# Hyperglycemia and diaphragmatic weakness in ICU patients

**Maria Gabriela Suarez MD, Avinash Adiga MD**

Diaphragmatic weakness usually presents with dyspnea, orthopnea, rapid, shallow breathing, paradoxical inward motion of the abdomen during inspiration, and/or a restrictive pattern on lung function testing.[1] It can occur in diseases involving the motor cortex, spinal cord, phrenic nerves, and diaphragmatic muscle. Diaphragmatic weakness in ICU patients is associated with poor outcomes, including prolonged duration of mechanical ventilation and higher ICU mortality.[2,3] The incidence of diaphragmatic dysfunction in critically ill patients ranges from 40 % to 60 %, and when compared with normal individuals, these patients have 23% less diaphragmatic force generated during the respiratory cycle.[4,5] Several factors have been associated with diaphragmatic weakness, and these include sepsis, mechanical ventilation, and low albumin levels. [6-8] Hyperglycemia has also been reported to have a detrimental effect on respiratory muscle performance in ICU patients.[9,10] Twenty-five percent of all mechanically ventilated patients have difficulty weaning off mechanical ventilation.[8,11] The exact percentage of cases related to hyperglycemia is uncertain, because there is limited information on the association between diaphragmatic weakness, hyperglycemia, and delayed extubation in ICU patients.

Diaphragmatic weakness in the ICU patients could be secondary to neuropathy or myopathy induced by hyperglycemic states.[12,13] Most of the complications related to hyperglycemia are secondary to both microvascular and macrovascular complications induced by increased production of superoxide in endothelial cells of vessels and the myocardium resulting in decreased tissue perfusion.[13] Major pathways involved in pathogenesis of complications secondary to hyperglycemia induced superoxide overproduction include increased reactive oxygen species production from mitochondrial electron transport chain, polyol pathway flux, increased formation of advanced glycation end products, increased expression of receptors for these end products and its activating ligands, increased activity of hexosamine pathway, and activation of protein kinase C isoforms.[13-15]

***Corresponding author:*** **Maria Gabriela Suarez**
***Contact Information:*** gabriela.suarez@ttuhsc.edu
***DOI:*** 10.12746/swrccc2016.0413.168

Increased reactive oxygen species (ROS) generated from hyperglycemia alter single fiber contractile protein function evidenced by loss of diaphragm troponin T. In skeletal muscles, ROS activate signaling kinases, like JNK, PKR, and p38, which trigger downstream pathways, most importantly the caspase pathway, the proteasomal degradation pathway, and factors regulating protein translation.[16,17] Du and Russel reported that hyperglycemia activates skeletal muscle caspase-3 degrading myofibrillar proteins, specifically actin which leads to subsequent activation of the ubiquitin-proteasomal degradation pathway causing muscle atrophy and a decrease in protein synthesis.[18] Vincent, et al. also noted that two hours of high glucose exposure (20 mM added glucose) resulted in severe oxidative stress, mitochondrial disruption, activation of caspase 3, and apoptosis in cultured neurons, leading to neuronal and tissue damage.[19]

Animal studies on hyperglycemia and diaphragm dysfunction report that N-acetylcysteine and other thiol containing compounds can reverse hyperglycemia induced diaphragm weakness by detoxifying a variety of reactive electrophiles and by inhibiting the cytotoxic effects of tumor necrosis factor alpha (TNFα) on the diaphragm.[20]These results suggest that diaphragmatic weakness in hypergly-

cemia is mediated by TNFα or oxidative stress. Administration of scavengers and free radical inhibitors have also shown to reduce endotoxin/infection related diaphragm dysfunction.[21] An immunomodulatory chemical, eicosapentaenoic acid, has been shown to decrease the endotoxin mediated diaphragm dysfunction by altering sarcoplasmic reticulum function and calpain activation thereby reducing diaphragm weakness.[22]

Clinical studies have demonstrated that strict glucose control reduces ICU acquired diaphragm weakness and shortens the duration of mechanical ventilation and ICU length of stay in critically ill patients.[2] Hermans, et al. studied the effect of intensive insulin therapy on polyneuropathy/myopathy and prolonged mechanical ventilation in patients in the intensive care unit for at least 7 days. They showed that patients assigned to intensive insulin therapy had a reduced incidence of critical illness polyneuropathy/myopathy and required less mechanical ventilation.[23] Van den Berghe, et al. found that maintaining blood glucose in the 80 to 110 mg/dl range in ICU patients markedly reduced the time required to wean patients from mechanical ventilation, shortening the ICU stay. They also observed a reduction in the risk of polyneuropathy with intensive insulin therapy, suggesting that hyperglycemia, insulin deficiency, or both contribute to axonal dysfunction and degeneration.[24] The use of glucocorticoids to mitigate critical illness neuropathy is controversial. The anti-inflammatory properties of glucocorticoids may exert beneficial effects on neuromuscular system, but glucocorticoids can cause neuromuscular disorders, hyperglycemia, and insulin resistance, thereby worsening critical illness neuropathy. [23,25,26]

In summary, hyperglycemia may cause diaphragmatic dysfunction; avoiding hyperglycemia and improving glycemic control with insulin therapy have been associated with better outcomes and decreased ICU stay. Antioxidants, N-acetylcysteine, superoxide dismutase, and other agents have been used to reverse the diaphragm weakness in animal studies, but there have been no studies in humans. Clinicians need to consider the possible effects of hyperglycemia on diaphragmatic function when managing patients in intensive care units, especially patients requiring mechanical ventilation.[27-30]

**Author Affiliation:** Maria Suarez and Avinash Adiga are residents in the Department of Internal Medicine at Texas Tech University Health Sciences Center in Lubbock, TX.
**Received:** 10/24/2015
**Accepted:** 01/10/2016
**Reviewers:** Joaquin Lado MD
**Published electronically:** 01/15/2016
**Conflict of Interest Disclosures:** None

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