

Category : **Respiratory: mechanical ventilation**

**A215 - Non-acidotic hypercapnia limits the loss of diaphragm force at single fibers level in mechanically ventilated rats for 5 days**

**N Cacciani**<sup>1</sup> ; **A Addinsall**<sup>2</sup> ; **L Larsson**<sup>3</sup>

<sup>1</sup>Karolinska Institutet, Department of Physiology and Pharmacology (FyFa), Stockholm, Sweden, <sup>2</sup>Karolinska Institutet, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, <sup>3</sup>Viron Molecular Medicine Institute, Boston, MA, United States

## **Introduction:**

Acute exposure to hypercapnia has shown benefit to diaphragm function in porcine and rat ICU models of mechanical ventilation (MV), within 72 hours. Here, we hypothesize that normoxic and non-acidotic hypercapnic conditions (NAHCs) would limit the loss of diaphragm function during MV for longer duration.

## **Methods:**

Adult Sprague-Dawley rats were deeply sedated, pharmacologically paralyzed, hydrated, nourished and controlled mechanical ventilated (CMV) for 5 days in normoxic-normocapnic or normoxic and NAHCs (EtCO<sub>2</sub>: 55-70 mmHg with normal blood pH). Diaphragm fibers from euthanized rats were prepared for contractile function assessment and downstream signaling pathways analyses.

## **Results:**

Our results show that: 1) cross sectional area (CSA) was decreased by 40% following normocapnic CMV when compared with control sham operated (CTR) ( $p < 0.001$ ), which was unaltered by NAHCs; 2) Specific force (SF: force normalized to CSA) was decreased to 58% of CTR following normocapnic CMV ( $p < 0.001$ ). NAHCs increased SF by 15% compared with normocapnic rats ( $p < 0.05$ ); 3) Muscle E3 ligases Murf1 and Atrogin-1 protein expression is unchanged following 5 days of CMV, irrespective of CO<sub>2</sub> conditions. LC3B, a marker for autophagy, with LC3B II:I ratio signifying activation. Following 5 days normocapnic CMV LC3B II:I ratio ( $p < 0.05$ ) was reduced by 70% in diaphragm. NAHCs failed to alter the activation of LC3B or these muscle degradation pathways; 4) NAHCs however increased TNF $\alpha$  and IL-1 $\beta$  transcript expression in the diaphragm compared with normocapnic CMV and CTR groups; 5) As expected, NAHCs increased stability of respiratory peak pressure, peripheral oxygenation and perfusion, hemodynamic conditions.

## **Conclusion:**

Our results suggest that NAHCs have beneficial effects on single diaphragm fibers function irrespective of significant increase in muscle inflammation in non-septic animals. This, combined with the positive respiratory and hemodynamic effects, encourage further study of the therapeutic potential of CO<sub>2</sub> in ICU.