



HAL
open science

How We Would Treat Our Own Lung Transplantation: A Multidisciplinary and International Perspective

Archer K. Martin, Anna Katja Reed, Konrad Hoetzenecker, Julien Fessler

► To cite this version:

Archer K. Martin, Anna Katja Reed, Konrad Hoetzenecker, Julien Fessler. How We Would Treat Our Own Lung Transplantation: A Multidisciplinary and International Perspective. *Journal of Cardiothoracic and Vascular Anesthesia*, 2023, 37 (11), pp.2207-2214. 10.1053/j.jvca.2023.07.042 . hal-04229531

HAL Id: hal-04229531

<https://hal.science/hal-04229531>

Submitted on 23 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Journal of Cardiothoracic and Vascular Anesthesia

How We Would Treat Our Own Lung Transplantation: A Multidisciplinary and International Perspective

--Manuscript Draft--

Manuscript Number:	
Article Type:	Special Article
Keywords:	Lung transplantation; ECMO; multidisciplinary team; prehabilitation; analgesia; enhanced recovery; end-stage lung disease
Corresponding Author:	Archer Kilbourne Martin, M.D. Mayo Clinic Jacksonville, FL UNITED STATES
First Author:	Archer Kilbourne Martin, M.D.
Order of Authors:	Archer Kilbourne Martin, M.D. Anna Katja Reed, MD, PhD Konrad Hoetzenecker, MD, PhD Julien Fessler, MD
Abstract:	Lung transplantation is the ultimate treatment for end-stage lung disease (ESLD) arising from a wide variety of etiologies. This manuscript will focus on selected aspects of a theoretical perioperative lung transplantation plan, highlighting data-driven and theoretical techniques we would employ if we were the index patient undergoing surgery. Beginning with looking for a transplant center utilizing internet search, patient advocacy organizations, and artificial intelligence guidance, we lay out a course for multidisciplinary care throughout the entire patient journey, ending with ideal approaches to recovery 6-months post-transplantation. While the index case will focus on a theoretical patient with pulmonary fibrosis, the principles of general management will be applicable across the entire spectrum of patients with ESLD presenting for lung transplantation.

Dear Professor Kaplan:

On behalf of my co-authors, I am submitting this special article at the invitation of Dr. Gabor Erdoes regarding the following article in the *Journal of Cardiothoracic and Vascular Anesthesia*, "How We Would Treat Our Own Lung Transplantation: A Multidisciplinary and International Perspective". All authors agree and are responsible for the enclosed manuscript.

Thank you for your consideration of this special article submission to the *Journal of Cardiothoracic and Vascular Anesthesia* within the "How We Would Treat" series.

Dr. Archer Kilbourne Martin, M.D.

Dr. Anna Katja Reed, M.D., PhD

Dr. Konrad Hoetzenecker, M.D., PhD

Dr. Julien Fessler, M.D.

Statements of funding, Declarations of Interest, and Acknowledgements: No funding sources to declare. The authors JF, AKR, and KH have no interests to declare. AKM serves on the Scientific Advisory Board of Attgeno AB, with all consulting fees paid to Mayo Clinic.

Title of article: How We Would Treat Our Own Lung Transplantation: A Multidisciplinary and International Perspective

Full names of authors in preferred order: Archer Kilbourne Martin, MD^a, Anna Katja Reed, MD, PhD^b, Konrad Hoetzenecker, MD, PhD^c, Julien Fessler, MD^d

Author title and institution:

- A) Division of Cardiovascular and Thoracic Anesthesiology, Mayo Clinic College of Medicine and Science, Jacksonville, Florida
- B) Department of Cardiothoracic Transplantation and Mechanical Support, Harefield Hospital, Royal Brompton & Harefield Hospitals, Part of Guy's and St Thomas' NHS Foundation Trust & Imperial College, London, UK
- C) Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria
- D) Department of Anesthesiology, Hôpital Foch, Suresnes, France, and Université Versailles-Saint-Quentin-en-Yvelines, Versailles, France

Corresponding Author: Archer Kilbourne Martin, MD. Division of Cardiovascular and Thoracic Anesthesiology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida, USA. 32224. martin.archer@mayo.edu

Statements of funding, Declarations of Interest, and Acknowledgements: No funding sources to declare. The authors JF, AKR, and KH have no interests to declare. AKM serves on the Scientific Advisory Board of Attgeno AB, with all consulting fees paid to Mayo Clinic.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Abstract:

Lung transplantation is the ultimate treatment for end-stage lung disease (ESLD) arising from a wide variety of etiologies. This manuscript will focus on selected aspects of a theoretical perioperative lung transplantation plan, highlighting data-driven and theoretical techniques we would employ if we were the index patient undergoing surgery. Beginning with looking for a transplant center utilizing internet search, patient advocacy organizations, and artificial intelligence guidance, we lay out a course for multidisciplinary care throughout the entire patient journey, ending with ideal approaches to recovery 6-months post-transplantation. While the index case will focus on a theoretical patient with pulmonary fibrosis, the principles of general management will be applicable across the entire spectrum of patients with ESLD presenting for lung transplantation.

Keywords: Lung transplantation; ECMO; multidisciplinary team; prehabilitation; analgesia; enhanced recovery; end-stage lung disease;

Introduction:

The present manuscript aims to provide a review about selected aspects of the perioperative course of my own (AKM) theoretical transplantation, such as the selection of a world-renowned multidisciplinary team (AKR, KH, JF), optimal transplantation center, preoperative preparation of the journey, the adaptation of the intraoperative management of the specific end-stage lung disease (ESLD), pain management, blood management, utilization of extracorporeal life support (ECLS), and application of an enhanced recovery after surgery program. To illustrate this approach, the authors will use an index case that provides opportunity to examine a specific ESLD¹ and its various considerations throughout the perioperative course.

The management of a lung transplant recipient is particularly challenging due to the complex clinical situations requiring multidisciplinary coordination that can occur throughout the entire perioperative period. Adding to this challenge is the scarce evidence available to guide the multidisciplinary team (MDT) because of the difficulty of conducting high-quality, large volume studies examining lung transplantation. This research challenge results in most recommendations stemming from retrospective studies or database analyses that do not allow causal relationships to be established. Furthermore, the vast majority of these studies are single center, resulting in significant influence of the practices of each center and the profiles of the recipients recruited in each center.

Index Case:

The patient is a 40-year-old male with idiopathic pulmonary fibrosis who presents for bilateral lung transplantation. His baseline oxygen requirement has been steady over the past few months at 4 L/min, however, he has had an increase over the past 2 weeks in oxygen requirements on exertion to 8 L/min. Concomitantly, he has had a consistent decrease in functional capacity, with occasional orthopnea in the past few weeks. His past medical history is significant for gastroesophageal reflux. His transthoracic echocardiogram from 6 months ago showed a mildly increased right ventricle with intact systolic function, left ventricular ejection fraction of 65%, and mild tricuspid regurgitation. A right heart catheterization performed only a couple of days ago showed a pulmonary arterial pressure of 38/18 (mean 25), pulmonary capillary wedge pressure of 5 mm Hg, and calculated 4.2 Woods

1
2
3
4 Units. His current vital signs are as follows: heart rate 95, systemic blood pressure 122/59, respiratory rate 24,
5
6 oxygen saturation 94%.
7
8
9

10 **Review of the Clinical Context**

11 12 13 *How We Would Choose our Lung Transplantation Center*

14
15
16
17
18 Determining the selection of one's lung transplantation center focuses on many different factors including
19 personal preference, social support network, existing medical relationships, and expertise of the local center.
20 Utilizing online search, patient advocacy organizations, and artificial intelligence tools, we would prioritize the
21 foundational principles of selection for our theoretical center including the center outcomes and philosophy of care.
22 Centers are often judged on reported mortality outcomes, but a deeper theoretical evaluation would include a
23 composite assessment of long-term outcomes, rates of primary graft dysfunction (PGD), perioperative morbidity
24 related to complications, quality-of-life scores, return to work rates, and MDT philosophy of lung transplantation
25 care. Yang et al recently examined the relationship between 1-year survival outcome and lung transplantation center
26 volume.² The retrospective study of the United Network for Organ Sharing (UNOS) database examined over 10,000
27 patients at 71 transplant centers. Increasing transplant center volume was associated with improved 1-year survival
28 outcomes (hazard ratio [HR] 0.989, 95% confidence interval [CI], 0.980 to 0.999 per case), but no benefit was
29 observed once a center had crossed 33 lung transplantations per year.² Beyond 1-year survival metrics, our lung
30 transplantation center would also be evaluated on the composite outcomes of morbidity. PGD, most recently defined
31 by the International Society for Heart and Lung Transplantation (ISHLT) in 2017, is a multifactorial perioperative
32 syndrome (graded within 72 hours after transplantation) that is associated with increased rates of morbidity,
33 mortality, and chronic rejection when high grade at 72 hours.³ PGD, in combination with perioperative morbidity
34 related to procedural complications, should be minimized through careful attention to anesthetic and surgical
35 technique.⁴ In order to achieve a decrease in composite morbidity, our transplantation center would have an MDT
36 approach that would focus on improving communication⁵, coordinating specialized team-based training⁶, implement
37 the latest principles in resource stewardship⁷, and ultimately improving outcomes.⁸
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 Practical implementation of this diverse strategy within our lung transplantation center of choice would
5 start in the preoperative phase, with a tailored MDT approach to the recipient's etiology of ESLD^{9, 10} to include
6 optimal donor/recipient matching, short waiting list times, ex-vivo lung perfusion capabilities, pre-operative ECLS
7
8 bridging planning, physiotherapy, psychosocial resources, frailty assessment, and utilization of complementary
9
10 medicine.
11
12
13
14
15
16
17

18 *Preoperative Preparation for the Journey – Frailty Assessment and Improvement Through Pre-habilitation*
19
20
21
22

23 Pulmonologists are the team leads in charge of the patient optimization prior to official listing for lung
24 transplantation. One of the key assessments of frailty pre-listing is the utilization of multiparametric scores
25 reflecting a composite of physical, cognitive and social factors that quantify patient vulnerability to stressors that
26 result from an accumulation of physiologic deficits across multiple interrelated systems.¹¹ Physical assessment is
27 predominantly based on clinical markers such as sarcopenia¹², physical weakness, slow locomotion, easy
28 fatigability, and low baseline levels of physical activity. Such scales predict death during enrollment, early
29 complications, disability, poor quality of life, and postoperative mortality.^{13, 14}
30
31
32
33
34
35
36
37

38 The most commonly used tests are the short physical performance battery (SPPB)^{13, 15} and the Fried frailty
39 phenotype (FFP).¹⁶ The latter integrates the respiratory component of the disease, limiting physical capacities.
40 Moreover, this evaluation must be adapted to the heterogeneity of the candidates¹⁷ and the pathology.¹⁸ Interestingly,
41 Singer et al have developed a 3-candidate scale measure incorporating readily available clinical data, then adding
42 muscle mass, and finally, research-grade biomarkers in a multicentric cohort. They found that their lung transplant
43 frailty scale (LT-FS) model exhibited superior construct and predictive validity compared to the SPPB and FFP.
44 Thus, we choose the LT-FS model to assess our index patient for frailty and prepare him for pre-habilitation.
45
46
47
48
49
50
51
52

53 Our patient's frailty assessment must also make it possible to identify factors that can be reversed by pre-
54 habilitation programs.¹⁵ The aims of our assessment are to identify impairments and provide interventions that
55 increase baseline functional level, enhance quality of life, and provide psychological support to improve
56
57
58
59
60
61
62
63
64
65

1
2
3
4 repeated over time and consider the dynamic notion of frailty. Once evaluated with LT-FS, we would employ the
5
6 Toronto pre-habilitation program to increase our index patient's chances of having a positive outcome.¹⁹ Pre-
7
8 habilitation exercise programs should follow the 'FITT' principle, consisting of the cornerstones of frequency,
9
10 intensity, time (duration), and type of exercise. The use of adjunct technology to objectively track exercise progress,
11
12 such as accelerometers, would be utilized for our index patient.²⁰ Finet et al showed that such devices are feasible in
13
14 thoracic surgery and could encourage patients in a physical reconditioning program to clearly predefined goals.^{21, 22}
15
16 The multi-modal pre-habilitation program should also include nutritional optimization and psychological well-
17
18 being.²³
19
20

21 In lung transplantation, the anesthesiologist is an active stakeholder at an advanced stage of this preparation
22
23 phase, particularly during the synthesis of all the preoperative assessments and MDT decision concerning
24
25 perioperative strategy. A recent study discussed the importance of the preoperative anesthesia consultation to discuss
26
27 the different stages of a lung transplantation and initiate the appropriate complementary techniques to aid the
28
29 recipient during the potentially painful events related to the procedure. This holistic engagement provides the
30
31 opportunity to make the patient an actor in their own care and provides them various tools to adapt to their own
32
33 personal strategy including self-hypnosis, sophrology, relaxation, or transcutaneous electrical stimulation.²⁴ While
34
35 their study was not designed²⁵ to demonstrate the effectiveness of this strategy on pain or quality of life, we would
36
37 decide to utilize it for our index patient as a complementary strategy within our comprehensive pre-habilitation
38
39 program.
40
41

42 Finally, psychosocial pre-habilitation based on supportive behavioral therapies and improved mental
43
44 wellbeing have been shown to improve outcomes in cancer and reduce postoperative chronic pain.²⁶ For example, in
45
46 this present case, the index patient would choose to enter the operating room in a calm and benevolent atmosphere,
47
48 where the team would play his preferred choice of music: Zuill Bailey's rendition of Bach's Cello Suite No. 1
49
50 Prelude in G Major. This choice highlights the importance of tailoring even the most minute details of the
51
52 prehabilitation plan to the individual patient's objective disease and subjective preferences by the MDT.
53
54
55
56

57 *From Bedside to Operating Room: Pre-Anesthetic Evaluation and Induction Adapted to End-Stage Lung Disease*
58
59
60
61
62
63
64
65

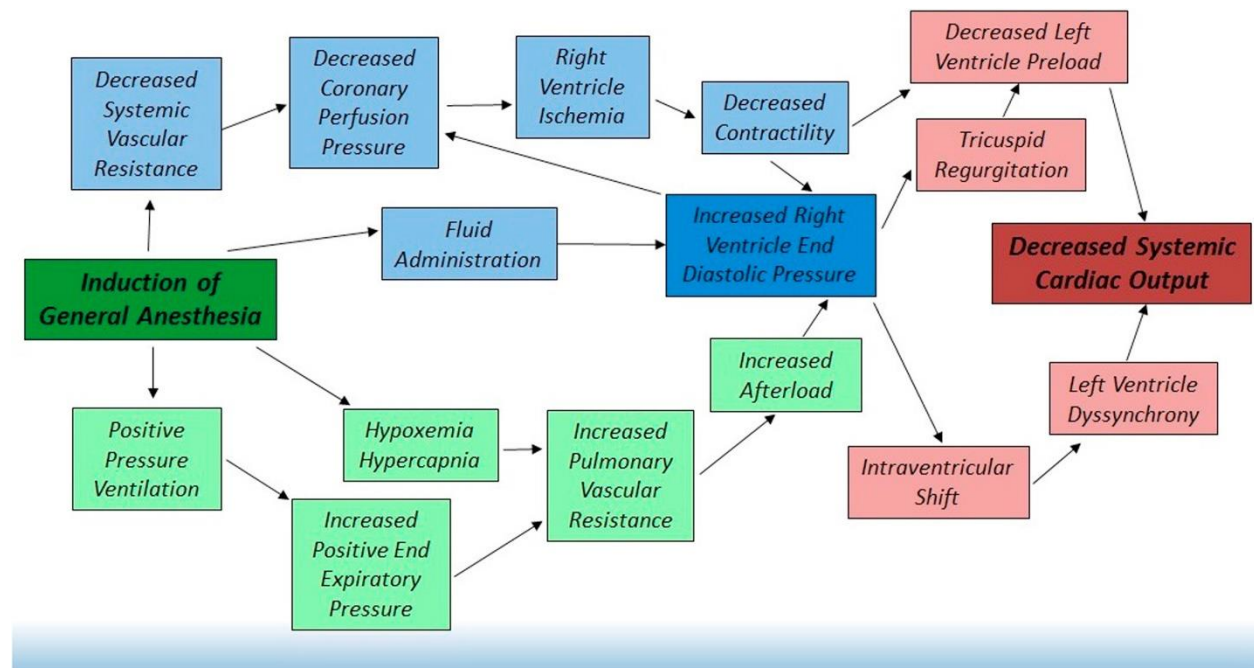
1
2
3
4 Our index case patient suffers from idiopathic pulmonary fibrosis (IPF), which is a disease process with
5
6 unique comorbidities to consider when evaluating for an anesthetic.^{9, 10} Prior to evaluating the patient, the
7
8 anesthesiologist should review the history and preoperative diagnostic work-up for signs of IPF-related co-
9
10 morbidities including gastroesophageal reflux, gastroesophageal dysmotility, coronary artery disease, right
11
12 ventricular dysfunction, or signs of adhesions on preoperative thoracic imaging.^{9, 10} Combining these factors as well
13
14 as published predictors for intraoperative course related to recipient ESLD should inform the anesthesiologists'
15
16 discussion with the patient in the preoperative area. Data have shown that cystic fibrosis (CF) and chronic
17
18 obstructive pulmonary disease/emphysema (CE) have a simpler intraoperative journey, leading to an increased
19
20 likelihood in extubation in the operating room as compared to IPF patients, with IPF patients also having a higher
21
22 incidence of unplanned intraoperative and postoperative extracorporeal membrane oxygenation (ECMO).²⁷
23
24 Preparing for an informed discussion with the patient, one should consider discussing the entire range of
25
26 possibilities, ranging from a fast-track extubation to a prolonged ECMO course.²⁸
27
28

29
30 One of the primary aspects of the clinical exam is to determine the impact of the etiology of ESLD on the
31
32 function of the cardiopulmonary unit. Our index patient's history suggests numerous things that point towards a
33
34 relatively acute decline in cardiopulmonary function in the past several weeks – decreased functional capacity,
35
36 increased supplemental oxygen requirements, worsening orthopnea, and elevated pulmonary arterial pressures on
37
38 the recent right heart catheterization. These recently obtained clinical data must be considered within the temporal
39
40 context of the transthoracic echocardiogram, which was performed 6 months prior to the hospitalization. Abu et al
41
42 described the differences between echocardiography versus right heart catheterization in preoperative evaluation of
43
44 lung transplantation patients. Utilizing a retrospective cohort of nearly 400 recipients, the echocardiographic
45
46 estimation of pulmonary arterial systolic pressure was limited as compared to right heart catheterization.²⁹
47
48 Combining these data with the temporal decline or improvement of the patient's clinical status allows the
49
50 anesthesiologist to better formulate a real-time assessment of the cardiopulmonary unit function.
51

52
53 However, these data do not preclude the utilization of real-time echocardiography during the immediate
54
55 preoperative evaluation phase. On the contrary, the utilization of point of care ultrasound (POCUS) is a necessity for
56
57 the anesthesiologist during the immediate preoperative evaluation.³⁰ Evaluation of the impact of increased right
58
59 ventricular afterload secondary to pulmonary hypertension should look for both acute and chronic changes in right
60
61
62
63
64
65

ventricular anatomy and function. Acute changes include the presence of a relative increase in right ventricular chamber diameter, new onset flattening of the interventricular septum, relative increases in tricuspid regurgitation, and relative decrease within indices of right ventricular function. The most important chronic change to assess for is right ventricular hypertrophy, as these patients may present with dynamic right ventricular outflow obstruction during the intraoperative phases of care including induction, implantation, or following pulmonary arterial clamp release.³¹ Beyond evaluation of the heart, the evaluation with POCUS should include gastric ultrasound to assess aspiration risk, lung ultrasound to assess for the presence or absence of pulmonary edema/effusion, pulmonary atelectasis, or diaphragmatic function.^{30, 32} Once a thorough history and physical has been performed, the induction strategy should focus on an approach tailored to ESLD in order for the anesthesiologist to predict and avoid pitfalls associated with the recipient ESLD co-morbidities.

Successful induction of our index patient should deploy appropriate pre-induction monitoring and anesthetic strategy for presumed worsening right ventricular dysfunction in the setting of increased acute pulmonary hypertension. Hargrave described the considerations for pre-induction monitor placement as well as strategy (Figure 1) in this patient population.³³



1
2
3
4 Figure 1: Possible physiologic effects of general anesthesia induction and positive-pressure ventilation on right
5
6 ventricular function in patients with pulmonary hypertension and compromised right ventricular function. Adapted
7
8 from Hargrave with permissions.³³
9

10
11 Data are lacking regarding ideal monitoring strategy, however, in our index patient we would place an
12
13 awake right arterial line to allow for real-time beat to beat monitoring. We would avoid placement of an awake
14
15 central venous cannula or pulmonary arterial cannula for several reasons. First, patient discomfort may lead to
16
17 increased sympathetic activity. This increased sympathetic activity may lead to increased pulmonary arterial
18
19 pressures, as would any potential hypoventilation resulting from sedating medications used to decrease patient
20
21 anxiety, although this may be attenuated by utilizing our self-hypnosis toolbox for the patient. Second, an acute
22
23 failing right ventricle may be prone to increased arrhythmias related to central venous wire and/or pulmonary
24
25 arterial catheter placement. Once monitors are placed, the induction strategy would focus on minimizing alterations
26
27 in systemic perfusion pressure, tachycardia, and right ventricular volume overload. While medication preferences
28
29 differ, the utilization of an ongoing low-dose norepinephrine infusion during induction would help our index patient
30
31 achieve these goals. The airway would be acquired as rapidly as possible, as hypoxic episodes during induction can
32
33 quickly lead to cardiac arrest in ESLD patients. In the immediate post induction period, caution would be noted to
34
35 maintain the balance of hemodynamics in the setting of positive pressure ventilation, which must be balanced to
36
37 avoid both decrease in right ventricular preload and increase in right ventricular afterload. Achieving this balance in
38
39 our index patient would be guided by a dynamic composite evaluation utilizing intraoperative transesophageal
40
41 echocardiography (TEE), pulmonary arterial pressures via a Swan-Ganz catheter, and systemic arterial pressures
42
43 while avoiding the integration of central venous pressure monitoring due to its inadequacy as a useful hemodynamic
44
45 monitor.³⁴
46
47

48 *Guiding Hemostasis with Coagulation Point of Care Management*

49
50
51
52

53 During dissection phase of lung transplantation, and in preparation for explantation, we would have a
54
55 special attention to optimizing perioperative hemostasis. Although perioperative transfusion to the donor and
56
57 recipient has been widely associated with an increased risk of PGD and 1-year mortality³⁵⁻³⁷, it is difficult to
58
59 determine whether the impact of transfusion is related to the nature of the products administered or to the bleeding
60
61
62
63
64
65

1
2
3
4 that led to the transfusion. Notwithstanding, the intraoperative hemoglobin threshold is not clearly defined, with
5 most centers advocating for a restrictive strategy. The first step in avoiding intraoperative transfusion is preoperative
6 optimization, and our index patient would undergo evaluation for and correction of any underlying anemia at a
7 specialized outpatient clinic. The next step focuses on intraoperative strategy, where a goal-directed transfusion
8 strategy would be deployed based on point-of-care coagulation testing (POCCT). Smith et al evaluated POCCT in
9 lung transplantation when they examined a retrospective cohort of 93 patients comparing a specific algorithm based
10 on rotational thromboelastometry (ROTEM) and platelet aggregometry assays to standard of care. All lung
11 transplantations were conducted with cardiopulmonary bypass (CPB), and the POCCT-based strategy resulted in
12 fewer blood transfusions without significant changes in outcome. They also performed a cost-analysis, which
13 demonstrated an overall reduction of cost of transfusion after introducing this strategy.³⁸ A randomized controlled
14 trial by Durila et al also examined POCCT in lung transplantation when they compared ROTEM to standard of care.
15 Although the study was complicated by differing fluid resuscitative strategies between the two arms (albumin 5% in
16 POCCT group versus crystalloids in non-POCCT), the study was stopped prematurely after interim statistical
17 analysis due to superior results in the POCCT/ROTEM group.³⁹ Their findings of decrease in perioperative blood
18 loss and blood product consumption guide our recommendation to engage a POCCT-based strategy within our index
19 patient's case. While ROTEM has been the predominantly studied POCCT, an ongoing multicentric randomized
20 controlled trial (NCT05798286) with Quantra technology may provide another POCCT monitor to guide
21 coagulation strategy in lung transplantation.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

44 *Strategy for Choosing and Managing Intraoperative ECLS*

45
46 Lung transplantation can be performed with or without ECLS. Strategies vary from center to center, with
47 some preferring an off-ECLS approach, while others prefer a variety of ECLS ranging from veno-venous (VV)
48 ECMO, veno-arterial (VA) ECMO, or CPB. CPB was the first ECLS approach used historically in lung
49 transplantation. Mohite et al retrospectively examined outcomes between an off-ECLS approach with an “elective
50 CPB” versus “unplanned conversion to CPB” group.⁴⁰ A total of 302 patients across a 7-year cohort were examined,
51 and the reported conclusion was that off-ECLS improved early outcomes and survival as compared to CPB
52 utilization. Subsequently, Hoetzenecker et al compared off-ECLS approach with a planned VA ECMO approach in a
53 retrospective analysis.⁴¹ Their reported findings showed a greater survival in the planned VA ECMO group as
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 compared to the off-ECLS approach at 1-, 3-, and 5-year time intervals. Finally, Magouliotis et al reported a meta-
5
6 analysis of 7 studies comparing CPB and ECMO.⁴² They reported improved rates of PGD and decreased rates of
7
8 morbidity in the ECMO group as compared to the CPB group.
9

10
11 These reported data helped to shape our approach in considering how to choose and manage our index
12
13 patient's lung transplantation ECLS strategy. Considerations for choosing the appropriate ECLS strategy include
14
15 patient factors, ECMO cannulation strategy, and requisite team expertise for intraoperative management. Our index
16
17 patient, suffering from IPF complicated by an acutely worsening cardiopulmonary unit secondary to increased
18
19 pulmonary pressures, would clearly benefit from the environment of hemodynamic stability and protective
20
21 ventilation strategy that VA ECMO provides.⁴¹ Additionally, the attenuation of the ischemic-reperfusion injury
22
23 provided by VA ECMO has been suggested to decrease rates of PGD across multiple etiologies of recipient
24
25 ESLD.^{43,44} The cannulation for ECMO, which can vary significantly across ECMO types⁴⁵, would be a planned
26
27 central VA ECMO after induction of anesthesia. In order to reduce the risk for ECLS-associated bleeding,
28
29 anticoagulation would be limited to a single dose of 3,000 units of heparin before ECLS cannulation. Coated ECLS
30
31 cannulas would be used, therefore activated clotting time (ACT) monitoring or repeated doses of heparin during the
32
33 procedure would not be necessary.
34
35

36
37 Intraoperative management of ECMO should be guided through an organ-system based strategy to optimize
38
39 cardiac, respiratory, neurological, and hematological function.⁴⁶ The balance of intrinsic cardiac output with VA
40
41 ECMO flow can be guided by indices of systemic perfusion such as urine output, acid-base balance, lactate and end-
42
43 tidal carbon dioxide combined with ongoing TEE assessment of the perfused pulmonary vein velocity time
44
45 integral.⁴⁶ In general, ECMO blood flow of 40-50% of the calculated cardiac output should be the perfusion goal.
46
47 This level of flow generally promotes hemodynamic support and facilitates protective ventilation strategies whilst
48
49 maintaining a low transpulmonary flow, thus avoiding stasis and the risk of in situ thrombosis of the new implanted
50
51 donor organ. We would choose to utilize a hybrid VA ECMO circuit, which provides the ability to perform VA
52
53 ECMO at a significantly reduced cost as compared to a standard ECMO circuit.⁴⁷ Our cardiac strategy would focus
54
55 on maintaining hemodynamic stability and systemic perfusion. Our respiratory strategy would employ a lung
56
57 protective ventilation strategy tailored to both recipient ESLD pre-explantation and standard practice to protect the
58
59 new grafts post-implantation.⁴⁸ Anesthetic depth would be monitored with electroencephalogram monitoring, with
60
61
62
63
64
65

1
2
3
4 cerebral oximetry employed to ensure localized perfusion of the brain.⁴⁶ Finally, appropriate hematological
5
6 monitoring, both to limit transfusion burden as well as guide ECMO anticoagulation, would employ point of care
7
8 techniques which have been shown to decrease perfusion and perhaps improve outcomes.^{39, 49}
9

10
11 ECMO circuit considerations include the impact on TEE measurement accuracy⁴⁶, dosing of antibiotic
12
13 therapy⁵⁰, and management of vasoplegia. Once the lungs are implanted, measuring the vascular anastomoses to
14
15 assess their diameter and peak velocities is vital to ensure they are patent.⁵¹ However, due to the diversion of
16
17 intracardiac preload to the ECMO circuit, measurements should be made once completely separated from VA
18
19 ECMO. Two systematic reviews, separately reporting pulmonary arterial and venous recommendations, provide
20
21 guidance for our assessment of anastomotic adequacy.^{52, 53} The ECMO circuit has been noted to sequester anti-
22
23 infective medications, which may theoretically impact overall dosing regimens. Lyster et al studied sequestration of
24
25 commonly used anti-fungal medications within ECMO circuits using an ex-vivo model.⁵⁰ The results were notable
26
27 in that the authors concluded it was possible that therapeutic levels of anti-fungal agents may possibly not be
28
29 achieved with general standardized doses for patients whilst undergoing ECMO therapy. These data would lead us
30
31 to consider a theoretical dosing strategy that would attenuate such a risk. Finally, vasoplegia has been reported to be
32
33 associated with any form of ECLS in cardiothoracic surgery and was reported by Sef et al to be associated with poor
34
35 outcomes.⁵⁴ While ideal treatment for vasodilatory shock associated with cardiothoracic transplantation has not been
36
37 elucidated in the literature, we would prefer an early vasopressin⁵⁵ and angiotensin II strategy.⁵⁶
38
39
40
41
42

43 *From Operating Room to Discharge: Strategy to Enhance Recovery and Pain Management*

44

45
46 At the end of the surgery, we would aim de-escalate ECMO and try to extubate the index patient in the
47
48 operating room to reduce the risk of morbidity as related to ongoing ECLS and mechanical ventilation. A recent
49
50 study examined the results of an operating room extubation strategy, with 36% of their cohort achieving it across a
51
52 wide variety of ESLD.²⁸ Prior to extubation, all patients had to pass a structured de-escalation trial. First, they
53
54 reduced the ECMO to a minimum flow (around 1.5 L/min) and evaluated the patients for any ongoing deterioration
55
56 in their right ventricular function or global cardiac output. The adequacy of the patient's intrinsic macrocirculation
57
58 was assessed with TEE and mixed venous oxygen saturation while microcirculation was evaluated by evolution in
59
60
61
62
63
64
65

1
2
3
4 blood lactate levels.⁵⁷ The assessment also included evaluation of graft function, utilizing arterial blood gas draws at
5
6 minimal ECMO flows to ensure adequacy of proper gas exchange (PaO₂/FiO₂ > 200). Second, ECMO was
7
8 removed and the patient was extubated if they met criteria for the Paul S. Myles magic bullet points.⁵⁸ Combining
9
10 these published approaches, we would aim for our index patient to be normothermic, on a low-dose of vasopressor,
11
12 blood lactate level below 2.6 mmol/L, de-curarized, and weaned from sedation utilizing a target control infusion
13
14 based on anesthetic depth sedation monitoring.⁵⁹ Apart from reducing ventilator-induced lung injury, early
15
16 extubation in the operating room would be helpful to quickly begin the post-rehabilitation program consisting of
17
18 tailored physiotherapy, early oral feeding, and removal of invasive hemodynamic monitoring.^{60, 61}
19
20

21 A key part of the post-transplantation recovery strategy for our patient is the control of analgesia.⁶² This is
22
23 based on multi-modal analgesia, with a key focus on loco-regional tailored to surgical incision approach. The
24
25 deployment of loco-regional must not only be aimed at attenuating pain at rest but also with movement
26
27 postoperatively, thus allowing for active post-rehabilitation. This active post-rehabilitation, and the role multi-modal
28
29 analgesia plays in optimizing it, is key to limit muscular deconditioning. In our case, preoperative epidural
30
31 placement is the preferred approach. Combining a low-heparin VA ECMO strategy with preoperative catheter
32
33 placement should have minimal hematoma risk, and the overall benefit/risk balance favors preoperative
34
35 placement.^{63, 64} A possible less invasive alternative would be chest wall blocks, such as a bilateral serratus block at
36
37 the end of the procedure⁶⁵, although this would avoid the benefit of pre-emptive analgesia.⁶⁶ A final alternative to
38
39 consider is cryoablation⁶⁷, but it remains controversial because of the risk of nerve damage, loss of respiratory
40
41 muscle contraction, and chronic neuropathic pain.
42
43

44 A final consideration in the recovery of our index patient is the assessment and treatment of chronic pain,
45
46 which has a high prevalence in the lung transplantation population. Laurent et al recently reported a prospective
47
48 cohort study of 72 patients who had chronic pain (score > 3/10 in 57%) and chronic neuropathic pain in 26.5% of
49
50 recipients at the 6-month post-surgical checkup.²⁶ This pain was associated with a poor quality of life and predicted
51
52 only by maximal preoperative pain score. Smith et al examined the psychosocial consequences of poor quality of
53
54 life in transplant recipients' mortality, and found that both depression and distress at the 6-month post-surgical
55
56 checkup were associated with increased mortality risk.⁶⁸ The postoperative recovery strategy of our index patient,
57
58 with immediate foundations of attenuating PGD and optimizing pain control, would also include an early enrollment
59
60
61
62
63
64
65

1
2
3
4 within a parallel psychosocial program to encourage mental health, social engagement, and medication adherence in
5
6 the outpatient setting.
7

8 9 **Conclusion**

10
11 The foundation of how I would treat my own lung transplantation is the multidisciplinary team. The
12 integration of the multidisciplinary team, which consists of a diverse set of physician/non-physician members and
13
14 the patient, across the entire perioperative spectrum is key for optimizing patient outcomes. While our index case
15
16 was theoretical, the evaluation of the topics discussed included data-driven recommendations as well as theoretical
17
18 topics that demand investigation. As such, members of the lung transplantation team should always approach
19
20 clinical strategy with a mix of humility and science, allowing for nuance to be discussed amongst ongoing
21
22 collaborations between centers across the globe.
23
24
25
26
27
28
29

30 **References**

- 31
32
33 1) Narula T, Martin AK, Asif AA, et al. (2023). "Outcomes of Lung Transplantation in Patients With Combined
34 Pulmonary Fibrosis and Emphysema: A Single-Center Experience." Transplant Proc **55**(2): 449-455.
35
36
37 2) Yang Z, Subramanian MP, Yan Y, et al. (2022). "The Impact of Center Volume on Outcomes in Lung
38 Transplantation." Ann Thorac Surg **113**(3): 911-917.
39
40
41 3) Snell GI, Yusef RD, Weill D, et al. (2017). "Report of the ISHLT Working Group on Primary Lung Graft
42 Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for
43 Heart and Lung Transplantation." J Heart Lung Transplant **36**(10): 1097-1103.
44
45
46 4) Martin AK, Yalamuri SM, Wilkey BJ, et al. (2020). "The Impact of Anesthetic Management on Perioperative
47 Outcomes in Lung Transplantation." J Cardiothorac Vasc Anesth **34**(6): 1669-1680.
48
49
50 5) Martin AK, Shah SZ, Guru PK, et al. (2022). "Multidisciplinary Approach for Lung Transplantation due to
51 COVID-19." Mayo Clin Proc Innov Qual Outcomes **6**(3): 200-208.
52
53
54 6) Wilkey BJ, Abrams BA, Del Rio JM, et al. (2020). "Statement From the Society for the Advancement of
55 Transplant Anesthesia: White Paper Advocating Desirable Milestones and Competencies for Anesthesiology
56 Fellowship Training in the Field of Lung Transplantation." Semin Cardiothorac Vasc Anesth **24**(1): 104-114.
57
58
59 7) Whitney L, Armstrong-James D, Lyster HS, et al. (2022). "Antifungal stewardship in solid-organ transplantation:
60 What is needed?" Transpl Infect Dis **24**(5): e13894.
61
62
63
64
65

- 1
2
3
4
5 8) Martin AK, Fritz AV and Ramakrishna H (2022). "Multidisciplinary collaboration: the key to advancing lung
6 transplantation outcomes." Indian J Thorac Cardiovasc Surg **38**(Suppl 2): 209-210.
7
8
9 9) Martin AK, Fritz AV and Wilkey BJ (2020). "Anesthetic management of lung transplantation: impact of
10 presenting disease." Curr Opin Anaesthesiol **33**(1): 43-49.
11
12
13 10) George PM, Patterson CM, Reed AK, et al. (2019). "Lung transplantation for idiopathic pulmonary fibrosis."
14 Lancet Respir Med **7**(3): 271-282.
15
16
17 11) Fried LP, Tangen CM, Walston J, et al. (2001). "Frailty in older adults: evidence for a phenotype." J Gerontol A
18 Biol Sci Med Sci **56**(3): M146-156.
19
20
21 12) Rozenberg D, Wickerson L, Singer LG, et al. (2014). "Sarcopenia in lung transplantation: a systematic review."
22 J Heart Lung Transplant **33**(12): 1203-1212.
23
24
25 13) Singer JP, Diamond JM, Gries CJ, et al. (2015). "Frailty Phenotypes, Disability, and Outcomes in Adult
26 Candidates for Lung Transplantation." Am J Respir Crit Care Med **192**(11): 1325-1334.
27
28
29 14) Koutsokera A, Sykes J, Theou O, et al. (2022). "Frailty predicts outcomes in cystic fibrosis patients listed for
30 lung transplantation." J Heart Lung Transplant **41**(11): 1617-1627.
31
32
33 15) Wickerson L, Rozenberg D, Gottesman C, et al. (2020). "Pre-transplant short physical performance battery:
34 Response to pre-habilitation and relationship to pre- and early post-lung-transplant outcomes." Clin Transplant
35 **34**(12): e14095.
36
37
38 16) Singer JP, Diamond JM, Anderson MR, et al. (2018). "Frailty phenotypes and mortality after lung
39 transplantation: A prospective cohort study." Am J Transplant **18**(8): 1995-2004.
40
41
42 17) Singer JP, Calfee CS, Delucchi K, et al. (2023). "Subphenotypes of frailty in lung transplant candidates." Am J
43 Transplant **23**(4): 531-539.
44
45
46 18) Singer JP, Christie JD, Diamond JM, et al. (2023). "Development of the Lung Transplant Frailty Scale (LT-
47 FS)." J Heart Lung Transplant 2023 Feb 20;S1053-2498(23)00049-9. Online ahead of print.
48
49
50 19) Wickerson L, Brooks D, Reid WD, et al. (2018). "Exertional Oxygen Requirements During Exercise Training in
51 Advanced Interstitial Lung Disease." J Cardiopulm Rehabil Prev **38**(6): 419-424.
52
53
54 20) Wickerson L, Mathur S, Singer LG, et al. (2015). "Physical activity levels early after lung transplantation." Phys
55 Ther **95**(4): 517-525.
56
57
58 21) Finet M, Bellicha A, Sage E, et al. (2023). "Comprehensive assessment of postoperative mobility during the first
59 days after mini-invasive lung surgery: A prospective observational study." J Clin Anesth **86**: 111048.
60
61
62
63
64
65

- 1
2
3
4 22) Huang L, Kehlet H and Petersen RH (2022). "Functional recovery after discharge in enhanced recovery video-
5 assisted thoroscopic lobectomy: a pilot prospective cohort study." Anaesthesia **77**(5): 555-561.
6
7
8 23) Scheede-Bergdahl C, Minnella EM and Carli F (2019). "Multi-modal prehabilitation: addressing the why, when,
9 what, how, who and where next?" Anaesthesia **74 Suppl 1**: 20-26.
10
11
12 24) Michel-Cherqui M, Szekely B, Fessler J, et al. (2022). "Feasibility and Usefulness of Self-Hypnosis in Patients
13 Undergoing Double-Lung Transplantation During the Pre- and Postoperative Periods: A Randomized Study." J
14 Cardiothorac Vasc Anesth **36**(8 Pt A): 2490-2499.
15
16
17 25) Michel-Cherqui M, Fessler J, Szekely B, et al. (2023). "Complementary Therapy Learning in the Setting of
18 Lung Transplantation: A Single-Center Observational Study of Appropriation and Efficacy." J Clin Med **12**(5):
19 1722.
20
21
22 26) Laurent Q, Michel-Cherqui M, Szekely B, et al. (2022). "Prevalence, Characteristics and Preoperative Predictors
23 of Chronic Pain After Double-Lung Transplantation: A Prospective Cohort Study." J Cardiothorac Vasc Anesth
24 **36**(2): 500-509.
25
26
27 27) Fessler J, Davignon M, Sage E, et al. (2021). "Intraoperative Implications of the Recipients' Disease for Double-
28 Lung Transplantation." J Cardiothorac Vasc Anesth **35**(2): 530-538.
29
30
31 28) Fessler J, Fischler M, Sage E, et al. (2021). "Operating room extubation: A predictive factor for 1-year survival
32 after double-lung transplantation." J Heart Lung Transplant **40**(5): 334-342.
33
34
35 29) Abu T, Levi A, Hasdai D, et al. (2022). "Preoperative evaluation of pulmonary hypertension in lung transplant
36 candidates: echocardiography versus right heart catheterization." BMC Cardiovasc Disord **22**(1): 53.
37
38
39 30) Kalagara H, Coker B, Gerstein NS, et al. (2022). "Point-of-Care Ultrasound (POCUS) for the Cardiothoracic
40 Anesthesiologist." J Cardiothorac Vasc Anesth **36**(4): 1132-1147.
41
42
43 31) Prada G, Vieillard-Baron A, Martin AK, et al. (2019). "Echocardiographic Applications of M-Mode
44 Ultrasonography in Anesthesiology and Critical Care." J Cardiothorac Vasc Anesth **33**(6): 1559-1583.
45
46
47 32) Prada G, Vieillard-Baron A, Martin AK, et al. (2021). "Tracheal, Lung, and Diaphragmatic Applications of M-
48 Mode Ultrasonography in Anesthesiology and Critical Care." J Cardiothorac Vasc Anesth **35**(1): 310-322.
49
50
51 33) Hargrave J (2017). "Con: Preinduction Pulmonary Artery Catheter Placement Is Advisable in Patients With
52 Right Ventricular Dysfunction Secondary to Severe Pulmonary Hypertension." J Cardiothorac Vasc Anesth **31**(4):
53 1514-1518.
54
55
56 34) De Backer D and Vincent JL (2018). "Should we measure the central venous pressure to guide fluid
57 management? Ten answers to 10 questions." Crit Care **22**(1): 43.
58
59
60 35) Borders CF, Suzuki Y, Lasky J, et al. (2017). "Massive donor transfusion potentially increases recipient
61 mortality after lung transplantation." J Thorac Cardiovasc Surg **153**(5): 1197-1203 e1192.
62
63
64
65

- 1
2
3
4
5 36) Elmaleh Y, De Tymowski C, Zappella N, et al. (2021). "Blood transfusion of the donor is associated with stage
6 3 primary graft dysfunction after lung transplantation." Clin Transplant **35**(9): e14407.
7
8
9 37) Subramaniam K, Loor G, Chan EG, et al. (2023). "Intraoperative Red Blood Cell Transfusion and Primary Graft
10 Dysfunction After Lung Transplantation." Transplantation 2023 Mar 24, Online ahead of print.
11
12
13 38) Smith I, Pearse BL, Faulke DJ, et al. (2017). "Targeted Bleeding Management Reduces the Requirements for
14 Blood Component Therapy in Lung Transplant Recipients." J Cardiothorac Vasc Anesth **31**(2): 426-433.
15
16
17 39) Durila M, Vajter J, Garaj M, et al. (2021). "Rotational thromboelastometry reduces blood loss and blood product
18 usage after lung transplantation." J Heart Lung Transplant **40**(7): 631-641.
19
20
21 40) Mohite PN, Sabashnikov A, Patil NP, et al. (2016). "The role of cardiopulmonary bypass in lung
22 transplantation." Clin Transplant **30**(3): 202-209.
23
24
25 41) Hoetzenecker K, Schwarz S, Muckenhuber M, et al. (2018). "Intraoperative extracorporeal membrane
26 oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation." J
27 Thorac Cardiovasc Surg **155**(5): 2193-2206 e2193.
28
29
30 42) Magouliotis DE, Tasiopoulou VS, Svokos AA, et al. (2018). "Extracorporeal membrane oxygenation versus
31 cardiopulmonary bypass during lung transplantation: a meta-analysis." Gen Thorac Cardiovasc Surg **66**(1): 38-47.
32
33
34 43) Hoetzenecker K, Benazzo A, Stork T, et al. (2020). "Bilateral lung transplantation on intraoperative
35 extracorporeal membrane oxygenator: An observational study." J Thorac Cardiovasc Surg **160**(1): 320-327 e321.
36
37
38 44) Halpern SE, Wright MC, Madsen G, et al. (2022). "Textbook outcome in lung transplantation: Planned
39 venoarterial extracorporeal membrane oxygenation versus off-pump support for patients without pulmonary
40 hypertension." J Heart Lung Transplant **41**(11): 1628-1637.
41
42
43 45) Martin AK, Jayaraman AL, Nabzdyk CG, et al. (2021). "Extracorporeal Membrane Oxygenation in Lung
44 Transplantation: Analysis of Techniques and Outcomes." J Cardiothorac Vasc Anesth **35**(2): 644-661.
45
46
47 46) Martin AK, Harrison BA, Fritz AV, et al. (2020). "Intraoperative management of a hybrid extracorporeal
48 membrane oxygenation circuit for lung transplantation." J Card Surg **35**(12): 3560-3563.
49
50
51 47) Thomas M, Martin AK, Allen WL, et al. (2020). "Lung Transplantation Using a Hybrid Extracorporeal
52 Membrane Oxygenation Circuit." ASAIO J **66**(10): e123-e125.
53
54
55 48) Thakuria L, Davey R, Romano R, et al. (2016). "Mechanical ventilation after lung transplantation." J Crit Care
56 **31**(1): 110-118.
57
58
59 49) Vajter J, Vachtenheim J, Jr., Prikrylova Z, et al. (2023). "Effect of targeted coagulopathy management and 5%
60 albumin as volume replacement therapy during lung transplantation on allograft function: a secondary analysis of a
61 randomized clinical trial." BMC Pulm Med **23**(1): 80.
62
63
64
65

- 1
2
3
4
5 50) Lyster H, Pitt T, Maunz O, et al. (2023). "Variable Sequestration of Antifungals in an Extracorporeal Membrane
6 Oxygenation Circuit." ASAIO J **69**(3): 309-314.
7
8
9 51) Abrams BA, Melnyk V, Allen WL, et al. (2020). "TEE for Lung Transplantation: A Case Series and Discussion
10 of Vascular Complications." J Cardiothorac Vasc Anesth **34**(3): 733-740.
11
12
13 52) Kumar N, Essandoh M, Bhatt A, et al. (2019). "Pulmonary cuff dysfunction after lung transplant surgery: A
14 systematic review of the evidence and analysis of its clinical implications." J Heart Lung Transplant **38**(5): 530-544.
15
16
17 53) Kumar N, Hussain N, Kumar J, et al. (2021). "Evaluating the Impact of Pulmonary Artery Obstruction After
18 Lung Transplant Surgery: A Systematic Review and Meta-analysis." Transplantation **105**(4): 711-722.
19
20
21 54) Sef AV, Yin Ling CN, Aw TC, et al. (2023). "Postoperative vasoplegia in lung transplantation: incidence and
22 relation to outcome." Br J Anaesth **130**(6):666-676.
23
24
25 55) Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. (2017). "Vasopressin versus Norepinephrine in Patients
26 with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial." Anesthesiology **126**(1):
27 85-93.
28
29
30 56) Khanna A, English SW, Wang XS, et al. (2017). "Angiotensin II for the Treatment of Vasodilatory Shock." N
31 Engl J Med **377**(5): 419-430.
32
33
34 57) Fessler J, Vallee A, Guirimand A, et al. (2022). "Blood Lactate During Double-Lung Transplantation: A
35 Predictor of Grade-3 Primary Graft Dysfunction." J Cardiothorac Vasc Anesth **36**(3): 794-804.
36
37
38 58) Myles PS (1999). "Early extubation after lung transplantation." J Cardiothorac Vasc Anesth **13**(3): 247-248.
39
40
41 59) Liu N, Chazot T, Trillat B, et al. (2008). "Closed-loop control of consciousness during lung transplantation: an
42 observational study." J Cardiothorac Vasc Anesth **22**(4): 611-615.
43
44
45 60) Fuller LM, El-Ansary D, Button BM, et al. (2018). "Effect of Upper Limb Rehabilitation Compared to No
46 Upper Limb Rehabilitation in Lung Transplant Recipients: A Randomized Controlled Trial." Arch Phys Med
47 Rehabil **99**(7): 1257-1264 e1252.
48
49
50 61) Ulvestad M, Durheim MT, Kongerud JS, et al. (2020). "Effect of high-intensity training on peak oxygen uptake
51 and muscular strength after lung transplantation: A randomized controlled trial." J Heart Lung Transplant **39**(9):
52 859-867.
53
54
55 62) Azem K, Mangoubi E, Zribi B, et al. (2023). "Regional analgesia for lung transplantation: A narrative review."
56 Eur J Anaesthesiol 2023 May 29. Online ahead of print.
57
58
59 63) McLean SR, von Homeyer P, Cheng A, et al. (2018). "Assessing the Benefits of Preoperative Thoracic Epidural
60 Placement for Lung Transplantation." J Cardiothorac Vasc Anesth **32**(6): 2654-2661.
61
62
63
64
65

1
2
3
4
5 64) Kupersztych-Hagege E, Dubuisson E, Szekely B, et al. (2017). "Epidural Hematoma and Abscess Related to
6 Thoracic Epidural Analgesia: A Single-Center Study of 2,907 Patients Who Underwent Lung Surgery." J
7 Cardiothorac Vasc Anesth **31**(2): 446-452.
8

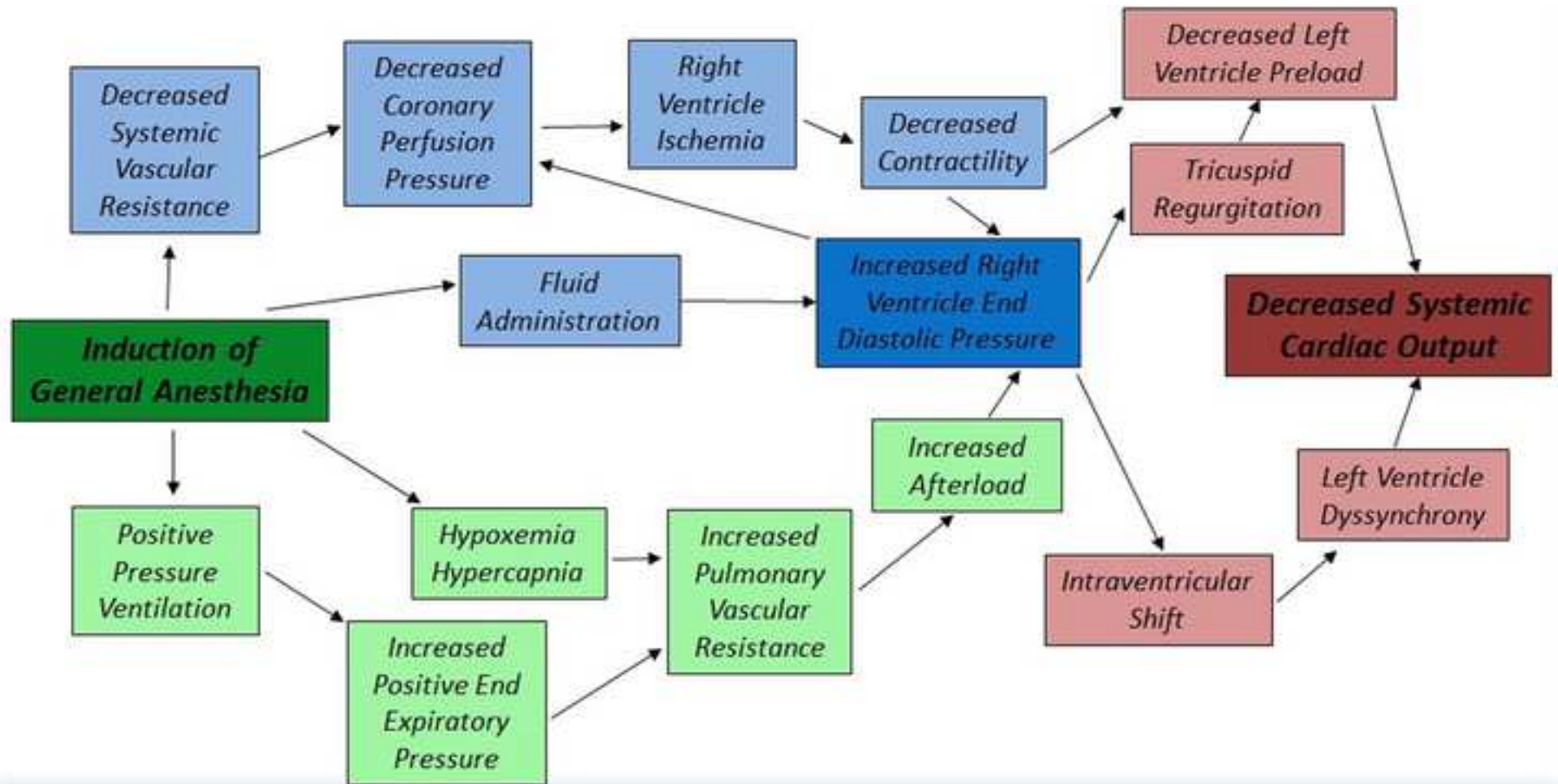
9
10 65) Sekandarzad MW, Konstantatos A and Donovan S (2019). "Bilateral Continuous Serratus Anterior Blockade for
11 Postoperative Analgesia After Bilateral Sequential Lung Transplantation." J Cardiothorac Vasc Anesth **33**(5): 1356-
12 1359.
13

14
15 66) Park SK, Yoon S, Kim BR, et al. (2020). "Pre-emptive epidural analgesia for acute and chronic post-
16 thoracotomy pain in adults: a systematic review and meta-analysis." Reg Anesth Pain Med **45**(12): 1006-1016.
17

18
19 67) Koons B, Suzuki Y, Cevasco M, et al. (2023). "Cryoablation in lung transplantation: Its impact on pain, opioid
20 use, and outcomes." JTCVS Open **13**: 444-456.
21

22
23 68) Smith PJ, Blumenthal JA, Trulock EP, et al. (2016). "Psychosocial Predictors of Mortality Following Lung
24 Transplantation." Am J Transplant **16**(1): 271-277.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure 1



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49