Bronchoscopic volume reduction techniques are naturally compared with the outcomes of volume reduction surgery. However, only a minority of patients with emphysema would ever be suitable for surgery, so the majority of patients must rely on medical therapies. Therefore, how do the end points reported by Slebos et al[3] compare with both standard inhaled medical therapies and alternative emerging bronchoscopic therapies? Slebos et al[3] report a 15% (86 mL) improvement in FEV_1. In the Understanding Potential Long-term Impacts on Function With Tiotropium (UPLIFT) study with inhaled tiotropium, we witnessed an initial improvement of 47 to 65 mL in FEV_1, which then drifted back to baseline after 1 year.[5] In the Towards a Revolution in COPD Health (TORCH) study evaluating inhaled fluticasone and salmeterol in combination, the impact of treatment was characterized by a prevention in decline of FEV_1 by a net amount of 15 mL per year.[6] Consequently, the data reported by Slebos et al[3] relative to inhaled therapy are very encouraging, as are data emerging from other forms of endoscopic therapy for emphysema. The deployment of one-way Zephyr valves in selected patients with intact fissures and achieving lobar occlusion can result in a 16% improvement in FEV_1.[7] Bronchoscopic thermal vapor ablation therapy using a water-based energy system to induce unilateral localized injury with resulting lung volume reduction is reported as achieving a 139-mL (17%) improvement in FEV_1 and a reduction of 400 mL in residual volume at 6 months.[8]

These changes in end points are particularly impressive given that stage IV emphysema is characterized by extensive lung destruction. Therefore, minimally invasive bronchoscopic therapeutic strategies would appear to offer meaningful change relative to inhaled pharmacologic therapy. This is a critical issue for regulatory authorities to consider when these therapies are being evaluated for approval. The study presented by Slebos et al[3] is important because it addresses a large unmet patient need and potentially offers a meaningful alternative to volume reduction surgery and transplant.

Jim J. Egan, MD
Dublin, Ireland

Affiliations: From the National Advanced Lung Disease and Lung Transplantation Program, Mater Misericordiae University Hospital; St Vincent's University Hospital; Our Lady's Children's Hospital; and the National Organ Donation and Transplantation Office, Dr Stevens Hospital.
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Correspondence to: Jim J. Egan, MD, Mater Misericordiae University Hospital, Eccles St, Dublin, D7, Ireland; e-mail: jegan@mater.ie

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The Homogeneous and Robust Clinical Phenotype of Severe Lung Injury

Acute-onset severe lung injury, regardless of etiology or associated risk factors, is universally recognized in terms of its sameness. Patients with this condition share many similarities, including younger age, few comorbidities, recovery of lung function in those without preexisting lung disease, ICU-acquired weakness (ICUAW), and neuropsychologic dysfunction. These patients also share resilience and recovery from a profound, multisystem, and exuberant inflammatory response. These outcomes are robust over time and across different countries and investigators.

In this issue of *CHEST* (see page 583), Luyt et al[1] report on a cohort of survivors of severe ARDS related to the 2009 influenza A(H1N1) (A[H1N1]) pandemic and compare outcomes between those receiving extracorporeal lung assist (ECLA) or not and their respective and detailed health-related quality-of-life (HRQoL), pulmonary, functional, and neuropsychologic outcomes at 1-year follow-up. This very important and rigorous study shows that outcomes in this patient sample are comparable whether ECLA was used or not and that patients with severe lung injury

had near-normal pulmonary function with a decrease in diffusion capacity; minor changes on CT imaging; and decrements in HRQoL and prevalent anxiety, depressive symptoms, and risk for posttraumatic stress disorder. These findings bear a striking similarity to other cohorts of patients with severe ARDS, most notably the group evaluated at 6 months as part of the Conventional Ventilation vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial[2] and other cohorts reported over the past 10 to 15 years.[3-10]

The authors did an admirable job of addressing in detail the various limitations of their work, acknowledging the modest and highly selected study sample, the possibility of selection bias in the no-ECLA follow-up group, and the use of ECLA as an ARDS surrogate. In addition, this study, like so many other ICU outcomes studies, was compromised by loss to follow-up and, therefore, potential challenges to internal validity. However, the rigor of the in-person follow-up, the fact that the criteria for ECLA were prespecified and derived by content experts, and the depth of information collected on the survivors of severe ARDS after A(H1N1) are clear strengths and underscore the importance of this contribution to the literature.

Luyt et al[1] used manual muscle testing to support the contention that there are no important differences in weakness between ECLA and no-ECLA groups at 1 year. The inference here is that there never were differences between the groups. Muscle and nerve injury and resultant ICUAW represent major morbidities of critical illness[11-13] and may be permanent in some cases.[14] As highlighted by Levine et al[15] and De Jonghe et al,[16] there is a continuum of ICUAW that starts within hours of ICU admission and continues with demonstrable weakness by manual muscle testing at 1 week after mechanical ventilation and that persists over time. It is still not clear how best to capture this disability in recovering patients and whether we can rely on a single serially administered measure or need multiple complementary measures to more fully characterize differential weakness across muscle groups and how this translates into functional disability. There is some concern about the responsiveness and sensitivity of the Medical Research Council score and that it may not be wholly informative in the ICU or the early recovery period.[17] The sole reliance on the Medical Research Council score may represent another significant limitation in this study in terms of our ability to be confident that there were no subtle strength differences between groups.

Several ARDS cohort studies have evaluated functional improvement over time, and each reports that functional and HRQoL outcomes appear to plateau at 6 months to 1 year after ICU discharge and that most improvements occur within the first 3 to 6 months.[3,14] One notable strength of the study by Luyt et al[1] is that patients were followed up in their nearest center for clinical investigation and assessed in person. However, patients were evaluated only at 1 year after their critical illness, so there was no opportunity to understand the trajectory of recovery or barriers to rehabilitation along the way. Measurement of outcome at only one time point, which was quite distant from the illness event, may have obscured the ability to detect more-nuanced differences in outcome between the ECLA and the no-ECLA groups. Disability may change over time, and patients may not report or remember more remote issues that have since resolved. One noted difference between groups was the degree of weight loss sustained. The ECLA group lost a median of 6 kg, and the no-ECLA group showed no weight loss. It is possible that this finding may represent an important residual clue that muscle and nerve injury may be heightened or exacerbated by some aspect of ECLA treatment. The authors establish that there are few differences in multiple morbid outcomes at 1 year between patients who did or did not receive ECLA, but they have not helped the reader to know whether the trajectory of recovery was similar or whether important morbidities occurred early that may have impeded return to functional independence or favorable HRQoL. Knowledge of these more proximate outcomes, and especially those believed to be related to mechanical complications (eg, cannula placement, distal limb ischemia, compartment syndromes, ischemic foot drop) or the necessary anticoagulation of ECLA, may influence decision-making about choice of acute treatment modality for these patients.

Another important limitation in our understanding of differences between the ECLA and the no-ECLA groups is the lack of translational work on how ECLA affects muscle and nerve and how injury on a cellular and molecular level correspond to function. It is not clear whether there is something intrinsically different about the nature or distribution of muscle injury in those with a severe systemic inflammatory response who are supine and on a circuit and are preferentially receiving blood and oxygen delivery to more-dependent muscle groups. Further, there is uncertainty about whether any short- and long-term consequences of this unusual distribution of potential injury exist and whether we need to implement a different rehabilitation strategy for these patients. The uptake of early mobility[18,19] and ICU-based rehabilitation[19] has been extended to patients receiving ECLA, and it remains to be seen whether this will help to modify muscle injury and functional disability. Other ICU-based modalities, such as electrical muscle

stimulation, may prove to be important adjuncts to early mobility intervention and may need to be applied differentially if muscle injury appears to be a greater risk in ECLA. We are definitely in need of more sensitive and responsive diagnostic tools and a comprehensive and translational approach to evaluating muscle and nerve injury and determining whether important differences exist in residua between patients receiving and not receiving ECLA.

Outcomes across different cohorts of severely ill patients with ARDS are remarkably stable over time. Luyt et al[1] have made many comparisons to earlier ARDS and ECLA studies and, in particular, they discuss and reference the 5-year Toronto ARDS cohort.[14] Similar to their cohort, the patients in the Toronto ARDS cohort were relatively young, had few comorbidities, and were high functioning prior to their critical illness. Like the French A(H1N1) cohort, the Toronto patients became abruptly and catastrophically ill, and the majority had pneumonia and sepsis as the risk factor for severe lung injury. Patients had a median lung injury severity score of 3.7 out of 4.0 and had four-quadrant airspace changes by chest radiograph. These patients were recruited between 1998 and 2001, and many received a low tidal volume ventilation strategy, but more patients received some form of high-frequency ventilation with nitric oxide, proning, or both. This unusual practice pattern for severe lung injury in the late 1990s is still not the standard of care in 2012, but the unmistakable phenotype of the patient with severe lung injury and the associated outcomes are constant. There appears to be a marked homogeneity in this group that transcends time.

Severe lung injury is a reproducible and homogeneous clinical phenotype but not a generalizable one. It is an ideal study sample for evaluating the efficacy of different ventilation strategies and ECLA. The study by Luyt et al[1] contributes important new knowledge from its in-person and in-depth evaluation of multiple morbidities at 1-year follow-up. Because of the limitations discussed, it is still unclear whether there are differences in early morbidity between ECLA and no-ECLA groups, and this will require a similar commitment to detailed in-person evaluation proximate to ICU discharge and with serial follow-up to determine whether the functional recovery associated with each group is, in fact, similar. Furthermore, we need to understand the potential muscle injury associated with ECLA and to develop or adopt muscle strength and function measures that fully capture muscle group weakness and how this translates into different types of limitations. We need to understand the cost of cannulation, anticoagulation, and the potential for immobility and to determine whether these risks are favorable compared with the potential to accrue more lung damage and perpetuation of the systemic inflammatory response and propagation of organ dysfunction. This study represents just one group of patients, and our challenge is to eventually construct, study, and establish different risk groups from the heterogeneous critically ill population and link these to specific morbidities and outcome. We need to work toward an understanding of a spectrum of disability after critical illness and the identification of different and easily recognizable clinical phenotypes for this. Patients with severe lung injury are a unique group in this spectrum.

Margaret S. Herridge, MD, MPH
Toronto, ON, Canada

Affiliations: From the University of Toronto, University Health Network.
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Correspondence to: Margaret S. Herridge, MD, MPH, University of Toronto, University Health Network, 11NCSB-1180, 585 University Ave, Toronto, ON, M5G 2C4, Canada; e-mail: margaret.herridge@uhn.on.ca

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Scleroderma Lung-Associated Cough

More Than Meets the Eye?

In this issue of *CHEST* (see page 614), Theodore et al[1] examined whether cough is related to disease activity and its response to immunosuppressive therapy. Most of the subjects in the study had dry, intermittent, mild to moderate cough. Only 5% (n = 6) reported severe persistent cough, and only 9% had productive cough. They found that only cough frequency, but not severity or phlegm production, correlated with lower physical quality of life, more dyspnea, and lower diffusing capacity of the lung for carbon monoxide. Subjects who reported cough as a symptom had more fibrosis (higher lung and skin fibrosis scores) when compared with subjects without cough. After 1 year of treatment with cyclophosphamide, the percentage of subjects reporting cough decreased over the 6- to 18-month time period. The improvement was not sustained and was gone by 24 months. Based on these findings, the authors suggest that cough may be a surrogate measure of ongoing fibrosis and alveolar inflammation.

Cough, as a symptom of interstitial lung diseases, has not received a lot of attention in the literature. Cough in scleroderma interstitial lung disease is particularly challenging. Aside from cough generated by pulmonary processes, patients often have distal esophageal dysmotility and gastroesophageal reflux,[2] are taking angiotensin-converting enzyme inhibitors, and may have xerotrachea.[3] In this study, there was no significant difference between subjects with scleroderma interstitial lung disease with and without cough in terms of gastroesophageal reflux disease (GERD). Does this mean that GERD-associated cough is excluded? Patient self-reported GERD symptoms were used in the study. Objective measurements of esophageal reflux or laryngeal examination for laryngopharyngeal reflux were not included. In a study using 24-h esophageal pH impedance monitoring, pathologic reflux was more common in those with lung involvement (80%) than in those without lung involvement (59%).[4] Fifty percent of subjects had silent reflux. Recently, the association of nonspecific interstitial pneumonitis with centrilobular fibrosis and foreign bodies in one-third of lung biopsy specimens from patients with scleroderma interstitial lung disease led researchers to suspect that microaspiration may be a contributor to lung disease progression.[5] Can GERD-associated cough be absolutely excluded in this study? Probably not, but until there are data to suggest that microaspiration responds to cyclophosphamide, we have to discount GERD as a major trigger for cough in this study. As the authors pointed out, cyclophosphamide should not have affected cough due to GERD.

The cause of cough in scleroderma interstitial lung disease and in other interstitial lung diseases is poorly understood. The reported association between cough and lung fibrosis in this study is intriguing. When noxious stimuli are applied to the airways, they trigger cough and not pain. Cough may be the pain equivalent of the airways and reflect epithelial nerve irritation. There is circumstantial evidence to suggest that neurogenic inflammation may be involved in lung fibrosis[6] and in cough.[7-9] Subjects with idiopathic pulmonary fibrosis and scleroderma interstitial lung disease have heightened cough response to capsaicin.[10,11] Capsaicin stimulates chemosensory-induced cough reflex mediated by unmyelinated C fibers within the airway epithelium via transient receptor potential cation channel member V 1 (TRPV1) (capsaicin receptor). Stimulation of TRPV1 and transient receptor potential cation channel, subfamily A, member 1 (mustard oil receptor) on unmyelinated nerve fibers can induce cough.[7,12] Activation of TRPV1 receptors is accompanied by the release of sensory neuropeptides. Among these, calcitonin gene-related peptide causes vasodilatation,[13] whereas neurokinin A (NKA) and substance P can induce plasma protein extravasation. In vitro, substance P and NKA can stimulate human lung fibroblasts to proliferate. NKA is chemotactic to fibroblasts.[14] Increased circulating levels