COMMENTARY

Exercise: Alternative Therapy for Heart Failure-Associated Sleep Apnea?

Commentary on Ueno et al. Effects of exercise training in patients with chronic heart failure and sleep apnea. Sleep 2009:32:637-647.

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IN INDIVIDUALS WITH HEART FAILURE SECONDARY TO SYSTOLIC DYSFUNCTION, THE PREVALENCE OF SLEEP DISORDERED BREATHING IS QUITE HIGH (~50%).[1] Central sleep apnea (CSA) is the most common form of disordered breathing in this patient population; nevertheless, a substantial fraction of patients with chronic heart failure experience obstructive sleep apnea (OSA).[1] In this issue of SLEEP, Ueno and colleagues report the effects of a 4-month exercise training program in chronic heart failure patients with and without sleep disordered breathing.[2] As expected, exercise training improved peak oxygen consumption and quality of life and, consistent with their previous findings,[3] decreased sympathetic vasoconstrictor outflow to skeletal muscle and increased limb blood flow. In addition, they observed a training-induced reduction in the severity of sleep disordered breathing, as indicated by a decrease in the apnea-hypopnea index and an increase in minimum oxygen saturation. Interestingly, these beneficial effects of exercise were observed in patients with sleep apnea of the obstructive subtype, whereas no change in sleep disordered breathing was noted in patients with CSA. This study was not a randomized, placebo-controlled trial; nevertheless, the experimental design has several strengths. The authors demonstrated stability of outcome measures in the absence of intervention during the 4 months prior to exercise training, and they compared effects of training in heart failure patients with OSA, CSA, those without sleep apnea, and normal control subjects.

The findings of Ueno and colleagues suggest several interdependent putative mechanisms for exercise-related amelioration of sleep apnea in patients with chronic heart failure. First, the reduction in sympathetic outflow following exercise training points to a normalization of chemoreflex hypersensitivity. An impressive collection of studies by Schultz and coworkers indicates that carotid chemoreflex sensitization is an important cause of heightened sympathetic outflow in heart failure,[4-7] and these investigators have also shown that exercise training normalizes chemoreflex sensitivity and lowers basal sympathetic outflow.[8] Reductions in sympathetic outflow would be expected to improve structure and function of resistance vessels in the peripheral circulation. Enhanced flow-mediated dilation has been documented following exercise training in patients with heart failure,[9] and in the present study, basal forearm vascular conductance was increased following exercise training. System-wide increases in conductance, if present, could positively impact cardiac function by reducing afterload.

In addition to its negative effects on cardiovascular function, it is likely that chemoreflex hypersensitivity destabilizes breathing during sleep. A chemoreflex-induced augmentation of the ventilatory response to CO_2 would heighten susceptibility to reaching the apneic threshold.[10] How might exercise training improve breathing stability during sleep? In addition to normalization of chemoreflex sensitivity, exercise-induced improvements in cardiac function may stabilize breathing via decreased circulation time[11] and/or reduced pulmonary vascular pressures.[12,13] Breathing stability may also be improved as the result of enhanced endothelial function in the cerebral circulation and increased brain blood flow reactivity to CO_2.[14,15]

One of the most intriguing findings of Ueno and colleagues is that exercise training reduced the severity of sleep disordered breathing in heart failure patients with OSA, but not those with CSA. Based on comparable decreases in muscle sympathetic nerve activity and increases in forearm vascular conductance, it appears that exercise training normalized chemoreflex function to the same extent in the two groups of patients. Assuming that training intensity and compliance with the exercise program were the same in the two groups, what might explain the differential effect of exercise on sleep disordered breathing severity? We believe that the explanation is related to ventricular function. Exercise training produced an increase in left ventricular ejection fraction that approached statistical significance ($P = 0.056$) in patients with OSA, whereas no change was seen in patients with CSA. As the authors speculate, this increase in cardiac function may have reduced upper airway edema, thereby decreasing the tendency for obstruction. Furthermore, this improvement in cardiac function may have increased breathing stability during sleep by decreasing circulation time[11] and/or reducing cardiac filling pressures.[12,13]

The reason left ventricular function did not improve with training in the CSA patients is not readily apparent. Baseline values for ejection fraction and peak VO_2 were slightly lower in CSA vs. OSA, so perhaps their heart failure was somewhat more severe. At the same time, their sleep disordered breathing appears to have been less severe. Even though the apnea-hypopnea index was similar in CSA and OSA patients, the minimum oxygen saturation during sleep was higher in CSA, suggesting that their sleep disordered breathing events were shorter in duration and/or there was a higher proportion of hypopneas vs. apneas. It is interesting to note that minimum saturation in heart

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failure patients with CSA was similar to that of heart failure patients without sleep apnea. After training, the improved minimum oxygen saturation in OSA patients was roughly the same as the baseline values in the other two groups.

This study is expected to generate a considerable amount of clinical interest; however, it is critical that these findings, which were obtained in a relatively small number of subjects, be confirmed in larger, placebo-controlled trials. The mechanisms of exercise-induced amelioration of sleep disordered breathing in patients with heart failure must also be explored. Suggestions for further study include evaluation of the effects of exercise training on: 1) chemoreflex control of muscle sympathetic nerve activity and ventilation and 2) vascular endothelial function, including assessment of cerebral blood flow responses to hypoxia and hypercapnia. Also, the potential for synergistic effects of exercise and continuous positive airway pressure (CPAP) treatment must be investigated. In future studies it will be important to quantify sleep disordered with a metric that reflects the level of nocturnal hypoxemia more precisely than does the apnea-hypopnea index (e.g., time spent with oxygen saturation <90%).

The findings of Ueno et al. have substantial clinical importance because sleep disordered breathing is thought to contribute to the progression of ventricular dysfunction via hypoxemia, sympathetic overactivity, increased afterload, and hypertension. CPAP is the treatment of choice for OSA; however, many people fail to tolerate it. The present findings have important implications for all patients with sleep disordered breathing, not just those with concomitant heart failure.

DISCLOSURE STATEMENT

Dr. Morgan has indicated no financial conflicts of interest.

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