Cardiac diastolic and autonomic dysfunction are aggravated by central chemoreflex activation in heart failure with preserved ejection fraction rats

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Key points: Heart failure with preserved ejection fraction (HFpEF) is associated with disordered breathing patterns, and sympatho-vagal imbalance. Although it is well accepted that altered peripheral chemoreflex control plays a role in the progression of heart failure with reduced ejection fraction (HFrEF), the pathophysiological mechanisms underlying deterioration of cardiac function in HFpEF are poorly understood. We found that central chemoreflex is enhanced in HFpEF and neuronal activation is increased in pre-sympathetic regions of the brainstem. Our data showed that activation of the central chemoreflex pathway in HFpEF exacerbates diastolic dysfunction, worsens sympatho-vagal imbalance and markedly increases the incidence of cardiac arrhythmias in rats with HFpEF. Abstract: Heart failure (HF) patients with preserved ejection fraction (HFpEF) display irregular breathing, sympatho-vagal imbalance, arrhythmias and diastolic dysfunction. It has been shown that tonic activation of the central and peripheral chemoreflex pathway plays a pivotal role in the pathophysiology of HF with reduced ejection fraction. In contrast, no studies to date have addressed chemoreflex function or its effect on cardiac function in HFpEF. Therefore, we tested

whether peripheral and central chemoreflexes are hyperactive in HFpEF and if chemoreflex activation exacerbates cardiac dysfunction and autonomic imbalance. Sprague-Dawley rats (n = 32) were subjected to sham or volume overload to induce HFpEF. Resting breathing variability, chemoreflex gain, cardiac function and sympatho-vagal balance, and arrhythmia incidence were studied. HFpEF rats displayed [mean ± SD; chronic heart failure (CHF) vs. Sham, respectively] a marked increase in the incidence of apnoeas/hypopnoeas (20.2 ± 4.0 vs. 9.7 ± 2.6 events h?1), autonomic imbalance [0.6 ± 0.2 vs. 0.2 ± 0.1 low/high frequency heart rate variability (LF/HFHRV)] and cardiac arrhythmias (196.0 ± 239.9 vs. 19.8 ± 21.7 events h?1). Furthermore, HFpEF rats showed increase central chemoreflex sensitivity but not peripheral chemosensitivity. Accordingly, hypercapnic stimulation in HFpEF rats exacerbated increases in sympathetic outflow to the heart (229.6 ± 43.2% vs. 296.0 ± 43.9% LF/HFHRV, normoxia vs. hypercapnia, respectively), incidence of cardiac arrhythmias (196.0 ± 239.9 vs. 576.7 ± 472.9 events h?1) and diastolic dysfunction (0.008 ± 0.004 vs. 0.027 ± 0.027 mmHg ?l?1). Importantly, the cardiovascular consequences of central chemoreflex activation were related to sympathoexcitation since these effects were abolished by propranolol. The present results show that the central chemoreflex is enhanced in HFpEF and that acute activation of central chemoreceptors leads to increases of cardiac sympathetic outflow, cardiac arrhythmogenesis and impairment in cardiac function in rats with HFpEF.

autonomic imbalance

cardiac function

central chemoreflex

heart failure preserved ejection fraction

respiratory disorders

propranolol

adult

animal cell

animal experiment

animal model

animal tissue

apnea hypopnea index

arrhythmogenesis

Article

autonomic dysfunction

brain stem

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heart rate variability

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Rats, Sprague-Dawley

Stroke Volume