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REVIEW

Applied physiological principles in the management of a lung allograft to thoracic cavity size mismatch in severe emphysema

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In this review, we discuss physiological principles that guided the management of a lung transplant for emphysema related to alpha-1-antitrypsin deficiency, where a lung allograft to thoracic cavity size mismatch occurred (donor-to-recipient predicted total lung capacity [pTLC] ratio was 0.89, donor pTLC-to-recipient actual-TLC ratio 0.62). In emphysema, the loss of lung elastic recoil and airway obstruction leads to air trapping and lung hyperinflation. Remodeling of the thoracic cavity ("barrel chest") develops, which has implications for donor-to-recipient sizing and postoperative management of lung transplantation. We discuss the physiology of a relatively undersized allograft and the impact on chest tube, mechanical ventilation, and respiratory system mechanics management. This case also illustrates how chronic adaptations of the ventilatory pattern to advanced lung diseases are reversible and the chest cavity size can remodel back to normal after lung transplantation.
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Background

In this review, we discuss 5 physiological principles (I-V) that guided the management of a lung transplant for severe emphysema related to alpha-1-antitrypsin deficiency. In emphysema, the loss of lung elastic recoil and airway obstruction leads to air trapping and lung hyperinflation. Remodeling of the thoracic cavity ("barrel chest") (I) develops, which has implications for donor-to-recipient sizing and postoperative management of lung transplantation. Collateral ventilation (II) pathways in emphysema can complicate the intraoperative course. During the postoperative period of lung transplantation, numerous changes and adaptions occur in lung and chest cavity physiology. We discuss the physiology of a relatively undersized allograft and the impact on chest tube (III), mechanical ventilation and respiratory system mechanics management. The increased thoracic cavity volume can return to more normal size following lung transplantation (IV). The time course for such a reduction in thoracic cavity size toward normal size takes months. Managing the post-transplant period based on physiological principles can allow for an excellent long-term outcome and our recipient experienced excellent long-term allograft function with supranormal expiratory airflows (V).

Case presentation

A 57-year-old male, 180 cm tall, with alpha-1-antitrypsin deficiency (ZZ-genotype) developed severe emphysema

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Table 1 Spirometry and Lung Volumes Over Time

Lung function parameter	Pre-Tx recipient	Donor	D-to-R ratio	6 mo post-Tx	8 mo post-Tx	10 mo post-Tx	12 mo post-Tx
Spirometry							
FVC (liter)	1.62			2.45	3.00	3.22	3.42
FVC % pred.	31			50	59	63	69
FEV_1 (liter)	0.77			2.37	2.96	3.16	3.28
FEV_1% pred.	20			63	76	81	86
FEV_1/FVC	47			97	99	98	96
FEF_{25-75} (liter/s)	0.29			5.93	6.26	5.89	5.98
$FEF_{25-75\%}$	9			190	194	182	186
Lung volumes							
Height (cm)	180	170	0.95				180
FRC (liter)	8.15	3.43[a]	0.42				3.48
FRC % pred.	197						96
RV (liter)	7.54	1.6[a]	0.20				2.65
RV % pred.	309						106
RV/TLC	75						23
Actual TLC (liter)	10.03	6.3[a]	0.62				6.52
pTLC (liter)	7.1	6.3	0.89				7.1
TLC % pred.	141						91

Abbreviations: D, donor; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; Pred., predicted; pTLC, predicted total lung capacity; R, recipient; RV, residual volume; TLC, total lung capacity; Tx, transplant.

[a]Based on recipient-predicted values calculated from regression equations based on sex, age, and height.

(forced expiratory volume in 1 second [FEV_1]: 17% predicted, diffusion capacity for carbon monoxide: 17% predicted) and lung hyperinflation (TLC: 10.03 liters [141% predicted], functional residual capacity [FRC]: 8.15 liters [197% predicted]) (Table 1). Computed tomography (CT) imaging of the chest demonstrated severe emphysema at the bases as well as a barrel chest (Figure 1A and B). He required 8 liters per minute of O_2 at rest and intermittently assisted mechanical ventilation via a mask interface for baseline hypercarbia (partial pressure of carbon dioxide in arterial blood: 63 mm Hg). The patient also exhibited pulmonary hypertension (pulmonary arterial pressure: 70/38 mm Hg).

A suitable donor for a bilateral lung transplant became available. After clamshell incision, the native lungs protruded out of the chest (Figure 1C). Pulmonary arterial pressures decreased to 44/20 mm Hg, oxygenation and hemodynamics improved, allowing an off-pump bilateral sequential lung transplant. Following surgical pneumonectomy, the native lung explant was neither deflated nor fitted into the specimen container (volume 3.5 liters, Figure 1D). Puncturing the upper lobe had no significant effect. Only after puncturing the pleura of the lower lobe did the explant deflate (Figure 1E and F, Supplemental Video 1).

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The donor (18-year-old male, 170 cm tall) had a predicted total lung capacity (pTLC) of 6.3 liters. The donor-to-recipient pTLC ratio was 0.89 and the donor pTLC-to-recipient actual-TLC ratio was 0.62 (Table 1). Residual pleural space was noted after implantation (Figure 2).

There was excellent early allograft function with primary graft dysfunction grade 0 at all time points. The recipient was extubated 9 hours post-transplant. During the first 24 hours, 1.7 liters of serosanguineous drainage from the chest tubes (−20 cm H_2O suction) was recorded. There was no evidence of active bleeding. Over the next 24 hours, chest tube output remained high at 2.1 liters. The recipient had minimal oxygen requirements (2 liters per minute via nasal cannula). However, on bedside exam, he did exhibit evidence of high work of breathing, using accessory respiratory muscles. The chest tubes were placed to waterseal, which was associated with a substantial decrease in chest tube output to on average 300 ml per 24 hours. The work of breathing improved as the chest tubes were placed on waterseal, however remained high. Hypercarbic respiratory failure (pH 7.29 and partial pressure of carbon dioxide in arterial blood of 76 mm Hg) necessitated reintubation and subsequent tracheostomy on postoperative day 4. A CT scan of the chest on postoperative day 4 demonstrated a size mismatch between the recipient's chest cavity and smaller allografts (Figure 2), with significant residual pleural space.

The post-transplant period was complicated by a chest wall hematoma complicated by hemorrhagic shock requiring massive transfusions of blood products and surgical evacuation. He developed acute lung allograft dysfunction from antibody-mediated rejection, which resolved after treatment with plasma-exchange, rituximab and intravenous immunoglobulin. Likely as a complication of his blood product transfusion, he had a primary infection with cytomegalovirus (CMV, serostatus donor, and recipient negative) and CMV pneumonitis complicated by acute lung allograft dysfunction. Secondary to the above complications, he required a prolonged period of ventilatory support. By postoperative month 3, he was weaned from nocturnal mechanical ventilation. By postoperative month 4, the tracheostomy tube was removed. He underwent surgical closure of the tracheostomy stoma 5 months post-transplant. His first pulmonary function studies 6 months post-transplant showed supranormal

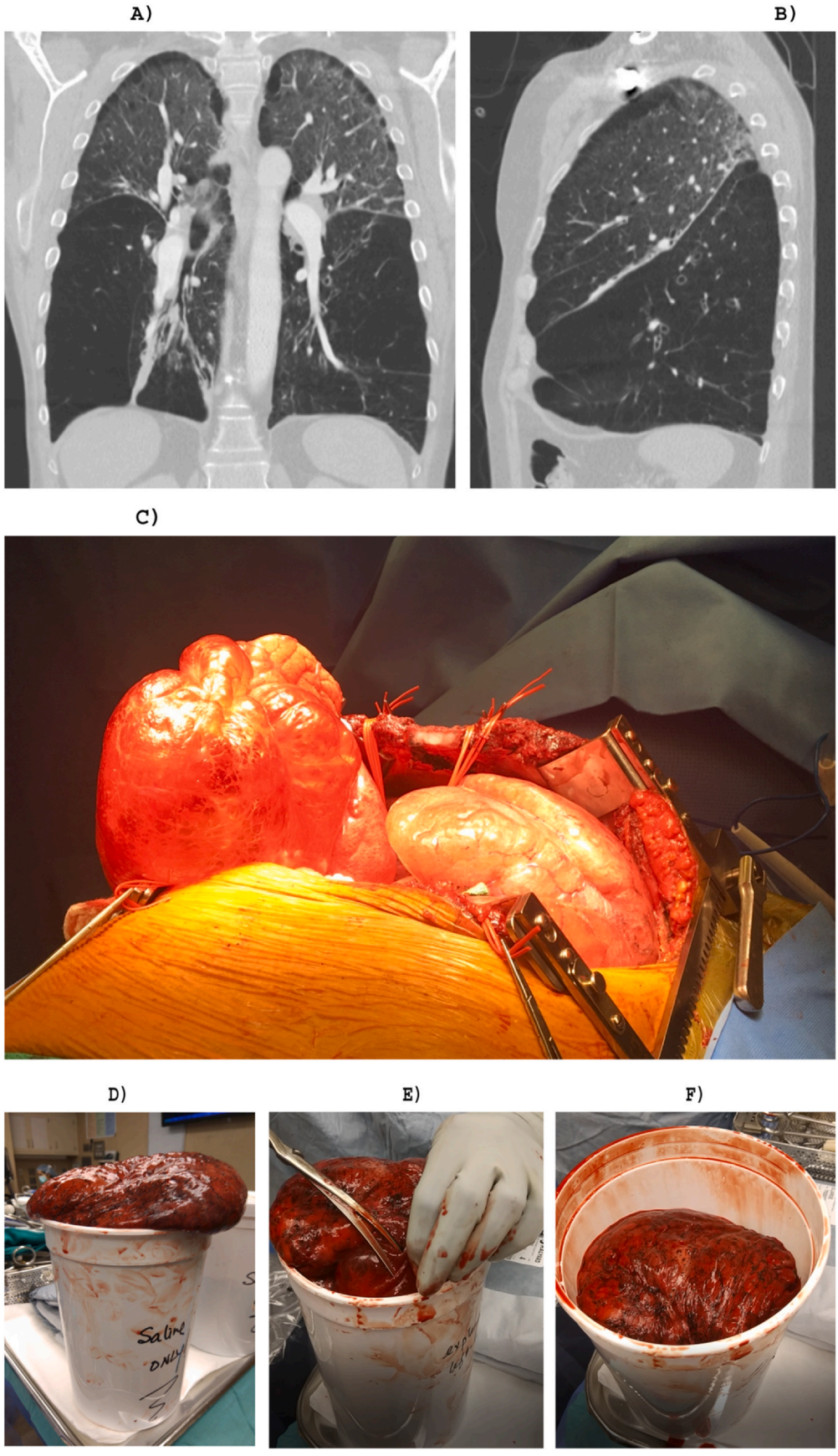

Figure 1 (A, B) Pretransplant computed tomography of the chest. (A) Coronal view showing lower lobe predominant emphysematous changes. (B) Sagittal view showing intact major fissure and lower lobe predominant emphysematous changes. (C) Intraoperative situs following clamshell incision. (D) Left explanted native recipient lung. The explant remained hyperinflated following pneumonectomy and did not fit into a 3.5-liters specimen container. (E) The pleura of the left lower lobe is punctured and immediately following the pleural puncture (F) the explant fully deflated.

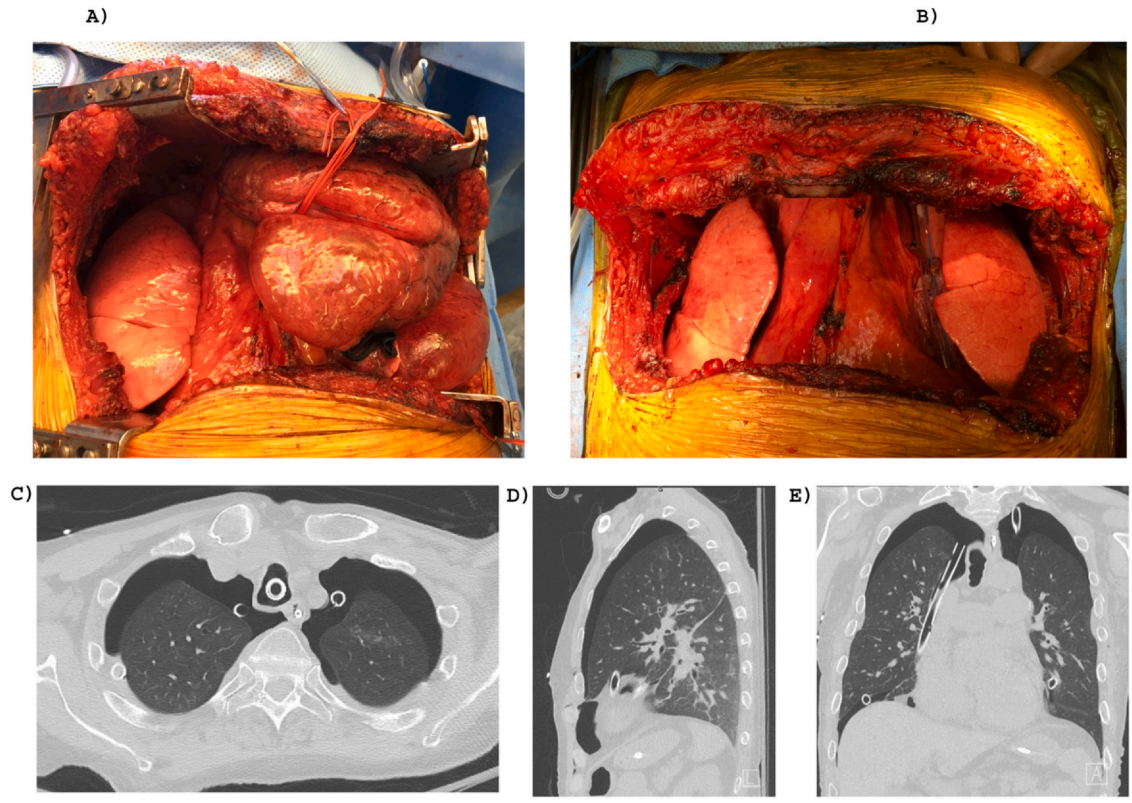

Figure 2 (A) Intraoperative situs following right allograft implantation. The hyperinflated left native lung is filling the entire left hemithorax, while the right allograft is not fully reaching the apex in the right hemithorax. (B) Intraoperative situs following bilateral allograft implantations. Bilateral allografts are not fully reaching the apex of the hemithoraces and a size mismatch is apparent. (C) Post-transplant computed tomography of the chest. Residual pleural space from a significant size mismatch between a smaller allograft and a larger recipient's chest cavity is shown in axial view (C), sagittal view (D), and coronal view (E).

expiratory airflow (Figure 3) with FEV_1/forced vital capacity (FVC) ratio of 97%, forced expiratory flow $(FEF)_{25-75\%}$ of 5.93 liters/s (190% of predicted), FVC of 2.45 liters (50% predicted), and FEV_1 of 2.37 liters (63% predicted) (Table 1). He had a gradual increase in his FVC and FEV_1 to 3.22 (63% predicted) and 3.16 (81% predicted) respectively, by 10 months after transplant. However, he maintained supranormal expiratory airflow (FEV_1/FVC ratio 98%, $FEF_{25-75\%}$ 6.26 liter/s [194% predicted]) (Table 1). A follow-up chest CT at 11 months post-transplant showed normal lung parenchyma and complete resolution of previous pneumothoraces (Figure 3).

Discussion

The transplant of our recipient highlights a series of physiological phenomena and the importance of applying basic physiological principles to the clinical management at the bedside. Throughout the discussion, we aim to highlight the general applicability of these physiological principles in end-stage lung disease from COPD/emphysema (I and II) and lung transplantation (III-V).

Air trapping and hyperinflation in emphysema

Loss of lung elastic recoil and air trapping from severe emphysema can lead to significant lung hyperinflation, which can cause intrinsic (or "auto") positive end-expiratory pressure in the lung, which may result in substantial elevation of intrathoracic pressure. This can have adverse hemodynamic consequences, leading to pulmonary arterial hypertension and diastolic dysfunction. Our patient likely had significant auto-positive end-expiratory pressure and elevations in intrathoracic pressure preoperatively. After clamshell incision and decompression of his chest cavity by the protrusion of his native lungs out of his chest (Figure 1C), his pulmonary arterial pressures significantly decreased, and his hemodynamics improved. This allowed an off-bypass bilateral sequential lung transplant (Figure 1A-F).

Collateral ventilation in emphysema

In severe emphysema, collateral ventilation can be a lower resistance pathway for airflow compared to the airway tree. Collateral ventilation can connect airspaces of an entire lung lobe and if there are incomplete lung fissures present it can connect airspaces of an entire lung. When the pleura is punctured in the setting of a severely emphysematous and hyperinflated lung, transpleural airflow through the pleural tear can be a pathway of least resistance. In such circumstances, we have previously reported complete transpleural exhalation via pleural tears during lung transplantation for severe emphysema.[1-4] Such a phenomenon can be characterized by complete loss of the end-tidal CO_2 waveform,

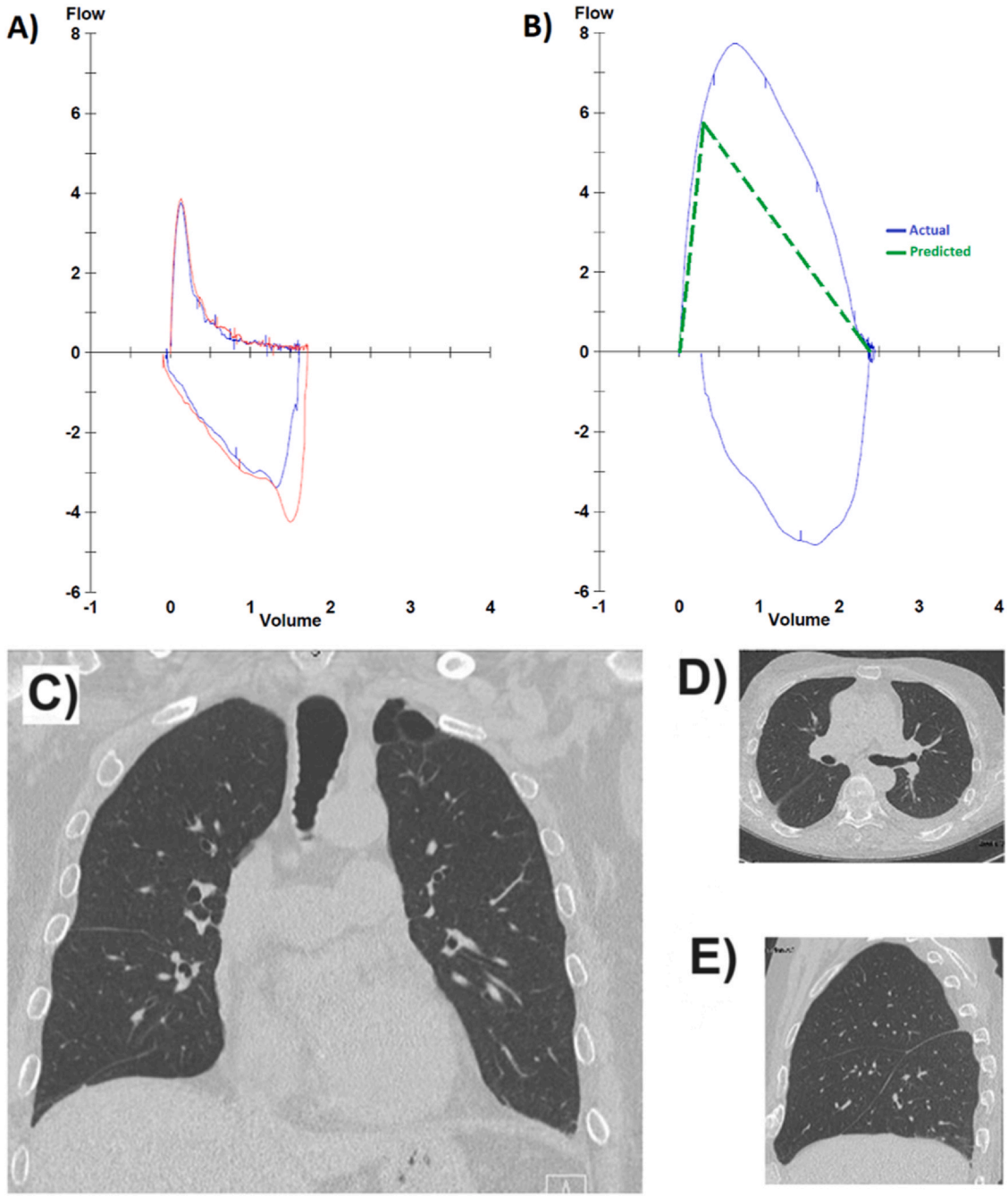

Figure 3 (A) Pretransplant FVL and (B) first post-transplant FVL. (C) Follow-up chest CT at 11 months post-transplant shows normal lung parenchyma and resolution of previous pneumothorax. (D) Axial and (E) sagittal views. CT, computed tomography; FVL, flow volume loop.

as well as complete loss of measured expiratory volume in the breathing circuit.[1] The measured inspiratory volume, however, may exhibit no change. Intraoperative loss of expiratory airflow and detectable end-tidal CO_2 during mechanical ventilation would ordinarily be considered an anesthetic emergency. However, some patients may maintain stable oxygenation and ventilation in such circumstances.[1] Alveolar ventilation becomes more effective for CO_2 elimination via "transpleural" exhalation, often requiring reduced minute ventilation to maintain normal pH and eucapnia.[2]

This physiology of collateral ventilation and severe emphysema is highlighted in this case by the significant deflation that occurred after the explanted lung's lower lobe was punctured in only 1 defined location (Figure 1D-F, Supplemental Video 1).

Physiology of an undersized allograft

Size matching based on pTLC indicated an almost ideal size match, with a donor-to-recipient pTLC ratio of 0.89. However long-standing hyperinflation in our patient resulted in a barrel chest, with a substantial increase in total thoracic volume. The FRC of our patient was elevated at 8.15 liters, which was higher than the pTLC of the allograft at 6.3 liters.

The measurement of the recipient's FRC was confounded by severe emphysema. However, in the setting of a barrel chest, the recipient's FRC in the immediate postoperative period was likely similar in magnitude to the preoperative TLC of the allograft. The residual pleural space on a CT of the chest on postoperative day 4 supports the presence of a significant donor-to-recipient size mismatch (Figure 2A-F). An allograft expanded in the range of its TLC would be associated with a substantial increase in elastic recoil and would be limited by its physical boundaries to further inflation. This physiology of an undersized allograft has implications for post-transplant patient management.[5-10]

Chest tube management

Chest tubes are frequently placed on continuous regulated suction in the immediate postoperative period of lung transplantation, to facilitate the removal of intrapleural air and fluid. However, high negative pleural pressure applied to a large residual pleural space, as may occur with an undersized allograft, can lead to severe hyperinflation of the graft.[5] Such hyperinflation may predispose the allograft to volutrauma, inflammation, and pulmonary edema.[5] A similar situation is often reported when suction is applied to a postpneumonectomy residual pleural space and is referred to as "postpneumonectomy" pulmonary edema. Thus, if chest tube suction is applied to a residual pleural space in the setting of a very undersized allograft, hydrostatic shifts of fluid into the allograft and pleural space may occur, resulting in pulmonary edema and high chest tube drainage. Instead of placing the chest tubes on continuous suction, it may be more appropriate to place them on waterseal if clinically feasible.[5]

Mechanical ventilation

In the setting of an undersized allograft, it is important to manage mechanical ventilation according to the characteristics of the donor lung.[6-10] Specifically setting the size of the tidal volume based on donor lung size, rather than recipient predicted body weight, is critical to assure lung-protective ventilation (Figure S1). We previously described the relationship between donor-recipient lung-size mismatch and postoperative mechanical ventilation tidal volumes according to recipient- and donor-predicted body weights in a cohort of bilateral lung transplant patients and highlighted that undersized allografts received relatively higher tidal volumes compared with oversized allografts when the tidal volumes were related to donor-predicted body weights (as a measure of allograft size) (Figure S1).[7] It is common practice to set tidal volumes based on recipient characteristics.[8] However, in our opinion, the mechanical ventilation strategy should be based on donor characteristics (using donor-predicted body weight as a parameter of actual allograft size), rather than recipient characteristics.[8-10] Donor–based lung-protective ventilation is associated with decreased risk of primary graft dysfunction grade 3 at 48 to 72 hours and decreased 1-year mortality.[10]

Work of breathing

An allograft inflated in the range of its TLC significantly increases the work of breathing for the recipient (Figure S2).[11] At TLC, the lung elastic recoil is in the range of 30 cmH_2O (Figure S2). In addition, the compliance of the lung at TLC is substantially reduced. Attempts to further inflate the lung will be associated with substantial increases in the work of breathing and may be limited by the physical boundaries of the allograft (Figure S2). Such factors may increase the required work of breathing in the early postoperative period, leading to hypercarbic respiratory failure as we observed in this patient (Figure S2). It has been shown that the changes in the thoracic cavity based on the underlying lung disease are not permanent.[12] On the contrary, irrespective of the underlying lung disease, it has been shown that the thoracic cavity remodels to near-normal size in the postoperative period.[12,13] Certainly, vigilance during the early postoperative period is mandated given the mechanical limitations of the undersized allograft and risk for acute respiratory failure. However, the long-term prognosis for our recipient, at least regarding the mechanical synergy between the lungs and chest wall, was predicted to be excellent. After the thoracic cavity of the recipient returns to a more normal size, the allograft is better matched, as indicated by the donor-to-recipient pTLC ratio of 0.89.

Time course of remodeling of the thoracic cavity size

After lung transplantation, the chronic adaptations of the ventilatory pattern to advanced lung diseases are reversible and indicate that the main contributing factor is the lung itself rather than the systemic effects of the disease.[12] The exact time course of chest cavity remodeling toward normal has not been described. Using CT chest and lung volume measurements before and 1 year after transplant, Yu et al have shown that disease-specific chest remodeling caused by lung fibrosis in restrictive lung disease and lung hyperinflation in obstructive lung disease is reversible after lung transplant.[13] After lung transplant, the chest remodeling occurs in the opposite direction to the lung disease-specific remodeling caused by the underlying lung disease in recipients (Figure S3).[13] In our patient, CT imaging and lung volume measurements returned to normal at around 1 year after transplant (Table 1). The period of prolonged ventilatory support in this patient is best explained by the postoperative course complicated by chest wall hematoma, antibody-mediated rejection with allograft dysfunction, and CMV pneumonitis.

Supranormal expiratory airflow following lung transplantation

All our recipient's post-transplant pulmonary function studies showed supranormal expiratory airflow (Figure 3, Table 1). We have previously defined and described the supranormal expiratory airflow pattern following lung

transplantation and found that it was associated with improved survival after lung transplantation and a lower risk of bronchiolitis obliterans syndrome.[14,15]

In our previous studies, we found that restriction of donor lungs in a relatively smaller recipient thorax was the likely cause of the supranormal expiratory airflow pattern, as a higher pTLC ratio (suggestive of oversized allografts) was strongly associated with it.[14] Increased elastic recoil from limitations on inspiration and lower airway resistance from larger transplanted airways may explain the supranormal expiratory flow associated with an oversized allograft. The physiology of an oversized allograft restricted in a smaller recipient thorax has similarities to the old physiological experiment of chest wall strapping, which also causes increased elastic recoil and increased expiratory airflow.[16,17] In our recipient, the donor allograft was undersized relative to the recipient's chest cavity size. Elastic recoil of the lung is the key determinant of expiratory airflow capacity. Lung recoil can be from tissue forces (elastic structures of the parenchyma) and surface forces (at the air-liquid interface of the alveoli) (Figure S4). In the case of the relatively undersized allograft in our recipient, it is likely that increased tissue forces (from stretch of collagen and elastin fibers) are the source of increased lung recoil and the supranormal expiratory airflow.

Conclusion

The transplant journey of our recipient highlights a series of lung physiological phenomena and the importance of applying basic physiological principles to the clinical management at the bedside. We have previously shown that undersized allografts are associated with an increased risk of complications, primary graft dysfunction, and increased resource utilization.[18-21] However, we believe that an understanding of the physiology of an undersized allograft may allow for adjustments to postoperative mechanical ventilation and chest tube management strategies to protect the allograft, as highlighted in our recipient. After lung transplantation the chronic adaptations of the ventilatory pattern to advanced lung diseases are reversible and the chest cavity size can remodel back to normal. This indicates that the main contributing factor to chest cavity changes before transplant is the diseased lung itself rather than systemic effects of the disease leading to permanent chest wall and chest cavity changes.

Ethics statement

Patient consent was obtained.

CRediT authorship contribution statement

Michael Eberlein: Writing - Original draft (Conception, drafting, and revision of manuscript). John C. Keech: Writing - Review and editing. Robert M. Reed: Writing - Review and editing.

Disclosure statement

All authors have no relevant conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100124.

References

1. Eberlein M, Larson CD, Parekh KR, Terry P, Schmidt GA. Complete transpleural exhalation during a bilateral lung transplant operation. Ann Am Thorac Soc 2015;12:948-51.
2. Chahla M, Larson CD, Parekh KR, et al. Transpleural ventilation via spiracles in severe emphysema increases alveolar ventilation. Chest 2016;149:e161-7. https://doi.org/10.1016/j.chest.2015.12.032.
3. Khauli S, Bolukbas S, Reed RM, Eberlein M. Interlobar collateral ventilation in severe emphysema. Thorax 2016;71:1168-9.
4. Khauli S, Abston E, Sajjad H, et al. Incomplete fissures are associated with increased alveolar ventilation via spiracles in severe emphysema. Interact Cardiovasc Thorac Surg 2017;25:851-5.
5. Kozower BD, Meyers BF, Ciccone AM, Guthrie TJ, Patterson GA. Potential for detrimental hyperinflation after lung transplantation with application of negative pleural pressure to undersized lung grafts. J Thorac Cardiovasc Surg 2003;125:430-2.
6. Eberlein M, Reed RM. Donor to recipient sizing in thoracic organ transplantation. World J Transplant 2016;6:155-64.
7. Dezube R, Arnaoutakis GJ, Reed RM, et al. The effect of lung-size mismatch on mechanical ventilation tidal volumes after bilateral lung transplantation. Interact Cardiovasc Thorac Surg 2013;16:275-81.
8. Barnes L, Reed RM, Parekh KR, et al. Mechanical ventilation for the lung transplant recipient. Curr Pulmonol Rep 2015;4:88-96.
9. Beer A, Reed RM, Bölükbas S, et al. Mechanical ventilation after lung transplantation. An international survey of practices and preferences. Ann Am Thorac Soc 2014;11:546-53.
10. Tague LK, Bedair B, Witt C, et al. Lung protective ventilation based on donor size is associated with a lower risk of severe primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2021;40:1212-22. https://doi.org/10.1016/j.healun.2021.06.016.
11. Loring SH, Garcia-Jacques M, Malhotra A. Pulmonary characteristics in COPD and mechanisms of increased work of breathing. J Appl Physiol (1985) 2009;107:309-14.
12. Wilkens H, Weingard B, Lo Mauro A, et al. Breathing pattern and chest wall volumes during exercise in patients with cystic fibrosis, pulmonary fibrosis and COPD before and after lung transplantation. Thorax 2010;65:808-14. https://doi.org/10.1136/thx.2009.131409.
13. Yu WS, Park CH, Paik HC, et al. Changes in thoracic cavity volume after bilateral lung transplantation. Front Med 2022;9:881119. https://doi.org/10.3389/fmed.2022.881119.
14. Eberlein M, Permutt S, Brown RH, et al. Supranormal expiratory airflow after bilateral lung transplantation is associated with improved survival. Am J Respir Crit Care Med 2011;183:79-87.
15. Eberlein M, Permutt S, Chahla MF, et al. Lung size mismatch in bilateral lung transplantation is associated with allograft function and bronchiolitis obliterans syndrome. Chest 2012;141:451-60.
16. Eberlein M, Schmidt GA, Brower RG. Chest wall strapping. An old physiology experiment with new relevance to small airways diseases. Ann Am Thorac Soc 2014;11:1258-66.
17. Taher H, Bauer C, Abston E, et al. Chest wall strapping increases expiratory airflow and detectable airway segments in computer tomographic scans of normal and obstructed lungs. J Appl Physiol (1985) 2018;124:1186-93.

18. Eberlein M, Reed RM, Maidaa M, et al. Donor-recipient size matching and survival after lung transplantation. A cohort study. Ann Am Thorac Soc 2013;10:418-25.
19. Eberlein M, Arnaoutakis GJ, Yarmus L, et al. The effect of lung size mismatch on complications and resource utilization after bilateral lung transplantation. J Heart Lung Transplant 2012;31:492-500.
20. Eberlein M, Reed RM, Permutt S, et al. Parameters of donor-recipient size mismatch and survival after bilateral lung transplantation. J Heart Lung Transplant 2012;31:1207-13.
21. Eberlein M, Reed RM, Bolukbas S, et al. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. J Heart Lung Transplant 2015;34:233-40.