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**Title:** Gender-related association between respiratory stability and Cheyne-Stokes respiration in chronic heart failure – A matched control study

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Body: Introduction: Hypersensitive ventilatory feedback loop has major impact on the manifestation of Cheyne-Stokes respiration (CSA) in chronic heart failure (CHF). As CSA mainly affects male CHF patients (pts), this study aims to clarify the role of respiratory stability in the evolution of CSA in men and women. Methods: We investigated 563 pts with CHF (91 female, LVEF ≤45%, NYHA-class ≥2) using echocardiography, cardiopulmonary exercise testing (CPX), cardiorespiratory polygraphy, measurement of hyperoxic, hypercapnic ventilatory response (HCVR), and standard laboratory. Adjusted for age (±2 years), body mass index (BMI; ± 2), and LVEF (± 3%) 79 matched pairs (male/female) were eligible for analysis. Results: Obstructive sleep apnoea (AHI ≥5/h) was present in 12 female (15.2%) and 13 male (16.4%) pts (p=n.s.), CSA (AHI ≥5/h) in 30 (37.9%) female and 54 (68.4%) male pts (p<0.001). Parameters of respiratory instability (female vs. male: daytime pCO<sub>2</sub> 36.7 (interquartile range (IQR) 34.4-39.4) vs. 36.7 (IQR 34.8-38.7), VE/VCO<sub>2</sub> slope during CPX 34 (IQR 30-40) vs. 35 (IQR 31-40), HCVR 2.32 (IQR 1.71-3.49) vs. 2.69 (IQR 2.01-4.45) did not show a significant difference. Adjusted for age, NYHA-class, BMI, heart rate, LVEF, CRP, creatinine, NT-proBNP stepwise regression analysis revealed HCVR (p=0.03) an independent predictor for CSA in male pts while NYHA-class (p=0.04) was the only independent predictor for CSA in female pts. Conclusion: These data suggest gender-related differences in the evolution of CSA. Additional studies are warranted to figure out a more sophisticated pathophysiological concept that may elucidate these findings.