Exercise training reduces brainstem oxidative stress and restores normal breathing function in heart failure

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Abstract
Enhanced central chemoreflex drive and irregular breathing are both hallmarks in heart failure (HF) and closely related to disease progression. Central chemoreceptor neurons located within the retrotrapezoid nucleus (RTN) are known to play a role in breathing alterations in HF. It has been shown that exercise (EX) effectively reduced reactive oxygen species (ROS) in HF rats. However, the link between EX and ROS, particularly at the RTN, with breathing alterations in HF has not been previously addressed. Accordingly, we aimed to determine: i) ROS levels in the RTN in HF and its association with chemoreflex drive, ii) whether EX improves chemoreflex/breathing function by reducing ROS levels, and iii) determine molecular alterations associated with ROS generation within the RTN of HF rats and study EX effects on these pathways. Adult male Sprague-Dawley rats were allocated into 3 experimental groups: Sham (n = 5), volume overloaded HF (n = 6) and HF (n = 8) rats that underwent EX training for 6 weeks (60 min/day, 25 m/min, 10% inclination). At 8 weeks post-HF induction, breathing patterns and chemoreflex function were analyzed by unrestrained plethysmography. ROS levels and anti/pro-oxidant enzymes gene expression were analyzed in the RTN. Our results showed that HF rats have high ROS levels in the RTN which were closely linked to the enhanced central chemoreflex and breathing disorders. Also, HF rats displayed decreased expression of antioxidant genes in the RTN compared with control rats. EX training increases antioxidant defense in the RTN, reduces ROS formation and restores normal central chemoreflex drive and breathing regularity in HF rats. This study provides evidence for a role of ROS in central chemoreception in the setting of HF and support the use of EX to reduce ROS in the brainstem of HF animals and reveal its potential as an effective mean to normalize chemoreflex and breathing function in HF. © 2021

Author keywords
Central chemoreflex; Exercise training; Heart failure; Oxidative stress; Retrotrapezoid nucleus