Orthostatic stress and postural transitions are present in day to day life, yet for many people, provide substantial challenges. Evidence continues to emerge that suggests young women regulate blood pressure differently from young men (Hart et al. 2012) and are traditionally more prone to orthostatic intolerance. Many studies attribute such differences to the vasoactive effects of sex hormones because the disparity between young men vs. women is much more striking than the difference between post-menopausal women vs. older men. However, the effect of sex hormones is still unclear because of the difficulty in accounting for within-subject day-to-day variations and between-subject differences in endogenous oestrogen. In this issue of The Journal of Physiology, Wenner et al. (2013) isolated the effect of oestradiol in young women using a novel methodology to examine blood pressure regulation during orthostatic challenge. The authors suppress endogenous hormones utilizing a GnrH antagonist (to concentrations similar to those in post-menopausal women) with and without a 17β-oestradiol (E2) patch. This unique experimental approach is particularly useful to tease out the effect of a loss of sex hormones, independent of the effect of ageing, on cardiovascular function.

The results demonstrate that women with low orthostatic tolerance had greater sensitivity to the vasodilating effects of oestradiol and demonstrated lower peripheral vasoconstriction when exposed to E2 during orthostatic challenge. Although cardiovagal baroreflex sensitivity (BRS) was not impaired, exposure to E2 increased BRS only in women with low orthostatic tolerance. In a previous study by this laboratory, they also demonstrate no effect of oestradiol or oestrogen combined with progesterone on the cutaneous vasoconstrictor response to noradrenaline in women with low orthostatic tolerance (Wenner et al. 2011). This is in contrast to the healthy young women with high orthostatic tolerance. Thus, when sex hormones are experimentally controlled, women with low tolerance do not vasoconstrict to maintain blood pressure and paradoxically vasodilate to exogenous oestrogen, despite the presence of significant orthostatic challenge. Taken together, this suggests that not only do young women regulate blood pressure differently from men, but considerable variability in underlying mechanisms of blood pressure control exists between young women.

The question of interest is what effect ageing has on women with divergent compensatory mechanisms to maintain pressure during an orthostatic challenge. Hormone replacement therapy in post-menopausal women attenuates the blood pressure response to lower body negative pressure (LBNP) so that post-menopausal women given oestrogen had similar responses to the young women with an E2 patch in this present study (Harvey et al. 2005). This indicates that older women with chronically low endogenous sex hormones have a systemic cardiovascular response comparable to that of young women. Thus far, no study has separated post-menopausal women by orthostatic tolerance so it is unknown if this group is as heterogenous as their younger counterparts. In addition, the β-adrenergic receptors appear to offset α-adrenergic vasoconstriction only in pre-menopausal women (Hart et al. 2012). Will women with low tolerance continue to regulate blood pressure differently from women with high tolerance into the peri- and post-menopausal years? Will the low tolerant women (with presumably low sympathetic nerve activity) be less likely to develop hypertension? Will one group be more or less predisposed to cardiovascular risk? These questions are difficult to address because of the integrative nature of this problem. The provocative data demonstrating the interaction between sex hormones and fluid-balance hormones (particularly ANP and ANGII) in the article by Wenner et al. (2013) adds more complexity to these questions.

Another consideration is the potential role of regular exercise training in altering the compensatory response to orthostatic challenge. Whether aerobically trained individuals have improved orthostatic tolerance is unclear, with studies reporting both higher tolerance, lower tolerance, or no change in exercise trained individuals. The women in the study by Wenner et al. were all untrained and it will be important to determine whether physically active or endurance trained young women are more similar to women with low or high tolerance to LBNP. Exercise training is often associated with higher cardio-vagal BRS, lower arterial stiffness of the carotid artery (which potentially safeguards the afferent signal transduction from the carotid baroreceptors), and enhanced nitric oxide-mediated peripheral vasodilation. Exercise training is associated with blood volume expansion and may reduce the magnitude of decline in stroke volume during orthostatic challenges. In this context, a recent study examined orthostatic tolerance using head up tilt (HUT) in trained and untrained adults. The untrained adults had greater reductions in cardiac output and increases in total peripheral resistance compared with the untrained adults (Murrell et al. 2011). Although HUT tolerance time was not improved, this nevertheless suggests that endurance training modifies the cardiovascular compensatory mechanisms to orthostatic challenge.

In summary, the insightful collection of studies from Wenner and colleagues highlights the complexity of sex-specific vs. sex hormone-related differences in humans and the integrative nature of blood pressure regulation. The authors provide numerous questions that will drive future research and encourage investigators to carefully consider the effect of sex and sex hormone exposure when conducting integrative physiology studies.

References


