

COMMENTARY

The role of inflammation in ICU-acquired weakness

Chris Winkelman*

See related research by Weber-Carstens *et al.*, <http://ccforum.com/content/14/3/R119>

Abstract

A pilot observational study by Weber-Carstens and colleagues contributes to a mechanistic explanation of the puzzling and complex phenomena of ICU-acquired weakness (ICU-AW). The authors suggest systemic, inflammatory-mediated pathology is the most significant risk factor for ICU-AW. While this finding is somewhat equivocal, it provides important direction for future investigations and illustrates the challenges of interpreting significance in small observational studies.

The pilot observational study by Weber-Carstens and colleagues [1] provides important contributions to a mechanistic explanation of the puzzling and complex phenomena of ICU-acquired weakness (ICU-AW). Earlier findings from this research group suggested that ICU-AW is primarily a myopathy [2] and confirmed that initial pathology manifests, on average, 7 days after ICU admission among the most severely ill [2-4]. In the current subanalysis with 40 of the original 52 subjects, multiple factors were examined for association with myopathy: molecular (IL-6, C-reactive protein (CRP), and insulin growth factor binding protein (IGFBP)-1); serum osmolarity; medication use (norepinephrine, dobutamine, hydrocortisone, aminoglycosides, analgesics, sedatives and neuromuscular blocking agents); and multi-system factors (simplified acute physiology (SAPS-2) and sequential organ failure assessment (SOFA) scores).

The authors suggest systemic, inflammatory-mediated pathology is the most significant risk factor for ICU-AW. The results on IL-6 show that its effects are actually quite modest. While IL-6 had a significant contribution to the statistical model, the hazard ratio of 1.006 indicated a higher IL-6 (>230 picograms/ml) is little better than chance in predicting inexcitable muscle membranes (see

Figure 7 in [1]). CRP, the second inflammatory biomarker, was not associated with abnormal muscle excitability ($P = 0.075$). However, the sample size for this analysis was small. It may simply be that there are insufficient numbers of results to derive a meaningful Cox regression equation - allowing a reasonable 10 samples per factor/covariate, a sample size of 160 would provide more value to the statistical model (16 covariates; see Table 2 in [1]).

The authors also report a hazard ratio for norepinephrine similar to that for IL-6. Along with the relative differences in the presence of septic shock and organ dysfunction in Table 1 in [1] among participants with/without inexcitable muscle membrane, this finding lends support to oxidative stress or the interaction of oxidative stress and pro-inflammatory biomarkers as risk factors for myopathy in ICU patients [5]. Findings from this study illustrate the challenges of translating basic science to clinical settings. Multiple measures and more complex clinical data, such as a heterogeneous sample as in this report, make it difficult to derive important conclusions from small samples.

Building a framework to identify ICU-AW early and to evaluate efficacy of treatments is essential. Between 25 and 50% of patients who receive mechanical ventilation for 7 or more days experience neuromuscular abnormalities and these abnormalities can result in weakness and impaired function years after discharge from the ICU [6]. In the United States, from 1997 to 2006, the number of ICU patients who received mechanical ventilation and were subsequently discharged to home has decreased while transfers to long-term acute care increased significantly without concomitant changes in survival [7]. For older adults discharged with new or additional dependency in daily activities after hospitalization, less than 31% return to prehospital function [8]. Determining interventions that alter muscle pathology and associated dysfunction among patients who experience prolonged mechanical ventilation, whether from a mechanistic or a holistic perspective, has the potential to reduce the duration of mechanical ventilation and length of hospital stay [9].

The role of IL-6 and other cytokines in muscle dysfunction is not yet clear. In healthy adults, very high levels can be myogenic after intense exercise [10]. Yet

*Correspondence: Chris.Winkelman@case.edu
Frances Payne Bolton School of Nursing, Case Western Reserve University,
10900 Euclid Ave, Cleveland, OH 44106, USA

IL-6 is also associated with proteolysis and myosin loss [11]. Among patients with chronic inflammatory conditions/diseases, serum IL-6 is related to muscle wasting and dysfunction [12]. In ICU patients, IL-6 can be unconnected to illness severity yet predictive of mortality [13,14]. The sources of IL-6 - muscle versus leukocyte - may also be important to muscle pathology.

Developing understanding of basic pathology and establishing predictive biomarkers will provide the opportunity for new hypothesis testing. In this exploratory report of risk factors associated with abnormal responses to direct muscle stimulation, molecular to multisystem levels of covariates were examined [1]. Future studies will be more compelling when focused on single-level, inter-related pathways. Investigations related to molecular cascade interactions are providing insight into the genetic, signaling, bioenergetic, and metabolic processes that contribute to muscle health and disease. Understanding of molecular determinants of common diseases encountered in the critically ill can provide the rationale for selection of therapeutic targets [15]. If a serum IL-6 value >230 picograms/ml is confirmed in future studies as an early indicator of muscle dysfunction, then the efficacy of prevention and treatment strategies may be measured rapidly and inexpensively by IL-6.

Observational data like this report provide important information with which to calculate effect size and determine promising biologic pathways for future investigations. Results also suggest that the timing of interventions to prevent ICU-AW may need to occur earlier than typically occurs in many settings as serum IL-6 and muscle stimulation responses were abnormal quite early in the majority of patients who went on to manifest ICU-AW.

Abbreviations

CRP = C-reactive protein; ICU-AW = ICU-acquired weakness; IGF1 = insulin growth factor binding protein; IL = interleukin; SAPS = simplified acute physiology; SOFA = sequential organ failure assessment.

Competing interests

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