JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 25, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.04.042

ORIGINAL INVESTIGATIONS

Cumulative Blood Pressure in Early Adulthood and Cardiac Dysfunction in Middle Age

The CARDIA Study

Satoru Kishi, MD,* Gisela Teixido-Tura, MD, PhD,† Hongyan Ning, MD,‡ Bharath Ambale Venkatesh, PhD,* Colin Wu, PhD,§ Andre Almeida, MD,* Eui-Young Choi, MD,* Ola Gjesdal, MD,* David R. Jacobs, Jr, PhD,‖ Pamela J. Schreiner, PhD,‖ Samuel S. Gidding, MD,¶ Kiang Liu, PhD,‡ João A.C. Lima, MD*

ABSTRACT

BACKGROUND Cumulative blood pressure (BP) exposure may adversely influence myocardial function, predisposing individuals to heart failure later in life.

OBJECTIVES This study sought to investigate how cumulative exposure to higher BP influences left ventricular (LV) function during young to middle adulthood.

METHODS The CARDIA (Coronary Artery Risk Development in Young Adults) study prospectively enrolled 5,115 healthy African Americans and whites in 1985 and 1986 (baseline). At the year 25 examination, LV function was measured by 2-dimensional echocardiography; cardiac deformation was assessed in detail by speckle-tracking echocardiography. We used cumulative exposure of BP through baseline and up to the year 25 examination (millimeters of mercury × year) to represent long-term exposure to BP levels. Linear regression and logistic regression were used to quantify the association of BP measured repeatedly through early adulthood (18 to 30 years of age) up to middle age (43 to 55 years).

RESULTS Among 2,479 participants, cumulative BP measures were not related to LV ejection fraction; however, high cumulative exposure to systolic blood pressure (SBP) and diastolic blood pressure (DBP) were associated with lower longitudinal strain rate (both $p < 0.001$). For diastolic function, higher cumulative exposures to SBP and DBP were associated with low early diastolic longitudinal peak strain rate. Of note, higher DBP (per SD increment) had a stronger association with diastolic dysfunction compared with SBP.

CONCLUSIONS Higher cumulative exposure to BP over 25 years from young adulthood to middle age is associated with incipient LV systolic and diastolic dysfunction in middle age. (J Am Coll Cardiol 2015;65:2679–87)

From the *Division of Cardiology, Johns Hopkins University, Baltimore, Maryland; †Department of Cardiology, Hospital Vall d'Hebron, Barcelona, Spain; ‡Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; §Office of Biostatistics Research, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ‖Division of Epidemiology and Community Health, School of Public Health, University of Minnesota School of Public Health, Minneapolis, Minnesota; and the ¶Nemours Cardiac Center, Alfred I. duPont Hospital for Children, Wilmington, Delaware. The CARDIA Study is supported by Contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C from the National Heart, Lung, and Blood Institute, the Intramural Research Program of the National Institute on Aging, and an intra-agency agreement between the National Institute on Aging and the National Heart, Lung, and Blood Institute (AG0005). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received October 23, 2014; revised manuscript received March 25, 2015, accepted April 20, 2015.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CI = confidence interval

DBP = diastolic blood pressure

Ecc = circumferential peak systolic strain

Ecc_SRe = circumferential peak early diastolic strain rate

Ecc_SRs = circumferential peak systolic strain rate

Ell = 4-chamber longitudinal peak strain

Ell_SRe = 4-chamber longitudinal peak early diastolic strain rate

Ell_SRs = 4-chamber longitudinal peak systolic strain rate

Err = radial peak strain

Err_SRs = radial peak systolic strain rate

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

LVMI = left ventricular mass index

MAP = mean arterial pressure

OR = odds ratio

PP = pulse pressure

SBP = systolic blood pressure

STE = speckle-tracking echocardiography

Blood pressure (BP) at the higher end of the population distribution may represent a chronic exposure that injures the cardiovascular system. Cumulative BP exposure from young adulthood to middle age may adversely influence myocardial function and predispose individuals to heart failure (HF) and other cardiovascular disease later in life. The 2005 guidelines for the diagnosis and treatment of HF from the American College of Cardiology and American Heart Association highlighted the importance of early recognition of subclinical cardiac disease and of noninvasive tests in the clinical evaluation of HF (1).

SEE PAGE 2688

Speckle-tracking echocardiography (STE) offers the opportunity to evaluate subclinical markers of left ventricular (LV) dysfunction, and global myocardial strain assessed by STE has been described as a better predictor of future HF and other cardiovascular endpoints compared with left ventricular ejection fraction (LVEF) (2,3). Hypertension has been related to reduced global myocardial deformation as a precursor of HF (4,5), and, in turn, global myocardial deformation parameters (longitudinal and circumferential shortening and radial thickening) have been directly related to HF (6,7).

Our main objective was to investigate how cumulative exposure to high BP from young to middle adulthood influences LV function. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, multiple repeated measures of BP and other cardiovascular risk factors were recorded over a 25-year timespan, starting during early adulthood (ages 18 to 30 years). In this report, we demonstrate the cumulative effect of BP exposure to conventional echocardiographic measures of LV systolic and diastolic function, as well as LV strain measures assessed by STE, also used as markers of subclinical LV dysfunction.

METHODS

PARTICIPANTS. The CARDIA study is a multicenter prospective investigation that enrolled 5,115 healthy African-American and white men and women in 1985 and 1986 (year 0) from 4 U.S. field centers (Birmingham, Alabama; Oakland, California; Chicago, Illinois; Minneapolis, Minnesota). Participants were followed prospectively in 7 subsequent examinations. The Institutional Review Boards at each study site approved the study protocols, and written informed consent was obtained from all participants. Of 3,498 participants attending the year 25 (2010 to 2011) examination, 3,474 underwent standard echocardiography and STE assessment. We excluded participants with incomplete BP measurement during 25 years of follow-up (n = 995). The remaining 2,479 participants with complete longitudinal datasets were included in the analyses. At baseline, the included participants were slightly older (25.3 vs. 24.5 years) and more female than male (1,409 vs. 1,070), and had a lower percentage of blacks (41.4% vs. 61.1%), higher educational attainment (14.2 vs. 13.4 years), and lower baseline systolic blood pressure (SBP) (109.8 vs. 110.9 mm Hg; all $p < 0.01$) compared with those not included in this study (n = 2,636) (Online Table 1).

Standardized protocols were used to measure height, weight, heart rate, BP, lipids, glucose, smoking status, educational level, and physical activity (8,9). Weight and height were measured using a standard balance beam scale. Body mass index was calculated as weight (kilograms) divided by height in meters squared. We used the average of the second and third of 3 BP measurements using random-zero sphygmomanometry performed at 1-min intervals after the participant had been sitting quietly for 5 min in a still room (year 0 to 15) and a BP monitor (year 20 to 25; Omron Healthcare Inc., Lake Forest, Illinois) (10). A calibration study was performed, and values calibrated to the sphygmomanometric measures were used for year 20 and year 25 BP measurements. We used recalibrated measures (10). Pulse pressure (PP) as the index of pulsatile component of BP was calculated as SBP minus diastolic blood pressure (DBP); mean arterial pressure (MAP) was calculated as: DBP + (1/3 PP). The presence of diabetes was assessed at each examination on the basis of a combination of medication use for diabetes (every examination), fasting plasma glucose ≥126 mg/dl (examination years 0, 7, 10, 15, 20, and 25), 2-h glucose ≥200 mg/dl (years 10, 20, and 25), or glycosylated hemoglobin ≥6.5% (years 20 and 25). Total cholesterol was measured in fasting plasma samples and determined by enzymatic procedures.

We calculated the cumulative exposure of BP for each participant over 25 years from age 18 to 30 years to age 43 to 55 years as millimeters of mercury × year at each clinic visit to represent long-term exposure to BP levels. We defined this BP product for each participant's accumulated exposure to BP. We used the area under the BP curve over 25 years as a covariate in the univariable and multivariable analyses. Calculations were performed for SBP, DBP, PP, and MAP.

ECHOCARDIOGRAPHIC AND SPECKLE-TRACKING ANALYSIS. Experienced sonographers performed Doppler echocardiography and 2-dimensional-guided M-mode echocardiography using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) using standardized protocols across all field centers. The sonographers made measurements from digitized images using a standard off-line image analysis software system (Digisonics, Inc., Houston, Texas). LVEF and left atrial volume were measured from the apical 4-chamber view on the basis of the American Society of Echocardiography guidelines; LV mass was derived from the Devereux formula using the American Society of Echocardiography guidelines (11). Left atrial volume and LV mass were indexed to body surface area (left atrial volume index and left ventricular mass index [LVMI]). In the diastolic functional parameters, peak velocities of the early phase (E), late phase (A) of the mitral inflow, and their ratio (E/A ratio) were measured from pulsed Doppler echocardiography recordings of transmitral flow; early peak diastolic mitral annular velocity (e') at the septal mitral annulus was measured using tissue Doppler imaging (12). E/e' ratio was calculated as an index of LV filling pressures.

STE for myocardial strain and strain rate measurements was performed offline with dedicated semiautomated 2-dimensional STE software (Toshiba Medical Systems) only at year 25 (13). Three cardiac cycles from each view were recorded for offline analyses. Average frame rate was 46.2 frames per second with mean heart rate <70 beats/min on the basis of consensus (14). Strain was calculated as the peak systolic change in segment length relative to its end-diastolic value. Longitudinal strain and strain rate curves were assessed from 4-chamber views. Circumferential strain and strain rate were assessed from the short-axis view at mid-ventricular level. STE images were analyzed on a 6-segment basis for endocardial, mid-wall, and epicardial contours for each view. The mid-wall layer in each segment was analyzed for global longitudinal and circumferential strain and strain rate. The image set in each view was considered inadequate for STE if 4 or more segments had been excluded because of less optimal tracking. Global strain values were calculated as the average of segmental peak strains. Global strain rate values were also calculated from the average of segmental peak values for each phase (in s^{-1}). STE indices of systolic cardiac deformation at the year 25 examination included 4-chamber longitudinal peak systolic strain (Ell), circumferential peak systolic strain (Ecc), radial peak systolic strain (Err), 4-chamber longitudinal systolic strain rate (Ell_SRs), circumferential systolic strain rate (Ecc_SRs), and radial systolic strain rate (Err_SRs). Diastolic STE indices were peak early diastolic strain rate in the 4-chamber longitudinal (Ell_SRe), circumferential (Ecc_SRe), and radial (Err_SRe).

STATISTICAL ANALYSIS. Descriptive statistics were displayed using means and standard deviations for continuous variables and group proportions for categorical variables. Student *t* tests were used to compare means between blacks and whites of both sexes. Multivariable linear regression models assessed the longitudinal associations between year 0 BP parameters and STE parameters and conventional echocardiographic parameters measured at the year 25 examination. Multivariable models were adjusted for the following traditional cardiovascular disease risk factors: Model 1 included age at year 25, sex, race, and field centers as demographic variables; Model 2 included Model 1 and average level of body mass index (kilograms/meters squared), physical activity (exercise unit), alcohol intake (milliliters), heart rate (beats/min), total cholesterol (milligrams/deciliter), diabetes, and current smoking status at year 25 as cardiovascular risk factors; Model 3 included Model 2 and LVMI as an LV structural parameter; and Model 4 included Model 3 and use of antihypertensive medication at year 25.

For categorical analyses of clinically significant cardiac dysfunction, systolic dysfunction was defined as LVEF <50% and diastolic dysfunction as E/e' ratio >15 (15–17). We explored relationships between BP (per SD higher) over 25 years and clinically relevant LV dysfunction at year 25 using multivariable logistic regression analysis, which we evaluated accounting for similar covariates, reporting odds ratios (ORs) and 95% confidence intervals (CIs).

We explored the relationship between the deciles of cumulative BP exposure and standardized LV function. We compared the deciles of cumulative BP for LV function compared with the lowest BP decile (0% to 10%) group.

A 2-sided p value of <0.05 was considered for statistical significance. All statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute Inc., Cary, North Carolina).

RESULTS

Cohort characteristics at year 25 are shown in **Table 1**. The mean age at this time point was 50 ± 3.6 years, 56.8% of all participants were women, and 60.0% were white. Mean values for conventional echocardiographic parameters were within the normal range in mid-age (43 to 55 years). In this CARDIA cohort,

TABLE 1 Participant Characteristics at Year 25 (n = 2,479)

	n	Men	n	Women	p Value
Age, yrs	1,070	50.4 ± 3.6	1,409	50.4 ± 3.5	0.7788
Black	381	35.6	644	45.7	<0.0001
Weight, kg	1,070	93.2 ± 20.0	1,409	82.2 ± 22.0	<0.0001
BMI, kg/m^2	1,067	29.4 ± 5.8	1,409	30.4 ± 8.0	0.0007
Heart rate, beats/min	1,070	65.6 ± 7.34	1,409	69.0 ± 6.8	<0.0001
SBP, mm Hg	1,070	121.2 ± 14.2	1,409	117.5 ± 17.2	<0.0001
DBP, mm Hg	1,070	75.3 ± 10.6	1,409	73.6 ± 11.6	0.0002
Cumulative exposure to SBP, mm Hg × yr	1,070	2,875.1 ± 228.9	1,409	2,721.1 ± 256.8	<0.0001
Cumulative exposure to DBP, mm Hg × yr	1,070	1,834.0 ± 181.4	1,409	1,741.5 ± 192.9	<0.0001
Cumulative exposure to PP, mm Hg × yr	1,070	1,041.0 ± 137.7	1,409	979.5 ± 143.1	<0.0001
Cumulative exposure to MAP, mm Hg × yr	1,070	2,181.1 ± 187.6	1,409	2,068.0 ± 205.5	<0.0001
Diabetes	82	7.7	97	6.9	0.4578
Current smoker	155	14.7	188	13.5	0.4242
Drinker	693	65.1	683	48.9	<0.0001
Antihypertensive medication	279	26.1	365	25.9	0.9239
Educational level, yrs	1,067	15.3 ± 2.8	1,406	15.4 ± 2.6	0.3294
Physical activity, EU	1,066	414.7 ± 295.2	1,401	285.3 ± 244.2	<0.0001
Fasting glucose, mg/dl	1,065	104.4 ± 33.7	1,401	95.6 ± 23.7	<0.0001
Total cholesterol, mg/dl	1,065	189.0 ± 37.4	1,402	195.2 ± 35.9	<0.0001
HDL cholesterol, mg/dl	1,065	50.5 ± 15.6	1,402	63.8 ± 17.5	<0.0001
LDL cholesterol, mg/dl	1,049	113.0 ± 33.5	1,396	111.5 ± 31.6	0.2736
Echocardiographic parameters					
LVEF, %	1,003	60.8 ± 7.3	1,285	62.5 ± 6.8	<0.0001
E/A ratio	1,055	1.33 ± 0.35	1,376	1.29 ± 0.38	0.0228
Deceleration time, ms	1,049	179.4 ± 40.1	1,371	176.9 ± 39.4	0.1292
LAV/BSA ml/m^2	1,054	25.34 ± 7.08	1,386	25.05 ± 7.16	0.3217
e', cm/s	1,045	10.45 ± 2.20	1,377	10.65 ± 2.36	0.0328
E/e' ratio	1,043	7.48 ± 2.13	1,361	8.03 ± 2.29	<0.0001
Ell, %	941	−14.70 ± 2.30	1,222	−15.50 ± 2.44	<0.0001
Ecc, %	943	−15.02 ± 2.70	1,259	−15.67 ± 2.85	<0.0001
Err, %	943	37.80 ± 12.02	1,259	37.18 ± 12.38	0.2378
Ell_SRs, sec^{-1}	941	−0.65 ± 0.12	1,222	−0.67 ± 0.12	0.0013
Ecc_SRs, sec^{-1}	860	−0.69 ± 0.15	1,125	−0.69 ± 0.15	0.9715
Err_SRs, sec^{-1}	860	1.81 ± 0.64	1,125	1.74 ± 0.62	0.0138
Ell_SRe, sec^{-1}	937	0.77 ± 0.21	1,219	0.87 ± 0.27	<0.0001
Ecc_SRe, sec^{-1}	859	0.77 ± 0.31	1,122	0.84 ± 0.31	<0.0001
Err_SRe, sec^{-1}	860	−2.27 ± 1.30	1,125	−2.32 ± 1.29	0.4201

Values are n, mean ± SD, or %. Comparisons across sex or race were by Student *t* test.

BSA = body surface area; BMI = body mass index; DBP = diastolic blood pressure; e' = peak early diastolic mitral annular velocity; E/A = peak velocities of the early phase and late phase of the mitral inflow; Ecc = circumferential peak systolic strain; Ecc_SRe = circumferential peak early diastolic strain rate; Ecc_SRs = circumferential peak systolic strain rate; E/e' = ratio of early peak diastolic mitral velocity/peak early diastolic mitral annular velocity; Ell = longitudinal peak systolic strain; Ell_SRe = longitudinal peak early diastolic strain rate; Ell_SRs = longitudinal peak systolic strain rate; Err = radial peak systolic strain; Err_SRe = radial peak early diastolic strain rate; Err_SRs = radial peak systolic strain rate; EU = exercise unit; HDL = high-density lipoprotein; LAV = left atrium volume; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

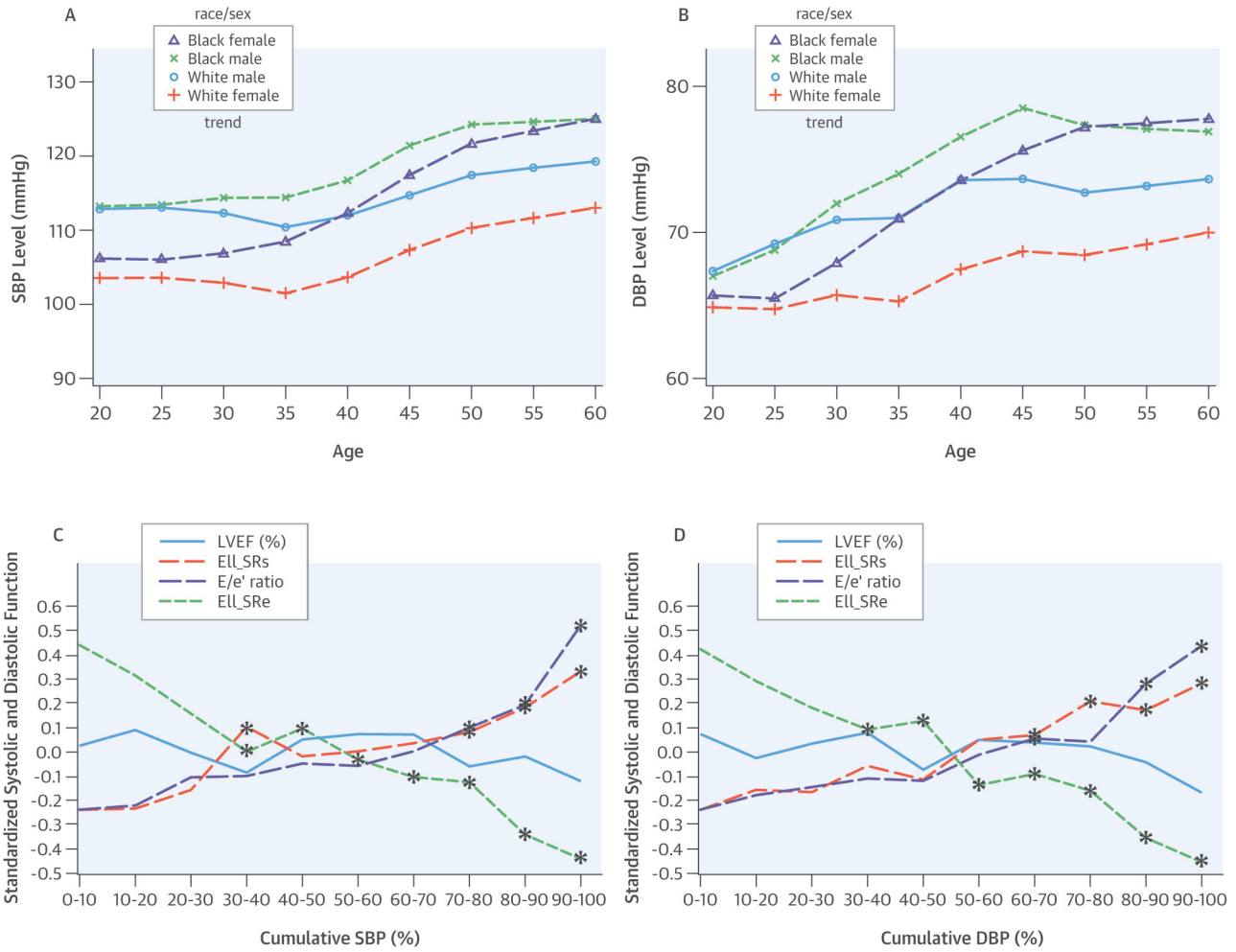
SBP increased gradually after 35 years of age and DBP and MAP increased from baseline to the fourth decade and then plateaued (**Central Illustration**, Online Figure 1). PP decreased until 40 years of age and then increased after age 40 years. Black men and women had higher SBP, DBP, and MAP levels compared with whites more than 25 years of age. Men had higher PP than women.

LV SYSTOLIC AND DIASTOLIC FUNCTION. LV systolic dysfunction (LVEF <50%) was present in 70 participants, diastolic dysfunction (E/e' ratio >15) was present in 69 participants, and systolic or diastolic dysfunction was present in 135 participants. Cumulative BPs (SBP, DBP, MAP, and PP) were not associated with the likelihood of having an ejection fraction <50% measured by conventional echocardiography (**Table 2**, Online Table 2); meanwhile, higher SBP (OR: 1.46; 95% CI: 1.09 to 1.94), DBP (OR: 1.69; 95% CI: 1.23 to 2.33), and MAP (OR: 1.40; 95% CI: 1.10 to 1.78) were predictors of diastolic dysfunction after full adjustment. Higher DBP had the strongest association with diastolic dysfunction. Both higher SBP (OR: 1.38; 95% CI: 1.10 to 1.73) and DBP (OR: 1.34; 95% CI: 1.05 to 1.70) were predictors of the presence of systolic or diastolic dysfunction after full adjustment.

Higher deciles of cumulative SBP and DBP were associated with low Ell_SRs ($p < 0.05$) compared with the lowest BP decile; however, neither SBP nor DBP was associated with LVEF (**Central Illustration**). Results for MAP were similar (Online Figure 2). Cumulative exposure to BP parameters (SBP, DBP, and PP) was not related to LVEF measured by conventional echocardiography (**Table 3**, Online Table 3); however, high cumulative exposure to SBP, DBP, and MAP were independently associated with low Ell and Ell_SRs. The magnitudes of the standardized β-coefficients for DBP (0.119 for Ell and 0.107 for Ell_SRs; all $p < 0.001$) in relation to Ell and Ell_SRs were higher than those for SBP (0.078 for Ell; $p < 0.05$; and 0.086 for Ell_SRs; $p < 0.005$) and MAP (0.112 for Ell; $p < 0.001$; and 0.080 for Ell_SRs; $p < 0.005$). High cumulative exposure to PP was independently associated with Ecc (standardized β-coefficient = −0.06; $p < 0.05$). High cumulative exposure to SBP (0.118 for Err and 0.115 for Err_SRs; all $p < 0.001$) and PP (0.105 for Err and 0.106 for Err_SRs; all $p < 0.001$) was independently associated with high Err and Err_SRs. LVMI attenuated the relationship of BP to LV systolic function in Model 3, but antihypertensive medications did not attenuate these relationships in Model 4. Prediction of LV function from BP at year 0 (baseline) was less powerful than cumulative BP over 25 years (Online Table 4).

Higher deciles of cumulative SBP and DBP were associated with increased E/e' ratio ($p < 0.05$), and higher deciles of cumulative SBP and DBP were associated with reduced Ell_SRe ($p < 0.05$) compared with the lowest BP decile (**Central Illustration**). Similar relationships were found for MAP (Online Figure 2).

CENTRAL ILLUSTRATION **Early Adulthood Blood Pressure and Middle-Age Left Ventricular Function**



Kishi, S. et al. J Am Coll Cardiol. 2015; 65(25):2679–87.

Blood pressure (BP) trends with increasing age. The trajectory slope shows mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) with increasing age for white and black men and women. All BP measurements over 25 years were within guideline acceptable range **(A and B)**. Systolic and diastolic function with increasing cumulative SBP and DBP. **(C)** For left ventricular (LV) systolic function, there were no differences in left ventricular ejection fraction (LVEF) among cumulative SBP deciles; meanwhile, higher deciles of cumulative SBP produced a lower 4-chamber longitudinal peak systolic strain rate (Ell_SRs) compared with the lowest SBP (0% to 10%) decile. For LV diastolic function, early peak diastolic mitral velocity/peak early diastolic mitral annular velocity (E/e') ratio increased in higher deciles of cumulative SBP compared with the lowest decile. Higher deciles of cumulative SBP were associated with lower 4-chamber longitudinal peak early diastolic strain rate (Ell_SRe) versus the lowest decile. **(D)** In considering cumulative DBP deciles, the same trends were seen for LVEF, as well as when comparing the higher deciles with the lowest group for Ell_SRs, E/e' ratio, and Ell_SRe.

High cumulative exposure to SBP, DBP, and MAP was independently associated with low E/A ratio (SBP: −0.157, DBP: −0.217, MAP: −0.212; all $p < 0.001$), Ell_SRe (SBP: −0.151, DBP: −0.181, MAP: −0.185; all $p < 0.001$), and high E/e' ratio (SBP: 0.183, DBP: 0.161, MAP: 0.186; all $p < 0.001$) (**Table 4**, Online Table 5). High cumulative exposure to SBP and PP was independently associated with high left atrial volume index (SBP: 0.068; $p < 0.05$; PP: −0.127; $p < 0.001$). LVMI attenuated the relationship of BP to LV diastolic function parameters in Model 3, but use of antihypertensive medications did not (Model 4).

DISCUSSION

This study demonstrates the effects of chronically elevated BP—expressed as cumulative exposure to hypertension from young adulthood to middle age—

TABLE 2 LV Systolic and Diastolic Dysfunction at Year 25 Predicted from Cumulative Exposure to SBP and DBP

		Cumulative Exposure to SBP* OR (95% CI)				Cumulative Exposure to DBP* OR (95% CI)			
	n	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Systolic dysfunction (LVEF <50%)	70	1.37 (1.07–1.75)	1.14 (0.88–1.50)	1.04 (0.77–1.41)	1.15 (0.83–1.58)	1.25 (0.97–1.61)	1.00 (0.74–1.33)	0.92 (0.67–1.26)	0.99 (0.70–1.38)
Diastolic dysfunction (E/e' ratio >15)	69	1.68 (1.34–2.10)	1.66 (1.30–2.13)	1.41 (1.08–1.84)	1.46 (1.09–1.94)	1.86 (1.44–2.39)	1.89 (1.42–2.51)	1.62 (1.20–2.18)	1.69 (1.23–2.33)
Systolic or diastolic dysfunction	135	1.57 (1.32–1.87)	1.45 (1.20–1.75)	1.30 (1.05–1.60)	1.38 (1.10–1.73)	1.53 (1.28–1.85)	1.40 (1.14–1.72)	1.26 (1.01–1.58)	1.34 (1.05–1.70)

Model 1 adjusted for age, race, sex, and field center. Model 2 adjusted for Model 1 + average body mass index (kg/m^2), average physical activity (EU), educational level (year) at year 25, average alcohol intake (ml), current smoking at year 25, average heart rate (beats/min), average total cholesterol (mg/dl), diabetes at year 25 (yes). Model 3 adjusted for Model 2 + LV mass/body surface area at year 25 to the systolic and diastolic indices. Model 4 adjusted for Model 3 + antihypertensive medications at year 25 (yes). *Per SD increment.

CI = confidence interval; LV = left ventricular; OR = odds ratio; other abbreviations as in Table 1.

on LV function measured at middle age. The study documents a greater effect of cumulative BP exposure on diastolic versus systolic myocardial function in a population of healthy adults, with a greater effect of diastolic as opposed to SBP elevation on both systolic and diastolic LV dysfunction.

CUMULATIVE EFFECTS OF BP ON MYOCARDIAL DEFORMATION. LV function has been reported to be associated with the effects of hypertension and other chronic factors such as obesity (13,18–21). In our study, cumulative BP was not associated with reduced LVEF (<50%); however, cumulative exposure to elevated BP, especially high DBP and MAP, was independently associated with reduced global systolic myocardial LV function as assessed by Ell and Ell_SRs. In addition, Ell_SRe was affected by mildly elevated cumulative BP compared with E/e' ratio, which was affected by high cumulative BP exposure (**Central Illustration**). Thus, Ell_SRe may be a good predictor of diastolic LV dysfunction even when compared with E/e' ratio.

In an older population, the MESA (Multi-Ethnic Study of Atherosclerosis) demonstrated a relation between elevated DBP and decreased regional myocardial function using cardiac magnetic resonance (5). Likewise, high DBP at an older age was associated with reduced longitudinal myocardial shortening as measured by STE in the Framingham Study (22). In hypertensive patients with LV hypertrophy and normal ejection fraction, Palmon et al. (23) reported reduced intramural (endocardial) longitudinal and circumferential shortening. Worse longitudinal and circumferential myocardial deformation also have been associated with adverse outcomes (6).

Echocardiographic measurement of worsening of longitudinal and circumferential strain mostly represents reduced longitudinal and circumferential deformation of endocardial fibers, respectively. This may reflect a chronic process that begins with cumulative BP effects increasing afterload and aortic stiffness, thus increasing systolic LV wall stress and inducing LV remodeling (4,24). Compensatory mechanisms activated to maintain cardiac contraction include: 1) an increase in LV mass with concentric remodeling (25); and 2) an increase in LV torsion (4). Increased LV wall stress damages the oblique fiber structure in the endocardium; this may lead

TABLE 3 Relationship of Cumulative Exposure to BP Over 25 Years to Systolic LV Functional Indices

	Cumulative Exposure to SBP				Cumulative Exposure to DBP			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)
LVEF, %	−0.001 (0.024)	0.039 (0.025)	0.016 (0.027)	0.005 (0.030)	−0.024 (0.023)	0.032 (0.025)	0.016 (0.027)	0.005 (0.029)
Ell, %	0.175 (0.023)§	0.097 (0.024)§	0.086 (0.026)‡	0.078 (0.029)†	0.218 (0.022)§	0.132 (0.024)§	0.120 (0.025)§	0.119 (0.028)§
Ecc, %	0.046 (0.024)*	−0.009 (0.025)	−0.033 (0.026)	−0.035 (0.029)	0.086 (0.023)‡	0.024 (0.025)	0.011 (0.026)	0.018 (0.028)
Err, %	0.080 (0.024)‡	0.098 (0.025)‡	0.088 (0.027)‡	0.118 (0.029)§	0.015 (0.023)	0.039 (0.026)	0.026 (0.026)	0.043 (0.029)
Ell_SRs, sec^{-1}	0.127 (0.024)§	0.112 (0.026)§	0.081 (0.027)‡	0.086 (0.030)‡	0.125 (0.023)§	0.125 (0.025)§	0.099 (0.026)‡	0.107 (0.029)‡
Ecc_SRs, sec^{-1}	−0.013 (0.024)	−0.018 (0.025)	−0.038 (0.027)	−0.025 (0.029)	0.014 (0.023)	0.016 (0.026)	0.0003 (0.026)	0.021 (0.029)
Err_SRs, sec^{-1}	0.116 (0.024)§	0.1004 (0.025)§	0.097 (0.027)‡	0.115 (0.029)§	0.064 (0.023)†	0.387 (0.026)	0.033 (0.027)	0.039 (0.029)

Models adjusted as indicated in Table 2. *p < 0.10. †p < 0.05. ‡p < 0.005. §p < 0.001.

BP = blood pressure; SE = standard error; standardized β = standardized β-coefficients; other abbreviations as in Tables 1 and 2.

TABLE 4 Relationships of Cumulative Exposure to BP Over 25 Years to Diastolic LV Functional Indices

	Cumulative Exposure to SBP				Cumulative Exposure to DBP			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)	Standardized β (SE)
E/A ratio	−0.255 (0.022)§	−0.157 (0.022)§	−0.158 (0.024)§	−0.157 (0.027)§	−0.324 (0.021)§	−0.209 (0.022)§	−0.209 (0.024)§	−0.217 (0.027)§
e', cm/s	−0.271 (0.020)§	−0.208 (0.021)§	−0.148 (0.022)§	−0.127 (0.024)§	−0.322 (0.019)§	−0.266 (0.021)§	−0.225 (0.022)§	−0.218 (0.023)§
E/e' ratio	0.260 (0.020)§	0.227 (0.022)§	0.183 (0.023)§	0.183 (0.026)§	0.226 (0.020)§	0.200 (0.022)§	0.165 (0.023)§	0.161 (0.025)§
LAV/BSA, ml/m^2	0.120 (0.022)§	0.134 (0.023)§	0.068 (0.024)‡	0.068 (0.026)†	0.000 (0.022)	0.028 (0.024)	−0.026 (0.024)	−0.004 (0.026)*
Ell_SRe, sec^{-1}	−0.186 (0.023)§	−0.162 (0.025)§	−0.139 (0.026)§	−0.151 (0.029)§	−0.200 (0.022)§	−0.185 (0.025)§	−0.167 (0.026)§	−0.181 (0.028)§
Ecc_SRe, sec^{-1}	−0.05 (0024)†	−0.003 (0.025)	0.020 (0.026)	0.020 (0.029)	−0.066 (0.023)‡	−0.026 (0.025)	−0.012 (0.026)	−0.017 (0.028)
Err_SRe, sec^{-1}	0.016 (0.024)*	0.014 (0.025)	0.018 (0.027)	0.005 (0.030)	0.032 (0.023)	0.031 (0.026)	0.034 (0.027)	0.024 (0.029)

Models adjusted as indicated in Table 2. *p < 0.10. †p < 0.05. ‡p < 0.005. §p < 0.001.
Abbreviations as in Tables 1 and 3.

to myocardial fibrosis (26). Moreover, long-term exposure to high BP stimulates reactive interstitial fibrosis, as shown in hypertensive cardiomyopathy (25,27). Reduced subendocardial shortening, observed in this study using STE, is the first sign of impairment of longitudinal myocardial function. Compensation by mid-wall fibers with resultant improvement in radial contractility maintains overall cardiac function and explains the lack of relation to conventional systolic function parameters (28).

In young adulthood (before 40 years of age), aging is associated with an increase in DBP and a decrease in PP up to age 40 years (**Central Illustration**, Online Figure 1). After age 40 years, aging is associated with a decrease in DBP and an increase in PP; in the latter half of the human life span SBP increases with each decade of life (29,30). Of note, our findings show a turning point for PP that occurs earlier than that demonstrated in the Framingham Study (30). Furthermore, BP, especially elevated DBP, already produced worsening myocardial function in healthy young adulthood. An elevation in DBP may be useful as an outcome predictor in young adulthood in contrast to the greater importance of SBP in older individuals (31).

CLINICAL IMPLICATIONS. This study shows that the use of speckle-tracking data and LV dysfunction help us better understand the adverse effects of cumulated BP exposure that ejection fraction alone does not identify.

In prior CARDIA reports, Pletcher et al. (32) and Allen et al. (33) demonstrated that a higher BP trajectory beginning in young adulthood increased the risk of the prevalence of coronary calcium in middle age. These studies suggest that long-term BP control in early young adulthood may be important to prevent coronary heart disease. Our findings suggest that the relationship of long-term exposure to higher BP and LV dysfunction is similar to that for subclinical atherosclerosis and provides further support for the importance of good risk factor control early in life. In the CARDIA study, potentially modifiable antecedents of HF were present in African Americans more than a decade before the onset of clinical HF (31). Each increase of 10 mm Hg in DBP among African Americans 20 to 29 years of age had a 2-fold greater risk for development of HF at 40 to 49 years of age.

Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF (34,35). Of patients with hypertension, 20% to 30% are unaware of their condition (36,37). In addition, 50% to 70% of all patients with hypertension do not achieve their target BP (36–38). In the National Longitudinal Study of Adolescent Health, Nguyen et al. (39) reported that approximately 1 in 5 young adults had high BP. In our cohort, many participants were not hypertensive at age 18 to 30 years; however, chronic exposure to higher BP, even within what is considered the normal range, is independently related to LV dysfunction 25 years later. Young adults may prevent the development of LV dysfunction by reducing sodium intake, keeping ideal body weight, and performing adequate levels of physical activity, as well as by adhering to medical treatment (40–42). Clinical trials of earlier treatment for hypertension may be warranted to determine whether favorable cardiac function can be maintained by decreasing cumulative BP exposure. Our findings and those of some previous studies suggest that prehypertension throughout early adulthood is harmful to cardiac function (4,20,22).

STUDY LIMITATIONS. We relied on a subclinical endpoint (LV systolic and diastolic dysfunction measured by echocardiography); our findings will need validation using clinical endpoints. We did not aim to expose the potential effect of differences

between classes of antihypertensive medication on LV function. Our participants were 18 to 30 years of age at baseline (year 0); thus, our study could not assess cumulative BP exposure at earlier ages. This study was not designed to identify a specific BP early in age that was associated with future myocardial dysfunction. Also, all analyses were performed on a single system (Toshiba Medical Systems). Recently, the inter/intrasonographer reproducibility for STE analysis using the Artida cardiac ultrasound scanner in the CARDIA Study has been published (43). The results were highly reproducible in this large cohort study. However, recent publications have shown significant intervendor variability of strain (14).

CONCLUSIONS

Cumulative exposure to BP over 25 years from young adulthood to middle age is associated with incipient LV systolic and diastolic dysfunction in middle age. In early adulthood, DBP control may be of particular importance to prevent LV dysfunction and HF.

ACKNOWLEDGMENTS The authors thank the other investigators, staff, and participants of the CARDIA study for their valuable contributions.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. João A.C. Lima, Johns Hopkins University School of Medicine, Division of Cardiology, 600 North Wolfe Street, Blalock 524, Baltimore, Maryland 21287-8222. E-mail: jlima@jhmi.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: BP in early adulthood is related to later systolic and diastolic ventricular dysfunction.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether specific lifestyle interventions implemented to reduce DBP in early adulthood prevent HF from developing later in life.

REFERENCES

1. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.

2. Orhan AL, Uslu N, Dayi SU, et al. Effects of isolated obesity on left and right ventricular function: a tissue Doppler and strain rate imaging study. Echocardiography 2010;27:236–43.

3. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004;110:3081–7.

4. Yoneyama K, Gjesdal O, Choi EY, et al. Age, sex, and hypertension-related remodeling influences left ventricular torsion assessed by tagged cardiac magnetic resonance in asymptomatic individuals: the multi-ethnic study of atherosclerosis. Circulation 2012;126:2481–90.

5. Rosen BD, Saad MF, Shea S, et al. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic: individuals the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;47:1150–8.

6. Ersbøll M, Valeur N, Mogensen UM, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 2013;61:2365–73.

7. Choi EY, Rosen BD, Fernandes VR, et al. Prognostic value of myocardial circumferential strain for incident heart failure and cardiovascular events in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J 2013;34:2354–61.

8. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41:1105–16.

9. Jacobs DR Jr., Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of short physical activity history: Cardia and the Minnesota Heart Health Program. J Cardiopulm Rehabil 1989;9:448–59.

10. Jacobs DR, Yatsuya H, Hearst MO, et al. Rate of decline of forced vital capacity predicts future arterial hypertension: the Coronary Artery Risk Development in Young Adults Study. Hypertension 2012;59:219–25.

11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

12. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.

13. Kishi S, Armstrong AC, Gidding SS, et al. Association of obesity in early adulthood and middle age with incipient left ventricular dysfunction and structural remodeling: the CARDIA Study (Coronary Artery Risk Development in Young Adults). J Am Coll Cardiol HF 2014;2:500–8.

14. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D Speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183–93.

15. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. J Am Med Assoc 2003;289:194–202.

16. Goldberg LR, Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. Circulation 2006;113:2851–60.

17. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction. a population-based study. J Am Coll Cardiol 2010;55:300–5.

18. Huffman MD, Berry JD, Ning H, et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. J Am Coll Cardiol 2013;61:1510–7.

19. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure factors associated with lack of blood pressure control in the community. Hypertension 2000;36:594–9.

20. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart

failure: the Framingham Heart Study. Circulation 2002;106:3068–72.

21. Kishi S, Reis JP, Venkatesh BA, et al. Race-ethnic and sex differences in left ventricular structure and function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. J Am Heart Assoc 2015;4:e001264.

22. Cheng S, Larson MG, McCabe EL, et al. Age- and sex-based reference limits and clinical correlates of myocardial strain and synchrony: the Framingham Heart Study. Circ Cardiovasc Imaging 2013;6:692–9.

23. Palmon LC, Reichek N, Yeon SB, et al. Intramural myocardial shortening in hypertensive left ventricular hypertrophy with normal pump function. Circulation 1994;89:122–31.

24. Roman MJ, Ganau A, Saba PS, Pini R, Pickering TG, Devereux RB. Impact of arterial stiffening on left ventricular structure. Hypertension 2000;36:489–94.

25. Rossi MA. Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. J Hypertens 1998;16:1031–41.

26. Rosen BD, Edvardsen T, Lai S, et al. Left ventricular concentric remodeling is associated with decreased global and regional systolic function: the Multi-Ethnic Study of Atherosclerosis. Circulation 2005;112:984–91.

27. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891–903.

28. Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol 2010;56:89–97.

29. Franklin SS, Gustin W Iv., Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. Circulation 1997;96:308–15.

30. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham Heart Study. Hypertension 2012;60:1393–9.

31. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. N Engl J Med 2009;360:1179–90.

32. Pletcher MJ, Bibbins-Domingo K, Lewis CE, et al. Prehypertension during young adulthood and coronary calcium later in life. Ann Intern Med 2008;149:91–9.

33. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA 2014;311:490–7.

34. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on epidemiology and prevention, clinical cardiology, cardiovascular nursing, and high blood pressure research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544–65.

35. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. J Am Med Assoc 1996;275:1557–62.

36. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. J Am Med Assoc 2003;289:2560–72.

37. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245.

38. Valderrama AL, Gillespie C, King SC, George MG, Hong Y, Gregg E. Vital signs: awareness and treatment of uncontrolled hypertension among adults–United States, 2003-2010. MMWR Morb Mortal Wkly Rep 2012;61:703–9.

39. Nguyen QC, Tabor JW, Entzel PP, et al. Discordance in national estimates of hypertension among young adults. Epidemiology 2011;22:532–41.

40. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10.

41. Blumenthal JA, Babyak MA, Hinderliter A, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. Arch Intern Med 2010;170:126–35.

42. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr., Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. J Am Med Assoc 2003;290:3092–100.

43. Armstrong AC, Ricketts EP, Cox C, et al. Quality control and reproducibility in M-mode, two-dimensional, and speckle tracking echocardiography acquisition and analysis: the CARDIA study, year 25 examination experience. Echocardiography 2014 Nov 9 [E-pub ahead of print].

KEY WORDS echocardiography, hypertension, left ventricular function, speckle tracking

APPENDIX For supplemental tables and a figure, please see the online version of this article.