

# Therapeutic exercise in improving acute lung injury: a long distance to be covered

Nikoletta Rovina, Antonia Koutsoukou, Nikolaos Koulouris

Intensive Care Unit, 1st Department of Respiratory Medicine, National & Kapodistrian University of Athens Medical School, "Sotiria" Hospital for Chest Diseases, Athens, Greece

Correspondence to: Nikoletta Rovina. Lecturer in Respiratory and Critical Care Medicine. 152 Mesogeion Ave, 11527, Athens, Greece.

Email: nikrovina@med.uoa.gr.

Submitted Aug 14, 2015. Accepted for publication Aug 18, 2015.

doi: 10.3978/j.issn.2305-5839.2015.09.13

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.09.13>

Skeletal muscle weakness is a common finding among critically ill patients, and many factors have been recognized to trigger its initiation early in the patients' course in intensive care unit (ICU) (1). In acute respiratory distress syndrome (ARDS), a clinical condition which is characterized by acute respiratory failure, skeletal muscle weakness acquired in ICU is present in 25-50% of patients, and is independently associated with mortality and long term morbidity in survivors (2). Several clinical research studies suggest that early mobilization of critically ill patients improves clinically meaningful outcomes for the patient (3), however, without having clarified the mechanisms underlying this implementation. We read with interest the study by Files *et al.* (4) who through their experiments suggest a unifying mechanism underlying the beneficial effects of therapeutic exercise in mice with lung injury. In their study authors exercised ALI mice for 2 days after lipopolysaccharides (LPS) instillation. They found that a short duration of moderate intensity exercise attenuated muscle ring finger 1 (MuRF 1)-mediated atrophy of the limb and diaphragm and improved limb muscle force generation. Importantly, exercise also limited neutrophilic influx into the alveolar space through modulation of a co-ordinated systemic neutrophil chemokine response. Furthermore, in ALI mice exercise reduced granulocyte colony-stimulating factor (G-CSF), and *in vivo* blockade of the G-CSF receptor lead to recapitulation of the lung. Similarly, in humans with acute respiratory failure, early mobility therapy led to greater decrements over time in G-CSF plasma levels compared to control patients, confirming the relevance of G-CSF as a mediator of the

improved outcomes of mobilized/exercised critically ill patients.

Although multiple factors may contribute to ALI-induced muscle wasting including inadequate nutrition, prolonged inactivity due to bed rest, and systemic inflammation, the pathophysiology of ALI-related skeletal muscle atrophy remains obscure. Understanding the molecular mechanisms that promote and control ALI-associated skeletal muscle wasting is essential in designing therapeutic approaches targeting this syndrome. Files *et al.* (5) have previously presented a mouse model of ALI-associated skeletal muscle wasting in which they demonstrated that muscle specific E3 ubiquitin ligase MuRF 1, is a critical mediator of the ALI-associated skeletal muscle wasting that occurs in this model. Initiation of muscle atrophy in this model is temporally tied to lung injury and the persistence of muscle weakness after resolution of lung injury, that is present in a large percentage of patients at least 5 years post-hospitalization (6). These changes were associated with increased MuRF 1 mRNA and protein expression, and high levels of NF- $\kappa$ B activity in ALI mice, which has been correlated with tumor cachexia and denervation. Interestingly, genetic inactivation or biochemical suppression of MuRF 1 in ALI muscles suppressed MuRF 1 transcriptional activation in ALI mice.

In the work of Files *et al.* (4) exercise seems to have specific immunomodulatory effects, most notably on limiting the mobilization and recruitment of neutrophils from the bone marrow to the lung, with G-CSF being a key mediator of this process. The role of G-CSF on mobilization and activation of neutrophils is well described (7) and is supported in this study, too. G-CSF seems to be a pathogenic biomarker in

ARDS since it was proved to contribute in neutrophilic injury and exercise helped in reducing its levels over time. Authors propose that therapeutic exercise in mice and humans may act as rheostat that controls neutrophilic invasion in the lung by reducing G-CSF. However, the mechanism responsible for G-CSF decrease during exercise is not fully understood, and furthermore, its role in other models of critically ill, such as sepsis for example, should be addressed in future studies. It is apparent that the limitation of neutrophilic recruitment to the lung in response to exercise in mice and humans favorably modulates the local immune response however, it gives no clue on potential functional changes that may concern neutrophils *per se*, and this is an important issue that should be further explored. Furthermore, the roles of other differentially regulated cytokines besides G-CSF should be examined in future studies, in order to clarify the pathways implicating in the improvement seen in ALI mice after exercise.

Although this study provides a mechanism whereby early mobility therapy attenuates muscle wasting and limits ongoing alveolar neutrophilia there are several issues we should take in account when we relate the experimental ALI model with critically ill patients with ARDS. In ventilated critically ill patients with ARDS several factors contribute to the degree and type of inflammation in the lungs, i.e., the oxygen supply, the type of ventilation, infections, etc. Thereby, many other pathways may interfere with the local (in the lungs) and systemic inflammation (which contributes to muscle wasting) differentiating the response in mobilization. Another important issue which was pointed out in this study is that timing and intensity of early mobility therapies may have a different response (detrimental or protective). The results of this study imply that mobility in the critically ill should start as early as possible, with low to moderate exercise intensity (5-25 min twice daily) which seems to be protective. This study suggests that early mobilization of patients with ARDS is a promising therapy to improve the outcomes of these patients; this would be extremely interesting in clinical practice, if for example, it proves to favorably assist the easier and earlier weaning by enhancing the diaphragmatic strength. Therapeutic exercise is shown to improve neutrophilic lung injury and skeletal muscle wasting in ALI mice, however there is a long distance to be covered until the mechanisms underlying its benefits are fully elucidated in critically ill patients with

ARDS, in order new therapeutic targets to be explored.

## Acknowledgements

None.

## Footnote

*Provenance:* This is a Guest Editorial commissioned by the Section Editor Hui Kong, MD, PhD (Department of Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References

1. Ali NA, O'Brien JM Jr, Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med* 2008;178:261-8.
2. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
3. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82.
4. Files DC, Liu C, Pereyra A, et al. Therapeutic exercise attenuates neutrophilic lung injury and skeletal muscle wasting. *Sci Transl Med* 2015;7:278ra32.
5. Files DC, D'Alessio FR, Johnston LF, et al. A critical role for muscle ring finger-1 in acute lung injury-associated skeletal muscle wasting. *Am J Respir Crit Care Med* 2012;185:825-34.
6. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293-304.
7. Greenbaum AM, Link DC. Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. *Leukemia* 2011;25:211-7.

**Cite this article as:** Rovina N, Koutsoukou A, Koulouris N. Therapeutic exercise in improving acute lung injury: a long distance to be covered. *Ann Transl Med* 2015;3(18):273. doi: 10.3978/j.issn.2305-5839.2015.09.13