Letters to the Editor

To the Editor:

The pathophysiology of menopause related vasomotor symptoms remains an enigma. Recently, authors have hypothesized about the effect of endogenous peripheral nitric oxide (NO) and these symptoms.

Alison J. Huang et al[1] postulate that continuous use of nitroglycerin rapidly leads to tolerance to the drug's vasodilatory effects and cross-tolerance to endogenous nitrates, as a result of enhanced NO degradation.[2-7] Although this tolerance limits the usefulness of nitroglycerin for chest pain, it offers a potentially innovative approach to treating hot flashes, because women who develop cross-tolerance should experience a marked reduction in hot flashes as a result of suppression of NO-mediated peripheral vasodilation.

On the other hand, Bailey et al,[8] explain that exercise training reduces thermoregulatory dysfunction via stabilization of central thermoregulatory control, that is, lowering core body temperature and improving heat dissipation thresholds, alongside improvements in peripheral mechanisms that allow for greater heat dissipation (sweating sensitivity). These adaptations likely include increases in the number of sweat expulsions per minute, sweat gland hypertrophy, increased NO availability, and others.[9] The reduction in estrogen associated with menopause causes endothelial dysfunction via decreased NO bioavailability[10] and/or increased reactive oxygen species scavenging NO.[11] Exercise increases endothelial NO synthase expression via similar mechanisms of transcriptional regulation to that of estrogen[12] and augments NO-mediated vasodilation.[13]

It appears that these hypotheses are in conflict. Further discussion by the authors may clarify the existing knowledge base regarding the role of nitric oxide and vasodilatation. This information may aid menopause practitioners in educating and caring for their patients.

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In Reply:

We thank Professor Steiner for her interest in our recent publication and the opportunity to discuss the role of nitric oxide (NO) in menopausal hot flush mechanisms and treatment.

Initially, it is important to highlight that while the two studies investigate the effects of "treatment" via different interventions (exercise training[1] and nitrogylcerin therapy[2]) to improve the frequency and severity of self-reported hot flushes in postmenopausal women; both interventions alter NO availability. In the following text, we have outlined how the two interventions potentially impact hot flushes, potentially via NO pathways.

During a bout of exercise the endothelium releases NO in response to episodic increases in blood flow, and subsequently shear stress along the artery wall. NO diffuses into the smooth muscle cells causing relaxation and artery vasodilation, which

is endothelium-dependent. Exercise training, as performed in our study,[1] causes regular, episodic increases in vascular shear stress that causes NO release during each exercise session[3] and thus has been shown to improve both local[3] and systemic[4,5] NO-mediated endothelial function. Nitroglycerin is an NO donor that causes increased systemic NO availability that acts directly on smooth muscle cells causing endothelium-independent vasodilation when administered acutely. Huang et al,[2] administered a daily dose of nitroglycerin for 6 weeks and inferred that cross-tolerance to organic nitrates occurred with the continuous nitroglycerin administration that surpressed NO-mediated vasodilation. Endothelial function, microvascular function (eg, cutaneous vasodilation) or other thermoregulatory variables (e.g. core body temperature) were not measured by Huang,[2] nor was the frequency and severity of hot flushes prior to the onset of cross-tolerance where NO availability would have been elevated.

There is evidence that acute alterations in NO have a role in cutaneous vasodilation during an individual hot flush,[6] but it is currently unknown whether NO is involved in the trigger for hot flushes. Nevertheless, the self-report data from ours[1] and Huang's[2] studies suggest that both interventions reduce the frequency of hot flushes, which may provide evidence that NO availability is involved in the trigger for hot flushes; the specific mechanism(s) are unclear however it is plausible that NO impacts on the thermoregulatory system,[7] the sympathetic nervous system[8] or neurotransmitters in the brain[9,10]; all of which have been shown to be involved in the hot flush trigger.

The self-report data from ours[1] and Huang's[2] studies also suggest that both interventions reduce the severity of hot flushes. Physiological severity was not measured in the Huang study, but we have direct evidence that exercise training reduces the physiological severity of hot flushes by reducing the amount of cutaneous vasodilation and sweating during a hot flush.[11] We suggest that this is due to more efficient thermoregulation, including endothelial dependent NO-mediated vasodilation. Huang infers that cross tolerance to NO would reduce cutaneous vasodilation during a hot flush.

There are a number of distinct differences between the two interventions that are noteworthy. Exercise training enhances endothelial function,[1] which has been shown to be impaired in postmenopausal women and especially in symptomatic women,[12] whereas chronic daily administration of nitroglycerin can cause "cross tolerance" to organic nitrates and possibly negate the requirement for endothelial dependent vasodilation, both of which may lead to endothelial dysfunction, that might have implications for those with coronary artery disease.[13,14] Furthermore, exercise does not cause headaches like nitroglycerin, and exercise training has additional benefits to reducing hot flush frequency and severity (eg, improved thermoregulation, neural activity[15]) as well as several well-known multifaceted benefits for improving health in postmenopausal women.[16]

It is also important to emphasize that both of these studies[1,2] require confirmation with full randomized control trials to determine efficacy, ideally which include outcomes measurements of both self-reported and physiologically measured hot flushes that include cutaneous vasodilation, sweating, and vascular function.[11]

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In Reply:

We agree that the pathophysiology of menopause-related vasomotor symptoms remains frustratingly unclear. However, our exploration of continuous nitroglycerin as a treatment strategy for hot flashes is not predicated on any particular hypothesis about the causal trigger for these symptoms.[1] We only assume that, once triggered, hot flashes manifest in the form of cutaneous vasodilation that is likely mediated by nitric oxide (NO) activation of vascular smooth muscle.[2] If this is true, then treatment strategies directed at dampening NO-mediated vasodilation (such as induction of nitrate cross-tolerance) may suppress the primary physical manifestations of hot flashes, regardless of the original stimulus for these symptoms.

We appreciate that menopause may be associated with changes in vascular endothelial function that are in turn associated with decreased NO bioavailability, and that a prior study has suggested that changes in endothelial-dependent flow-mediated dilation are associated with more severe vasomotor symptoms.[3] However, evidence is lacking that these changes are specifically responsible for development of menopausal vasomotor symptoms. Similar changes in flow-mediated dilation have also been observed in other populations such as aging men[4] or cardiac patients using long-term oral nitrates,[5] and yet high rates of vasomotor symptoms are not reported in these populations. Even if decreased endothelial response to endogenous NO is associated with vasomotor symptoms, it is unlikely that it is the primary cause of these symptoms.

With regard to the exercise study by Bailey et al,[6] larger-scale randomized trials of exercise-based interventions have unfortunately failed to demonstrate a reduction in vasomotor symptoms relative to controls.[7] But even if we assume that exercise is effective in reducing hot flashes, it does not necessarily follow that this is mediated by exercise-induced increase in NO availability.[6] Regular exercise has a multitude of effects—not just at the tissue-specific level, but also at the level of the organ system and the individual woman and her perception of vasomotor symptoms. Reported reductions in hot flashes among women who exercise may (and probably do) arise from other mechanisms.

Two things are certain—hot flashes involve vasodilation, and NO is a vasodilator. If we go one step further and accept laboratory-based evidence that NO is the primary vasodilator implicated in hot flashes,[2] then interventions that target NO-mediated vasodilation may offer promise for treatment. Of course, this does not lessen the need for a better understanding of the upstream stimuli that give rise to these perplexing symptoms in the first place.

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