Myocardial Dysfunction in Hypertrophic Cardiomyopathy

To The Editor:

We note with interest Nagueh et al’s recent observation that the reduction of tissue Doppler (TD) velocities in mitral annulus excursion was highly sensitive and specific for the detection of individuals carrying hypertrophic cardiomyopathy (HCM)—causing mutations in HCM families, even in the prehypertrophic phase. Any clinical tool that can reliably identify subtle functional impairments as a marker of future disease will be of enormous significance in HCM management and counseling. The authors should be warmly congratulated for delineating a potential approach.

The authors attribute the reduced TD velocities to myocardial dysfunction resulting from intrinsic myocyte abnormalities, disarray, or interstitial fibrosis. They also highlight the apparent discordance between changes in TD velocity and the preserved ejection fraction in HCM, particularly in the prehypertrophic phase, and attribute this finding to a smaller cavity that decreases stroke volume and, hence, reduces afterload. We contend that no evidence exists for a decrease in afterload. Furthermore, in subclinical mutation carriers, a decreased left ventricle cavity size does not occur. An alternative explanation exists.

TD measurement of mitral annulus velocity assesses long-axis function. Long-axis function predominantly reflects longitudinal fiber contraction. The myocardium is composed of interwoven fiber sheets, with longitudinal fibers occupying the subendocardium (and subepicardium). Thus, TD velocity impairment reflects subendocardial dysfunction. It is recognized that this regional dysfunction is often partly compensated for by contraction of the midwall circumferential fibers.

Therefore, the findings of an impaired long-axis function but preserved ejection fraction suggest a specifically subendocardial defect in the early stages of HCM. We agree with the authors that the fibrosis and myofiber disarray are probably late features and that the functional pathology lies at the myocyte level. What distinguishes the myocytes in the subendocardium, bearing in mind that all cardiomyocytes carry the causative mutation? It is well recognized that because of pressure, flow, and vascular anatomical characteristics, the subendocardium is relatively less well perfused, even in conditions of normal afterload and cavity pressure. Thus, the subendocardium is a site of relative oxygen deprivation and, hence, bioenergetic vulnerability.

Therefore, we contend that the striking TD defects offer another layer of support for the suggestion that sarcomeric and other HCM mutations act through a unifying myocyte energetic deficit rather than through a specific contractile abnormality. Energetic decompensation and mechanical dysfunction that starts in the subendocardium will lead to longitudinal muscle dysfunction and, hence, reduced mitral annulus excursion velocity, whereas the circumferential fibers maintain a compensated ejection fraction.

Houman Ashrafian, MA, BM, BCH
Hugh Watkins, MD, PhD, FRCP
Department of Cardiovascular Medicine
University of Oxford
John Radcliffe Hospital
Oxford, United Kingdom
ashrafian@hotmail.com

Response

We appreciate the very kind comments of Ashrafian and Watkins regarding our finding of reduced tissue Doppler (TD) velocities in the preclinical stage of hypertrophic cardiomyopathy (HCM). Further, we agree that this finding could be of enormous significance in the management and counseling of patients with HCM.

Ashrafian and Watkins raise 2 points. The first relates to the state of afterload in HCM. We would like to clarify their statement that afterload is reduced only because left ventricular hypertrophy leads to a smaller left ventricular cavity and increased wall thickness. In fact, in a subgroup of patients with HCM, afterload increased as the phenotype evolved into that of dilated cardiomyopathy. In the absence of hypertrophy, ie, the preclinical stage of HCM, afterload is expected to be normal.

The second point relates to the reduced TD velocities in the preclinical stage of HCM. We have proposed that a reduction in TD velocities is primarily due to myocyte dysfunction secondary to mutant contractile protein. As noted in the article, we believe, as Ashrafian and Watkins assert, that interstitial fibrosis and/or disarray are less likely to be responsible for the reduced TD velocities because they often occur late in the course of HCM. Ashrafian and Watkins also propose that pressure, flow, and vascular anatomical characteristics in the subendocardium result in reduced TD velocities in the early stages of HCM because of impaired myocyte bioenergetics rather than transmural myocyte dysfunction. This theory is another potentially plausible hypothesis that requires proof through experimentation.

Sherif F. Nagueh, MD
Linda L. Bachinski, PhD
Denise Meyer, MT (ASCP)
Rita Hill, RN
William A. Zoghbi, MD
James W. Tam, MD
Miguel A. Quiñones, MD
Robert Roberts, MD
A.J. Marian, MD
Department of Medicine
Section of Cardiology
Baylor College of Medicine
Houston, Texas

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Houman Ashrafian and Hugh Watkins

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