Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay. A Pilot Study.


Abstract

RATIONALE: Critical illness survivors often experience permanent functional disability due to intensive care unit (ICU)-acquired weakness. The mechanisms responsible for long-term weakness persistence versus resolution are unknown.

OBJECTIVES: To delineate cellular mechanisms underlying long-term weakness persistence in ICU survivors.

METHODS: We conducted a nested, prospective study of critically ill patients mechanically ventilated for 7 days or longer. The patients were recruited from the RECOVER program and serially assessed over 6 months after ICU discharge. Twenty-seven of 82 patients consented to participate; 15 and 11 patients were assessed at 7 days and 6 months after ICU discharge, respectively.

MEASUREMENTS AND MAIN RESULTS: We assessed motor functional capacity, quadriceps size, strength, and voluntary contractile capacity and performed electromyography, nerve conduction studies, and vastus lateralis biopsies for histologic, cellular, and molecular analyses. Strength and quadriceps cross-sectional areas were decreased 7 days after ICU discharge. Weakness persisted to 6 months and correlated with decreased function. Quadriceps atrophy resolved in 27% patients at 6 months. Muscle mass reconstitution did not correlate with resolution of weakness, owing to persistent impaired voluntary contractile capacity. Compared with Day 7, increased ubiquitin-proteasome system-mediated muscle proteolysis, inflammation, and decreased mitochondrial content all normalized at 6 months. Autophagy markers were normal at 6 months. Patients with sustained atrophy had decreased muscle progenitor (satellite) cell content.

CONCLUSIONS: Long-term weakness in ICU survivors results from heterogeneous muscle pathophysiology with variable combinations of muscle atrophy and impaired contractile capacity. These findings are not explained by ongoing muscle proteolysis, inflammation, or diminished mitochondrial content. Sustained muscle atrophy is associated with decreased satellite cell content and compromised muscle regrowth, suggesting impaired regenerative capacity.

KEYWORDS: autophagy; mitochondria; muscle atrophy; satellite cell; ubiquitin–proteasome system
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