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Association Between Migraine Headache and Cardiac Syndrome X



In the October 2015 issue of the *Journal*, Pepine et al. (1) presented the current concepts on non-obstructive coronary artery disease as an origin of ischemic heart disease and associated adverse outcomes among women. The authors emphasized the need for further evaluation to clarify the emerging paradigm of nonobstructive coronary artery disease especially in women to define proper short-term and long-term treatment. To expand this point further, we would like to add our novel project to increase the level of knowledge about the dilemma of cardiac syndrome X (CSX) (2,3), which is currently deficient.

In our study, we assessed the prevalence of migraine headache, according to the International Classification of Headache Disorders, in 3 groups: a CSX group (n = 50), a coronary artery disease group (n = 50), and a healthy group (n = 50) using a well-designed prospective study. The prevalence of migraine was 60% in CSX patients, 16% in the coronary artery disease group and 22% in the healthy group (p < 0.0001). The frequency of migraine headache in women with CSX was 70.4% and in men was 52.2%. Our study concluded that CSX may presumably be a manifestation of migraine as another migraine equivalent.

The connection between CSX and migraine headache has not yet been fully addressed. One of the suggested mechanisms in relation to migraine and angina pectoris is vasospasm, as has been seen previously in the coronary and cerebral arteries of patients with migraine headache (4,5). This occurrence can be clarified using functional brain imaging during the symptomatic phase of CSX to reveal cerebral perfusion changes similar to the migraine complex. Endothelial disturbance and different reactions to mediators, such as endothelin, is another probable theory that connects CSX and migraine headache (3). The third presumable mechanism causing chest pain in migraine patients is mitochondrial dysfunction. It may occur in the myocardial tissue of patients with migraine headache, which may eventually present with a clinical manifestation similar to CSX (2,5). However, there are many debates about the connection of CSX and migraine, and future studies are needed.

After the ongoing evidence on the multifaceted pathophysiology of CSX, it became even more clear that there is a need for a pragmatic approach to education and training of medical practitioners in the management of patients, especially in refractory patients using the current treatment.

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REPLY: Association Between Migraine Headache and Cardiac Syndrome X



We appreciate the interest in our State-of-the-Art Review on nonobstructive coronary artery disease (CAD) (1) and the interesting data about migraine, and are pleased to add our comments.

In a previous report from the original Women's Ischemia Syndrome Evaluation (WISE) cohort, among 905 women, mean age 58 years, 220 reported a migraine history (2). They had lower angiographic CAD severity scores and less severe ($\geq 70\%$ stenosis) angiographic CAD versus women without migraine history ($n = 685$). These differences remained significant after adjustment for important cardiac risk factors. We prospectively followed 873 of the WISE cohort and found that migraine was not associated with a significant increase in adverse outcomes after 4.4 years. In addition, a preliminary analysis of that cohort concluded migraine was not linked to alterations in endothelial function (unpublished observations).

We have since reported WISE 10-year outcomes that now included a National Death Registry search (3). In response to this letter we updated our prior analyses, and now note that of a total cohort of 902 women included in extended follow-up 177 women died. Among those reporting migraine headaches, 32 of 220 (14%) died (all-cause) versus 145 of 682 (21%) in those without migraine (hazard ratio: 0.66; 95% confidence interval: 0.45 to 0.96; $p = 0.031$ [unadjusted]). However, when adjusted for age, diabetes, body mass index, smoking, family history of CAD, race, aspirin use, dyslipidemia, and CAD severity score, absence of migraine is no longer a significant predictor for either all-cause death (hazard ratio: 1.12; 95% confidence interval: 0.73 to 1.72; $p = 0.60$) or cardiovascular death.

We also use this opportunity to reemphasize that it is no longer possible to support use of the term "cardiac syndrome X" for the rationale described in our recent article (1). A comprehensive review confirmed that there were no standard definitions for this terminology among published data (4). Furthermore, at least 1 pathophysiological mechanism present in many of these patients is attributable to coronary microvascular dysfunction, and therefore no longer "unknown" as implied by this term.

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Caveat Emptor

Antibiotics, Endocarditis, and Statistical Artifacts



In October 2007, the American Heart Association published guidelines that recommended against the use of prophylactic use of antibiotics before oral surgery among patients at moderate risk of adverse outcomes from infective endocarditis (IE) (1). Analyzing the Nationwide Inpatient Sample dataset for IE hospitalizations, Pant et al. (2) noted an increase in rates of streptococcal IE and "speculate(d) that this may be related to the decrease in the use of