Case report

Spirometry testing for extracorporeal membrane oxygenation (ECMO) bridge to transplant patients

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ARTICLE INFO

Keywords:
Spirometry
Extra-corporeal membrane oxygenation (ECMO)
Pulmonary function test
Lung transplantation
Lung allocation score

ABSTRACT

Purpose: ECMO can provide a bridge to transplantation and improve survival for patients with advanced lung disease. Although pulmonary function testing (PFT) is an important component of the lung allocation score (LAS), it is not always feasible on patients requiring ECMO. While generally safe, PFT testing has contraindications and is not recommended in unstable patients. Currently there are no recommendations regarding the performance of spirometry in ECMO patients.

Study design: and Methods: We reviewed data on five patients with advanced lung disease requiring ECMO-bridge to transplant. After careful consideration of the theoretical physiologic risks associated with forced expiratory maneuvers, bedside spirometry was performed in order to update the patients’ LAS.

Results: All patients successfully completed three forced expiratory maneuvers in the seated position with a bedside spirometer. Vital signs and ECMO flow were stable during testing and without complication. In 2 patients who had both a LAS pre and post spirometry, the LAS increased by 3–5 points.

Conclusion: Spirometry results are pivotal to organ allocation under current organ sharing protocols. This case series demonstrates that bedside spirometry testing may be performed safely in patients on ECMO awaiting lung transplantation without appreciable side effects, leading to a more accurate LAS score.

List of abbreviations

ATS American Thoracic Society
BP Blood Pressure
COPD Chronic Obstructive Pulmonary Disease
FEV1 Forced Expiratory Volume in One Second

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https://doi.org/10.1016/j.rmcr.2021.101577
Received 29 September 2021; Accepted 30 December 2021
Available online 3 January 2022
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1. Introduction

Lung transplantation is the treatment of choice for selected patients suffering from end-stage lung disease \[1-6\]. Advances in surgical techniques have significantly reduced post-operative complications, resulting in 1-year survival that often exceeds 90% \[7\]. Patients with acute respiratory failure requiring respiratory support with invasive mechanical ventilation while awaiting lung transplantation have a significantly increased risk of dying, with wait list mortality for lung transplantation ranging from 5% to 10% \[8\].

In an effort to facilitate lung transplantation to more urgent and critically ill patients, the lung allocation score (LAS) system was implemented in 2005 \[9\]. The LAS involves a mathematical model that gives a quantitative score to a patient, representing their need of transplantation and their likely survival after transplantation, giving priority to patients with higher scores, and therefore sicker patients. The LAS is calculated on the basis of clinical data collected for each patient, including information such as functional status, exercise capacity, lung function, hemodynamic data, and the need for oxygen or ventilatory support \[10\]. If spirometry results are not available or updated in the prior 6 months, the lung function parameters included in the LAS calculation will default to normal and the result will be a lower overall LAS score which may underestimate the disease severity and decrease the chance of timely transplantation \[11\].

Extracorporeal Membrane Oxygenation (ECMO) can be the only lifesaving procedure for selected high-risk patients with respiratory failure due to advanced lung disease refractory to maximal mechanical ventilation \[12\]. However, there are inherent risks associated with performing testing in these patients, including pulmonary function tests (PFT) \[13,14\], that may limit the ability to appropriately update the LAS for those that need lung transplantation the most. While generally safe, spirometry poses physiologic demands that could make performance unsafe in patients currently receiving ECMO. During spirometry, the forced expiratory maneuver results in increased intrathoracic, intraabdominal, and intracranial pressures \[15-17\]. The main potential risks of spirometry are related to maximal pressures generated in the thorax and the subsequent impact on abdominal and thoracic organs, venous return and systemic blood pressure \[18\]. Patient safety incidents are reported in 5 of every 10,000 routine PFTs, with the most common event being syncope \[19\]. While many of these known physiologic impacts and safety incidents are usually well-tolerated, the effect in patients on mechanical augmentation of blood flow may not be. Thus, it is important to determine whether spirometry can be performed safely in these patients.

2. Materials and methods

2.1. Patient selection

After receiving an exemption from the Institutional Review Board at the University of Maryland, we retrospectively reviewed data on five ECMO patients evaluated for lung or heart-lung transplantation. Demographic, clinical data and surgical procedures were collected from the electronic medical record. Data detailing spirometry values, ECMO parameters and vital signs during the forced expiratory maneuvers were recorded.

2.2. Spirometry evaluation

Bedside spirometry was conducted in accordance with published guidelines \[14,19\] by an experienced, certified PFT technician using a spirometer, either the Microloop (CareFusion, Mettawa, Illinois, USA) or SpiroPro (ERT, Estenfeld, Germany). The patients were seated in chairs with the feet touching the ground. Three forced expiratory maneuvers were attempted by all patients. Forced vital capacity maneuvers were made according to the American Thoracic Society guidelines \[19\]. The patients took a deep breath in, as large as possible, and blew out as hard and as fast as possible. The patients were encouraged to keep blowing until no more air came out and the volume–time trace reached a plateau with <50 mL being exhaled in 2 seconds.
2.3. ECMO characteristics

ECMO circuits for all 5 patients included Maquet rotaflow centrifugal pump and quadrox oxygenator (Cardiopulmonary AG, Hirrlingen, Germany). Four patients required veno-venous (VV) ECMO support with cannulas placed in the common femoral vein (for drainage) and right internal jugular or femoral vein (for infusion). Patient 5 required veno-arterial (VA) ECMO with blood removed from the right atrium or vena cava (for drainage) and returned to the arterial system through peripheral cannulations via femoral arteries (for infusion).

3. Results

3.1. Case 1

A 62-year-old woman with combined chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and severe pulmonary hypertension (PH) presented to the hospital with acute on chronic hypoxemic respiratory failure. She had increased oxygen requirements 40 LPM, 100% FiO2 at humidified high flow nasal cannula (HFNC) (Vapotherm Precision Flow Plus, Exeter, NH, USA) alternating with non-invasive ventilation. She had progressive deterioration requiring VV ECMO cannulation ten days after presentation and was awaiting transplant. No spirometry data was available in the past six months. She was able to actively participate in physical therapy after ECMO cannulation and breathe without invasive ventilation. Spirometry was performed 11 days after ECMO cannulation in order to update her LAS and accurately reflect the severity of her disease (Table 2). She completed three forced maneuvers, one of which was useable (Table 3). Her vital signs and ECMO flow were stable during testing and there were no complications. Her LAS score did not significantly change after updating her spirometry results. She underwent bilateral lung transplantation one month later.

3.2. Case 2

A 49-year-old woman with sarcoidosis and PH presented with respiratory failure due to underlying disease progression with increased oxygen requirements, FiO2 90–100% (50LPM) on HFNC, compared to baseline of 4–6 LPM oxygen per nasal cannula (NC) at home. She was evaluated and listed for lung transplantation seven days after admission. For one month she had some improvement in O2 requirements (65–70% FiO2/35–40 LPM) HFNC that allowed her to ambulate daily. The patient had acute decompensation and required VV ECMO cannulation 58 days from admission. Despite a high LAS of 82, she did not have a suitable donor. In an attempt to update her score, bedside spirometry was performed, and her results were of high quality (Table 2 and 3). Her vital signs and ECMO flow were stable during testing and there were no complications. Her results were included in the updated LAS. Unfortunately, despite increasing her LAS score there was no suitable donor. She decompensated and was delisted 104 days later.

3.3. Case 3

A 53-year-old man diagnosed with pulmonary fibrosis 2 years prior to presentation was admitted with acute on chronic respiratory failure and increased O2 requirements - FiO2 90% HFNC (50 LPM) and FiO2 100% via non-rebreather mask. His baseline O2 requirement was 5–8 LPM per nasal cannula prior to admission. Ten days later he completed the transplant evaluation and was listed for lung transplant. The following day he decompensated and required cannulation for VV ECMO. There were no PFT results available prior to admission. Two days post ECMO cannulation, he was in a stable condition and underwent bedside spirometry testing in order to update his LAS score (Table 2 and 3). Both vital signs and ECMO parameters were stable during the spirometry (Table 1). Unfortunately, 7 days later he had a cardiorespiratory arrest due to overwhelming sepsis and died.

3.4. Case 4

A 62-year-old man with combined COPD, ILD, and PH was admitted with hypoxemic respiratory failure initially requiring 45–50% FiO2 HFNC and flow 50 LPM. Seventeen days after the admission, the patient had progressive deterioration requiring cannulation for VV ECMO. Two days after ECMO cannulation, the patient was able to participate with physical therapy/ambulate on ECMO and

| Patients: | HR (Beats/ min) | BP(mmHG) | RR (breath/ min) | O2 saturation (FiO2%) | Oxygen requirement (FiO2/LPM or LPM) | Flow (LPM) | Sweep (LPM) | RPM (RPM) | O2 saturation (FiO2%) |
|-----------|----------------|----------|----------------|----------------------|--------------------------------------|------------|-------------|-----------|----------------------|
| Patient 1 | 94             | 141/60   | 26            | 91%                  | 55%/40LPM                            | 4.04       | 4           | 3062      | 100                  |
| Patient 2 | 104            | 131/97   | 12            | 96%                  | 50%/40LPM                            | 3.86       | 3.5         | 3825      | 100                  |
| Patient 3 | 87             | 131/49   | 39            | 97%                  | 80%/50LPM                            | 4.88       | 4.5         | 3130      | 100                  |
| Patient 4 | 136            | 126/84   | 26            | 91%                  | 50%/30LPM                            | 4.72       | 2           | 2990      | 100                  |
| Patient 5 | 100            | 106/75   | 16            | 97%                  | 2LPM                                 | 4.73       | 2.5         | 3855      | 100                  |

HR: Heart Rate; Beats/min: beats per minute BP: Blood Pressure; RR: Respiratory rate; Breath/min: breath per minute; O2 saturation: Oxygen saturation HFNC: high flow nasal cannula; LPM: liter per minute; RPM: revolutions per minute; the parameters were recorded during the procedure and remained stable for 1 hour following the procedure.
| Patients: | PFT Time prior admission | Pre-ECMO FEV1 (L) | Pre-ECMO FEV1% | Pre-ECMO FVC (L) | Pre-ECMO FVC % | Pre ECMO FEV1/FVC % | LAS-Before PFT | On ECMO FEV1 (L) | On ECMO FEV1% | On ECMO FVC (L) | On ECMO FVC % | On ECMO FEV1/FVC % | LAS After Spirometry |
|-----------|--------------------------|------------------|----------------|-----------------|----------------|---------------------|----------------|-----------------|----------------|-----------------|----------------|---------------------|----------------------|
| Patient 1 | 21 months prior          | 1.43             | 64             | 1.99            | 70             | 72                  | 77             | 0.77            | 33             | 1.45            | 46             | 53                  | 77                   |
| Patient 2 | 7 months prior           | 0.735            | 29             | 0.75            | 35             | 90                  | 83             | 0.41            | 18             | 0.46            | 15             | 89                  | 89                   |
| Patient 3 | No PFTs                  |                  |                |                 |                |                     | 85             | 0.64            | 16             | 0.64            | 13             | 100                 | 87                   |
| Patient 4 | 6 months prior           | 0.91             | 39             | 0.93            | 31             | 78                  | 1.01           | 36              | 1.02           | 26              | 99             | No LAS              |                     |
| Patient 5 | 25 months prior          | 1.36             | 35             | 2.53            | 51             | 43                  | 0.80           | 22              | 1.02           | 22              | 78             | 85                  |                     |

ECMO: Extracorporeal Membrane Oxygenation; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; LAS: lung allocation score.
underwent spirometry testing with return of high-quality results (Table 2 and 3). Both vital signs and ECMO parameters (Table 1) were stable during the spirometry. The patient completed the transplant evaluation but 15 days later he developed sepsis and had progressive decompensation. He was deemed not to be a suitable transplant candidate and was not placed on the transplant list.

### 3.5. Case 5

A 56-year-old man with sarcoidosis and PH presented with acute respiratory failure due to worsening PH with increased oxygen requirements 85–90% FiO\(_2\)/30–35 LMP on HFNC compared to baseline 1–2 LPM oxygen by NC at home. He had a progressive decline requiring cannulation for VA ECMO 3 days after admission. As part of the transplant evaluation, he underwent bedside spirometry three days after ECMO cannulation, producing high quality test results (Table 2 and 3). He was listed for heart-lung transplantation shortly after spirometry was performed and was transplanted one month after ECMO cannulation. Vital signs and ECMO parameters (Table 1) were stable during the spirometry.

### 4. Discussion

This case series describes our experience with bedside spirometry on five ECMO bridge-to-transplant patients as part of their pre-transplant evaluation. The patients were able to tolerate spirometry well without changes in vital signs and ECMO hemodynamics. The additional data allowed the care team to update their LAS score and provide a more accurate representation of their pulmonary pathophysiology and disease severity. LAS score was increased in two out of five patients because of the ability to perform this testing. To our knowledge the performance of spirometry in patients requiring ECMO has not been reported before.

Patients with advanced lung disease who are otherwise excellent candidates for lung transplantation frequently develop acute decompensations before a donor organ becomes available [20]. ECMO support has evolved as a bridge to lung transplantation for patients with advanced lung disease failing invasive or non-invasive ventilation strategies [21].

Despite significant improvement in prioritizing organ donation after the introduction of the LAS, the mortality rate for waitlist patients with acute end-stage exacerbations continues to remain unacceptably high [22]. In fact, patients with pulmonary fibrosis with acute exacerbation can have mortality reaching up to 85% [23].

Parameters included in LAS calculation include assisted ventilation (NIV, Continuous Positive Airway Pressure –CPAP-, continuous or intermittent mechanical ventilation), supplemental oxygen and FVC % predicted. Currently, ECMO is not included in the LAS calculator and therefore the score does not reflect disease severity for those patients [24]. Additionally, for many patients admitted with rapid progression of their underlying disease, FVC % predicted is usually measured prior to acute decompensation and frequently it does not reflect the current level during the acute illness.

This case series demonstrates that bedside spirometry evaluation is feasible and can be performed safely in ECMO bridge to transplant patients in an attempt to document the severity of their disease. Spirometry allowed us to update LAS score and prioritize for lung transplantation accordingly.

Increasing evidence is proposing ECMO as the most suitable bridging strategy to increase the possibility to identify an appropriate donor. More than fifteen studies describe post-transplant experience and survival rate in ECMO bridge to transplant patients. One of the first articles presented the outcome of 26 ECMO bridge to transplant patients [25]. ECMO proved to be more effective in increasing chances to receive a transplant with an 80% survival at 6 months. A similar survival rate (74% versus 78%) was described in patients who received ECMO support compared to the control group that required mechanical ventilation before transplant [26]. Toyoda et al. also found comparable survival in ECMO vs control patients (74% vs 83%) despite significantly higher LAS score (87 ± 9 versus 44 ± 15) [27]. Recently, due to significant technological advancements, the survival of ECMO patients continues to improve as centers become more comfortable in managing those patients [28]. Therefore, a more recent study reported survival rates of 84% at two years post-transplant for ECMO bridge to transplant patients [29]. Survival is better when the ECMO bridge duration was shorter than 14 days compared to longer cannulation times (82% versus 29%) underlining the importance of an accurate updated LAS score to adequately represent the severity of illness in ECMO bridge patients [29]. We saw similar results in our small cohort as a longer cannulation time was associated with worse outcomes. Three of the five patients had significant decompensation and died while awaiting a suitable donor. Two patients underwent successful bilateral lung and heart lung transplantation respectively.

Although spirometry is a relatively safe procedure, negative consequences can still occur. At the present time high-risk

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**Table 3**

| Patient | Details | FVC repeatability (ml) | FEV1 repeatability (ml) | Quality grade |
|---------|---------|------------------------|-------------------------|--------------|
| 1       | Single useable FVC, not repeatable. FEV1 repeatable within 150 ml | 680 | 70 | U |
| 2       | 3 FVC maneuvers reach plateau, although none achieve 6 seconds | 40 | 50 | A |
| 3       | Single FVC maneuver achieves plateau and occurs <6 seconds; Shape of flow-volume loops all appear similar. | 10 | 40 | U |
| 4       | 3 FVC maneuvers reach plateau, although none achieve 6 seconds | 40 | 50 | A |
| 5       | 3 FVC maneuvers do not plateau or achieve 6 seconds, but best FVCs within 150 ml (satisfying end of forced expiration criteria). | 100 | 80 | A |

FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second. Quality grade details: A = ≥ 3 acceptable maneuvers, and two largest FVCs and two largest FEV1 values within 150 ml(13); U = ≥ 1 useable maneuvers but no additional scoring applied due to lack of maneuvers meeting acceptability criteria; F = no maneuvers meeting acceptability or usability criteria.
contraindications to PFT are cardiovascular complications such as myocardial infarction, pulmonary embolism or ascending aortic aneurysm. Potential harm from spirometry evaluation is considered to be related to the following factors: 1) the maximal pressures generated in the thorax can impact the function of the thoracic or abdominal organs; 2) large swings in blood pressure can cause stresses on distant tissues in the body (head, limbs, etc.); and 3) the spirometry maneuvers can cause expansion of the chest wall and lungs [25]. Currently there is no published literature evaluating the feasibility and safety of performing spirometry testing in patients cannulated for ECMO. Despite possible concerns that an increased intrathoracic pressure generated during a forced expiratory maneuver can cause variations in intra-thoracic pressure resulting in hemodynamic instability and/or hypoxia, our study demonstrated that bedside FVC values can be safely obtained in patients requiring ECMO support.

While spirometry was able to be performed safely, none of the participants were able to exhale for 6 seconds. All, however, produced maneuvers that satisfied end of forced expiration criteria thought to reliably assure a true FVC has been achieved [18]. Two out of the five patients (patients 1 and 3) had maneuvers that did not meet ATS quality criteria for acceptable and repeatable spirometry. These patients’ results, however, were considered useable, or grade “U” results. This category was added in the 2019 official ATS and European Respiratory Society update on Standardization of Spirometry to acknowledge the clinical utility of spirometry maneuvers from patients who may not be able to achieve the acceptability and repeatability criteria expected [19]. Patients that are impaired enough to require ECMO might lack the musculoskeletal strength or pulmonary capacity required to complete spirometry meeting traditional quality standards. Still, clinicians must check the quality of test results when determining usefulness in decision-making about lung transplant listing status.

Based on our experience with these five cases, we propose a protocol to assess a patient’s safety to perform spirometry testing in those requiring ECMO (Fig. 1).

Limitations

Our study is a single center small case series. Nonetheless, our results support the premise that bedside spirometry can be safely performed in patients with advanced lung disease requiring ECMO bridge to lung transplantation. The study was performed by a respiratory therapist with substantial clinical experience in close collaboration with the clinical team caring for the patient.

Strengths

The study addresses a clinically relevant question, as having an updated FVC and FVC % predicted measurement and revising the LAS score to reflect disease severity can improve a patient’s chance to receive an organ transplant in a timely manner. That would potentially decrease the chance of decompensation and death while awaiting a suitable organ to become available.

Implications and future directions

Development of progressive respiratory failure requiring maximal noninvasive or invasive mechanical ventilation has a significant

![Algorithm to assess a patient’s safety prior to perform spirometry testing.](image-url)

Cxray: chest radiography; KUB: Kidney, Ureter, Bladder radiography; ECMO: Extracorporeal Membrane Oxygenation; VS: Vital Signs; HR: Heart Rate; BP: Blood Pressure; O2 saturation: Oxygen saturation.

Fig. 1. Algorithm to assess a patient’s safety prior to perform spirometry testing.

Cxray: chest radiography; KUB: Kidney, Ureter, Bladder radiography; ECMO: Extracorporeal Membrane Oxygenation; VS: Vital Signs; HR: Heart Rate; BP: Blood Pressure; O2 saturation: Oxygen saturation.
impact on wait list mortality. Current therapeutic strategies to improve survival include ECMO cannulation in an attempt to decrease sedation requirements and increase participation in physical therapy. The goal is to decrease progression to decomposition and multi-organ dysfunction while waiting for an organ to become available. Performing testing required by United Network for Organ Sharing (UNOS) for updating the LAS score, like spirometry testing or 6-min walk testing, can be challenging while on ECMO. Despite that, accurately increasing the LAS score to reflect disease severity for patients requiring ECMO bridge to lung transplantation can be lifesaving.

Additional clinical studies designed to investigate the safety of performing spirometry in patients cannulated for ECMO and the association with clinical outcomes are necessary. If our findings can be replicated, bedside spirometry could be routinely used and have a meaningful impact in improving the chance for lung transplantation and overall survival in critically ill patients with advanced lung disease.

**Author contributions**

Irina Timofte MD was involved in conceptualization, study design and methodology, data collection, analysis, and writing the paper. Montserrat Diaz-Abad MD was involved in study design, data collection, and writing the paper. Fahid Alghanim MD was involved in study design, writing, editing, and reviewing the paper. Jordan Assadi MD was involved in study design, data collection, and writing the paper. Christine Lau MD was involved in data collection and writing the paper. Ronson Madathil MD was involved in study design and writing the paper. Bartley Griffith MD was involved in data collection and writing the paper. Daniel Herr, MD was involved in study design, data analysis, and writing the paper. Aldo Iacono MD was involved in study design, data analysis, and writing the paper. Stella Hines MD was involved in study design, data analysis, and writing the paper.

**Financial support**

None.

**Declaration of competing interest**

The authors whose names are listed in the manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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