Association of Aortic Root Dilation from Early Adulthood to Middle Age with Cardiac Structure and Function: The CARDIA Study

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Background: The human aorta dilates with advancing age. However, the association between progressive aortic dilation with aging and cardiac remodeling has not been established in studies of community-dwelling adults. The aim of this study was to test the hypothesis that there would be a relationship between aortic size increase over the early adult life span with left ventricular (LV) structural remodeling and subclinical LV dysfunction in middle age, even in the absence of overt cardiovascular and valvular disease.

Methods: Included were Coronary Artery Risk Development in Young Adults study participants (N = 2,933) aged 23 to 35 years with available transthoracic echocardiographic measurements during 20 years of follow-up. Multivariate linear regression models assessed sex-specific associations between 20-year change in aortic root diameter with LV structure and function.

Results: Larger aortic root diameter at 20-year follow-up was associated with greater LV mass (2.77 vs 2.18 g/mm in men and women, respectively, $P < .001$). In longitudinal analyses, increase in aortic root diameter over 20-year follow-up was associated with a greater 20-year increase in LV mass and ratio of LV mass to LV end-diastolic volume ratio in both sexes. In women but not in men, increased aortic root diameter over 20 years was associated with increased left atrial dimension, impaired E/E′, and impaired early diastolic longitudinal and circumferential strain rates assessed by speckle-tracking echocardiography.

Conclusions: Progressive increase in aortic root diameter from early adulthood to middle age was associated with increased LV mass and LV concentric remodeling in both sexes and impaired diastolic function predominantly in women. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Aorta, Left ventricle, Systolic function, Diastolic function, Aging, Cardiac remodeling

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Aortic remodeling with advancing age has been described in population and postmortem studies.[1-5] These aging-related changes are thought to be mediated in part by collagen deposition in the aortic wall, aortic stiffness, and progressive thinning and fragmentation of elastin fibers, ultimately resulting in aortic root enlargement.[2,6,7] Structural alterations in the aorta are exacerbated by chronic pressure load and exposure to cardiovascular risk factors.[1,5,8-11]

In the Coronary Artery Risk Development in Young Adults (CARDIA) study, we have previously demonstrated that aortic root size increases from early adulthood to middle age, with a greater increase in men than women, and that key determinants that may accelerate this aging-related increase in aortic size include obesity, cigarette smoking, and blood pressure.[12] Recent studies have shown that larger aortic root diameter (AoD) independently predicts adverse cardiovascular outcomes.[13-15] However, studies evaluating the association between longitudinal aortic size increase and cardiac structural, systolic, and diastolic functional indices in later life are notably lacking.

Observational studies have shown a greater incidence of heart failure with preserved ejection fraction with aging, especially among women.[16] Adverse vascular-ventricular interactions and elevated

Abbreviations

AoD = Aortic root diameter

CARDIA = Coronary Artery Risk Development in Young Adults

LV = Left ventricular

LVM = Left ventricular mass

STE = Speckle-tracking echocardiography

left ventricular (LV) filling pressures with predominant but not isolated diastolic dysfunction may be contributory mechanisms that are theorized to play a role in the pathophysiology of heart failure with preserved ejection fraction.[17,18] This may suggest differential arterial and ventricular interactions with aging and by gender that may be reflected in associations of change in aortic root size with markers of LV remodeling and subclinical function.

Accordingly, we posited that there would be a relationship between AoD increase over the early adult life span with LV structural remodeling and subclinical LV function in middle age. We tested these hypotheses in CARDIA, a community-based cohort study that provides a unique opportunity to explore these relationships over the early adult life course and also to assess for race- and gender-specific effects.

METHODS

Study Design and Participants

The selection criteria and study design of the CARDIA study have been described in detail elsewhere.[19] Briefly, CARDIA is a multicenter, biracial cohort study that enrolled 5,115 men and women from four US field centers (Birmingham, Alabama; Oakland, California; Chicago, Illinois; and Minneapolis, Minnesota), aged 18 to 30 years at baseline (1985–1986) with 25 years of follow-up in seven subsequent visits up until 2010–2011 (year 25 examination). For this study, we evaluated 3,239 CARDIA participants with echocardiograms obtained 20 years apart, 1990–1991 (year 5, baseline) and 2010–2011 (year 25, follow-up). One hundred seventy participants were excluded because of suboptimal images for AoD assessment. Participants with clinical cardiovascular disease events ($n = 93$) and moderate or severe valvular dysfunction ($n = 43$) were excluded. The final analytic cohort had 2,933 participants (91% of total year 5 and year 25 participants). All study participants gave written informed consent, and the institutional review board of each participating institution approved study.

Echocardiographic Assessments

The echocardiographic protocols for CARDIA year 5 and year 25 were designed to ensure consistency across examinations and followed existing American Society of Echocardiography guidelines at each period.[20-23] Briefly, trained sonographers, following standardized protocols across all four field centers, acquired images. Experienced readers interpreted digitized images using standard software offline image analysis system transmitted to a core reading laboratory (videotape in year 5 to the University of California, Irvine, and digitally in year 25 to the Johns Hopkins University Echocardiography Reading Center in Baltimore, Maryland). AoD was measured from two-dimensionally guided parasternal M-mode tracings at the level of the sinuses of Valsalva, using the leading edge–to–leading edge approach in end-diastole. LV and left atrial dimensions were acquired using two-dimensionally guided M-mode obtained from parasternal views.[22] LV mass (LVM) was derived according to American Society of Echocardiography guidelines. LV volumes were estimated from apical views using the Simpson method. LV ejection fraction was calculated from LV end-diastolic and end-systolic volumes.[24] Peak early diastolic velocity (E) and peak late diastolic velocity (A) were measured from pulsed Doppler recordings of transmitral flow. Early peak diastolic mitral annular velocity (E′) was derived from tissue Doppler as the average of septal and lateral mitral annular velocities.[25]

Speckle-Tracking Echocardiography

The speckle-tracking echocardiographic protocol and quality control procedures for CARDIA have been previously described.[23,26] In a retrospective analysis of prospectively collected data, speckle-tracking echocardiography (STE) for LV myocardial strain and strain rate measures were performed offline with dedicated semiautomated two-dimensional wall motion tracking software (Toshiba Medical Systems, Tokyo, Japan). Three cardiac cycles were recorded for apical and parasternal views at an average frame rate of 46.2 frames/sec. After manual tracing of LV endocardial border, a midwall region of interest was automatically defined and adapted when necessary. Lagrangian strain was derived from the change in regional length relative to the length at end-diastole: strain $= (L[t] - L_0)/L_0 \times 100$, in which $L(t)$ is the length at time t, and L_0 is the length of the segment at the beginning of the QRS complex. Strain rate was defined as the rate of deformation, estimated from the strain temporal derivative. Strain rate parameters were presented as deformation per second. Global strain values were calculated as the average of segmental peak systolic strain. More negative strain values imply better systolic function, whereas more negative diastolic strain rate values denote worse diastolic function.

Covariates

Assessments of risk factor variables in the CARDIA study have been previously described.[22,27] Briefly, the use of antihypertensive medication and smoking status (current smoker, former smoker, and never smoker) were self-reported, assessed using validated questionnaires. A physical activity score (exercise units) was obtained from the CARDIA physical activity history, a modified version of the Minnesota Leisure Time Physical Activity Questionnaire.[28] Three seated blood pressure measurements were obtained; the mean of the second and third readings was used. Diabetes mellitus was ascertained at each examination on the basis of one or more of a combination of history of medication use (every visit), fasting glucose $\geq$ 126 mg/dL, 2 hours from a glucose tolerance test (glucose $\geq$ 200 mg/dL) or glycated hemoglobin $\geq$ 6.5, and the absence of pregnancy. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, WA). Low-density lipoprotein cholesterol was derived using the Friedewald equation.[29]

Statistical Analysis

Descriptive characteristics of study participants were summarized for men and women at year 5 and year 25. Continuous variables are presented as mean ± SD or as medians and interquartile ranges, using Student's t test or the Wilcoxon rank sum (Mann-Whitney) test, as appropriate. Categorical variables were compared using χ^2 statistics for frequencies and proportions. AoD at the year 25 examination was used for cross-sectional analyses, and 20-year change in AoD