Cardiac “Morphomics”

Do We Need to Measure LV Mass and Geometry in Everyone?*

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Morphometry refers to the quantitative analysis of form, including parameters such as size and shape. The study of morphometrics enables investigators to test hypotheses about the factors that affect shape. Cardiovascular physiologists have had a long-standing interest in size, shape, and structure of the heart. Four morphologic categories have been defined based on left ventricular (LV) mass and relative wall thickness (normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy). All of the abnormal patterns have prognostic relevance (1). Gaasch and Zile (2) proposed a more granular classification system that adds 3 additional patterns (mixed hypertrophy, physiologic hypertrophy, and eccentric remodeling).

Traditional thinking holds that chronic pressure and volume overload lead to distinct LV geometric patterns. In reality, many patients have some combination of both, and the severity of each hemodynamic abnormality may vary over time. Obesity, present in at least 30% of adults, tends to produce a concentric pattern (3,4). However, the obesity-related changes in cardiac structure are only partially related to blood pressure (3). Interestingly, the degree of nocturnal hypoxemia in patients with sleep-disordered breathing is a predictor of LV hypertrophy, suggesting a role for oxidative stress (3). Hemodynamic factors that affect LV mass are interwoven with important modifiers such as sex, race, age, genetic variations (genomics), protein expression and function (proteomics), metabolic profiles (metabolomics), exercise habits, pharmacological treatments, and others (5). Perhaps the study of cardiac structure is a large enough endeavor to deserve its own name, for example, “cardiac morphomics.”

The presence of LV hypertrophy is predictive of an increased incidence of cardiac events as well as cardiac and total mortality (1). Arguments favoring a direct pathological role include the fact that LV hypertrophy can adversely affect myocardial perfusion, stiffness, and repolarization. In addition, regression of LV mass achieved by treatment of hypertension (6), aortic stenosis (7), and obesity (8) have been associated with improved outcomes (6,7).

In this issue of JACC, Hoang et al. (9) report relationships between indexed LV mass, determined by M-mode echocardiography, and outcomes (coronary heart disease, stroke, heart failure, cardiovascular death, and total mortality) in 3,724 older adults participating in the Cardiovascular Health Study. Over a mean follow-up period of 14.2 years, 58% of the subjects experienced a cardiovascular event, and 26% died of cardiovascular causes. Patients were categorized as having the following: 1) metabolic syndrome without diabetes; 2) diabetes; or 3) neither diabetes nor metabolic syndrome. The main finding was that M-mode-derived LV mass (adjusted for age, sex, ethnicity, body mass index, fasting glucose concentration, blood pressure, serum lipid levels, and medications) was positively associated with cardiovascular events in those patients with neither condition or with metabolic syndrome, but surprisingly not in those with diabetes. Several points are worthy of additional consideration.

First, methods of assessing LV mass have evolved from electrocardiography to M-mode, 2- and 3-dimensional echocardiography, to cardiac computed tomography and magnetic resonance imaging (MRI). This evolution has yielded increasingly more accurate and reproducible methods of measuring LV mass and volumes (1,10). The use of M-mode in the current study could have affected the results.

Second, determining whether LV mass is appropriate for body size is troublesome. Guidelines
recommend use of body surface area for indexing heart size to body size (11); however, this method tends to underestimate the degree of hypertrophy in obese patients and give false impressions of changes in LV mass if people gain or lose weight. Many investigators have used height (5) or height raised to a power between 1.7 and 2.7 to approximate lean body size from a parameter that does not change with adiposity (height) (12). Allometric scaling factors are intended to relate height to ideal body size by using a power law. Unfortunately, the human form is very complex, and there is currently no single allometric scaling factor that is widely accepted. The recently published Echo-NoRMAL (Echocardiographic Normal Ranges Meta-Analysis of the Left Heart) study (5), which attempted to establish normative values for LV and left atrial sizes in both the sexes and multiple ethnic groups, used the simple and easily understandable standard of height without allometric adjustment as the method of indexing.

Third, the study touches on the question of whether diabetes directly causes or contributes to LV hypertrophy. To this point, 1,017 type 1 diabetic subjects from the Diabetes Control and Complications Trial had cardiac MRI performed at a mean of 21 years after enrollment in the trial (13). Mean LV mass and LV mass/LV end-diastolic volume were within normal ranges and only weakly associated with mean glycosylated hemoglobin (HbA1c) concentrations over the prior 21 years. Thus, type 1 diabetes appears, at most, to be a rather weak contributor to the development of LV hypertrophy. In comparison, type 2 diabetes seems more strongly associated with LV hypertrophy, although it is likely that obesity and other comorbidities mediate some or all of this association (14). The findings of Hoang et al. (9) show a graded relationship between LV mass and cardiovascular event rates in the diabetic group, but this was no longer statistically significant after multivariate adjustment. This unexpected finding is most likely related either to statistical chance, given that the study was not designed to test this question, or to the overall high risk of adverse cardiac events in diabetics, which overwhelmed the predictive value of LV mass in this group.

How does measurement of LV mass help us clinically? Although measuring LV mass gives prognostic information, it does not directly guide many treatment decisions, including goals for blood pressure, body mass index, HbA1c, and low-density lipoprotein (LDL) cholesterol. Treatment of heart failure is guided mainly by measurement of LV ejection fraction to differentiate between subjects in whom it is preserved and those in whom it is reduced. Use of implantable cardioverter-defibrillators is also driven by LV ejection fraction, but rarely by LV mass. On the other hand, identification of LV hypertrophy may help to identify causes of symptoms. Increased LV mass is included as a diagnostic criterion for the diagnosis of heart failure with preserved ejection fraction (15). Measurement of LV mass is sometimes used as a means to assess long-term blood pressure control. Finally, documenting the presence or absence of LV hypertrophy may be helpful in assessing patients with aortic stenosis when traditional criteria for grading the severity are ambiguous.

Given that LV mass measurements are easy to obtain using modern imaging techniques, we should report this parameter when such tests are ordered for appropriate clinical indications. Absolute LV mass or LV mass indexed to some measurement of height is probably more meaningful than mass indexed to body surface area because of the high prevalence of obesity in our society. Using LV mass as a screening test does not appear to be warranted at this point in time. However, the dramatic advances occurring simultaneously in cardiac imaging, genomics, proteomics, metabolomics, and population science bode well for the resurgence of cardiac morphomics as a field of inquiry that has high potential to lead to important new discoveries and therapeutic opportunities.

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