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EDITORIAL

Sex differences in cardiovascular autonomic control: introduction to the special issue

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Cardiovascular disease remains the leading cause of morbidity and mortality in Western Populations. In the United States alone, ~ 300,000 women die from cardiovascular disease annually; the incidence and mortality of cardiovascular disease among women age 55 and younger remains unaltered, whereas cardiovascular morbidity and mortality in men continues to improve [1]. This is particularly true for racial minorities such as African Americans who suffer one of the highest mortality rates for cardiovascular disease [2].

The 2030 goal of the World Health Organization is to reduce mortality for non-communicable diseases in women. Similar country-specific organizations such as the National Institutes of Health have brought in policies for inclusion of women and minorities in clinical research, emphasising this should start with considering sex as a biological variable when developing study designs [3]. This is particularly important given known sex differences in blood pressure regulation and cardiovascular disease susceptibility, onset, clinical presentation, treatment responses, and outcomes. Despite this importance, there is a paucity of research in female animal models and clinical populations, leading to an incomplete understanding of mechanisms underlying sex differences in cardiovascular disease.

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In this special issue of *Clinical Autonomic Research,* we present a series of articles highlighting recent discoveries of sex differences in cardiovascular autonomic control. These manuscripts discuss: gender-specific effects of the renin-angiotensin system (RAS) in cardiovascular disease pathophysiology and treatment [4]; sex-specific differences in relationships between components of neurovascular control, such as vascular transduction, resting levels of sympathetic activity and baroreflex sensitivity [5]; neurohormonal control during different stages of pregnancy [6, 7]; race and sex-specific differences in cardiovascular autonomic regulation [8]; neurovascular control in post-traumatic stress disorder (PTSD) [9]; and sex differences in sympathetic reactivity during orthostatic stress [10] (Fig. 1).

In terms of physiological regulatory systems, the RAS provides an important mechanism contributing to sex differences in cardiovascular disease. Medina et al. [4] review cardiovascular actions of the RAS, including interactions with gonadal hormones and clinical implications. They describe protection of premenopausal women from cardiovascular derangements produced by angiotensin II pathway activation, while highlighting recent data for cardioprotective effects of angiotensin-(1-7) pathways in this population that appear mediated, in part, by estrogen interactions. Importantly, while targeting angiotensin-(1-7) and related components of the vasodilatory arm of the RAS seems to be a promising therapeutic target, there is a paucity of clinical data, as well as underrepresentation of women in clinical trials targeting the RAS.

In addition to sex differences in long-term regulation by the RAS, recent evidence indicates differences in short-term blood pressure regulation driven by the autonomic nervous system. Hissen and Taylor [5] review methods available for quantifying beat-to-beat transduction of muscle sympathetic nerve activity (MSNA). Whilst some evidence suggests that young women exhibit lower levels of vascular transduction, results vary depending on the method used and direction of the change in MSNA. One common theme was identified:

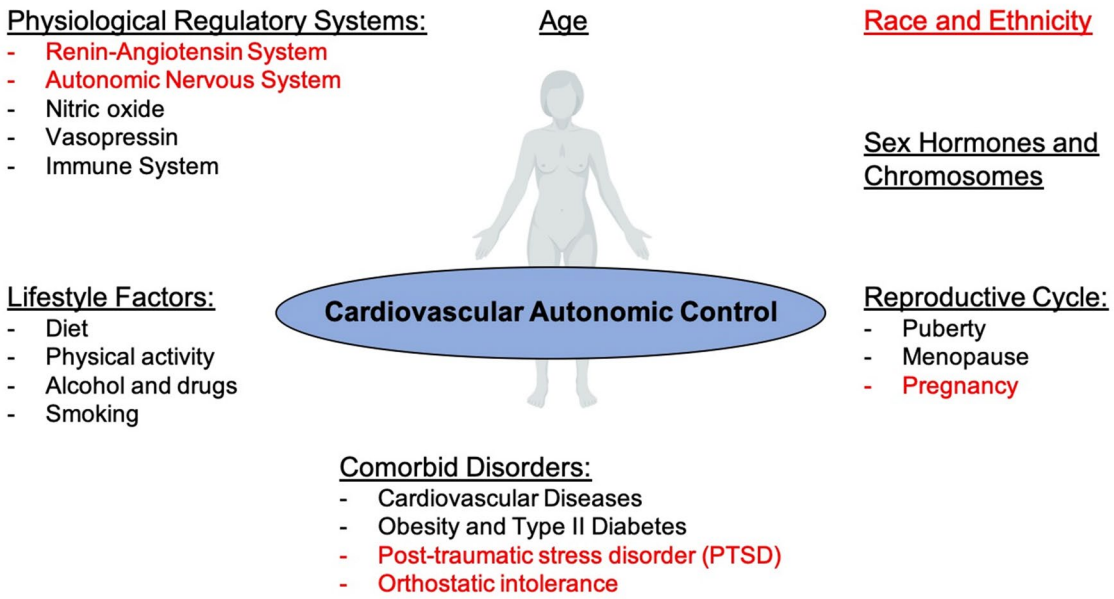

Fig. 1 Factors involved in cardiovascular autonomic control in women (red, factors addressed in this special issue)

the presence of relationships between components of neurovascular control, such as vascular transduction, resting levels of MSNA and baroreflex sensitivity. While causality cannot be confirmed, these negative correlations may reflect compensatory interactions that ensure appropriate blood pressure levels. Also consistent between studies is the presence of such relationships in young men but not young women, which may reflect a dominance of vasodilator mechanisms in pre-menopausal women.

These compensatory interactions in autonomic components of blood pressure control also come into play during pregnancy. Previous microneurographic studies indicate that MSNA is elevated in normotensive pregnant women and offset by blunted vascular transduction. MSNA is even higher in women with gestational hypertension and preeclampsia during the third trimester. Hissen and Fu [6] report that gestational hypertensive disorders are associated with augmented sympathetic nervous system activity in early and late pregnancy, as well as during postpartum. Importantly, the level of corin, an atrial natriuretic peptide-converting enzyme, is increased in the maternal circulation as a homeostatic response to elevated sympathetic activity. This may represent a biomarker for the detection of adverse pregnancy outcomes, especially in those women with a high risk of gestational hypertensive disorders.

Sex differences in cardiovascular disease are also driven by racial factors, with African American women having the highest cardiovascular mortality in the United States [2]. Farrell et al. [8] review racial differences in cardiovascular autonomic control that may predispose African American women to cardiovascular disease. Sympathetic activity in African American women is positively correlated with body mass index, but this correlation is not as strong as in non-Hispanic white women and does not contribute to hypertension by increasing peripheral vascular resistance. Evidence suggests that African American men and women have increased sympathetic vascular transduction and altered baroreflex sensitivity, which contribute to hypertension. Furthermore, African American men have generalized alpha-1 adrenergic receptor hypersensitivity in all vascular beds (arteries and veins) resulting in enhanced vasoconstriction and increased risk for hypertension. Finally, reduced heart rate variability, a known predictor of overall cardiovascular mortality, appears reduced in African Americana. These autonomic changes in African Americans have been found in early adolescence, particularly in women.

Women have twice the probability of developing PTSD after experiencing a traumatic event compared with men. However, as highlighted by Fonkoue et al. [9], most studies of autonomic function in PTSD have been conducted in males. Even recent studies involving women have not involved direct comparisons between sexes, and others have been conducted exclusively in women. This has made it difficult to discern whether findings of elevated sympathetic activity, blunted baroreflex sensitivity and increased inflammation reported in women with PTSD are on a par with men, or whether sex differences do indeed exist.

In summary, these articles highlight significant race and sex-specific differences in several aspects of cardiovascular autonomic regulation. This suggests that therapies targeting

cardiovascular disease, particularly hypertension, should be tailored to women and racial minorities such as African Americans. It is clear much more needs to be done to understand autonomic function in women across the lifespan, including pregnancy and menopause. Furthermore, the unexpected trauma inflicted by the current COVID-19 pandemic may lead to an increased incidence of PTSD, especially in women. We call for more preclinical and clinical research specifically designed to examine sex differences as well as interactions with race in cardiovascular disease, so that treatment strategies can be tailored appropriately.

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Compliance with ethical standards

Conflict of interest All author(s) declares that there is no conflict of interest.

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