Effect of Estrogen Replacement Therapy on Sympathetic Activity in Postmenopausal Women

To the Editor:

Two recent articles in Circulation described modulations of sympathetic nerve activity to the muscle vascular bed in postmenopausal women on long-term estrogen replacement therapy (ERT). Vongpatanasin et al.1 reported a decrease in resting muscle sympathetic nerve activity (MSNA) after transdermal but not oral estrogen administration. Furthermore, the diastolic blood pressure was significantly decreased after transdermal ERT. The authors concluded that the decrease in blood pressure was induced by a fall in MSNA to the muscle vascular bed.

These data confirm and extend the results of a recent study that administered 2-day transdermal ERT to postmenopausal women and measured MSNA to the muscle vascular bed in the superficial peroneal nerve using a placebo-controlled, within-subject crossover design.2 In this study, resting MSNA decreased from 37.1 ± 3.1 to 30.1 ± 3.1 bursts/min by the second day of estrogen treatment. Vongpatanasin and colleagues1 show that this effect is sustained for a treatment period of 8 weeks. In the short-term study by Weitz et al.,2 however, the identical decrease in MSNA was not accompanied by a fall in blood pressure. This finding casts doubt on the hypothesis that the decrease in blood pressure is the consequence of reduced sympathetic tone to the muscle vascular bed. Rather, other mechanisms, such as direct vascular effects, could account for the blood pressure–lowering effects of transdermal ERT after prolonged treatment. This effect, however, must be combined with an influence on baroreflex function in postmenopausal women, because otherwise a decrease in blood pressure would have resulted in an increase in MSNA. In fact, the effects of estrogens on baroreflex regulation have been repeatedly demonstrated, most recently in the study by Hunt et al.3 in postmenopausal women in the same issue of Circulation. However, in premenopausal women, an increased suppression of MSNA in response to an elevation of blood pressure has also been observed during phases of high estrogen levels during the menstrual cycle,4 although neither study showed any change in blood pressure. Thus, these studies indicate that estrogens lower sympathetic baroreflex gain, as suggested by Hunt et al.4 and Minson et al.5 MSNA should increase even further. Thus, our data strongly suggest that the reduction in MSNA is one of the causes of the reduction in BP induced by transdermal estrogen.

Although there is abundant evidence that the baroreceptor reflex resets very quickly to regulate MSNA during transient changes in BP, it remains to be seen whether such resetting occurs during a prolonged decrease in BP. In addition, the recent study by Hunt et al.4 demonstrating that the 6-month administration of oral estrogen had no effect on MSNA or BP in postmenopausal women further supports our observation of the superiority of transdermal over oral estrogen on neural control of BP.

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Response

In reply to the thoughtful comments by Dodt and colleagues, it is gratifying to know that while our article underwent revision for publication in Circulation, a study from his laboratory1 demonstrating a similar finding of suppression of muscle sympathetic nerve activity (MSNA) by transdermal estrogen was published. We think that the greater fall in MSNA and blood pressure (BP) in our study2 is due to a longer duration of estrogen administration. Transdermal estrogen administration for 8 weeks reduced muscle MSNA by 13 bursts/min, which is 33% below baseline. The decrease in MSNA was accompanied by a 4 mm Hg reduction in 24-hour ambulatory diastolic BP and a 5 mm Hg reduction in daytime diastolic BP. In the study by Weitz et al.,1 transdermal estrogen administration for 2 days reduced muscle MSNA by 7 bursts/min, which is 19% below baseline, whereas BP measured in a laboratory setting was unchanged. Failure to detect any change in BP may be due to the lack of effect of short-term estrogen on BP or the lack of adequate power to detect a small reduction in BP. In general, casual BP measurement has larger test-retest variability than 24-hour ambulatory BP measurement (3 to 6 mm Hg versus 2 to 3 mm Hg, respectively).3 Therefore, it would be extremely difficult to detect a reduction in BP of <5 mm Hg using casual BP measurement alone in a small number of subjects.

We agree that estrogen is known to have a direct vascular effect, which could have contributed to the reduction in BP in our study. However, the decrease in BP in our study was in part sympathetically mediated, because the reduction in BP would have triggered a baroreflex-mediated increase, not a decrease, in MSNA. If the reduction in BP in our study was due to the direct vasodilator effect of estrogen alone and estrogen increases sympathetic baroreflex gain, as suggested by Hunt et al.4 and Minson et al.5 MSNA should increase even further. Thus, our data strongly suggest that the reduction in MSNA is one of the causes of the reduction in BP induced by transdermal estrogen.

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References


Response

Dodt and colleagues address the extent to which reduced muscle sympathetic nerve activity (MSNA) might directly influ-
ence resting blood pressure (BP). This issue is an important, albeit largely unresolved, one. Vongpatanasin et al\(^1\) reported that 8 weeks of transdermal estrogen administration was associated with a significant decline in resting levels of MSNA ($\approx 32\%$) and BP ($\approx 4$ mm Hg), but not with a change in vascular sympathetic baroreflex gain.\(^1\) In contrast, we recently found that 26 weeks of oral estrogen administration was associated with improved baroreflex control of MSNA, without a change in either resting levels of BP or MSNA.\(^2\) Apparent contradictions between these studies may be explained simply by the route of administration. Nonetheless, each finding is consistent with the conclusion that estrogen affects BP control. The former study suggests that estrogen can lower the baroreflex set point (i.e., the resting MSNA/BP relation); the latter suggests that it can increase baroreflex gain. Furthermore, neither conclusion alone is physiologically inconsistent; changes in either set point or gain do not necessitate reciprocal changes in the other.\(^3\)

Dodt and coworkers propose that the declines in BP observed by Vongpatanasin et al\(^1\) may be secondary to estrogen affecting vascular function rather than resting MSNA. Although estrogen therapy in postmenopausal women may impact arterial compliance, it can do so without an attendant change in BP,\(^4\) suggesting that the direct vascular effects of estrogen alone may not be sufficient to lower BP. Given the integrated nature of human physiology, it is likely the effects of estrogen are multifactorial. Thus, simplistic, single-factor models will not suffice.

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