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Authors Response: Nutrition and Respiratory Muscle Weakness in Children

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We thank Dr. Shah and Lodha (1) for their interest in our paper regarding maximal inspiratory airway pressure during airway occlusion (aPiMax) and extubation failure in children. Our study highlighted that up to 35% of children have respiratory muscle weakness at the time of extubation, and that low aPiMax is an independent risk factor for extubation failure. Dr. Shah and Lodha (1) have asked specifically about the potential role of hypophosphatemia and nutritional status on the development of respiratory muscle weakness. They have recently performed an observational cohort study that found hypophosphatemia is associated with extubation failure.

Our study was primarily focused on the relationship between measures of respiratory muscle weakness and extubation outcomes, and was not specifically looking for risk factors for respiratory muscle weakness. Nevertheless, a crucial next step would be to identify the independent risk factors for respiratory muscle weakness in children, and develop strategies to prevent it. When looking at the pathophysiology of acquired respiratory muscle weakness (i.e. ventilator induced diaphragm dysfunction), mechanisms relate to the underlying disease status of the patient, the severity of inflammation, the use of therapies like neuromuscular blockade and corticosteroids, the degree of protein catabolism, the nutritional status of the patient, and the degree of diaphragm contraction during mechanical ventilation (2-8). However, the adaptations of malnutrition on diaphragmatic function are unclear and may be disparate based on whether the malnutrition is acute or chronic. In rodent models of acute malnutrition there is loss of cross sectional area, but preserved diaphragm contractility and improved fatigue resistance with restoration of cross sectional area with re-feeding. In contrast, in human CF patients with chronic malnutrition, there is a clear association between lower BMI (or weight for height for children < 2 years) z score and decreased diaphragmatic strength (9-11). As such, the nutritional status of the patient upon initiation of mechanical ventilation, as well as acquired nutritional deficiencies or electrolyte abnormalities during the course of mechanical ventilation may be important in the pathogenesis or preservation of diaphragmatic function. However, the development of

ventilator induced diaphragm dysfunction is likely multi-factorial, and the effects of individual risk factors may be additive or multiplicative.

Unfortunately, we did not specifically track electrolytes in our study, so we do not have phosphorous levels. However, on secondary analysis, we found that children who had weight for height z-score (for children <2) or BMI z-score (for children >2) two standard deviations above or below normal (i.e. chronic malnutrition or obesity) had a non-significant trend for higher rates of re-intubation ($p=0.07$, Table 1). However this relationship did not appear to be from low aPiMax, as a higher proportion of obese or malnourished children maintained aPiMax > 30 cmH₂O (the cut point we found to be most associated with extubation failure). While cardiac surgery patients may have more swings in their electrolytes, patients undergoing cardiac surgery were not at higher risk for re-intubation ($p=0.8$), although there was a trend for these patients to have lower aPiMax ($p=0.06$). However, because there is a larger proportion of neonates undergoing cardiac surgery, after controlling for age, this relationship was no longer present ($p=0.18$).

Accumulating data indicate that > 50 % of critically ill adults who are on mechanical ventilation > 72 hours have thinning of the diaphragm (based on ultrasound) within the first few days of mechanical ventilation, (4) and there is a dose response relationship between diaphragm atrophy and increasing ventilator driving pressure.(4) Moreover, low diaphragm contractile activity leads to atrophy, while diaphragm thickness is preserved when contractile activity during mechanical ventilation is normal (i.e., patient maintains normal work of breathing) (12). Observational data in pediatrics confirms that patient effort of breathing during mechanical ventilation is often 2-4 times lower than normal physiologic levels, and much lower than it is after extubation or even at the time of ICU discharge (13, 14). We believe this sub-physiologic effort of breathing is the major contributor to ventilator induced diaphragm dysfunction. We hypothesize that we may be able to prevent ventilator induced diaphragm dysfunction by changing our practice patterns with respect to patient effort of breathing during mechanical ventilation, to promote more physiologic levels throughout the entire ventilation course. We are about to begin a Phase II clinical trial to specifically test this hypothesis (15)(ClinicalTrials.gov NCT03266016). As a part of this study, we will gather detailed information related to acute and chronic nutritional status and electrolyte abnormalities, as well as surrogate variables related to all the major mechanisms thought to be important in the pathogenesis of ventilator induced diaphragm dysfunction.

Understanding the independent importance of all of these related factors is crucial to help us devise the best treatment or preventative strategies to maintain respiratory muscle capacity.

Sincerely,

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Table 1

Age for Height (or BMI) Z Score	Total N	Re intubated N (%)	aPiMax 30 cmH ₂ O
< -2	80	9 (11.3%)	22 (27.5%)
-2 to 2	293	19 (6.5%)	105 (35.8%)
> 2	29	4 (13.8%)	8 (27.6%)