論　文　内　容　要　旨

Neurally adjusted ventilatory assist mitigates ventilator-induced diaphragm injury in rabbits

（急性肺障害ウサギモデルにおける神経調節補助換気が人工呼吸器誘発横隔膜障害に与える影響の検討）

Respiratory Research, 20:293, 2019.

主指導教員：志馬 伸朗教授
（医系科学研究科　救急集中治療医学）
副指導教員：木原 康樹教授
（医系科学研究科　循環器内科学）
副指導教員：大下 慎一郎准教授
（医系科学研究科　救急集中治療医学）

島谷　竜俊

（医歯薬保健学研究科　医歯薬学専攻）

Background: Ventilator-induced diaphragm dysfunction (VIDD)occurs in 30%–80% of critically ill patients undergoing mechanical ventilation, and may be associated with prolonged mechanical ventilation and increased intensive care unit (ICU) and hospital mortality. Major mechanisms of VIDD appear to be related to disuse atrophy from excessive respiratory support, and sarcomere injury due to eccentric contraction or load-induced injury. Nevertheless, while preservation of spontaneous breathing may prevent atrophy, the risk of sarcomere injury remains, particularly if respiratory effort is high. Furthermore, there is biologic plausibility that eccentric contraction of the diaphragm leading to sarcomere injury can be exacerbated by patient-ventilator asynchrony. Although neurally adjusted ventilatory assist (NAVA) could be associated with lower patient-ventilator asynchrony compared with conventional ventilation, its effects on diaphragmatic dysfunction have not yet been well elucidated.

Methods: Twenty Japanese white rabbits were randomly divided into four groups, (1) no ventilation, (2) controlled mechanical ventilation (CMV) with continuous neuromuscular blockade, (3) NAVA, and (4) pressure support ventilation (PSV). Ventilated rabbits had lung injury induced, and mechanical ventilation was continued for 12 hours. Respiratory waveforms were continuously recorded, and the asynchronous events measured. Subsequently, the animals were euthanized, and diaphragm and lung tissue were removed, and stained with Hematoxylin-Eosin to evaluate the extent of lung injury. The myofiber cross-sectional area of the diaphragm was evaluated under the adenosine triphosphatase staining, sarcomere disruptions by electron microscopy, apoptotic cell numbers by the TUNEL method, and quantitative analysis of Caspase-3 mRNA expression by real-time polymerase chain reaction.

Results: Physiological index, respiratory parameters, and histologic lung injury were not significantly different among the CMV, NAVA, and PSV. NAVA had lower asynchronous events than PSV (median [interquartile range], NAVA, 1.1 [0–2.2], PSV, 6.8 [3.8–10.0]; $p = 0.023$). No differences were seen in the cross-sectional areas of myofibers between NAVA and PSV, but those of Type 1, 2A, and 2B fibers were lower in CMV compared with NAVA. The area fraction of sarcomere disruptions was lower in NAVA than PSV (NAVA vs PSV; area fraction: 1.6 [1.5–2.8] vs 3.6 [2.7–4.3] $p < 0.001$). The proportion of apoptotic cells was lower in NAVA group than in PSV (NAVA vs PSV; 3.5 [2.5–6.4] vs 12.1 [8.9–18.1], $p < 0.001$). There was a tendency in the decreased expression levels of Caspase-3 mRNA in NAVA groups. Asynchrony Index was a mediator in the relationship between NAVA and sarcomere disruptions.

Conclusions: We have demonstrated that preservation of spontaneous breathing prevents diaphragm atrophy and NAVA may be superior to PSV in preventing sarcomere injury and apoptosis of myofibrotic cells of the diaphragm, and that this effect may be mediated by patient-ventilator asynchrony mostly related to ineffective efforts, and not the degree of inspiratory load. These results suggest potential unfavorable effects of patient-ventilator asynchrony on diaphragm function.