EDITORIAL COMMENT

The Left Atrium

A Biomarker of Chronic Diastolic Dysfunction and Cardiovascular Disease Risk*

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Since Framingham Heart Study investigators first confirmed the existence and importance of cardiac risk factors in 1961 (1), clinicians and scientists have been seeking to refine our ability to predict cardiovascular disease risk. These efforts stem from an appreciation that atherosclerosis begins at a very young age but is clinically silent for many years and also that during this latent period it is possible to delay or prevent the onset of its devastating and systemic clinical manifestations. Thus, efforts have focused on identifying risk factors, not for their own sake, but so that they may be modified and, through this modification, reduce the burden of disease. This trio—risk stratification, risk modification, and altered outcomes—is one of the foundations of cardiovascular medicine and defines a preventive paradigm of medical care that is increasingly receiving attention from caregivers across many specialties, patients, and the public.

At the present time, the state of the art in cardiovascular risk assessment and modification is the National Cholesterol Education Program Adult Treatment Panel III, a National Institutes of Health–convened, consensus panel–endorsed risk assessment tool based largely on age and counting major risk factors to estimate 10-year coronary heart disease (CHD) risk based on Framingham data. It is easy to perform and scientifically well validated for the middle-aged, Caucasian population from which it was derived. However, it is not perfect, particularly in predicting risk in other populations and in individuals. There are also other reasons why we should seek to improve our ability to estimate risk. In the Framingham risk score, the significance of advancing age overwhelms most risk factors, making it difficult to identify low-risk elderly individuals, even among those without risk factors. The Framingham risk score also fails to adjust for the severity of risk factors, their treatment, other genetic factors, lifestyle, and interactions between risk factors. Finally, because CHD is so common, many affected individuals actually fall within the normal range of variables such as cholesterol, making it even harder to predict individual risk.

In this issue of the Journal, Tsang et al. (2) propose that transthoracic echocardiography adds significantly to our current ability to assess risk. Drawing on a moderately sized (for epidemiologic studies) community–based population of elderly patients undergoing clinically indicated echocardiograms, the authors compare a variety of clinical and echocardiographic variables to the development of virtually any form of cardiovascular disease. Of the clinical variables, age, gender, diabetes, and high blood pressure predict outcomes, whereas smoking, cholesterol levels, or a family history of CHD does not. Although some of these findings are expected, the lack of significance of some known risk factors is of concern. Other limitations relate to the cohort studied, particularly their homogeneity and that they were clinically referred rather than being a community sample.

Of the echocardiographic variables examined, reduced ejection fraction, left ventricular (LV) hypertrophy, and diastolic dysfunction score were associated with poorer outcomes, as has been noted by others. However, left atrial (LA) volume (but not dimension) was also associated with poorer outcomes. Because LA diameter would be expected to track with LA volume, it is unclear why there should be this disconnect. Nevertheless, the finding that LA size is related to prognosis is new and of interest. Perhaps its novelty is related to the fact that few evaluations of cardiac risk in otherwise healthy individuals have considered detailed echocardiographic findings as predictive variables. Exceptions include the Framingham study, which pronounced LV hypertrophy a risk factor 13 years ago (3) and, along with the present authors, has noted a poorer outcome in those with asymptomatic systolic and/or diastolic dysfunction (4). The Tsang et al. (2) data suggest that echocardiography in general, and evaluation of LA size in particular, should be included among tests and variables offering insight into cardiovascular risk.

There is substantial biologic plausibility to the prognostic significance of LA volume. The left atrium (LA) is most commonly thought of as a transporting chamber, receiving blood from the pulmonary veins and conveying it to the left ventricle (LV) through both passive and active diastolic filling. However, the LA also functions as a volume sensor of the heart, releasing natriuretic peptides in response to stretch and other neurohormones and generating a reflex tachycardia in response to increased venous return (Bainbridge reflex). The LA also reflects LV filling pressure and is capable of remodeling (enlarging) in response to its elevation. It is in this final role, as an ongoing biomarker or transducer of sustained elevations in LV filling pressures, that LA size captures our attention.

A great deal of research has been conducted on noninvasive assessments of diastolic function. Investigators and clinicians alike have struggled with the load dependence of easy-to-obtain measures, such as rapid filling rates and...
mitral E and A velocities, and with the technical difficulties of obtaining pulmonary vein flows and assessing the angle of the color M-mode LV inflow. At best, these techniques present only a snapshot view of diastolic function—the pattern would be altered if loading conditions changed. Clinicians need a measure of diastolic dysfunction that is easy to obtain, adequately reflects underlying abnormalities, and has similar prognostic significance. The Tsang et al. (2) data suggest that this elusive measure is LA volume.

Left atrial size is certainly easy to assess. With the advent of hand-carried ultrasound, it can be a bedside or point of care measure, possibly routinely obtainable as part of a comprehensive physical examination. Even more important, the Tsang et al. (2) data suggest that the hypothesis that LA size represents the integration of LV diastolic performance over time is clinically valid. Left atrial volume thereby provides a long-term view of whether or not the patient has the “disease” of diastolic dysfunction, regardless of whatever loading conditions are present at the time of the examination. Drawing a parallel to two of the most commonly used diagnostic tests in diabetes is nearly irresistible. Just as serum glucose is used to assess transient diabetic control, LV filling pressure is used to assess transient loading conditions. In turn, the diastolic function corollary of measurement of hemoglobin A1C (a long-term biomarker of average metabolic state) is LA size (a long-term biomarker of average LV diastolic pressure, and hence, when increased, of diastolic dysfunction). The message is simple: in the absence of other contributing pathology such as mitral valve disease, if the LA is large, the patient has had a sustained elevation in LV filling pressure, and hence has chronic diastolic dysfunction.

The Tsang et al. (2) report is of interest in other ways as well. Epidemiologic studies rarely include such large numbers of the elderly (average age 75 years), despite their growing demographic importance. More interestingly, few epidemiologic studies have considered and combined such a broad range of cardiovascular outcomes—heart failure, atrial fibrillation, myocardial infarction, surgical or percutaneous revascularization, stroke or transient ischemic attack—in addition to death. This novel combined end point allowed the authors to develop a single, unifying prediction model, rather than separate models for each type of event. This is arguably more clinically relevant than determining risk for any single one of its component events. Interestingly, in contrast to epidemiologic studies, randomized clinical trials routinely utilize a combined end point (MACE, or major adverse cardiovascular events), similar to the present study’s. The Tsang et al. (2) approach is worth keeping in mind for future studies. Many studies evaluating cardiovascular risk place an emphasis on the presence of clinical disease—diabetes, hypertension, hyperlipidemia—and minimize subclinical or mechanistic markers that may be more predictive. In this sense, the prognostic value of high sensitivity C-reactive protein is an important example, as it detects the inflammatory component of the disease process as it is occurring, and not simply its end point. Other “non-traditional” tests that detect the actual burden of subclinical disease are also of value. The best studied of these, carotid intima medial thickness, has been proven in multiple cohorts to prospectively predict both heart attack and stroke (5). A $68 million NIH-funded trial, the Multi-Ethnic Study of Atherosclerotic (MESA), involving six centers and 6,500 participants age 45 to 84 years, is examining the relative value of such tests, including cardiac magnetic resonance imaging, carotid intima medial thickness, ankle-brachial index, coronary calcium scores, and inflammatory and genetic markers. Echocardiography is not included in the trial, which could have made it an excellent validation of the Tsang et al. (2) data in a much larger population. Future studies will be needed to determine the relative value of LA size in relation to other noninvasive tests.

Tsang et al. (2) have taken the relationship between LA size and diastolic dysfunction and analyzed its clinical relevance. The association needs to be studied prospectively, and the applicability of these data to clinical care remains to be defined. Nevertheless, their findings suggest that echocardiographically determined LA size may become an important clinical risk stratifier in pre-clinical cardiovascular disease.

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