Acquired Weakness in Critically Ill Patients

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The number of patients populating critical care units in the United States has grown steadily over the past 2 decades. This growth has occurred as the result both of implementation of technological advances that can keep patients alive longer and also in response to the application of ever-more sophisticated therapies (ie, organ transplants and advanced chemotherapy) that often have complications that require intensive care. While there is an overall benefit to the use of increasing complex technologies to keep patients alive, substantial morbidity also is associated with use of these therapies.

One major cause of morbidity in this patient population is the development of significant limb and respiratory skeletal muscle weakness and atrophy. Recent work indicates that these patients develop far more severe weakness than usually is recognized by the clinicians taking care of them, and this weakness lasts far longer after discharge from the hospital than people realize.[1-3]

This phenomenon is best supported by data from a study by Herridge et al, which measured the post-discharge strength and exercise tolerance of patients who were hospitalized for adult respiratory distress syndrome (ARDS).[1] ARDS, characterized by acute lung injury, affects 200,000 Americans each year. Approximately 70,000 of these patients die during hospitalization, but 130,000 survive the syndrome and are eventually discharged.

Herridge et al found that, on average, these patients do not return to work until 8-12 months after hospital discharge, and at 1 year, have a level of exercise capacity that is only 66% of the normal level (Table). Moreover, pulmonary function returns to normal in the majority of these patients at an early point after discharge, and it appears that reductions in long-term exercise capacity are linked to peripheral skeletal muscle dysfunction. Herridge et al recently have updated these data and find that exercise capacity remains substantially lower than normal, even 5 years after hospital discharge. Anecdotally, many of these patients give histories of having the ability to walk only short distances (eg, 40 feet) immediately after discharge, with an impaired ability to perform many of the tasks of daily living.

Table. Walk Distance and Return to Work Status of Survivors of ARDS[1]

Outcome	3 Months	6 Months	12 Months
Distance walked in 6 minutes			
Number evaluated	80	78	81
Median (m)	28	396	422
Interquartile range (m)	55-454	244-500	277-510
Percentage of predicted value	49	64	66
Returned to work Number/total number (%)	13/83 (16)	26/82 (32)	40/82 (49)

m=meter

Adapted from "Canadian Critical Care Trials Group: One-year outcomes in survivors of the acute respiratory distress syndrome" by Herridge et al. *New England Journal of Medicine* 2003;348:683. ©2003 by New England Journal of Medicine.

Top panel presents distance walked in 6 minutes; bottom presents number returned to work. At 1 year after discharge, walk distance was only 66% of predicted, and the number that had returned to work was only 49%.[1]

In addition to this severe limb muscle weakness, some work suggests that many critically ill patients develop significant weakness of the respiratory muscles. This is of special concern, because weakness of this particular muscle group contributes to respiratory failure and can prolong the time these patients require mechanical ventilatory support. Theoretically, this problem could result in a downward spiral, with critical care illnesses engendering respiratory muscle weakness, respiratory muscle weakness necessitating continued ventilatory support, and continued ventilator support leading to complications that sustain or worsen the level of critical care illness.

In support of this concept, two recent studies reported that critically ill patients requiring sustained mechanical ventilation have surprisingly severe reductions in diaphragm strength.[2,3] Both studies used bilateral magnetic stimulation to activate the phrenic nerves in the neck, and both recorded the transdiaphragmatic pressure evoked by supramaximal twitch stimuli to achieve an objective index of respiratory muscle strength. Laghi et al found that the average patient requiring mechanical ventilation had diaphragm twitch transdiaphragmatic pressures that were only 23% of the level measured in a healthy control population.[2] Watson et al reported similar data, with transdiaphragmatic pressures decreased on average to levels only 36% of controls.[3] Furthermore, we have found some groups of critically ill patients to have even more severe reductions in diaphragm strength, with levels as low as 2%-5% of normal values recorded in individual patients.

Several factors appear to predispose critically ill patients to the development of skeletal muscle weakness and wasting. For one thing, these patients often are heavily sedated and relatively

immobile, with disuse atrophy probably a major factor contributing to the development of weakness. Moreover, the respiratory muscles seem especially prone to the development of disuse atrophy, such that use of ventilator modes that result in little or no respiratory muscle contraction (eg, controlled volume-cycled or pressure-limited ventilation in the presence of heavy sedation and/or paralytic agents) may rapidly induce severe diaphragm atrophy and weakness.[4] In addition, patients often fail to receive even minimal levels of nutrition because of procedural delays, and malnutrition may become a major factor contributing to skeletal muscle weakness and atrophy.

A high percentage of ICU patients are infected at some point during their ICU stay with infections, both precipitating the need for ICU admission (eg, pneumonia, urinary tract infection) and complicating ICU stay (eg, line infections, ventilator-associated pneumonia). It is known that infection-induced systemic inflammation has profound effects on muscle function because of the direct and indirect effects produced by cytokines, and even minor infections (eg, colds) can produce enormous reductions (30%-40%) in the functional capacity of respiratory and limb muscles.[5] More serious infections produce even larger reductions in muscle function, with reductions in strength up to 50%-80% observed in both human and animal studies of severe sepsis (Fig 1).[6] Other factors that are present in critically ill patients and are associated with the development of skeletal muscle weakness include hyperglycemia, congestive heart failure, vitamin D deficiency, uremia, hypophosphatemia, and steroid administration.

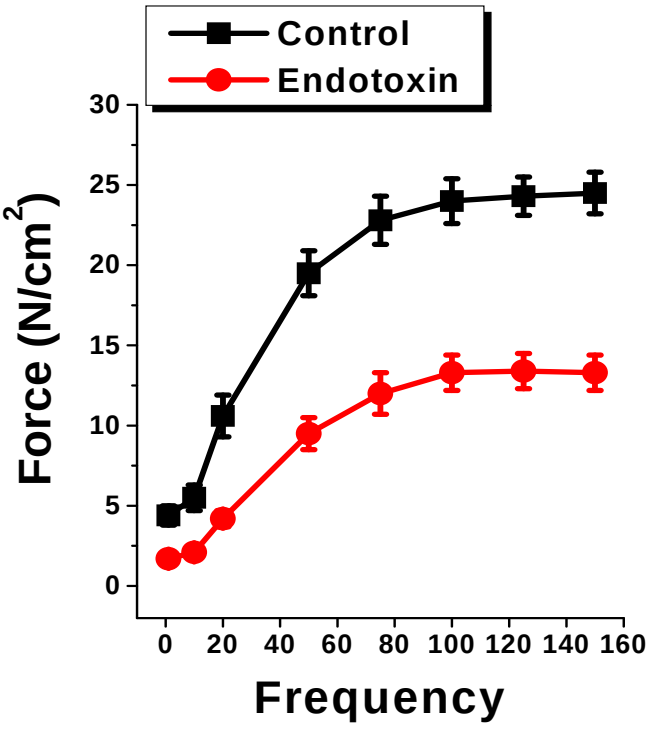


Fig 1. Skeletal muscle force-frequency curves with and without endotoxin treatment. Animals were treated with saline or endotoxin, killed at 24 hours, skeletal muscle excised, and muscle force determined in vitro in response to electrical excitation over a range of stimulation frequencies. Force was markedly reduced at all stimulation frequencies for muscle samples taken from lipopolysaccharide (LPS) (endotoxin)-treated animals.[7]

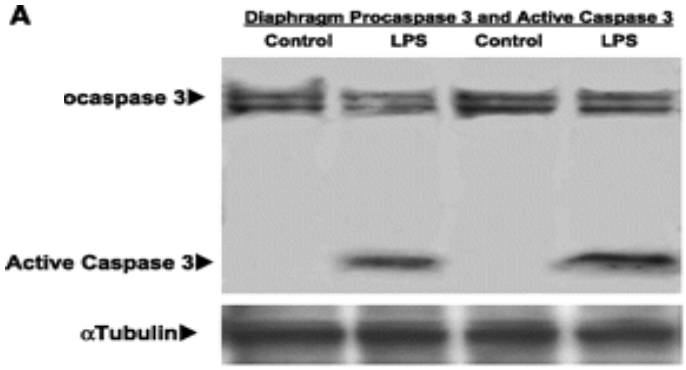
A substantial amount of recent work has examined the mechanisms by which these various stresses induce muscle weakness. Our own work has focused on the mechanisms by which infections alter muscle function, but many of the cellular pathways involved in sepsis-related muscle weakness also contribute to muscle dysfunction engendered by other pathophysiological processes (eg, disuse, hyperglycemia). Studies suggest that infection-induced muscle dysfunction does not result from activation of a single enzyme pathway and is not attributable to damage of a single subcellular structure, but probably represents the interacting effects of activation of a number of pathophysiological processes, which damage a number of subcellular organelles.

Animal models of infection, for example, are shown to cause a disruption of skeletal muscle sarcolemmal membranes, a depletion of sarcolemmal sodium-potassium ion exchange proteins, alterations in sarcoplasmic reticulum calcium turnover, a marked reduction in the intrinsic force-generating capacity of the contractile proteins, a reduction in mitochondrial adenosine triphosphate (ATP) synthesis rates, a reduction in mitochondrial ATP transport capacity, depletion of critical mitochondrial electron transport constituents, a reduction in creatine kinase levels, and depletion and dysfunction of skeletal muscle phosphofructokinase, a key enzyme required for glycolysis.[8-11] These subcellular alterations reduce the ability of muscle to both generate a single contraction and to sustain repetitive contractions.

Several pathophysiological processes are perhaps responsible for producing these multiple defects in skeletal muscle functional capacity. It is possible to broadly group these into two classes, factors that accelerate protein degradation in muscle and factors that impair protein synthesis. Recent studies demonstrate a marked increase in multiple elements of the proteasomal proteolytic pathway in sepsis, including an increase in ubiquitin, the 20S proteasome component, and several E3 ligases (atrogin and MuRF1 [ie, muscle ring finger 1]).[12,13] In keeping with the importance of the proteasome in sepsis, administration of proteasome inhibitors in an animal model of sepsis is shown to result in a marked reduction in protein degradation, as judged by use of the tyrosine release assay.[14]

In addition, calpain and caspase proteases are both shown to become activated in skeletal muscle in inflammatory states (Fig 2).[15,16] Both proteases can cleave important components of skeletal

muscle contractile apparatus and cytoskeleton, including actin, actinin, and spectrin in the case of caspase, and myosin, talin, and spectrin in the case of calpain. It is thought that calpain and caspase activation may result in destabilization of the contractile protein matrix, leading to a disruption of force generation and facilitating release of contractile elements that can be subsequently degraded by the proteasome.[17,18] These proteolytic pathways are regulated by signaling pathways, and recent reports indicate that several upstream kinases, including p38 and PKR (protein kinase R), play essential roles in regulating the activation of proteolytic processes in response to inflammatory stimuli.[19,20]



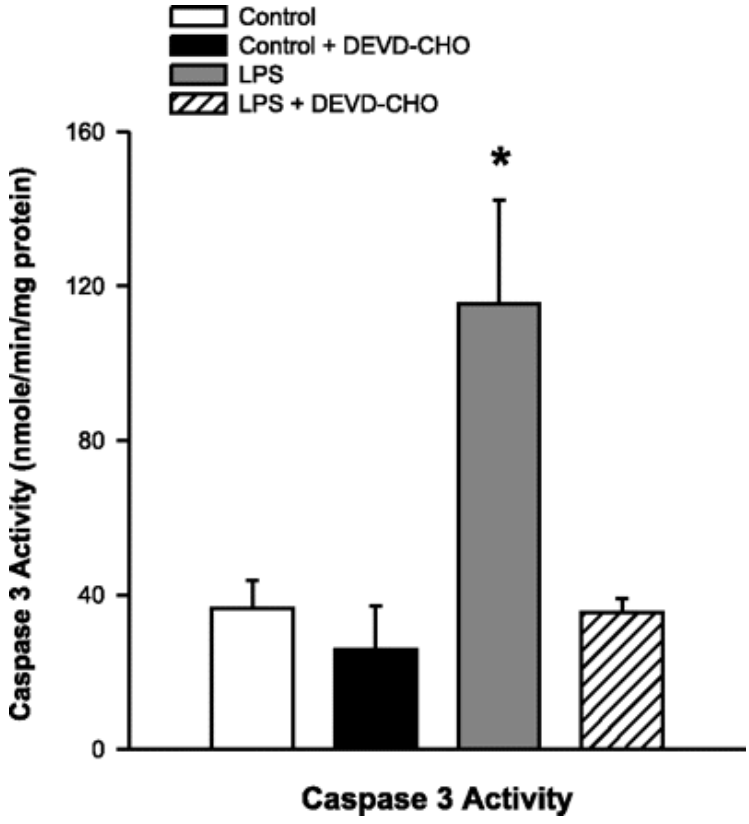


Fig 2. Skeletal muscle caspase activity following endotoxin administration. Top panel presents active caspase protein levels for skeletal muscle from control and endotoxin (LPS)-treated animals. LPS induced a large increase in active caspase protein. Bottom panel presents caspase activity levels assessed for muscle samples from control and LPS-treated animals; as an additional control, samples were run with and without addition of DEVD-CHO, an exogenous caspase inhibitor. LPS administration markedly increased muscle caspase activity.[16]

The precise mechanisms by which inflammation reduces protein synthesis also has undergone considerable recent study and appears to involve alterations in circulating hormone levels that normally modulate protein synthesis (eg, corticosteroid levels) and, in addition, muscle-specific alterations in the activity of regulators of translation, such as eIF2Bepsilon (eukaryotic initiation factor 2B epsilon) and eIF2α.[21,22] Reductions in protein synthesis by as much as 50% can occur within a few days in response to infection and other inflammatory stimuli, and this process alone may result in a significant reduction in skeletal-muscle protein stores.

Summary

Loss of functional capacity of skeletal muscle is a major cause of morbidity in patients with critical illnesses. Weakness in these patients can manifest as either severe limb muscle weakness and/or respiratory muscle weakness, requiring mechanical ventilatory support. Several factors appear to interact to induce weakness in these patients, including inactivity, poor nutrition, infection, drugs, and hyperglycemia. These various factors are thought to interact to activate several proteolytic pathways (ie, the proteasome, caspase, and calpain) and to impair protein synthesis. A complete understanding of the cellular pathways by which skeletal-muscle proteolysis is enhanced and protein synthesis is reduced in critically ill patients should lead to the

discovery of cellular pathways that can prevent weakness and wasting in this patient population through therapeutic targeting.

References

1. Herridge MS, Cheung AM, Tansey CM; Canadian Critical Care Trials Group: One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683-693.

2. Laghi F, Cattapan SE, Jubran A, et al: Is weaning failure caused by low-frequency fatigue of the diaphragm? *Am J Respir Crit Care Med* 2003;167:120-127.

3. Watson AC, Hughes PD, Louise Harris M, et al: Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. *Crit Care Med* 2001;29:1325-1331.

4. Levine S, Nguyen T, Taylor N, et al: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327-1335.

5. Poponick JM, Jacobs I, Supinski G, DiMarco AF: Effect of upper respiratory tract infections on respiratory muscle strength in patients with neuromuscular disease. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):659-664.

6. Lanone S, Mebazaa A, Heymes C, et al: Muscular contractile failure in septic patients: Role of the inducible nitric oxide synthase pathway. *Am J Respir Crit Care Med* 2000;162:2308-2315.
7. Supinski G, Nethery D, Nosek TM, et al: Endotoxin administration alters the force vs. pCa relationship of skeletal muscle fibers. *Am J Physiol Regul Integr Comp Physiol* 2000;278:R891-R896.

8. Callahan LA, Nethery D, Stofan D, et al: Free radical-induced contractile protein dysfunction in endotoxin-induced sepsis. *Am J Respir Cell Mol Biol* 2001;24:210-217.

9. Callahan LA, Stofan DA, Szweda LI, et al: Free radicals alter maximal diaphragmatic mitochondrial oxygen consumption in endotoxin-induced sepsis. *Free Radic Biol Med* 2001;30:129-138.

10. Callahan LA, Supinski GS: Downregulation of diaphragm electron transport chain and glycolytic enzyme gene expression in sepsis. *J Appl Physiol* 2005;99:1120-1126.

11. Callahan LA, Supinski GS: Diaphragm and cardiac mitochondrial creatine kinase are impaired in sepsis. *J Appl Physiol* 2007;102:44-53.

12. Roth GA, Moser B, Krenn C, et al: Heightened levels of circulating 20S proteasome in critically ill patients. *Eur J Clin Invest* 2005;35:399-403.

13. Wray CJ, Mammen JM, Hershko DD, Hasselgren PO: Sepsis upregulates the gene expression of multiple ubiquitin ligases in skeletal muscle. *Int J Biochem Cell Biol* 35:698-705, 2003.

14. Kadlciková J, Holecek M, Safránek R, et al: Effects of proteasome inhibitors MG132, ZL3VS and AdaAhx3L3VS on protein metabolism in septic rats. *Int J Exp Pathol* 2004;85:365-371.

15. Fareed MU, Evenson AR, Wei W, et al: Treatment of rats with calpain inhibitors prevents sepsis-induced muscle proteolysis independent of atrogin-1/MAFbx and MuRF1 expression. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R1589-R1597.

16. Supinski GS, Callahan LA: Caspase activation contributes to endotoxin-induced diaphragm weakness. *J Appl Physiol* 2006;100:1770-1777.

17. Du J, Hu Z, Mitch WE: Cellular signals activating muscle proteolysis in chronic kidney disease: A two-stage process. *Int J Biochem Cell Biol* 2005;37:2147-2155.

18. Powers SK, Kavazis AN, DeRuisseau KC: Mechanisms of disuse muscle atrophy: Role of oxidative stress. *Am J Physiol Regul Integr Comp Physiol* 2005;288:R337-R344.

19. Supinski GS, Callahan LA, Ji X: p38 MAP kinase modulates endotoxin induced diaphragm caspase activation. *Am J Respir Cell Mol Biol* 2009 Aug 28. [Epub ahead of print]

20. Supinski GS, Callahan LA: PKR kinase modulates endotoxin induced diaphragm caspase 8 activation [publication page A4201]. Presented at: American Thoracic Society Meeting; May 19, 2009; San Diego, CA. Available at: http://www.abstracts2view.com/ats09/view.php?nu=ATS09L_4547&terms. Accessed January 23, 2010.

21. Svanberg E, Frost RA, Lang CH, et al: IGF-I/IGFBP-3 binary complex modulates sepsis-induced inhibition of protein synthesis in skeletal muscle. *Am J Physiol Endocrinol Metab* 2000;279:E1145-E1158.

22. Vary TC, Deiter G, Kimball SR: Phosphorylation of eukaryotic initiation factor eIF2Bepsilon in skeletal muscle during sepsis. *Am J Physiol Endocrinol Metab* 2002;283:E1032-E1039.

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Q & A

Q: The data you show with LPS is very similar or maybe in a slightly different order to what I [Dr Tisdale] showed with the LPS in tissue culture. We also find, by the way, that hyperglycemia induces an activation of PKR; so, you could have the same mechanism.

The question I was going to ask was that I [Dr Tisdale] showed Tuesday that HMB [beta-hydroxy-beta-methylbutyrate] also was effective in attenuating the increase in caspase and PKR and preventing the muscle protein degradation in vitro. Did you consider using this, as well as EPA [eicosapentaenoic acid], in your animal model and maybe patients?

Dr Supinski: That is a great suggestion, and we would like to test a number of therapies in the animal model. That is a great therapy, because I think we could rapidly translate it to human use. We have found some other potential treatments in animals that are theoretically usable in people. Obviously, I can not give a calpain inhibitor 3 to a patient, but there are other ways to inhibit caspase and calpain. I think that is an excellent suggestion.

Q: My question is with the selectivity of the mediators, such as the caspase and calpain and p38. Are we talking about something at the receptor level?

Dr Supinski: Well, it is one of the things we focused on. We think that the receptors involved in this are probably cytokine receptors, TNF, and interleukin. In sepsis and in critical patients in general, use of receptor antagonists to cytokines has not worked out very well.

Our thesis and contention are that cytokine receptor antagonists block these pathways too far upstream, inhibiting the good as well as the bad effects of cytokines such as TNF [tumor necrosis factor]. You want TNF to activate neutrophils. You want neutrophils to kill bacteria. As a result, we believe that it may be an important therapeutic strategy to try to selectively block some of the far-downstream effects of cytokines, focusing on blocking detrimental effects alone. The processes we are trying to block (ie, caspase, calpain, and PKR) are fairly downstream. We believe this helps in two ways. First, we will not interfere with the normal functions of cytokines, such as TNF, and second because we are blocking later pathophysiological events, we have more time from the onset of illness to administer our treatments.

Q: You mentioned that force dropped as the first thing, and then mitochondrial function.

Dr Supinski: Yes, force drops first, then mitochondrial function declines, and finally we see loss of muscle mass and protein content (ie, muscle wasting).

Q: I was wondering if you could you speculate about what you think causes this drop in muscle function as the first thing?

Dr Supinski: It is profound, and we have seen it over and over again in every one of our infectious models. We think what is happening initially is that the contractile protein lattice is perturbed. I think it almost has to be this way, because you have to break the proteins out of that lattice before you can degrade them. When they first come out of the lattice or the lattice is

disrupted, the proteins remain in the cell. As a result, protein content and muscle mass remain normal initially. Subsequently, these proteins become fodder for the proteasome inhibition pathway.

Now, one of the other things we have seen, which I did not present, is if we give a proteasomal inhibitor, it does nothing to these reductions in strength. I think that protein degradation is a two-step process. First, relatively selective proteases, such as caspase and calpain, break apart the lattice. Afterward, the contractile proteins fall out and are available for degradation by the proteasome. Force drops when the lattice is initially disrupted; muscle mass and protein content decline when the removed proteins are degraded. Perhaps the proteasome may be largely degrading proteins that do not work anyway in our sepsis models. This is our interpretation.

Now, the mitochondrial alterations are also interesting. We observe increased free-radical generation from mitochondria very early (and far before we observe reductions in mitochondrial function). Is that part of the same process? Is that part of the triggering pathway for activation of all of these proteolytic pathways? I do not know.

Q: I did not catch how long you supplemented with EPA. Was it was long enough to change the membrane composition? I also wonder if you could speculate on EPA's inhibiting calpain activation, and in the backdrop of oxidative stress, if it is through neuroprostanes and isoprostanes.

Dr Supinski: I think it is a good bet that EPA may affect lipid constituents, including isoprostanes. Our initial hypothesis was that EPA administration to septic animals would not affect force. We thought it was going to affect wasting. We measured all these indices (force, mass, and protein content) just to be complete. We were shocked when we found that EPA was capable of inhibiting calpain and preventing force loss. We would speculate that EPA may stabilize membranes and in some way prevent calcium release as a potential explanation for its ability to inhibit calpain.

To answer your question, I am not completely sure. I will bet it is something related to isoprostanes or PLA2, or something to do with the membrane and calcium release through membranes. It probably is that mechanism. This is the first time anyone has shown, to my knowledge, that with EPA you can affect calpain activation. We certainly were not looking for it, but this is what we found.