Ventilator-induced Diaphragm Dysfunction

From Mice (Hopefully) to Men

In the 60 yr since Danish anesthesiologist Bjorn Ibsen initiated the widespread use of positive pressure ventilation during the Copenhagen poliomyelitis epidemic of 1951, the concerns have shifted beyond saving lives to minimizing iatrogenic harm. Webb and Tierney’s seminal 1974 report of ventilator-induced lung injury1 initiated 3 decades of research culminating in the ARDS (acute respiratory distress syndrome) Network trial that confirmed the survival benefit of lower versus higher tidal volumes.2 Although efforts over the last 10–20 yr have concentrated on minimizing damage to the lungs (i.e., ventilator-associated lung injury), harm to the diaphragm caused by mechanical ventilation (i.e., ventilator-induced diaphragm dysfunction [VIDD]) is becoming more widely appreciated. The study of VIDD receives an important boost with the report by Mrozek et al. in the current issue of Anesthesiology of a mouse model that enables reliable exploration of the mechanisms involved.3

The association between mechanical ventilation and respiratory muscle weakness was first reported in baboons by Anzueto et al. in 1997 (although reported in abstract a decade before)4; several studies have since replicated these findings in multiple species. All the models demonstrate that controlled mechanical ventilation results in a significant loss of respiratory (but not peripheral skeletal) muscle strength and endurance after hours or 2–3 days. VIDD is likely an important clinical problem. Diaphragm biopsy specimens from brain dead patients reveal characteristic histologic patterns; indeed, rapidly progressive inspiratory muscle weakness has been reported within 1–2 days of mechanical ventilation in intensive care unit patients. Inspiratory muscle weakness is highly prevalent among mechanically ventilated patients and is associated with a longer duration of ventilation. Because respiratory muscle strength is a key determinant of weaning success (or failure), VIDD probably prolongs mechanical ventilation and increases its associated complications.5

The report by Mrozek et al. provides additional evidence that suppression of respiratory muscle activity during controlled mechanical ventilation leads rapidly to diaphragmatic contractile dysfunction.5 In the study, mice were subjected to controlled mechanical ventilation, continuous positive airway pressure, or control conditions. The results are reassuringly similar to models reported previously: controlled mechanical ventilated mice demonstrated 40% lower maximal diaphragmatic force versus control, with no impact from continuous positive airway pressure; loss of diaphragm endurance paralleled these findings, and there were no effects on peripheral skeletal muscle.

Ventilator-induced diaphragm dysfunction is characterized by atrophy of type 1 and 2 muscle fibers, as well as by myofibrillar disarray, oxidative injury, and autophagy. Molecular explanations include altered gene expression, with stress-response and proteolytic genes up-regulated and structural and metabolic genes down-regulated.6 Proteolytic systems, such as calcium-dependent proteases (calpain) and caspase, modulate disassembly of the myofilament framework; cleaving these regulatory proteins renders muscle susceptible to ubiquitination and destruction by the ubiquitin-proteasome system. Autophagy, a self-degradative proteolytic pathway has been demonstrated in the diaphragms of brain dead organ donors after 18–69 h of mechanical ventilation. The imbalance between proteolysis and protein synthesis leads to atrophy; myofibrillar disarray produces loss of contractile force that is out of

“A pressing example awaiting explanation is how muscle inactivity triggers the cellular changes associated with [ventilator-induced diaphragmatic dysfunction].”


Accepted for publication March 29, 2012. Supported by a New Investigator Award from the Canadian Institutes of Health Research, Ottawa, Ontario, Canada (to Dr. Ferguson), and the Dr. Geoffrey Barker Research Chair in Critical Care Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada (to Dr. Kavanagh). The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Copyright © 2012, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2012; 117:463–4
proportion to the degree of atrophy. Although the precise events
that initiate the cascade of injury within the diaphragm myocyte
remain unidentified, oxidative stress resulting in injury to key
contractile elements (e.g., myosin and actin) appears to be a key
upstream trigger. That antioxidants such as N-acetylcyesteine
significantly attenuate muscle injury in vitro suggests that ox-
diative injury plays a role; indeed, reactive oxygen species seem to
originate from the myocyte mitochondria, and a mitochondrial-
specific antioxidant may attenuate diaphragmatic injury. Many
such mechanisms in the pathogenesis of VIDD need to be un-
derstood to formulate strategies for prophylaxis or therapy.

In the murine model of VIDD described by Mrozek et al.
there was no histologic evidence of muscle atrophy despite a
dramatic reduction in contractile function. Such uncoupling
of muscle weakness from atrophy has been reported previ-
ously in VIDD. This (early) weakness likely results from the
initial myofibril disassembly that is required before muscle pro-
tein can be ubiquitinated and degraded.7 Consistent with pre-
vious reports, the caspase-3 proteolytic system was found to be
up-regulated in the controlled mechanically ventilated mice.
Thus, this model seems to reflect well other models of VIDD.

How will this model facilitate increasing our understand-
ing of VIDD? The beauty of a murine model is that a wide
variety of molecular techniques and assays as well as geneti-
cally modified animals are available, allowing dissection of
potential molecular mechanisms. A pressing example await-
ing explanation is how muscle inactivity triggers the cellular
changes associated with VIDD. A postulated candidate is
titin, a long filamentous sarcomeric protein that functions as
a mechanosensor by altering its signaling kinase domain ac-
tivity in response to mechanical stretch8; selective expression
of this gene or mutation of its kinase domain would allow explo-
ation of its role in VIDD.

The study also supports the interesting hypothesis that the
risk of VIDD is proportional to the rate of protein turn-
aver. The authors predicted that the mice would develop
VIDD after only 6 h of mechanical ventilation by extrapo-
lating protein turnover rates from previous VIDD animal
models (piglet, rabbit, rat) to mice. They reported contractile
dysfunction (but no atrophy) at the 6-h point, suggesting that
the muscle injury pathways are not simply related to a
local imbalance in cellular protein synthesis and catabolism,
at least in the initial stages of VIDD. Nevertheless, organisms
with higher protein turnover rates may develop the lesion
more quickly; this hypothesis merits further confirmation.
Of course, some critically ill patients have extremely high
rates of protein catabolism, and these patients may be at
higher risk of VIDD; this could help to guide the selection
of high-risk patients for study.

One universally reported feature of VIDD is that it is
induced by suppression of diaphragm activity during me-
chanical ventilation, so-called disuse atrophy. The report by
Mrozek et al. supports the theory of disuse atrophy; mice
subjected to anesthesia and positive airway pressure that
maintained diaphragm activity (continuous positive airway
pressure mice) had no loss of contractile function. Because
maintenance of some respiratory muscle activity attenuates
the severity of VIDD, it has been suggested that spontaneous
modes of ventilation be used when possible.2 Multiple fac-
tors other than mechanical ventilation affect diaphragm
function (e.g., sepsis, corticosteroids, neuromuscular block-
ade, antibiotics, nutritional deficiency)9 and may compound
the VIDD lesion or limit the benefit of maintaining respira-
tory muscle activity; here the murine model might provide
insights into which conditions contribute most.

Whether attempts at preventing or treating VIDD ulti-
mately will help critically ill patients remains to be seen. But
it is likely that insights enabled by careful development of a
valid murine experimental model will help guide our pursuit
of better care for patients receiving mechanical ventilation.
Bjorn Ibsen would be pleased.

Ewan C. Goligher, M.D., F.R.C.P.(C),* Niall D. Ferguson,
M.D., M.Sc., F.R.C.P.(C),† Brian P. Kavanagh, M.B.,
F.R.C.P.(C)‡ Interdepartmental Division of Critical Care
Medicine, University of Toronto, Toronto, Ontario, Canada.
†Department of Medicine, Division of Respirology, Uni-
versity Health Network and Mount Sinai Hospital, and the
Interdepartmental Division of Critical Care Medicine, Uni-
versity of Toronto. ‡Department of Critical Care Medicine,
Hospital for Sick Children and the Department of Anesthe-
sia, University of Toronto. brian.kavanagh@utoronto.ca

References
1. Webb HH, Tierney DF: Experimental pulmonary edema due to
intermittent positive pressure ventilation with high inflation
pressures. Protection by positive end-expiratory pressure. Am
2. Ventilation with lower tidal volumes as compared with tradi-
tional tidal volumes for acute lung injury and the acute respi-
atory distress syndrome. The Acute Respiratory Distress Syn-
A, Cassan C, Thireau J, Molinari N, Futier E, Scheuermann V,
Constantin J-M, Matecki S, Jaber S: Rapid onset of specific
diaphragm weakness in a healthy murine model of ventilator-
duced diaphragmatic dysfunction. Anesthesiology 2012;
117:560–7
Moore G, Cox WJ, Coalson JJ: Effects of prolonged controlled
mechanical ventilation on diaphragmatic function in healthy
5. Tobin MJ, Laghi F, Jubran A: Narrative review: Ventilator-
153:240–5
6. Powers SK, Kavazis AN, Levine S: Prolonged mechanical ven-
tilation alters diaphragmatic structure and function. Crit Care
Med 2009; 37:S47–51
7. Sassoon CS, Caiozzo VJ, Manka A, Sieck GC: Altered dia-
aphragm contractile properties with controlled mechanical
8. Ottenheijm CA, van Hees HW, Heunks LM, Granzier H: Titin-
based mechanosensing and signaling: Role in diaphragm atro-
phy during unloading? Am J Physiol Lung Cell Mol Physiol
2011; 300:L161–6
Respir Crit Care Med 2003; 168:10–48