Sex, sex hormones and autonomic circulatory control

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Emerging evidence suggests that there are sex-specific differences in autonomic circulatory control in humans, which may account for the differences in incidence and prognosis of cardiovascular disease and stroke in men and women of a similar age. As the cardiovascular risk increases with the onset of menopause in women, sex hormones, in particular estrogen, have been implicated as protective against these diseases. Indeed, the beneficial effects of estrogen on neural and vascular health in premenopausal women have been well demonstrated. However, more recent research reveals that in post-menopausal women, estrogen replacement therapy increases, rather than decreases, the risks of cardiovascular disease and stroke. It is likely that endogenous and exogenous sex hormones have opposite effects on neural and vascular health in women. To further support this notion, previous studies have shown that in young women, use of hormonal contraceptives (most commonly prescribed as combined oral contraceptives, such as ethinyl estradiol plus levonorgestrel) is associated with elevated blood pressure with an increased risk for hypertension.

To better understand the effects of sex and sex hormones on autonomic circulatory control, in this issue of *Clinical Autonomic Research*, Nili et al. [1] examined the responses to deep breathing in healthy young men as well as young women taking and not taking oral contraceptives. The

authors found that deep breathing decreased end-tidal carbon dioxide and middle cerebral artery velocity and increased cerebrovascular resistance in all participants with no significant differences between the sexes; however, blood pressure decreased in men only. It was also found that the fluctuations of female sex hormones estrogen and progesterone during the normal menstrual cycle or the use of oral contraceptives did not affect autonomic responses to deep breathing in young women. These observations are important and provide some insights into the mechanisms underlying sex differences in autonomic control. Deep breathing induced hyperventilation decreases end-tidal carbon dioxide (i.e., hypocapnia), which, in turn, deactivates the central chemoreceptors. Jensen et al. [2] previously found that central chemoreflex sensitivity was greater in healthy young men compared with young women, while measures of peripheral chemoreflex sensitivity were similar between the sexes. These findings may explain, at least in part, why blood pressure was decreased in men but not in women during deep breathing in the study by Nili et al. [1]. On the other hand, Wallin et al. [3] demonstrated that in young men, respiratory rate correlated positively with sympathetic nerve activity and total peripheral resistance; however, in young women, there were no such relationships. Both sympathetic nerve activity and total peripheral resistance are involved in the regulation of blood pressure in humans. During deep breathing, respiratory rate decreases leading to reductions in sympathetic nerve activity, total peripheral resistance, and thereafter, blood pressure in young men.

The results of the study by Nili et al. [1] suggest that the relationship between breathing and blood pressure regulation is different between young men and young women. It is possible that sex hormones have direct influences on the central control of respiration. Moreover, the peripheral

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effects of estrogen on blood vessels (e.g., vasodilatory effect and increased nitric oxide bioavailability) may also be responsible for the lack of relationship between breathing and blood pressure in young women. As the authors mentioned in the paper that one man had hypertension and two men had prehypertension, it remains to be determined whether presence or absence of (pre)hypertension has a different impact on the relationship between breathing and blood pressure control in young men. Although Nili et al. [1] found that sex affected autonomic circulatory control during deep breathing, cyclic changes in estrogen and progesterone during the menstrual cycle did not affect the responses in young women. Also, despite the large fluctuations in hormonal levels during the placebo (low) and high hormone phase, the responses of women taking oral contraceptives remained similar between the phases. These results indicate that acute alterations in sex hormones in young women do not alter autonomic circulatory control during deep breathing, whereas long-term (chronic) effects of cyclical exposure to estrogen and/or progesterone contribute importantly to the overall sex differences reported by Nili et al. [1]. It should be noted that the influences of genes, age, or other factors on autonomic circulatory control may be much greater when compared with a sex effect. Whether sex differences in the responses to deep breathing can also be observed in older adults or patient populations needs to be determined.

The sex difference in the relationship between breathing and blood pressure (i.e., central chemoreflex sensitivity) may explain, at least in part, why the prevalence of

obstructive sleep apnea is higher in young men compared with young women [4]. Conversely, the finding that deep breathing decreased end-tidal carbon dioxide and lowered blood pressure in young men might set a new target for therapeutic approach(s) to be developed for the treatment of hypertension.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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