Rapid Vasomotor Effects of Estrogen

Men are Part of the Club

“We know of no culture that has said, articulately, that there is no difference between men and women except in the way they contribute to the creation of the next generation.”

Margaret Mead

Atherosclerotic coronary artery disease (CAD) is the leading cause of death for American men and women. Though the pathogenesis of CAD is multifactorial, recent work has identified endothelial dysfunction as an important early event in the atherosclerotic process. Endothelial dysfunction clinically is detected by a decrease in the normal vasodilatory response to acetylcholine (Ach) that results from partial or complete attenuation of the bioavailability of nitric oxide (NO). In the normal arterial wall, Ach stimulates endothelial cells to release NO, which induces vascular smooth muscle cell relaxation in a paracrine fashion. In the atherosclerotic vessel, the bioavailability of endothelium-dependent NO is lost, and Ach acts directly on vascular smooth muscle, causing “paradoxical” vasoconstriction. The same changes in vascular tone caused by Ach infusion are produced by a variety of stimuli (eg, cold exposure, ischemia) in a variety of vascular beds, forming the basis for several clinically useful provocative tests of vascular function. Using such tests, endothelial dysfunction has been shown to occur in a number of clinical settings, including hypercholesterolemia, diabetes, hypertension, and cigarette smoking. Treatment of such risk factors is accompanied by detectable improvement in endothelial function.

Over the past decade, a large body of observational data has accumulated demonstrating that long-term treatment of postmenopausal women with estrogen (E2) reduces the incidence of CAD by 35 to 50%. Both long- and short-term E2 administration is associated with improved endothelial function in animal and human studies. Williams and colleagues first showed that brief (15 min) exposure to IV E2 improves endothelial function in cholesterol-fed ovariectomized female monkeys. These effects of E2 have since been documented in postmenopausal women by several groups of investigators. The observed rapid (ie, occurring over 15 to 20 min) vasodilatory effects of E2 in female animals and humans raise a number of interesting questions. One important question is whether E2 can stimulate this same rapid vasodilatory pathway in men as it does in women. An early study examining this question failed to demonstrate an acute effect of 17β-estradiol in men. However, two more recent studies with larger patient populations demonstrate that IV administration of a mixture of conjugated equine estrogens improves the coronary response to Ach in men and to the cold pressor test in male cardiac allografts. In the current issue of CHEST (see page 1556), Reis and colleagues examine this issue further by demonstrating that a short exposure to conjugated equine estrogens also abolishes the abnormal coronary vasoconstrictor response to the cold pressor test in a group of 30 men, confirming the existence of the pathway for rapid E2-mediated vasodilation in men.

Intriguing mechanistic questions surround the observed rapid vasodilatory effects of E2. The cellular effects of E2 on gene expression occur over hours to days and are mediated by estrogen receptor-dependent effects on gene transcription. To date, two estrogen receptors (ER) are known, ERα and ERβ. These proteins, members of the larger family of steroid hormone receptors, act as ligand-activated transcription factors, and thus, alter gene transcription following binding of E2 to the receptor. Clearly, the rapid vasomotor effects of E2 such as those described by Reis and colleagues, occur too quickly to be mediated by this genomic mechanism. The nongenomic nature of the rapid effects of E2 is supported by in vitro studies demonstrating that gene transcription is not involved in the rapid vasodilatory effects of E2. How then, are these effects transduced? The following three likely explanations are presently being explored: (1) nonreceptor-mediated effects such as direct effects of E2 on membrane function or ion channels; (2) effects mediated by a novel, as yet undescribed estrogen receptor; and (3) effects mediated by one or both of the classical ERs acting in a novel manner. Though some in vitro and in vivo data suggest receptor-independent effects of E2, these only occur with supraphysiologic concentrations of E2 and are...
unlikely to be of physiologic relevance. More recent data better support the third possibility that known ERs, acting in a new way, can themselves mediate the rapid vasodilatory effects of E2.20,21 This exciting possibility is under active investigation in a number of laboratories and suggests that novel estrogen-like compounds may be developed that specifically activate vascular estrogen receptors to cause both rapid vasodilation and longer-term effects on the expression of beneficial vascular genes. Evidence such as that presented in this issue by Reis and colleagues suggests further that such compounds may prove useful in treating atherosclerotic vascular diseases in both men and women.

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Pneumonia in Japan

Another Piece to a Worldwide Puzzle

Because I know that time is always time
And place is always and only place
And what is actual is actual only for one time
And only for one place . . .

T. S. Eliot, “Ash Wednesday”

During the early 1880s, Carl Friedländer and Albert Fraenkel argued bitterly over whether the usual cause of community-acquired pneumonia was Klebsiella pneumoniae or Streptococcus pneumoniae (to use today’s nomenclature). The debate was settled in favor of the pneumococcus, which reigned for many years, but now there are many controversies. Why do we see classic lobar pneumonia less often? Why does the previous distinction between “typical” and “atypical” pneumonia seem