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LETTER TO THE EDITOR

Sex-related difference in sympathetic chemoreflex response: does it matter in clinical disease?

We read with great interest the work of Sayegh et al. (2022) recently published in *The Journal of Physiology*. In their elegant study, the authors aimed to assess, for the first time, the sex-related difference in the respiratory and sympathetic neurocirculatory responses (estimated through muscle sympathetic nerve activity, MSNA) to central, peripheral and combined chemoreflex activation in 10 male and 10 female healthy volunteers. The authors confirm that ventilatory and adrenergic responses to chemoreflex activation may be partially independent within the same individual. Although both responses are initiated at similar recruitment thresholds, the sympathetic response to chemoreflex stimulation cannot be predicted from the ventilatory response, as suggested by Keir and co-workers (2019). Further, the study shows a greater total MSNA response to hypercapnia (on either hyperoxic or hypoxic background) in women, as compared to men, despite an attenuated ventilatory response to hypercapnia (Sayegh et al., 2022). The greater sympathetic response to central chemoreflex activation in women unveils potential sex-related clinical implications in disease conditions.

A pathophysiological role for increased response to chemoreflex activation has long been observed in various cardiovascular diseases, including systemic hypertension, and, most notably, chronic heart failure (HF) (Shivkumar et al., 2016). Despite recent therapeutic advances, a substantial subset of HF patients shows an increased hypoxic (HVR) and/or hypercapnic (HCVR) ventilatory response, which is associated with sympathovagal imbalance, exercise intolerance and a significantly higher risk of HF-related hospitalizations and death (Giannoni et al., 2022). Such relations are even stronger when both peripheral and central chemoreflex responses are elevated (Giannoni et al., 2022). Furthermore, an increased ventilatory response to chemoreflex activation, together with an increased plant gain and circulatory delay, has been identified as a crucial pathophysiological determinant of highly prevalent breathing disorders in HF patients, such as period breathing, central apnoeas and Cheyne–Stokes respiration (PB/CA/CSR) (Giannoni et al., 2019). While PB/CA/CSR are well-known independent predictors of poor outcomes in HF patients, the repeated peripheral/central chemoreflex stimulation occurring during apnoeas has been proposed as a critical determinant of sympathovagal imbalance in these patients, likely increasing arrhythmic risk, clinical severity and worsening prognosis (Giannoni et al., 2020).

In a recent study (Gentile et al., 2022) enrolling 550 HF patients (mean left ventricular ejection fraction 32 ± 9%), women, compared with men, showed lower HVR and HCVR, and a lower burden of PB/CA/CSR across the 24-hour period. HCVR was an independent predictor of the apnoea–hypopnea index in both sexes. At adjusted survival analysis, PB/CA/CSR were independent predictors of the primary endpoint (a composite of cardiac death, appropriate implantable cardioverter–defibrillator shock or first HF hospitalization) only in women, but not in men (Gentile et al., 2022).

While the mechanism behind this finding had not been specifically investigated, the findings of Sayegh et al. (2022) may provide a reasonable explanation (Figure 1). The increased ventilatory response to chemoreflex activation observed in healthy men is in line with the higher HVR/HCVR observed in male HF patients, explaining the higher burden of PB/CA/CSR. On the other hand, a higher sympathetic response to chronic intermittent chemoreflex activation may explain the prognostic impact of such phenomena mainly observed in women. In line with this

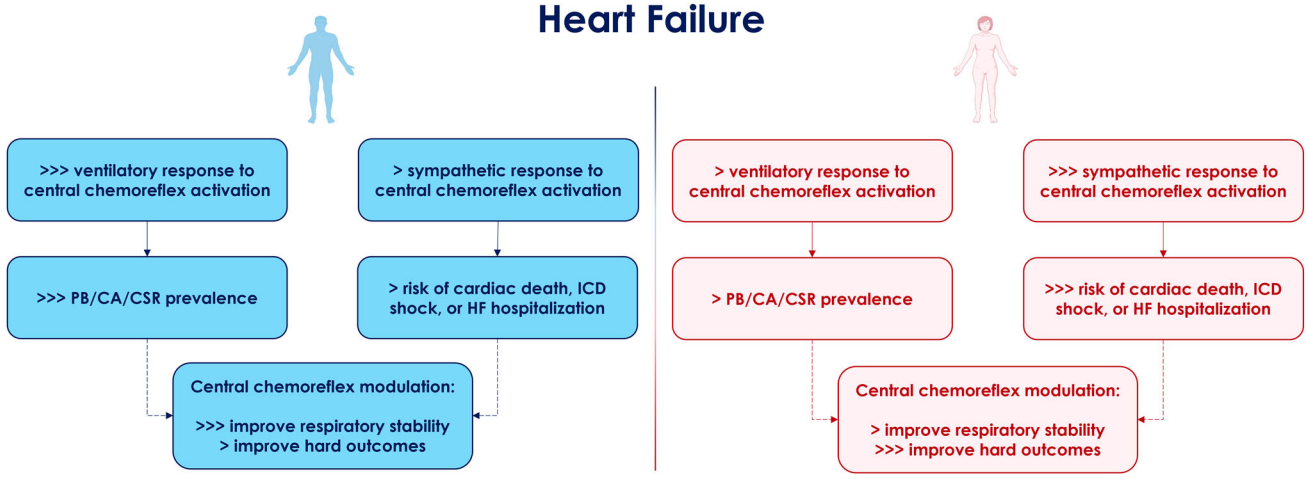

Figure 1. Hypothetical clinical implications of the sex differences in the ventilatory and sympathetic chemoreflex control in patients with heart failure (HF)
ICD, implantable cardioverter-defibrillator; PB/CA/CSR, periodic breathing/central apnoeas/Cheyne–Stokes respiration.

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hypothesis, also obstructive sleep apnoeas have been associated with a greater risk of cardiac damage and incident HF in women in the general population (Roca et al., 2015).

To the best of our knowledge, no studies have yet evaluated the sex-related differences in the sympathetic response to chemoreflex activation in HF patients. If confirmed also in patients with HF, the findings of Sayegh et al. (2022) may unravel important pathophysiological mechanisms with relevant clinical implications. Indeed, women have been extremely under-represented in the main clinical trials conducted in HF patients with PB/CA/CSR which tested the prognostic effects of non-invasive ventilation, yielding disappointing results (Bradley et al., 2005; Cowie et al., 2015). Furthermore, chemoreflex activation is emerging as an important therapeutic target to improve respiratory stability and, eventually, reduce the risk of hospitalization and mortality in HF patients (Langner-Hetmańczuk et al., 2022).

Evaluating the potential sex-related differences in the ventilatory and sympathetic responses may thus prove valuable when designing future clinical studies, which should, from now onward, also address rather than disregard the sex matter.

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Additional information

Competing interests

None.

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Supporting information

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