Anxiety as a risk factor in coronary artery disease among young women

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Abbreviations

CAD Coronary artery disease
SPECT Single-photon emission computed tomography

GAD Generalized anxiety disorder
FMM Fractional myocardial mass

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INTRODUCTION

Coronary artery disease (CAD) in women has several distinctive features from that in men. In addition to the traditional risk factors (e.g., diabetes, smoking), there are some ‘non-traditional’ risk factors for CAD in women including preterm delivery, gestational diabetes, gestational hypertension, autoimmune disease, and notably, psychiatric disorders.¹ Psychiatric disorders are not rare among patients with CAD and considered to be linked with CAD in pathophysiological aspects.^{2,3} The most highlighted psychiatric disorder regarding CAD is depression, which has already been extensively investigated and integrated into the clinical guidelines.^{4,5} Anxiety disorders have gained less attention than depression, but are getting more clinical relevance.⁶

In this issue of the Journal of Nuclear Cardiology, Bekendam et al.⁷ demonstrated an intriguing association

between anxiety and the severity of myocardial ischemia, which may explain the potential link between anxiety and poorer prognosis of CAD among women. They analyzed the association between anxiety and myocardial ischemia in relation to two demographic factors, gender and age. Trait anxiety was associated with severer myocardial ischemia on myocardial perfusion single-photon emission computed tomography (SPECT), which was significant only for younger women (≤ 65 years old). Younger women with high trait anxiety (General Anxiety Disorder [GAD]-7 score > 10) showed significantly severer myocardial ischemia as compared to those with low trait anxiety (GAD-7 score ≤ 10).

Anxiety exhibits chronic withdrawal of parasympathetic activity.⁸ As parasympathetic innervation mainly determines the chronotropic aspect of the heart, there is a significant decrease in high-frequency heart rate variability in patients with anxiety disorders. The high-frequency domain of heart rate variability represents the parasympathetic controls on the cardiac rhythm, and its impairment is associated with major symptoms of anxiety disorders—hypervigilance and worry. In addition, the impaired parasympathetic activity leads to impaired

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Figure 1. Mechanisms explaining the link between anxiety and poorer prognosis in CAD among women. Anxiety shows chronic withdrawal of parasympathetic activity, which induces sympathetic overdrive. This leads to exaggerated myocardial ischemia due to increased myocardial oxygen consumption by more prominent hemodynamic reactivity. At the same time, electrical instability due to sympathetic overdrive raises vulnerability to the incidence of heart failure. Anxiety itself may cause myocardial ischemia via mental stress. CAD coronary artery disease.

sympatho-excitatory inhibition. This might have contributed to the prominent chronotropic response to stress testing in patients with high trait anxiety in the present study. More marked increase in heart rate inevitably results in higher myocardial oxygen demand, which could exaggerate the extent and severity of myocardial ischemia despite similar severity of coronary artery disease.⁹

It is noteworthy that trait anxiety, not state anxiety, was associated with more prominent hemodynamic reactivity to stress testing and myocardial ischemia. State anxiety is defined as transitory anxious behaviors, cognitions, and/or affects that result from an interaction of person characteristics and situational influences.¹⁰ State anxiety in the present study was evaluated with a novel artificial intelligence technique, the FaceReader.¹¹ It read the facial expressions of anxiety to detect the timely evidences of state anxiety before stress, during stress, and at the recovery phase. However, neither increased hemodynamic reactivity nor demographic difference (gender or age) was associated with the presence of state anxiety. State anxiety did not affect the severity of myocardial ischemia, either. Instead, high trait anxiety was associated with increased hemodynamic reactivity and more extensive myocardial

ischemia. As trait anxiety is defined as a chronic, stable tendency to respond fearfully to a wide variety of unspecific stressors,¹² the anxiety–ischemia association should not be regarded as a transient, momentary phenomenon due to the nervous mood resulting from SPECT imaging and stress testing, so-called white-coat phenomenon.

Then, why was the anxiety–ischemia association found only for younger women? Aging is related to a decreased sympathetic reactivity to stress testing. Although the sympathetic activity is generally elevated (e.g., higher resting systolic blood pressure and heart rate), the sensitivity of the adrenergic receptors to sympathetic stimulation is declined in elderly patients. Thus, the physiologic increases in heart rate, cardiac output and vasodilation in response to adrenergic stimulation are diminished.¹³ Given the diminished sympathetic reactivity in the elderly people, it is not surprising that anxiety was associated with severe myocardial ischemia only for younger patients. Parallel decrease in anxiety is also noted in the elderly people.

However, the anxiety–ischemia association was not found for younger men, but only for younger women. Such female predisposition to higher hemodynamic

reactivity to stress testing and inducible myocardial ischemia have been consistently shown in previous studies.^{14,15} A possible explanation can be provided by the biological differences in hormonal homeostasis. The ovarian steroids are thought to control sympathetic drive on the heart and their monthly fluctuations may characterize the sex differences in myocardial ischemia as well as anxiety.^{16,17} Another explanation can be provided by the unique phenotypic features of CAD in women. Women have significantly smaller coronary luminal diameter and the mass of myocardium fed by a specific coronary branch (fractional myocardial mass [FMM]).^{18,19} Despite smaller FMM, the blood flow per unit mass of myocardium is significantly higher for women both at rest and during stress.²⁰ Thus, the shear stress against the coronary wall is higher for women. These in combination contribute to the unique CAD characteristics in women: more marked microvascular dysfunction, more common diffuse non-obstructive CAD, plaque erosion, thrombus formation, distal emboli, etc.¹ Although it is not clear how these features are associated with anxiety, hemodynamic reactivity to stress testing, and the severity of inducible ischemia, the study by Bekendam et al. adds potential explanations to the poorer prognosis of younger women with CAD.

Now, a schematic presentation of the pathophysiology can be built that sheds light on the link between anxiety and poorer prognosis of CAD among women (Figure 1). Anxiety incurs sympathetic overdrive; it directly stimulates cardiac sympathetic tone which can also lead to electrical instability and heart failure; it can also induce extensive myocardial ischemia, which has long been known as a marker of poor cardiovascular outcomes. Anxiety per se may induce myocardial ischemia via mental stress, to which women are particularly vulnerable.²¹ In such perspectives, it is desirable to screen mental health in the initial evaluation of CAD in women, and detect underlying functional impairment even if obstructive CAD is absent. Functional imaging studies (e.g, myocardial perfusion SPECT), will play important roles in the management of CAD in women.

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