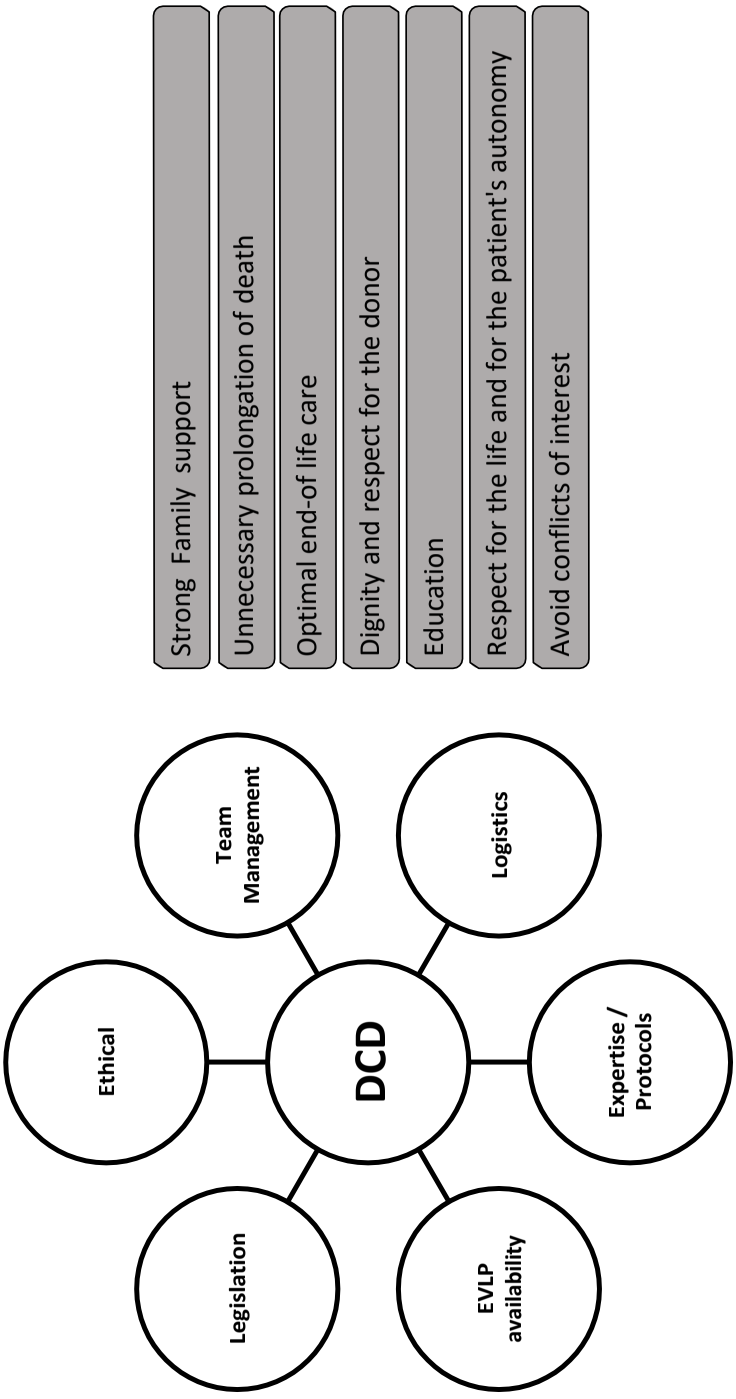


Figure 4- Potential Barriers for DCD implementation and key principles



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REVIEW AND UPDATE ARTICLE

Donation after circulatory death and lung transplantation

Pedro Augusto Reck dos Santos[1,2], Paulo José Zimermann Teixeira[1,3], Daniel Messias de Moraes Neto[4], Marcelo Cypel[5]

1. Department of Cardiothoracic Surgery, Mayo Clinic (AZ) USA.
2. Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
3. Departamento de Clínica Médica, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
4. Department of Cardiothoracic Surgery, Stanford (CA) USA.
5. Division of Thoracic Surgery, University of Toronto, University Health Network, Toronto (ON) Canada.

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ABSTRACT

Lung transplantation is the most effective modality for the treatment of patients with end-stage lung diseases. Unfortunately, many people cannot benefit from this therapy due to insufficient donor availability. In this review and update article, we discuss donation after circulatory death (DCD), which is undoubtedly essential among the strategies developed to increase the donor pool. However, there are ethical and legislative considerations in the DCD process that are different from those of donation after brain death (DBD). Among others, the critical aspects of DCD are the concept of the end of life, cessation of futile treatments, and withdrawal of life-sustaining therapy. In addition, this review describes a rationale for using lungs from DCD donors and provides some important definitions, highlighting the key differences between DCD and DBD, including physiological aspects pertinent to each category. The unique ability of lungs to maintain cell viability without circulation, assuming that oxygen is supplied to the alveoli—an essential aspect of DCD—is also discussed. Furthermore, an updated review of the clinical experience with DCD for lung transplantation across international centers, recent advances in DCD, and some ethical dilemmas that deserve attention are also reported.

Keywords: Tissue and organ procurement; Brain death; Lung transplantation; Respiratory insufficiency.

RATIONALE

Lung transplantation (LTx) is a life-saving therapy for managing patients with end-stage lung diseases such as COPD, cystic fibrosis, and pulmonary fibrosis. Unfortunately, this modality of treatment cannot be offered to more patients because of the lack of suitable donors, highlighting the disproportion of patients currently waiting for an organ transplant compared with the number of people on the waiting list.[1]

For example, although a significant number of liver and kidney transplants are performed every year in Brazil, cardiothoracic transplantation is still much lower than what is seen in other countries according to the Brazilian Association for Organ Transplantation.[2] In this context, given the number of active lung transplant centers in Brazil, an increment in the number of procedures performed every year is paramount.

The process of donation is always long and complex; it is necessary to deal with the emotions of the family of the donor, logistics, and expectations of the recipient, and constant attention needs to be paid to every single detail for this entire equation to move forward successfully. Regarding lungs, specifically, optimal donor management is so critical because a potential organ can be lost due to many factors. Less than ideal management leads to high numbers of potential donors becoming unsuitable for LTx.

In contrast to other organs, additional criteria need to be fulfilled for LTx to be considered[3,4] and are critical for the success of the process. The lungs are also susceptible to many insults, such as the intravascular volume status of the donor or the suboptimal management of secretions in the airways. Chart 1 highlights the criteria for lung acceptance for clinical LTx and the particular challenges that need to be considered. Thus, to avoid post-transplant complications, the acceptance rate of a donor for clinical LTx is low, making the relative scarcity of donors combined with low utilization a real challenge.

As the number of patients on the waiting list continues to rise, several strategies have been developed to increase the number of lung transplants. This includes the use of extended-criteria donors,[5] living-donor lobar LTx,[6] and ex vivo lung perfusion (EVLP) for organ rehabilitation.[7]

Another potential source to alleviate the shortage of donors is donation after circulatory death (DCD). This donation process has progressively gained acceptance, not only for LTx but also for kidney, liver, pancreas, and even heart transplantation.[8] This modality of donation has been shown to contribute to an increment in the number of transplants worldwide and represents a shift in a paradigm, given that the standard is donation after brain death (DBD). However, the number of DBD donors seems insufficient for the demand of patients in need of a life-saving transplant.[9,10] Advancements in the knowledge about DCD have bolstered the number of LTx, resulting in progressive increments in the number of DCD every year.[11,12] In the USA, DCD donors has incrementally been contributing to benefit more patients, and, specifically regarding the lungs, the number of DCD used for clinical

Correspondence to:
Pedro Augusto Reck dos Santos. Department of Cardiothoracic Surgery, Mayo Clinic Arizona, 5777 E Mayo Blvd, Phoenix, 85054, AZ, USA.
Tel.: 1 412 3989072. E-mail: reckdossantos.pedro@mayo.edu
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4.2 Artigo Científico – Journal of Heart and Lung Transplantation

O PDF do artigo – APROVADO – para publicação está disponível em:

https://www.jhltonline.org/article/S1053-2498(22)01812-5/fulltext

O artigo segue abaixo, exatamente conforme submetido ao Journal of Heart and Lung Transplantation:

Title: Donation after Circulatory Death Donors in High-Risk Recipients Undergoing Bilateral Lung Transplantation: an ISHLT Database Registry analysis

Authors: Pedro Augusto Reck dos Santos[a,f], Paulo José Zimermann Teixeira[b,f], Daniel Messias de Moraes Neto[c], Blake Langlais[d], Marcelo Cypel[e]

Running Title: Donation after Circulatory Death in High-Risk Recipients

Affiliations:

[a] Assistant Professor - Department of Cardiothoracic Surgery, Mayo Clinic, AZ, USA.

[b] Associate Professor of Medicine - Respirology - Department of Internal Medicine. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brasil.

[c] Clinical Assistant Professor – Department of Cardiothoracic Surgery, Stanford, CA, USA.

[d] Senior Biostatistician, Department of Quantitative Health Sciences, Mayo Clinic, AZ, USA.

[e] Professor of Surgery, Division of Thoracic Surgery. University of Toronto, University Health Network, Toronto, ON, Canada

[f] Programa de Pós-Graduação em Ciências da Saúde – Universidade Federal de Ciências da Saúde de Porto Alegre. Porto Alegre, RS, Brasil.

Orcid #: PARS 0000-0002-5497-3188 PJZT 0000-0002-4906-6970 DMMN 0000-0003-3721-2675 BL 0000-0001-8576-5851 MC 0000-0001-5652-1938

Corresponding Author:

Pedro Augusto Reck dos Santos MD MSc

Department of Cardiothoracic Surgery **-** Mayo Clinic Arizona. 5777 E Mayo Blvd. Phoenix, AZ 85054 - Tel: (412)3989072. Email: Reckdossantos.pedro@mayo.edu

List of non-standard abbreviations:

DCD: Donation after Circulatory Death

DBD: Donation after Brain Death

HR: High-Risk

LTx: Lung Transplantation

IPAH: Idiopathic Pulmonary Arterial Hypertension

ISHLT: International Society for Heart and Lung Transplantation

ECMO: Extra-corporeal Membrane Oxygenation

DLTx: Double Lung Transplants

CI: Confidence Intervals

NE: Not-estimable

FEV1: Forced Expiratory Volume in 1 Second

Word count: 1000

Abstract:

Lung transplantation (LTx) using donation after circulatory death (DCD) donors has demonstrated equivalent outcomes compared to donation after brain dead (DBD) donors. However, data from the use of DCDs for high-risk (HR) recipients is limited.

We performed a propensity match study to evaluate the impact of DCD transplantation on HR recipients. In addition, we assessed the effect of recipient profile (HR vs. non-HR) in DCDs and DBDs LTx. From 2009-2018, 1829 double lung transplants (DLTx) for HR recipients were identified. Of these, 131 were performed using DCD donors. There was no difference in survival between DCDs and DBDs among HR-DLTx recipients ($p=0.16$). However, HR recipients had worse survival compared to non-HR recipients in DBD ($p<0.001$) but not in DCD transplantation ($p=0.95$).

Our findings support that DCD lungs are appropriate for HR recipients and should not be considered inferior or higher-risk donors. Its use should be further stimulated rather than restricted.

Brief Communication:

Cumulative evidence demonstrates that the use of donation after circulatory death (DCD) lung transplants is safe and provides similar outcomes compared to donation after brain dead (DBD) transplantation (1,2). However, this source of donors is still underutilized, especially in the United States, where only about 5% of all lung transplants are performed from DCDs (3,4). Some concerns relate to the potential insults these organs could suffer during the interval between the withdrawal of life-support therapy and cardiac arrest (5,6).

One common concern is the combination of using a high-risk (HR) donor in an HR recipient as the compounded risk could typically lead to adverse outcomes. Levvey demonstrated the safety of performing DCD Lung Transplantation (LTx) in patients with Idiopathic Pulmonary Arterial Hypertension (IPAH); a population knowingly to have more graft dysfunction and complications early after transplantation (7). However, since DCDs are still considered HR donors by many centers, we wanted to evaluate the impact of using DCD donors on HR recipients using the ISHLT Database Registry.

We defined HR recipients as: 1)patients bridged with ECMO prior to LTx, 2)patients with IPAH, and 3)retransplants. These categories account for the highest risks of adverse patient outcomes with frequent perioperative complications where the quality of the graft becomes critically important (8-10).

Data were limited to single-organ double lung transplants (DLTx), occurred between 2009-2018. Single lung transplants were excluded as they are rarely used for these HR recipients. From 38,176 lung transplants, 1,829 DLTx for HR recipients were identified; 1698 DLTx were performed using a DBD donor, and 131 using DCD donors (Consort

diagram - Figure 1). DBDs were propensity score-matched 4:1 to DCDs to balance potential confounder bias associated with recipient age and diagnosis. Nearest-neighbor matching on the propensity score was performed using the software R (v4.0.3) and the "MatchIt" package(v4.3.0). Donor and recipient composition was compared between matched DCDs and DBDs, and between HR and non-HR recipients. Kruskal-Wallis and Chi-Square tests compared continuous and categorical characteristics between groups, respectively. Kaplan-Meier methods were used to compute survival estimates and 95% confidence intervals (CI). Undefined confidence bonds were denoted as not-estimable (NE). Log-rank tests compared survival distributions. P values less than 0.05 were considered statistically significant. Analyses were performed using the statistical software SAS(v9.4).

ISHLT Registry Datasets are available in:

https://ishlt.org/ishlt/media/documents/Registries/ISHLT_Registration_Data_Elements.xls

https://ishlt.org/ishlt/media/documents/Registries/ISHLT_Followup_Data_Elements.xls.

Double Lung Transplants in HR recipients – Propensity Matched Analysis

DCD donors were older than DBD donors, even though, based on age alone, both categories would still be considered as "ideal" donors. Also, DCD donors had longer ischemic time than DBDs (in the ISHLT Database, "ischemic time" means total organ ischemia time, which included cold and warm ischemic time). Results and additional analysis are available in Table 1. Within the sample, 240 (36.64%) patients died during

follow-up. There was no difference in survival between DCD and matched DBD recipients (Figure 2-A;p=0.1646). Median survival for DBD recipients was 5.6 years (95%CI:4.7-7.2). Median survival was not reached among DCD recipients. That is, more than 50% of DCD recipients survived to the end of the follow-up period. At the end of follow-up, DCD and matched DBD survival were 54% (95%CI:34-71) and 38% (95%CI:30-46), respectively. Composition of the DCD and matched DBD groups were similar (Supplementary Table S1).

Double Lung Transplants in DCD: Impact of HR Recipient

Compared to Non-HR, HR recipients less likely received organs from donors with a history of cigarette use (>20 pack/years). Furthermore, HR recipients were younger and more likely to be females (Supplementary Table S2). Within the sample, 376 (24.4%) patients died during the period of follow-up. There was no difference in survival between HR and non-HR recipients (Figure 2-B;p=0.9572). Median survival for non-HR DCD recipients was 9.4 years (95%CI:8.7-NE). As shown previously, median survival was not reached among HR DCD recipients. At the end of the follow-up, HR and non-HR DCD survival were 54% (95%CI:34-71) and 45% (95%CI:24-64), respectively.

Double Lung Transplants in DBD: Impact of HR Recipient

HR recipients more likely received lungs from younger donors and less commonly from donors with significant smoking history. In contrast, non-HR recipients were more

commonly matched to male donors. Also, HR recipients were younger, more likely females, had higher FEV1 (% prior to LTx), longer ischemic time, and less Six-minute walk test compared to non-HR recipients (Supplementary Table S3). Within the sample, 5317 (32.7%) patients died during the period of follow-up. Differently than DCD cohort, HR recipients had shorter survival (median 5.5 years, 95%CI:4.8-6.3) than non-HR recipients when using DBD lungs (median 7.3 years, 95%CI:7.2-7.6) (Figure 2-C; $p<0.0001$). At the end of follow-up, HR and non-HR DBD survival were 27% (95%CI:17-39) and 38% (95%CI:35-41), respectively.

This study demonstrates that HR recipients receiving DCD lungs have at least equivalent outcomes compared to recipients receiving DBD lungs. Interestingly, the adverse effect in survival seen in HR recipients was observed in DBD lungs but not in DCDs (lack of difference for DCDs may be due to power, considering sample size).

We recognize potential limitations inherent to a retrospective study evaluating a database that lacks granularity such as warm ischemic time, use of Ex Vivo Lung Perfusion, length of agonal time, and others. Also, no stratification into DCD Maastricht categories is available (ISHLT Database provides the information whether the donor was a DCD or not). However, based on literature and the infrequent practice of uncontrolled DCD, the vast majority of these donors are Maastricht Category III. Furthermore, since the analysis was performed in a univariate fashion, there may be confounding factors that may not been accounted for, even with the matched cohorts. For example, the significant effect seen here where DCD donors perform better than DBD in HR recipients may be biased by more experienced centers more commonly performing DCD LTx.

In conclusion, DCD LTx is appropriate for HR recipients, and maximum utilization of this organ pool should be accomplished. This data reinforces that DCD donors, when meeting quality criteria for transplantation, should not be considered as inferior or HR donors and should be used for any recipient type. Its use should be stimulated rather than restricted.

Author Contributions:

PARS - conception, design, data acquisition, analysis and interpretation, draft and review of the manuscript. PJZT – design, analysis, interpretation of data, revising the work, review of the manuscript. DMMN – interpretation of data, revising the work. BL – design of the work, analysis, and interpretation, review of the manuscript. MC - conception, design, analysis and interpretation, draft, and review of the manuscript. All authors have approved the final version of the manuscript.

Acknowledgments:

The authors would like to acknowledge the contribution of John Ryan, Statistical Project Manager, University of Pittsburgh.

Disclosure Statement:

The authors declare that they have no conflict of interest.

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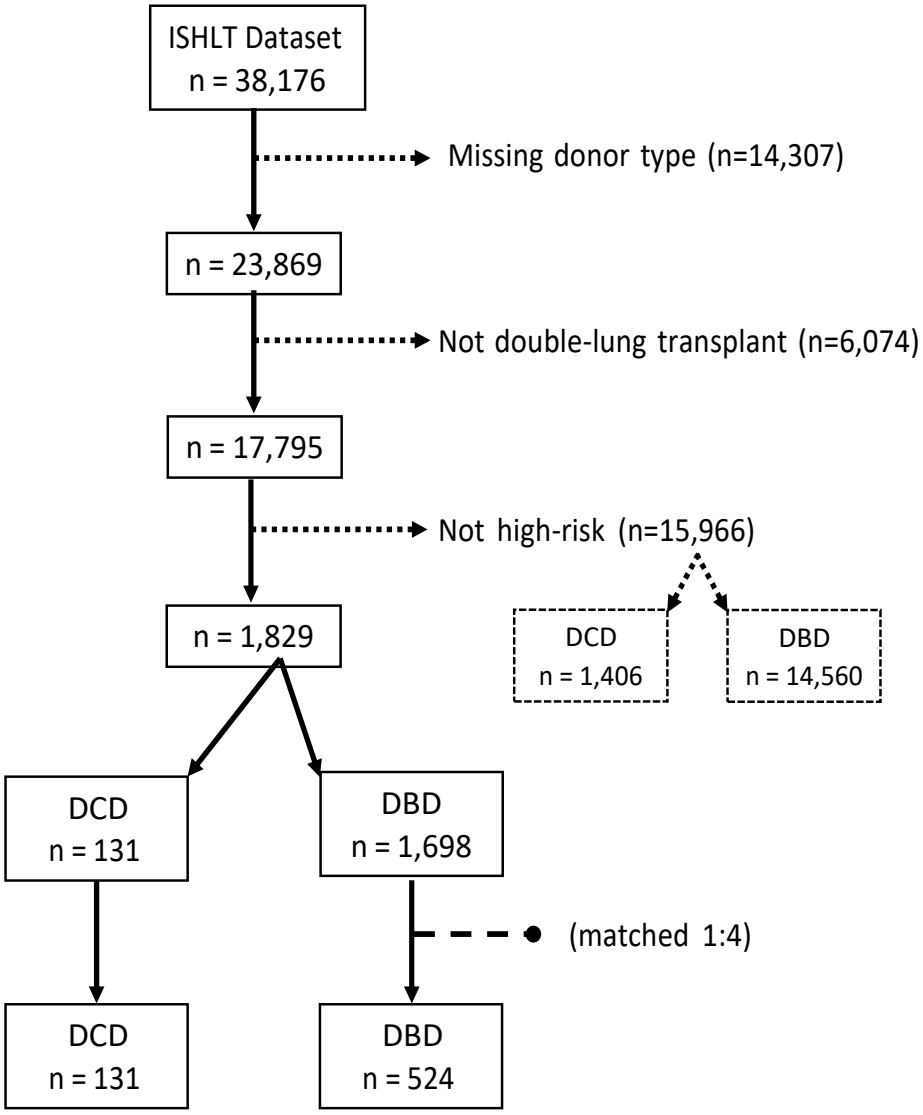

Figure 1 – Consort diagram

Table 1 - Univariate comparison of matched high-risk DCD and DBD donors. Data presented are mean (standard deviation) unless otherwise noted.

	DCD (N=131)	DBD (N=524)	Total (N=655)	p value
Donor age (years)				<0.0001[a]
mean (SD)	42.2 (14.6)	34.0 (13.8)	35.6 (14.3)	
Donor sex (male)				0.6942[b]
n (%)	68 (52.3%)	264 (50.4%)	332 (50.8%)	
Donor BMI (kg/m^2)				0.5803[a]
mean (SD)	26.6 (5.5)	26.2 (5.3)	26.2 (5.3)	
Donor history of cigarette use (>20 pack/years)				0.1663[b]
n (%)	2 (4.1%)	50 (10.2%)	52 (9.6%)	
Donor PO_2 (mmHg)				0.9458[a]
mean (SD)	376.4 (161.9)	377.8 (147.0)	377.6 (148.2)	
Recipient age (years)				0.8313[a]
mean (SD)	42.4 (14.9)	42.2 (14.8)	42.3 (14.8)	

Recipient sex (male)				0.7532[b]
n (%)	60 (45.8%)	232 (44.3%)	292 (44.6%)	
Recipient BMI (kg/m^2)				0.3618[a]
mean (SD)	22.7 (4.5)	23.4 (4.9)	23.3 (4.8)	
FEV1 (% prior to Tx)				0.4666[a]
mean (SD)	40.7 (24.1)	43.8 (25.8)	43.6 (25.7)	
Six-minute walk (meters)				0.1935[a]
mean (SD)	595.1 (532.9)	747.7 (507.6)	736.0 (510.4)	
Ischemic time (hours)				<0.0001[a]
mean (SD)	6.9 (2.0)	5.8 (1.8)	6.0 (1.9)	

[a]Kruskal Wallis [b]Chi-Square

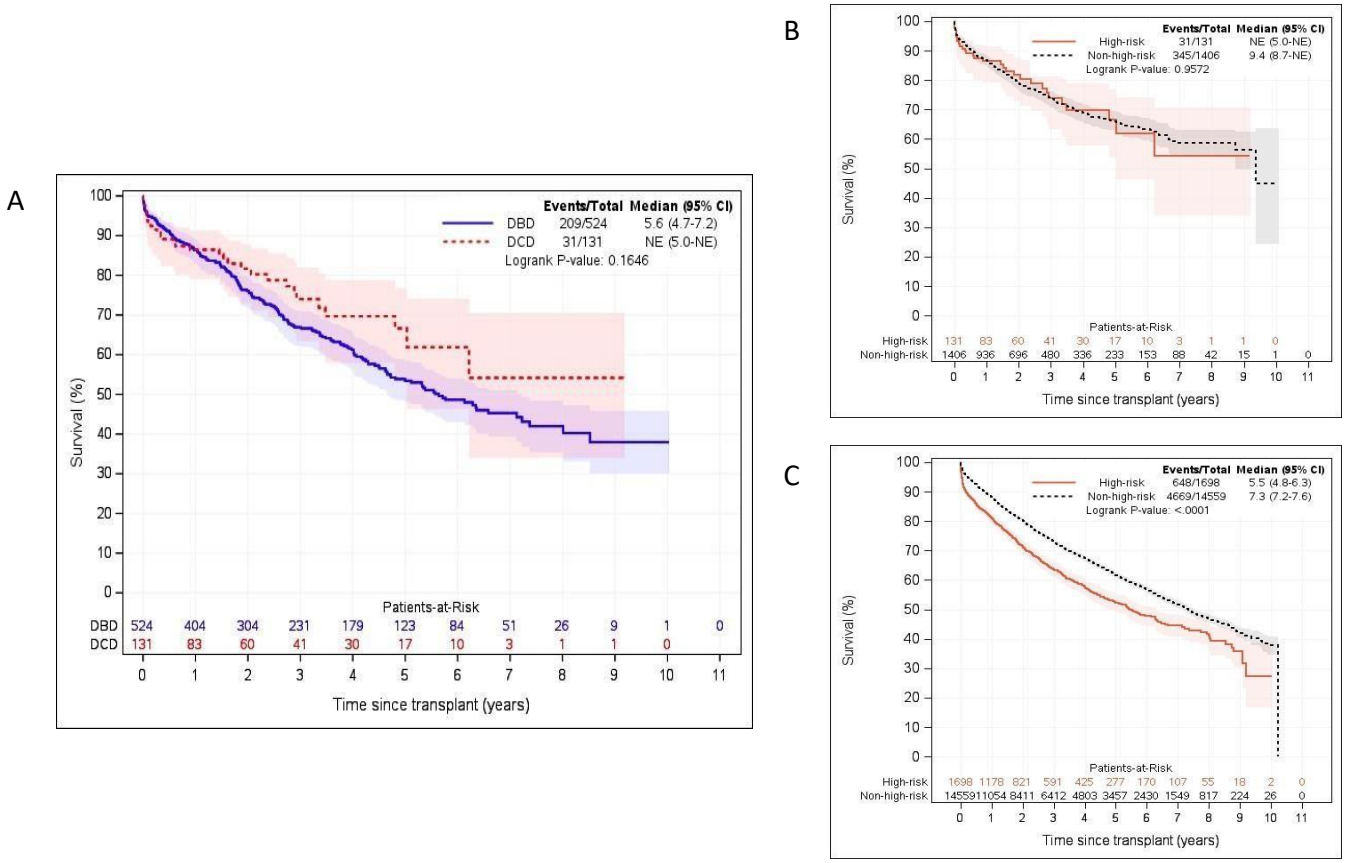

Figure 2 – A) High-Risk (HR) recipients receiving DCD lungs have at least equivalent outcomes compared to HR recipients receiving DBD lungs. When comparing the recipient profile, no adverse effect in survival was seen in HR recipients in DCD lungs (B) but identified in DBD lungs (C).

Os dados suplementares são enviados como um arquivo anexo no processo de submissão. São identificados abaixo:

Donation after Circulatory Death Donors in High-Risk Lung Transplant Recipients: an ISHLT Database Registry analysis

Authors: Pedro Augusto Reck dos Santos[a,f], Paulo José Zimermann Teixeira[b,f], Daniel de Messias Moraes Neto[c], Blake Langlais[d], Marcelo Cypel[e]

[a] Assistant Professor - Department of Cardiothoracic Surgery, Mayo Clinic, AZ, USA.

[b] Associate Professor of Medicine - Respirology - Department of Internal Medicine. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brasil.

[c] Clinical Assistant Professor – Department of Cardiothoracic Surgery, Stanford, CA, USA.

[d] Senior Biostatistician, Department of Quantitative Health Sciences, Mayo Clinic, AZ, USA.

[e] Professor of Surgery, Division of Thoracic Surgery. University of Toronto, University Health Network, Toronto, ON, Canada

[f] Programa de Pós-Graduação em Ciências da Saúde – Universidade Federal de Ciências da Saúde de Porto Alegre. Porto Alegre, RS, Brasil.

Supplementary Figures and Tables

Table of Contents:

Supplementary Table S1 – Composition of the DCD and DBD matched high-risk groups.

	DCD (N=131)	DBD (N=524)	Total (N=655)	p value
High-risk category, n (%)				0.1499[a]
ECMO	32 (24.4%)	108 (20.6%)	140 (21.4%)	
ECMO + IPAH	2 (1.5%)	16 (3.1%)	18 (2.7%)	
ECMO + Prev. Lung TX	0 (0.0%)	18 (3.4%)	18 (2.7%)	
IPAH	49 (37.4%)	210 (40.1%)	259 (39.5%)	
Prev. Lung TX	48 (36.6%)	172 (32.8%)	220 (33.6%)	
ECMO at TX				0.7914[a]
n (%)	34 (26.0%)	142 (27.1%)	176 (26.9%)	
Previous Lung TX				0.9353[a]
n (%)	48 (36.6%)	190 (36.3%)	238 (36.3%)	
IPAH				0.3843[a]
n (%)	51 (38.9%)	226 (43.1%)	277 (42.3%)	

[a]Chi-Square

Supplementary Table S2 - Univariate comparison of high-risk versus non-high-risk DCD recipients. Data presented are mean (standard deviation) unless otherwise noted.

	High-risk (N=131)	Non-high-risk (N=1406)	Total (N=1537)	p value
Donor age (years)				0.1798[a]
mean (SD)	42.2 (14.6)	43.9 (15.6)	43.7 (15.5)	
Donor sex (male)				0.2555[b]
n (%)	68 (52.3%)	808 (57.5%)	876 (57.0%)	
Donor BMI (kg/m^2)				0.2287[a]
mean (SD)	26.6 (5.5)	25.9 (5.5)	25.9 (5.5)	
Donor history of cigarette use (>20 pack/years)				0.0029[b]
n (%)	2 (4.1%)	125 (22.0%)	127 (20.6%)	
Donor PO_2 (mmHg)				0.2771[a]
mean (SD)	376.4 (161.9)	353.5 (153.8)	355.3 (154.4)	
Recipient age (years)				<0.0001[a]
mean (SD)	42.4 (14.9)	51.0 (14.0)	50.3 (14.3)	

Recipient sex (male)				0.0015[b]
n (%)	60 (45.8%)	845 (60.1%)	905 (58.9%)	
Recipient BMI (kg/m^2)				0.1343[a]
mean (SD)	22.7 (4.5)	23.5 (4.3)	23.5 (4.3)	
FEV1 (% prior to Tx)				0.4936[a]
mean (SD)	40.7 (24.1)	37.0 (21.2)	37.3 (21.5)	
Six-minute walk (meters)				0.9684[a]
mean (SD)	595.1 (532.9)	566.6 (471.2)	568.4 (474.7)	
Ischemic time (hours)				0.1616[a]
mean (SD)	6.9 (2.0)	6.6 (2.2)	6.7 (2.2)	

[a]Kruskal Wallis [b]Chi-Square

Supplementary Table S3 – Univariate comparison of high-risk versus non-high-risk DBD recipients. Data presented are mean (standard deviation) unless otherwise noted.

	High-risk (N=1698)	Non-high-risk (N=14560)	Total (N=16258)	p value
Donor age (years)				0.0039[a]
mean (SD)	34.7 (15.4)	36.0 (15.2)	35.8 (15.3)	
Donor sex (male)				0.0001[b]
n (%)	880 (51.8)	8292 (57.0)	9172 (56.4)	
Donor BMI (kg/m^2)				0.1471[a]
mean (SD)	25.7 (5.5)	25.9 (5.5)	25.9 (5.5)	
Donor history of cigarette use (>20 pack/years)				0.0144[b]
n (%)	155 (9.9)	1584 (12.0)	1739 (11.8)	
Donor PO_2 (mmHg)				0.3533[a]
mean (SD)	371.3 (147.3)	376.5 (146.6)	376.0 (146.7)	
Recipient age (years)				<0.0001[a]
mean (SD)	41.9 (16.3)	51.6 (15.0)	50.5 (15.5)	
Recipient sex (male)				<0.0001[b]
n (%)	823 (48.5)	8306 (57.1)	9129 (56.2)	

Recipient BMI (kg/m^2)				<0.0001[a]
mean (SD)	23.5 (5.3)	24.5 (4.8)	24.3 (4.8)	
FEV1 (% prior to Tx)				<0.0001[a]
mean (SD)	41.1 (23.3)	36.6 (20.4)	37.1 (20.7)	
Six-minute walk (meters)				0.0003[a]
mean (SD)	696.8 (530.9)	760.3 (477.2)	754.7 (482.5)	
Ischemic time (hours)				<0.0001[a]
mean (SD)	5.9 (1.8)	5.5 (1.7)	5.6 (1.7)	

[a]Kruskal Wallis [b]Chi-Square

Journal Pre-proof

Donation after Circulatory Death Donors in High-Risk Recipients Undergoing Bilateral Lung Transplantation: an ISHLT Database Registry analysis

Pedro Augusto Reck dos Santos , Paulo José Zimermann Teixeira , Daniel Messias de Moraes Neto , Blake Langlais , Marcelo Cypel

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Reference: HEALUN 7592

To appear in: *Journal of Heart and Lung Transplantation*

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5. Considerações Finais

O processo de Doação Após Morte Circulatória é importante para aumentar o número de doadores disponíveis e salvar vidas. Neste sentido, contribuímos para uma discussão inicial sobre este tópico no Brasil, aplicado ao Transplante Pulmonar. Existe a necessidade (pois o número de pacientes só aumenta) e certamente há o interesse. Porém há barreiras como a logística, a própria legislação do nosso País, além de conceitos religiosos que algumas vezes são difíceis de serem aceitos - como a retirada do suporte de vida de um paciente gravemente enfermo, sem chance de recuperação clínica.

Além disso, os achados reportados para a publicação internacional contribuirão para aumentar as evidências sobre a segurança do uso deste tipo de doação. O fato de Doadores Após Morte Circulatória terem resultados equivalentes (senão melhores) mesmo para os recipientes mais complexos, quando comparados aos Doadores Após Morte Encefálica (considerados o padrão “ouro” em todo o mundo) que demonstramos nesta pesquisa contribuirá ainda mais para a aceitação desta modalidade de doação. Doadores Após Morte Circulatória podem e devem ser considerados para qualquer tipo de receptor. E não devem ser considerados como doadores de alto risco ou doadores de qualidade inferior ou questionável. Seu uso deve ser estimulado e disseminado cada vez mais.

6. Dados suplementares

6.1 Processo de submissão

6.1.1 Jornal Brasileiro de Pneumologia

O processo de submissão de artigo para o Jornal Brasileiro de Pneumologia estão disponíveis no site:

http://www.jornaldepneumologia.com.br/journal/9

6.1.2 Journal of Heart and Lung Transplantation

O processo de submissão de artigo para o Jornal Brasileiro de Pneumologia estão disponíveis no site:

https://www.editorialmanager.com/jhlt/default1.aspx

6.2 Datasets – ISHLT Databases

Os dados utilizados para a pesquisa realizada e publicada no Journal of Heart and Lung Transplantation estão disponíveis nos seguintes links:

https://ishlt.org/ishlt/media/documents/Registries/ISHLT_Registration_Data_Elements.xls

https://ishlt.org/ishlt/media/documents/Registries/ISHLT_Followup_Data_Elements.xls.

Tais dados somente podem ser obtidos mediante solicitação para uso de dados para pesquisa científica. Esta solicitação é enviada para a ISHLT e discutida com o grupo de Bioestatística. A solicitação enviada consta abaixo:

ISHLT INTERNATIONAL THORACIC ORGAN TRANSPLANT REGISTRY
DATA USE AGREEMENT (DUA)

The ISHLT International Thoracic Organ Transplant (TTX) Registry will provide the individual identified below (Requestor) with the non-identifiable data derived from the ISHLT TTX Registry database, **solely for the use specified in the initial data request.**

Every effort has been made to exclude from the computer files identifying information on individual patients and facilities. Certain demographic information such as gender, age, etc. are provided for research purposes but may not be used to attempt to identify individuals or institutions.

In order for the ISHLT TTX Registry to provide a de-identified or another version of data to you, it is necessary that you agree to the following provisions.

1. DATA USE and DATA CONFIDENTIALITY

A. You will neither use **nor permit others** to use the data in any way other than for statistical reporting and analysis.

B. You will neither release **nor permit others** to release the files or data therein to any person (including media and subcontractors) except with the written approval of the ISHLT TTX Registry.

C. You will not present and/or publish data in which an individual or facility may be identifiable.

D. You will not attempt to sell this data set directly **nor permit others** to sell the data set.

E. You will neither attempt **nor permit others** to attempt to combine or link the data with individually identified records in another database or source of information or to learn the identity of any person or facility whose data is contained in the supplied file(s).

F. If the identity of any person or facility is discovered, then you must do the following: a) you will not use this knowledge in any way, b) you will notify the ISHLT TTX Registry of the incident.

G. If accessing the data from a centralized location on a time-sharing computer system or LAN with any statistical package, you will not share your logon name and password with any other individuals. You will also not allow any other individuals to use your computer account after you have logged on with your logon name and password.

H. As Primary Investigator, you certify that you are responsible for ensuring any staff assigned to this project with access to these data likewise will follow all of these provisions.

I. As Primary Investigator, you certify that you have appropriate institutional review board/ethics committee (or equivalent) approval or exemption for your proposed study.

J. You will respond to queries from the ISHLT TTX Registry for progress reports on the study and compliance with the terms of this agreement.

2. **RULES FOR PRESENTATION AND PUBLICATION of results based on ISHLT TTX Registry analyses**

A. **All abstracts, manuscripts and presentations must be reviewed by the ISHLT TTX Registry *before* submission. Abstract, manuscripts and presentations must be provided for review at least 14 days prior to presentation/submission.**

B. ISHLT TTX Registry Associate Medical Director may be assigned to your project to assist you along the completion of the project and preparation/review of the resulting abstract/manuscript prior to submission. The Registry associate director is well versed in the ISHLT TTX Registry structure and can provide important contributions and feedback with the goal of maximizing the project quality and validity. The assigned associate director must be involved in the project from the start, and if justified by his/her contributions, should be listed as coauthor on resulting work.

C. **All abstracts must be submitted for the ISHLT Annual Meeting and manuscripts must be submitted to the Journal of Heart and Lung Transplantation. If there is an important reason for submitting a sub-study of the main project for presentation or publication elsewhere, an approval must be obtained from the ISHLT TTX Registry director.**

D. All publications using the released data will contain the standard disclaimer, "The data have been provided by the ISHLT Thoracic Organ Transplant Registry. The interpretation and reporting of these data are the responsibility of the user(s)"

E. All publications or graphic presentations will note the effective date of the data. For example, "Based on ISHLT Thoracic Organ Transplant Registry data as of April 6, 2018, ..."

If a requestor does not comply with the any requirements in this agreement, the permissions granted for this DUA ma be revoked and the ISHLT TTX Registry may withhold data from future data requests from the investigator and his/her institution.

Project title: Trends in DCD Lung Transplantation over time: an ISHLT Registry Analysis

My signature indicates that I agree to comply with the above stated provisions.

Signature PAR

Name Pedro Augusto Reck dos Santos

Date Aug 22, 2019

Institution Name University of Pittsburgh Medical Center.

Street Address 200 Lothrop St, Suite C922

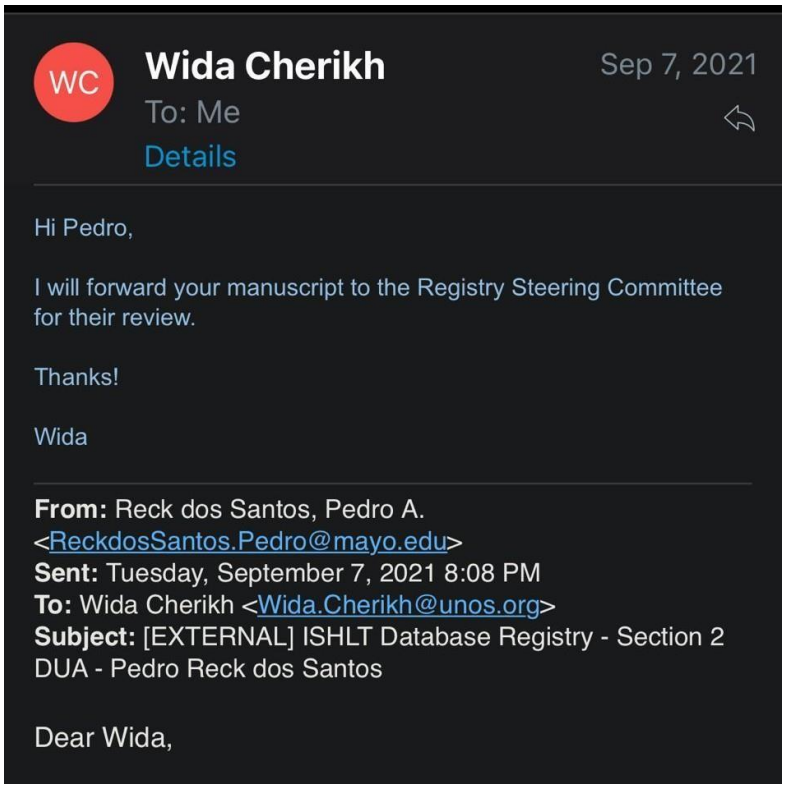
State/Country/Postal Code PA / USA / 15213

Phone Number (including country code) +1 4123989072

Email reck dos santos @upmc.edu

Após a pesquisa ser realizada, o arquivo e os dados precisam ser novamente enviados para a ISHLT para revisão e aprovação.

Abaixo, a comunicação realizada com a ISHLT para revisão dos dados antes da submissão.



WC

Wida Cherikh Sep 7, 2021

To: Me

Details

Hi Pedro,

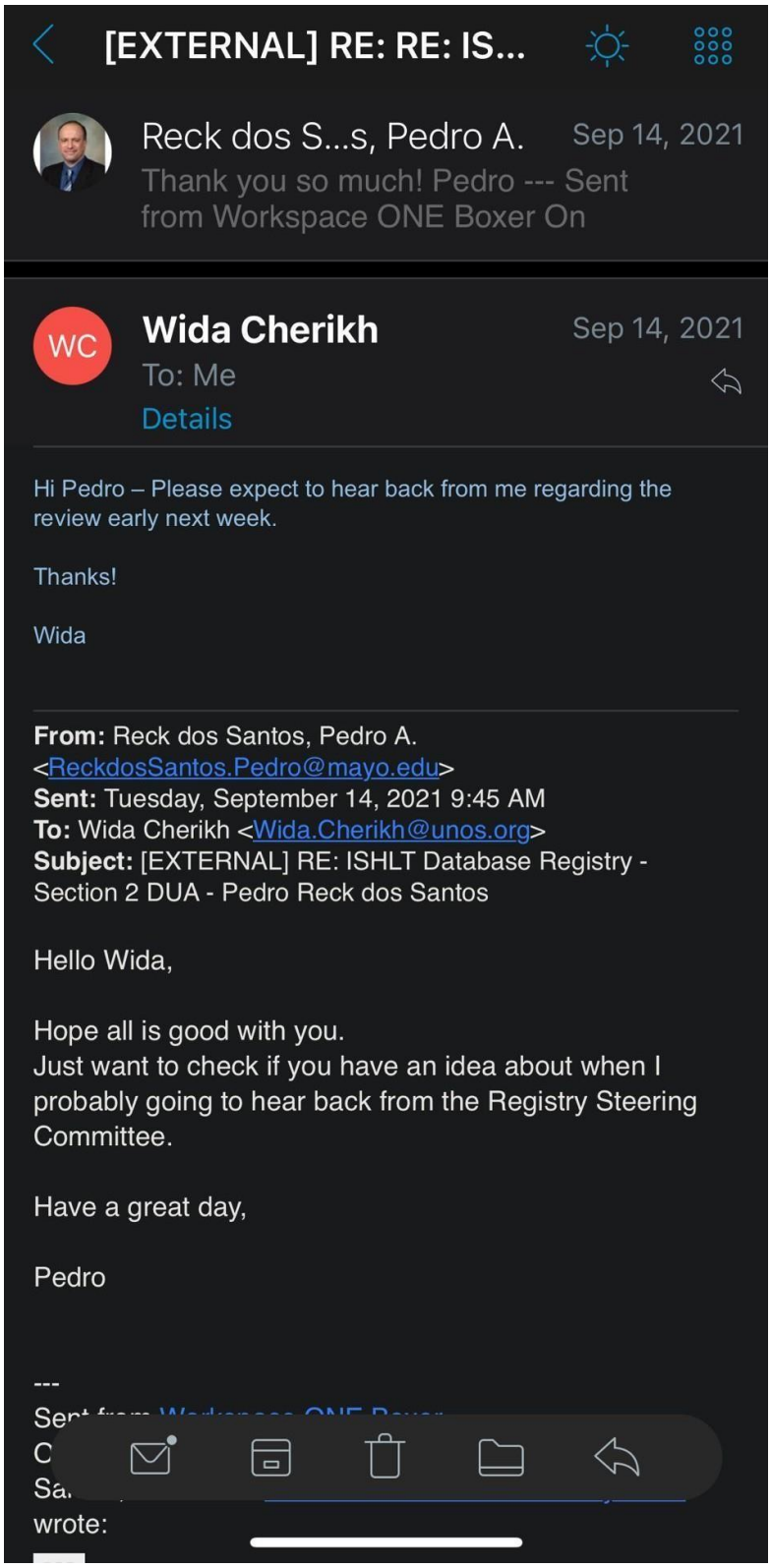
I will forward your manuscript to the Registry Steering Committee for their review.

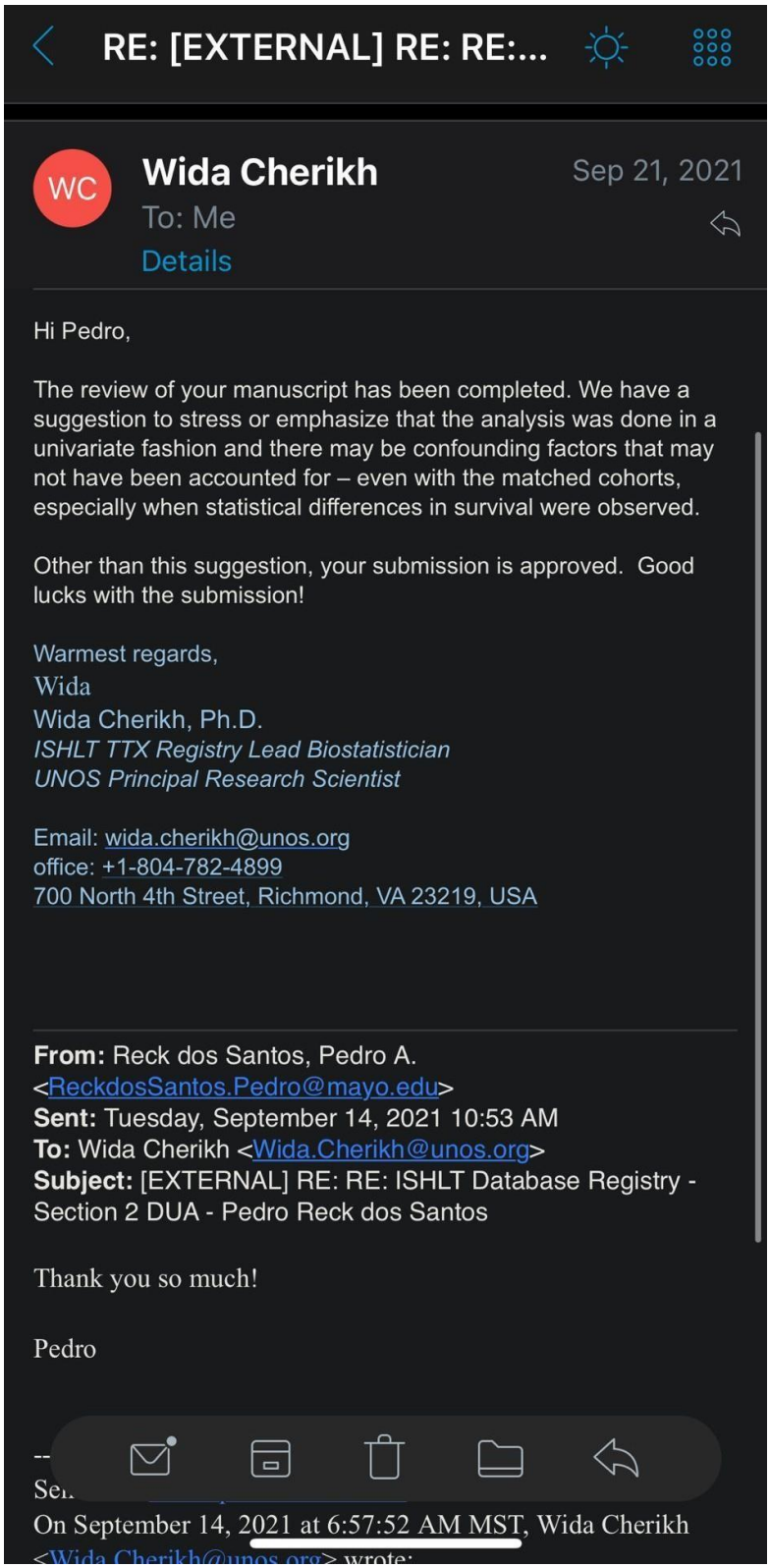
Thanks!

Wida

From: Reck dos Santos, Pedro A. <ReckdosSantos.Pedro@mayo.edu>
Sent: Tuesday, September 7, 2021 8:08 PM
To: Wida Cherikh <Wida.Cherikh@unos.org>
Subject: [EXTERNAL] ISHLT Database Registry - Section 2 DUA - Pedro Reck dos Santos

Dear Wida,


[EXTERNAL] RE: RE: IS...
Reck dos S...s, Pedro A.
Sep 14, 2021
Thank you so much! Pedro --- Sent from Workspace ONE Boxer On
WC
Wida Cherikh
Sep 14, 2021
To: Me
Details
Hi Pedro – Please expect to hear back from me regarding the review early next week.
Thanks!
Wida
From: Reck dos Santos, Pedro A. <ReckdosSantos.Pedro@mayo.edu>
Sent: Tuesday, September 14, 2021 9:45 AM
To: Wida Cherikh <Wida.Cherikh@unos.org>
Subject: [EXTERNAL] RE: ISHLT Database Registry - Section 2 DUA - Pedro Reck dos Santos
Hello Wida,
Hope all is good with you.
Just want to check if you have an idea about when I probably going to hear back from the Registry Steering Committee.
Have a great day,
Pedro
---
wrote:



RE: [EXTERNAL] RE: RE:...

WC **Wida Cherikh** Sep 21, 2021
To: Me
Details

Hi Pedro,

The review of your manuscript has been completed. We have a suggestion to stress or emphasize that the analysis was done in a univariate fashion and there may be confounding factors that may not have been accounted for – even with the matched cohorts, especially when statistical differences in survival were observed.

Other than this suggestion, your submission is approved. Good lucks with the submission!

Warmest regards,
Wida
Wida Cherikh, Ph.D.
ISHLT TTX Registry Lead Biostatistician
UNOS Principal Research Scientist

Email: wida.cherikh@unos.org
office: +1-804-782-4899
700 North 4th Street, Richmond, VA 23219, USA

From: Reck dos Santos, Pedro A. <ReckdosSantos.Pedro@mayo.edu>
Sent: Tuesday, September 14, 2021 10:53 AM
To: Wida Cherikh <Wida.Cherikh@unos.org>
Subject: [EXTERNAL] RE: RE: ISHLT Database Registry - Section 2 DUA - Pedro Reck dos Santos

Thank you so much!

Pedro

--
Se
On September 14, 2021 at 6:57:52 AM MST, Wida Cherikh
<Wida.Cherikh@unos.org> wrote: