Cardiac Calcium and Coronary Calcium—The Mitral Annulus Is Only Half the Story

We read with interest the report "Relation of Mitral Annular Calcium and Coronary Calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA])" in the May 1, 2011, issue of *The American Journal of Cardiology*.[1] As the investigators clearly demonstrate, mitral annular calcium (MAC) is associated with coronary artery calcium (CAC) and thereby coronary atherosclerosis. We agree that this finding, commonly noted on cardiac computed tomography, should figure more prominently in the clinical evaluation and management of patients. However, as pointed out by Roberts,[2] MAC is only part of the picture; it is frequently associated with calcific deposits in other structures, such as the submitral apparatus and the aortic root and valve. Conversely, patients may have a heavy burden of calcium (especially in the aortic valve), with little or no detectable calcium in the mitral annulus. Focusing on MAC alone underestimates the extent of the calcium.

We would also like to point out that MAC is most frequently detected on echocardiography, although currently, there is no echocardiographic standard for its evaluation. Various methods have been reported, most of them not very sophisticated. Most do not consider calcium of other cardiac structures. Accounting for calcium in all these areas, rather than limiting our examination to the mitral annulus, should allow better prediction of CAC. In a small series of patients with cardiac computed tomographic scans, we observed a significant correlation between global cardiac calcium and CAC as measured by the Agatston score.[3] In addition, we tested an echocardiographic score that semiquantitatively measures global cardiac calcium and found that this score too was useful in predicting CAC. In fact, a high echocardiographic score had a positive predictive value of 60% for a CAC score >400 (consistent with severe coronary atherosclerosis). In this study, the global calcium score performed better than MAC alone.

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Post-Traumatic Stress Disorder and Cardiovascular Disease Link: Time to Identify Specific Pathways and Interventions

Research suggests that post-traumatic stress disorder (PTSD) is associated with increased risks for chronic diseases, including cardiovascular disorders, rheumatoid arthritis, and other health conditions.[1–6] The study by Ahmadi et al[3] published in *The American Journal of Cardiology* adds to this research. This study, which was based on a sample of 637 veterans, goes beyond previous work; using coronary artery calcium scores, it suggests that PTSD is associated with the presence and severity of coronary atherosclerosis. In this study, PTSD also predicted future mortality independent of age, gender, and conventional risk factors, a finding reported several years earlier in a large national study.[2] The question now is not so much if there is a link between PTSD and chronic disease but why this association is found, especially for cardiovascular disease. Another important question is whether these disease outcomes can be prevented.

Studies suggest that PTSD could result in inflammatory injuries through overactivation of the hypothalamic-pituitary-adrenal stress axis, subsequently followed by hypocortisolism related to molecular downregulation of these systems.[1,7,8] Consistent with this, research suggests that systemic inflammatory activity appears common in patients with PTSD.[9] This PTSD-disease link also could be related to health behaviors, such as cigarette smoking and substance misuse, related to self-regulation of aversive psychological states brought on by PTSD psychopathology.[1,2] There are other variables that could also explain this association.[7] At this time, no single causal pathway has been identified. Recently, our research indicated that FKBP5, COMT, and CHRNA5 genetic loci encompassing pathways associated with inflammation, addiction, sleep, and anxiety are associated with PTSD,[10] suggesting that PTSD-related genes may be worthy of investigation related to these disease linkages. For example, researchers have reported that the CHRNA gene, which encodes components of the nicotinic acetylcholine receptor, were associated with lung cancer.[11] This gene was also associated with cigarette smoking, nicotine dependence, opioid misuse, and PTSD.[10,12] Thus, 1 pathway for lung cancer appears to include nicotine addiction associated with genetic variants of the CHRNA gene, without which there would be insufficient exposure to cigarette smoking to result in lung cancer in most cases. It is noteworthy that the CHRNA gene is associated not only with lung cancer but also with peripheral arterial disease.[13] Cigarette smoking is also commonly associated with PTSD.[10]

Similarly, other genetic components involved in PTSD onset, including the FKBP5, COMT, and CRH-R1 genes, may be associated with the pathophysiology of specific diseases after PTSD onset. The COMT gene has been associated with anxiety disorders, psychosis, depression, and other conditions involving catecholamine pathway regulation.[10] The FKBP5 gene regulates glucocorticoid receptor sensitivity, is functionally involved in hypothalamic-pituitary-adrenal axis activity, and has been associated with PTSD.[14] The CRH-R1 gene is involved in corticotropin-releasing hormone activity, a polypeptide hormone and neurotransmitter involved in the stress response. Studies have suggested that this gene also regulates hypothalamic-pituitary-adrenal axis function and is associated with the impact of traumatic stress exposure and PTSD onset.[15] Thus, current PTSD-genetic findings are consistent with the cardiovas-

cular disease links often reported for PTSD. Also noteworthy in this regard is that recent research suggests that trauma victims who received emergency counseling shortly after the traumatic event not only had better PTSD outcomes but also had improved outcomes in a number of clinical areas, including reductions in substance misuse.[16] Evidence suggests that these early interventions may prevent PTSD memory consolidation.[16] These PTSD findings may have implications for future cardiovascular disease prevention. Further research is advised.

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