News and Views From the Literature

Coronary Artery Disease

Tetrahydrobiopterin: A New Piece of the Postmenopausal Cardiovascular Puzzle

Reviewed by Paula Bernstein, PhD, MD
Cedars Sinai Medical Center, Los Angeles, CA

[Rev Cardiovasc Med. *2012;13(4):e209-e210 doi: 10.3909/ricm0651]*

A recent study by Moreau and colleagues[1] has shed new light on the mechanism by which estrogen affects vasodilatation in large elastic arteries. Tetrahydrobiopterin (BH_4) is a cofactor for endothelial nitric oxide synthase (e-NOS), the enzyme that produces nitric oxide (NO). It is well known that large elastic arteries stiffen with age and that NO is a potent vasodilator with a role in regulating arterial stiffness. Estrogen affects the vascular endothelium, producing increased levels of NO; postmenopausal women on hormone replacement therapy demonstrate improved vascular function compared with estrogen-deficient postmenopausal women.

This study examined the effect of the administration of BH_4 (10 mg/kg) in both premenopausal and estrogen-deficient postmenopausal women. Carotid artery compliance, brachial artery compliance, and flow-mediated dilation (FMD) were measured at baseline for both groups, and again 3 hours after administration of BH_4.

BH_4 had no effect in premenopausal women, but increased carotid artery compliance by 24% ± 5% and brachial artery FMD by 64% ± 11% in postmenopausal women. There was no change in brachial artery compliance in either group. Brachial artery compliance is mediated by vascular smooth muscle rather than vascular endothelium.

To further elucidate the relationship between estrogen and BH_4, the postmenopausal group was divided into estrogen versus placebo groups. The estrogen group received a .05 mg/d transdermal patch for 2 days, and the other group received a transdermal placebo. The estrogen group demonstrated increased carotid artery compliance and brachial FMD; there was no change in the placebo group. When BH_4 was administered, the placebo group demonstrated improved carotid artery compliance and FMD, but there was no further effect on the estradiol-treated women.

Estrogen is known to improve vasodilatation by increasing NO release and by preventing NO from being inactivated by reactive oxygen species. These results suggest that arterial stiffening in estrogen-deficient postmenopausal women may be partially due to reduced

levels of BH_4, and that the mechanism by which estrogen improves vascular compliance may involve an increase in bioavailable BH_4, thus leading to increased NO synthesis by e-NOS.

Neither estrogen treatment nor BH_4 supplementation restored compliance or FMD to premenopausal levels. Thus, additional factors must contribute to the vascular stiffening in large elastic vessels noted after menopause. These may include other vasoconstrictors, as well as structural changes of the arterial wall, which do not respond to short-term intervention. Further research looking at the dose response of BH_4 would be helpful in determining the degree of improvement in vascular function that can be achieved by supplementing this cofactor.

BH_4 has also been tested in patients with coronary artery disease, and has been found to prevent vasoconstriction induced by acetylcholine in angiographically normal vessel segments.[2] This study suggests several additional lines of future research, including the effects of BH_4 on the microvasculature of women with ischemic microvascular disease, and a possible pharmacologic role to improve large vascular function in women in whom hormone replacement is contraindicated. ■

References

1. Moreau KL, Meditz A, Deane KD, Kohrt WM. Tetrahydrobiopterin improves endothelial function and decreases arterial stiffness in estrogen-deficient postmenopausal women. *Am J Physiol Heart Circ Physiol.* 2012;302:H1211-H1218.
2. Maier W, Cosentino F, Lütolf RB, et al. Tetrahydrobiopterin improves endothelial function in patients with coronary artery disease. *J Cardiovasc Pharmacol.* 2000;35:173-178.

Age, Sex, Symptoms, and the Prevalence of Significant Coronary Artery Disease by Coronary Computed Tomographic Angiography

Reviewed by Nancy Mesiha, MD,[1,2] Usman Hashmi, MD,[1,2] Chatchawan Piyaskulkaew, MD,[1,2] Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP[1–3]

[1]*Department of Medicine, Division of Cardiology, St. John Hospital and Medical Center Detroit, MI;* [2]*St. John Providence Health System, Warren, MI;* [3]*Providence Hospital and Medical Centers, Southfield, and Providence Park Heart Institute, Novi, MI*

[Rev Cardiovasc Med. *2012;13(4):e210-e213 doi: 10.3909/ricm0652*]

The concept of "pretest probability" of coronary artery disease (CAD) is central dogma in the teaching and practice of cardiology. The likelihood of the presence of obstructive CAD based on age, sex, and quality of angina, as adopted by the Clinical Practice Guidelines for Management of Chronic Stable Angina by the American College of Cardiology (ACC) and American Heart Association (AHA) for predicting the presence of $>$ 50% stenosis, is challenged by Cheng and colleagues[1] in a recent analysis from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) registry.

Long before the work of Cheng and colleagues,[1] Diamond and Forrester[2] retrospectively collected data from angiograms performed in the 1960s and 1970s and discerned that the variables of age, sex, and type of pain were important in predicting the probability of CAD. Prospective studies from Duke University (Durham, NC) and Stanford University (Stanford, CA) in men and women who underwent cardiac catheterization[3,4] or stress testing[5] confirmed the power of these basic clinical variables. The Diamond and Forrester prediction model was compared with data from the large multicenter Coronary Artery Surgery Study, containing the angiographic data of more than 20,000 patients.[6] In both studies, age, sex, and character of pain were incorporated into probability tables, with an average difference of 5%. These similar results led to the adoption of one unified table that has served as the primary substrate in forecasting the likelihood of CAD (Table 1).

The large multinational CONFIRM registry studied 14,048 consecutive patients enrolled at the time of clinically indicated coronary computed tomography (CT) angiography. Patients with known CAD, suspected acute coronary syndrome, or age $<$ 30 years were excluded. Patients had their symptoms categorized as angina, atypical chest pain (ATCP), or nonanginal chest discomfort based on established criteria for angina pectoris, and were then grouped based on the current prediction score for $>$ 50% stenosis (CAD50). Those age $>$ 70 years and with a history of diabetes, smoking, and dyslipidemia were algorithmically placed into groups that projected a probability of $>$ 70% stenosis (CAD70).

CT angiography based on standardized protocols was performed to evaluate for coronary artery stenosis. A single-source 64-slice or dual-source scanner was used along with β-blockers and nitrates to enhance image quality prior to scanning. A concomitant noncontrast CT was performed in 11,727 (83%) patients for coronary calcium scoring. Data were processed in mid-diastole and end-systole (if available) with image enhancement if needed, and were then sent to an experienced reader who had interpreted at least $\geq$ 1000 prior CT angiograms to assess for the CAD50 or CAD70 in visible segments $\geq$ 1.5 mm in diameter. Images were read on an intent-to-diagnose basis, adherent to standards from prior studies. A 16-segment American Heart Association