Muscle Wasting and Early Mobilization in Acute Respiratory Distress Syndrome

Christopher J. Walsh, MD, FRCPC[a], Jane Batt, MD, FRCPC, PhD[a],
Margaret S. Herridge, MD, FRCPC, MPH[b],
Claudia C. Dos Santos, MD, FRCPC, MSc[a,*]

KEYWORDS

• Muscle weakness • Neuromuscular disease • Critical illness • ARDS • Intensive care unit
• Early rehabilitation

KEY POINTS

- Patients with acute respiratory distress syndrome frequently develop persistent muscle weakness and poor functional outcome attributed to intensive care unit (ICU)–acquired weakness (ICUAW).
- Risk factors for ICUAW include sepsis, immobility, and hyperglycemia.
- Clinical diagnosis of ICUAW by physical examination has limitations, even in cooperative patients.
- Early rehabilitation programs in the ICU have been shown to be safe and feasible and have resulted in improved functional status after ICU discharge.
- Few interventions are available for prevention of ICUAW. Elucidating the molecular pathways that cause ICUAW is critical to develop novel targeted therapeutics.

INTRODUCTION

Survivors of acute respiratory distress syndrome (ARDS) frequently develop substantial and persistent muscle weakness associated with impairments in physical function and health-related quality of life.[1–4] Intensive care unit (ICU)–acquired weakness (ICUAW), well described in the acute phase of critical illness, is increasingly recognized to contribute to long-term disability in survivors of critical illness.[2,4–6] Skeletal muscle wasting and weakness acquired during critical illness may result from muscle dysfunction, loss of myosin and less commonly, frank myofiber necrosis (critical illness myopathy [CIM]), axonal sensory-motor axonopathy (critical illness polyneuropathy [CIP]), or a combination of both. Both processes manifest clinically as muscle weakness, induced by the resultant and variable combination of muscle wasting and impaired muscle contractility.[6]

In the acute phase, ICUAW is associated with failure of ventilator weaning, prolonged ICU stay, and increased mortality.[7–10] In patients who survive, ICUAW may resolve completely over several weeks.[11] However, a large proportion of patients

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[a] Department of Medicine, Institute of Medical Sciences, Keenan Centre for Biomedical Science, Li Ka Shing Knowledge institute, St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada; [b] Interdepartmental Division of Critical Care, University of Toronto, Toronto General Hospital, NCSB 11C-1180, 585 University Avenue, Toronto, ON M5G 2N2, Canada
* Corresponding author.
E-mail address: dossantosc@smh.ca

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(40%–65%) have diminished functional capacity 5 years after ICU discharge (ie, reduced 6-minute walk [6MW]). The determinants of this persistent ICUAW remain inadequately defined.[2,9]

Inactivity has been shown to accelerate loss of muscle protein in severe illness and is a risk factor for ICUAW.[12,13] Early rehabilitation is hypothesized to prevent disuse atrophy and improve muscle strength in both short-term and long-term ICU survivors. An increasing number of interventional studies have emerged over the past decade examining muscle function and ICUAW as outcomes, notably trials implementing early rehabilitation in the ICU setting.

This article highlights the risk factors and molecular mechanisms associated with ICUAW and examines the current evidence for prevention and management of muscle weakness in critically ill patients, with a focus on early rehabilitation.

RISK FACTORS FOR INTENSIVE CARE UNIT–ACQUIRED WEAKNESS

Classification of ICU patients within clinical phenotypes has the potential to accurately stratify patients by likelihood of persistent weakness.[14] Several risks factors for ICUAW have been identified in multiple studies, including sepsis, immobility, and hyperglycemia. Age, burden of comorbid disease, and ICU length of stay have been recognized as major risk modifiers of long-term recovery of function after critical illness (Fig. 1).

Patients with sepsis and multiorgan dysfunction syndrome (MODS) are at high risk for ICUAW; a recent systematic review found a nearly 50% incidence of ICUAW in this population.[12] The severity and duration of both systemic inflammatory response syndrome (SIRS) and MODS have been associated with ICUAW in several studies and several investigators have concluded that ICUAW is one manifestation of MODS.[11,15–19] ICUAW has been associated with immobilization in several studies using the duration of mechanical ventilation (MV) and ICU stay as indirect measures of immobility.[11,15,20]

Hyperglycemia, a frequent complication of critical illness and inactivity, has been linked to ICUAW in multiple observational studies[12] and in 2 large randomized controlled trials (RCTs) of insulin therapy that examined the effect of intensive insulin therapy (IIT) versus conventional insulin therapy (CIT) on ICUAW as a secondary outcome.[21,22] The first RCT screened for ICUAW by electromyography weekly in 363 surgical patients requiring ICU stay for 1 week or more. The trial found a reduced incidence of ICUAW (28.7% vs 51.9%; $P<.001$) and a faster resolution of ICUAW in the IIT group versus CIT.[22] The second RCT enrolled 420 medical ICU patients requiring more than 1 week in the ICU and found similar outcomes.[22] Both trials showed reduced

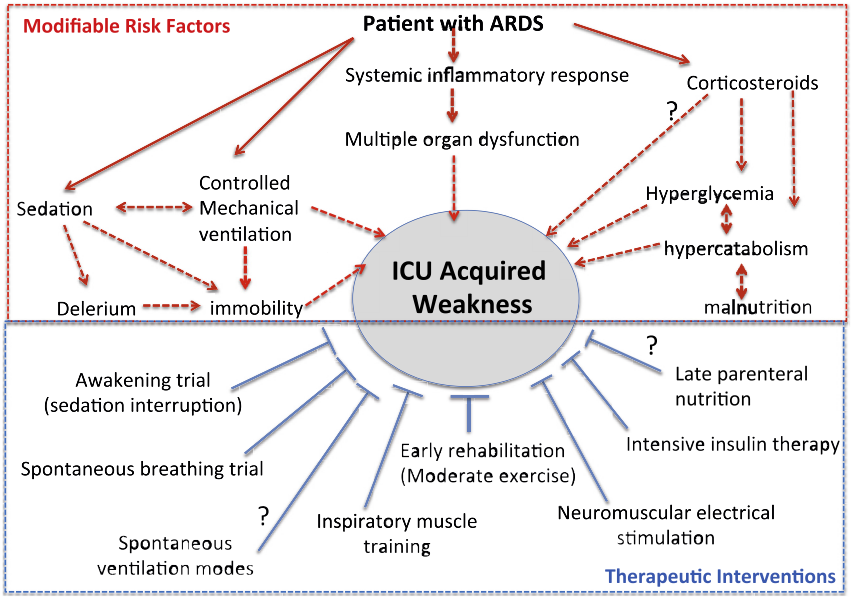

Fig. 1. Modifiable risk factors for muscle atrophy and ICUAW (*above*) and potential therapeutic interventions (*below*) in a mechanically ventilated patient with ARDS. Solid red arrows denote interventions for ARDS. Dashed arrows denote adverse effects of the intervention in addition to underlying critical illness/ARDS. Interventions with predominantly inconclusive or contradictory findings in the literature are denoted by a question mark (?).