Determinants of Doppler Indexes of Left Ventricular Diastolic Function in Normal Subjects (the Framingham Heart Study)

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Normative Doppler values and determinants of left ventricular (LV) diastolic function in healthy subjects have not been fully elucidated. Subjects from the Framingham Heart Study were examined to describe reference values and determinants of echocardiographic Doppler indexes of diastolic function. One hundred twenty-seven randomly selected, rigorously defined, normal subjects, approximately evenly distributed by sex and age from the third through the eighth decades were studied by Doppler echocardiography. Normative values for 7 frequently used Doppler indexes of LV diastolic function are presented. Doppler indexes of LV diastolic function change dramatically with age; the peak velocity of early filling divided by late filling (peak velocity E/A) ranges from a mean of 2.08 ± 0.55 for subjects in their third decade to 0.84 ± 0.29 for those in their eighth decade. A peak velocity E/A ratio <1 is abnormal in subjects aged <40 years, but occurs in most subjects aged ≥70 years. The high correlations between age and Doppler indexes of LV diastolic function are not greatly attenuated after adjustment for other clinical parameters associated with diastolic function; the multivariate partial correlation coefficient between age and peak velocity E/A is −0.80 (p <0.0001). Heart rate, PR interval, LV systolic function, sex and systolic blood pressure are minor determinants of Doppler indexes of diastolic function. Body mass index, left atrial diameter, and LV wall thickness, internal dimension and mass have little or no association with Doppler indexes in healthy subjects.

Age is the predominant determinant of Doppler indexes of LV diastolic function in normal subjects, whereas heart rate, PR interval, sex, systolic blood pressure and LV systolic function have a lesser impact. The independence of the age-diastolic function relation from changes in physiology and LV geometry is consistent with an intrinsic reduction in LV distensibility with advancing age. These findings indicate that Doppler diastolic function should be assessed with reference to age-specific normative values.

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An appreciation of the contribution of diastolic dysfunction to symptoms in various cardiac diseases has grown rapidly. At the same time, Doppler echocardiography has proved increasingly useful as a noninvasive method for characterizing alterations in the left ventricular (LV) diastolic properties of the heart.[1] The purpose of this investigation was twofold: (1) to assess the determinants of LV diastolic function in normal subjects and (2) to describe normal values for Doppler indexes of LV diastolic function in a well-characterized healthy subset of a population-based sample. The hypothesis that age-related changes in Doppler indexes of diastolic function in normal subjects are partially attributable to concomitant age-associated alterations in blood pressure and LV structure was also tested.

METHODS

Study population: The Framingham Study was begun in 1948 to prospectively examine factors that predispose a patient to cardiovascular disease. A sample of residents of Framingham, Massachusetts, aged 28 to 62 years was selected to undergo biennial examinations. The offspring of the original cohort (and their spouses) were recruited in 1971. Detailed descriptions of study design were previously reported.[2,3] From 1985 to 1987, 4,170 survivors of the original cohort and their offspring underwent their 19th and 3rd examinations, respectively. Histories, physical examinations, 12-lead electrocardiograms and echocardiograms were routinely performed at the index examinations. The Framingham Heart Study examination was approved by the investigational review board of Boston University Hospital. Informed written consent was obtained from all subjects at the beginning of the clinic examination.

Subjects were excluded from this study if they fulfilled the following clinical criteria: (1) history of cardiovascular disease (including chest pain at the current

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examination) or angina pectoris, recognized or unrecognized myocardial infarction, congestive heart failure, valvular heart disease, atrial fibrillation, pericardial disease, pacemaker or left bundle branch block (criteria for the various cardiac events and the event determination process were previously reviewed)[4] (n = 1,017); (2) borderline hypertension on current examination (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), or definite hypertension on any prior examination (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg on each of 2 successive determinations by a physician during a given examination) (n = 1,455); (3) current use of cardiac, blood pressure or diuretic medication (n = 31); or (4) renal failure, thyroid disease, diabetes mellitus or chronic lung disease (n = 182).

Of the original 4,170 subjects, 1,485 (35.6%) remained eligible after eliminating subjects for clinical exclusions. Eligible subjects were randomly selected to assure an approximately even distribution by age and sex. Subjects were assigned sequence numbers so that the investigators measuring the studies (EJB or DL) were unaware of the study subjects' sex and age. Of those who were eligible and randomly screened for study inclusion, subjects were excluded for the following echocardiographic findings: (1) valvular abnormalities (any degree of mitral or aortic stenosis, or > than mild mitral or aortic regurgitation) (n = 1); (2) LV abnormalities (dilation, wall motion abnormalities or hypertrophic cardiomyopathy) (n = 5). To examine the impact of alterations in LV geometry, mild isolated LV hypertrophy was not an exclusion criteria. Two subjects had mild septal thickening (1.2 cm), and none had increased LV mass (by Framingham criteria)[5]; (3) technically inadequate echocardiograms, defined as either unmeasurable LV dimensions (n = 43) or inadequate Doppler LV inflow (n = 52), or both (n = 18). Doppler transmitral waveforms were considered inadequate if any of the following conditions existed: the angle between the Doppler beam and the mitral waveform was ≥30°, the sample volume was inadequately positioned, or the Doppler envelope definition was too indistinct; or (4) tachycardia defined as heart rate >100 beats/min (n = 0).

Ascertainment of clinical parameters: For the analysis of determinants of diastolic function, all parameters were obtained from the index examinations. Heart rate was measured from Doppler recordings. PR interval (ms) was measured from the 12-lead electrocardiogram. Body mass index (weight in kg/height in m^2) was used as a measure of obesity. Diastolic and systolic blood pressures (mm Hg) were each calculated as the average of the clinic physicians' 2 blood pressure measurements. To define subject eligibility, blood pressure measurements for subjects from the original cohort were available from 19 examinations (from a 38-year span); for the offspring, blood pressure measurements were available from 3 examinations (from a 12-year span).

Echocardiographic methods: Subjects were examined by M-mode, 2-dimensional and pulsed-wave Doppler on a Hewlett-Packard (model 77020AC) ultrasound machine. Studies were reviewed until a minimum of 10 men and 10 women per decade were obtained. There was a paucity of eligible men in the eighth decade. To ensure blinding, category goals were monitored by investigators (DF and KC) uninvolved in obtaining echocardiographic measurements. Digitized images were obtained from analogue tape and stored on floppy disks for later analysis, using an off-line analysis system (Freeland Systems, Division of Prism Imaging Inc., Louisville, Colorado). M-mode, 2-dimensional and Doppler measurements were obtained from the digitized images, using the digital analysis system, from an average of 3 to 5 beats. M-mode measurements were obtained according to the American Society of Echocardiography guidelines, using a leading-edge-to-leading-edge method.[6] If the M-mode was unmeasurable, 2-dimensional measurements from the same view were substituted. The sum of the LV wall thicknesses was defined as IVS + LVPW, where IVS was interventricular septal thickness at end-diastole, and LVPW was LV posterior wall thickness at end-diastole. Percent LV fractional shortening was calculated as [100(LVIDed − LVIDes)]/LVIDed, where LVIDed was LV internal dimension at end-diastole, and LVIDes was LV internal dimension at end-systole.[7] LV mass was calculated from the modified cubed formula[8]: LV mass (g) = 0.8 $\{1.05[(\text{LVIDed} + \text{IVS} + \text{LVPW})^3 - (\text{LVIDed})^3]\} + 0.6$.

Doppler examination of LV inflow was performed from the apical 4-chamber view with the sample volume placed between the mitral leaflet tips. The ultrasound beam was lined up parallel to LV inflow to minimize the angle of the cosine (studies were ineligible if angle was ≥30°). Doppler was recorded at sweep speeds of 50 or 100 mm/s. Observers chose which 3 to 5 waveforms (of a maximum of 10) to measure from 2 digitized screens. Observers traced the modal velocities, and if the margins of the waveforms were indistinct, they ignored the "noise" artifact and traced the brightest portion of the waveform margin. The peak early diastolic inflow velocity coincident with the E wave, peak late diastolic inflow velocity coincident with the A wave, and the ratio of peak early to late velocities (E/A) were measured. Furthermore, time velocity integrals E and A and the ratio of time velocity integral E/A were also assessed. If there was overlap between the E and A waves, time velocity integral E was considered the area under the E wave extrapolated through the A wave to the baseline; the portion of time velocity integral A incorporated in time velocity integral E was not included in time velocity integral A. If heart rate was slower and E and A waves did not overlap, time velocity integral E was extrapolated through diastasis to the baseline; the remaining small amount of flow during diastasis was not included in the integral of the E or A wave. Atrial filling fraction was defined as time velocity integral A divided by the time velocity integral of total diastolic LV inflow.

Statistical analyses: Data analyses were performed using the Statistical Analysis System[9] and S-PLUS.[10] A *t* test for age and age-adjusted analysis of variance for other clinical parameters were used to evaluate the differences between subjects with adequate echocardiograms and those eligible for the study but not measured.

TABLE I Doppler Diastolic Function Indexes by Age (years)

	20–29 (n = 21)	30–39 (n = 20)	40–49 (n = 22)	50–59 (n = 21)	60–69 (n = 22)	≥70 (n = 21)	All Ages (n = 127)
Peak velocity E (m/s)							
Mean	0.71	0.66	0.63	0.61	0.55	0.53	0.61
SD	0.14	0.14	0.10	0.11	0.11	0.17	0.14
Peak velocity A (m/s)							
Mean	0.35	0.38	0.45	0.49	0.55	0.64	0.48
SD	0.06	0.06	0.08	0.11	0.10	0.14	0.14
Peak velocity E/A							
Mean	2.08	1.75	1.44	1.29	1.03	0.84	1.40
SD	0.55	0.40	0.26	0.28	0.26	0.29	0.54
Time velocity integral E (m)							
Mean	0.093	0.085	0.086	0.086	0.076	0.072	0.083
SD	0.022	0.018	0.016	0.017	0.015	0.023	0.019
Time velocity integral A (m)							
Mean	0.030	0.029	0.037	0.040	0.042	0.052	0.038
SD	0.005	0.006	0.007	0.009	0.009	0.014	0.012
Time velocity integral E/A							
Mean	3.24	3.02	2.35	2.23	1.89	1.45	2.35
SD	0.85	0.69	0.39	0.41	0.50	0.47	0.83
Atrial filling fraction							
Mean	0.24	0.25	0.29	0.30	0.35	0.42	0.31
SD	0.05	0.05	0.03	0.04	0.06	0.09	0.08

SD = ±1 standard deviation.

The decade-specific means and SD for Doppler indexes were also analyzed. Plots (by age) of peak velocity E/A, time velocity integral E/A and atrial filling fraction, with 95% intervals for predicted values, were constructed using a standard least-squares methodology.

Two-way Pearson correlation coefficients examined the univariate relation between age and Doppler indexes of diastolic function. Clinical and echocardiographic variables that potentially influenced Doppler indexes were entered in multivariate regression analyses, with each Doppler parameter considered as the dependent variable. Stepwise regression analyses with backwards elimination ($p < 0.10$) were used. The stepwise model was analyzed twice, first entering LV mass, then entering the determinants of LV mass (LV internal dimension and wall thickness) and omitting LV mass. For each independent clinical variable selected by the stepwise models, partial correlation coefficients (r values) adjusted for the other variables in the final models were derived. The change in R^2 provided an estimate of the amount of variance in the dependent Doppler variable explained by the independent clinical variable after adjusting for the other clinical variables selected in the stepwise multivariate model. The natural logarithm of the peak velocity E/A, time velocity integral E/A and atrial filling fraction were used for the Pearson correlations and multivariate analyses.

RESULTS

Characterization of subjects: Comparison of the clinical characteristics of the 127 subjects included in the study with the 1,358 eligible for the study but not measured demonstrates that the 2 groups were not significantly different in mean age (50 and 48 years, respectively), PR interval (16 ms for both) and systolic blood pressure (117 mm Hg for both). Subjects included in the study had slightly slower heart rates (63 vs 65 beats/min; $p = 0.02$) and were less obese (24.4 vs 25.3 kg/m^2; $p = 0.01$) than those eligible but not measured. The finding that subjects with adequate echocardiograms were less obese than the general population is in accordance with previous findings of the Framingham Study.[11]

Description of normal Doppler indexes of diastolic function: Mean and SD for the various Doppler LV inflow parameters stratified by age are shown in Table I. In normal subjects, peak velocities E and E/A, and time velocity integrals E and E/A decreased with age. In contrast, peak velocity and time velocity integral A, and atrial filling fraction increased with age. Figure 1 provides examples of Doppler LV inflow of a normal young and a normal old subject. Age nomograms for 3 of the most widely used Doppler indexes of diastolic function, peak velocity and time velocity integral E/A, and atrial filling fraction, are provided in Figures 2, 3 and 4, respectively. Mean peak velocity E/A ranged from 2.08 ± 0.55 for subjects in their third decade to 0.84 ± 0.29 for those in their eighth decade (Table I). A peak velocity E/A ratio <1 was abnormal at <40 years of age, but occurred in most normal subjects aged ≥70 years (Figure 2). A time velocity integral E/A ratio <1.5 was abnormal at <40 years of age, but occurred in half of normal subjects aged ≥70 (Figure 3).

Determinants of Doppler indexes of diastolic function: Multivariate analyses revealed that age is the most important determinant of Doppler LV filling in healthy subjects, with partial correlation coefficients (r values) ranging from −0.47 for peak velocity E to −0.80 for peak velocity E/A (Table II). The high univariate correlation between age and LV inflow parameters (Table II) was not markedly attenuated by adjusting for other clinical determinants of diastolic function. Furthermore, the percent variation in Doppler diastolic function indexes due to age was remarkably high. In the multivari-

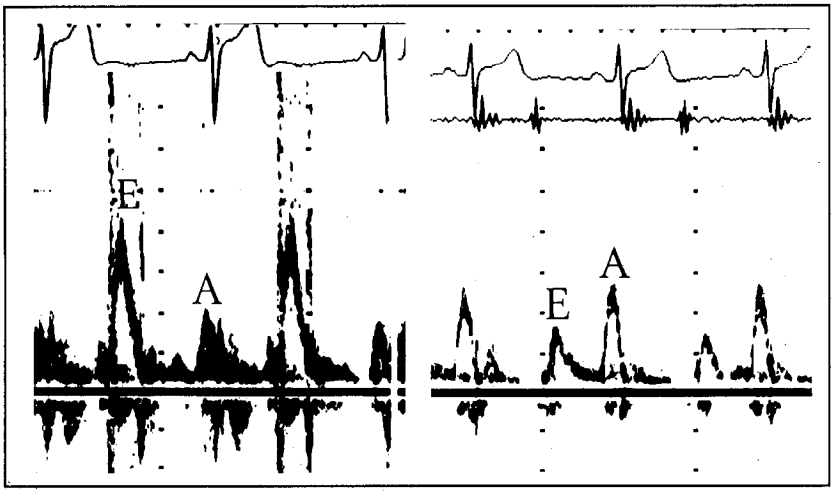

FIGURE 1. Doppler left ventricular inflow. *Left*, 21-year-old woman; *right*, 72-year-old man.

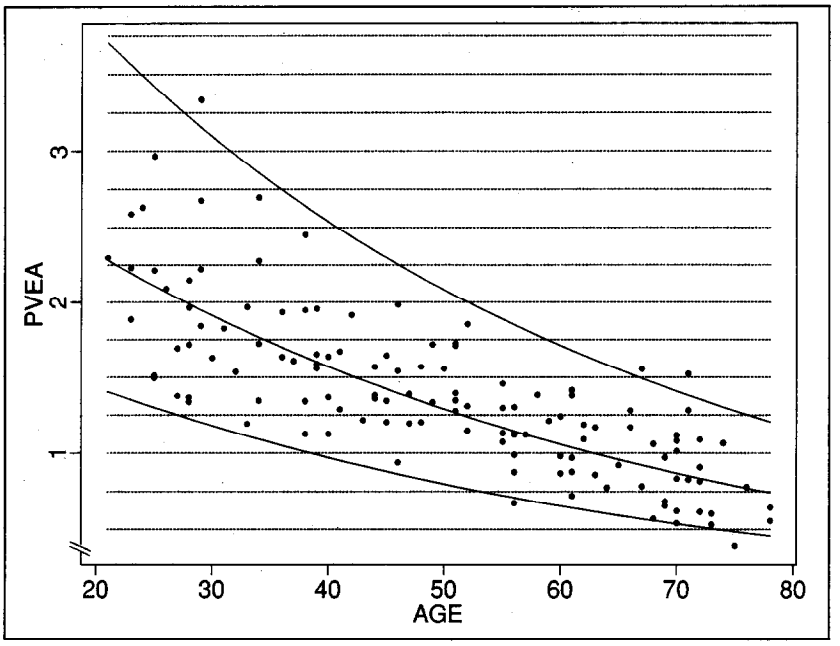

FIGURE 2. Plots of predicted values of peak velocity E/A (PVEA) by age with 95% confidence intervals. Individual data points are depicted by *closed circles*. Predicted values and 95% confidence intervals are shown by *solid lines*.

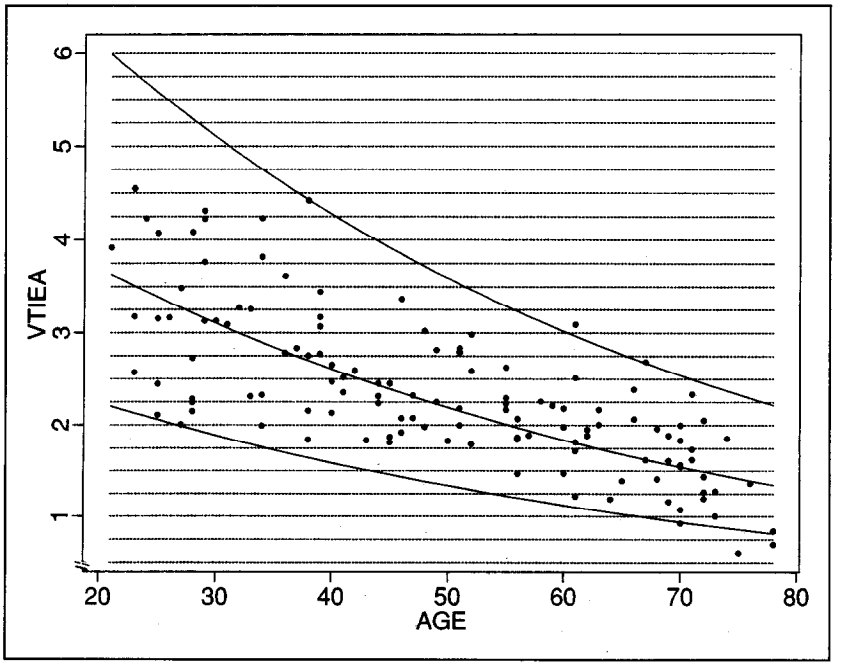

FIGURE 3. Plots of predicted values of time velocity integral E/A (VTIEA) by age with 95% confidence intervals. Individual data points are depicted by *closed circles*. Predicted values and 95% confidence intervals are shown by *solid lines*.

ate models, the variation due to age (partial R^2 for age after adjusting for other variables retained in the multivariate model) ranged from 19% for peak velocity E to 52% for peak velocity E/A.

In the multivariate model, sex was significantly associated with peak velocity E and marginally associated with peak velocity E/A and atrial filling fraction (peak velocity E and E/A being greater and atrial filling fraction being less in women than in men). However, sex accounted for only a minor portion of the variance of any Doppler parameter (4% for peak velocity E, and 1% for peak velocity E/A and atrial filling fraction).

In healthy subjects, heart rate and PR interval were also independent determinants of Doppler indexes of diastolic function. Heart rate was significantly associated with all LV inflow parameters, with partial correlation coefficients (r values) up to 0.39 for atrial filling fraction (Table II). Examining the partial R^2 values revealed that in healthy subjects the percentage of the variance attributable to heart rate ranged from 6% for atrial filling fraction to 3% for peak velocities E and A. PR interval was significantly correlated with all diastolic parameters except peak velocity A. The partial correlation coefficient for PR interval with atrial filling fraction was 0.29. However, the percentage of variance (partial R^2) attributable to PR in the multivariate models was ≤3%.

Blood pressure within the normal range did not make a major contribution to Doppler LV inflow in the multivariate models. Systolic blood pressure only significantly correlated with peak velocity A in the multivariate model (Table II), and the corresponding percent variance (partial R^2) explained by systolic blood pressure was only 2%. Neither diastolic blood pressure nor body mass index was significantly associated with any Doppler indexes in the multivariate models.

Left atrial size, and LV size and systolic function in normal subjects have at most only minor roles in determining Doppler diastolic function parameters (Table II). LV fractional shortening (a measure of systolic function) was significantly associated with peak velocities E and E/A, with adjusted correlation coefficients of 0.24 and 0.21, respectively; the corresponding variances attributable to systolic function were minor (R^2 values ≤4%). None of the following 4 variables were retained by any of the stepwise multivariate models: LV internal dimension at end-diastole, sum of the end-diastolic LV wall thicknesses, LV mass and left atrial size.

DISCUSSION

This study used a healthy reference subset of the Framingham Heart Study to provide insight into the contributions of various clinical parameters to Doppler indexes of diastolic function. Aging was associated with a decrease in passive early LV inflow (peak velocity E and time velocity integral E) and an increase in the contribution from active late LV inflow (peak velocity A

TABLE II Doppler Left Ventricular Diastolic Filling Determinants

	PVE	PVA	PVEA	TVIEA	AFF
Univariate Correlation Coefficients (r)					
Age	−0.45*	0.73*	−0.77*	−0.74*	0.74*
Multivariate Stepwise Regression Correlation Coefficients (r)					
Age	−0.47*	0.64*	−0.80*	−0.73*	0.74*
Sex	0.25†	‡	0.17§	‡	−0.17§
HR	−0.20¶	0.27†	−0.33‖	−0.33‖	0.39*
PR	−0.18¶	‡	−0.18¶	−0.27†	0.29‖
LVFS	0.24†	‡	0.21¶	‡	‡
SBP	‡	0.20¶	‡	‡	‡

*$p < 0.0001$; ‖$p < 0.001$; †$p < 0.01$; ¶$p < 0.05$; §$p \leq 0.10$; ‡ did not enter the model ($p > 0.10$).

The following variables did not enter any of the stepwise regression models: body mass index; sum of end-diastolic septal and posterior wall thicknesses; LV internal dimension at end-diastole, LV mass and left atrial size.

AFF = atrial filling fraction; HR = heart rate; LVFS = left ventricular fractional shortening; PR = PR interval; PVA = peak velocity A wave (m/s); PVE = peak velocity E wave (m/s); PVEA = ratio peak velocity E/A; SBP = systolic blood pressure; TVIEA = ratio time velocity integral E/A wave.

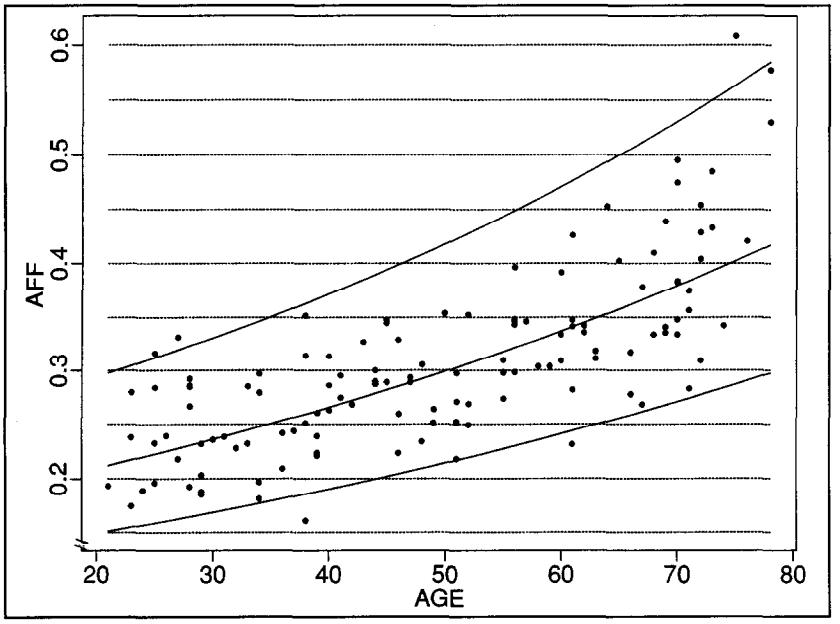

FIGURE 4. Plots of predicted values of atrial filling fraction (AFF) by age with 95% confidence intervals. Individual data points are depicted by *closed circles*. Predicted values and 95% confidence intervals are shown by *solid lines*.

and time velocity integral A), with a resultant decrease in the ratios of early to late filling (peak velocity E/A and time velocity integral E/A). Tables of normative values of Doppler LV inflow parameters are provided that may serve as reference values for echocardiography laboratories interested in assessing diastolic function. Decade-specific normal values of Doppler indexes of diastolic function have not been previously reported. The current analyses demonstrate that age is the overriding determinant of Doppler diastolic function in healthy subjects. Heart rate, PR interval, sex, LV systolic function and systolic blood pressure have less important contributions to diastolic filling parameters.

Correlations between Doppler left ventricular inflow and other variables; comparison with prior studies: ASSOCIATION BETWEEN AGE AND DOPPLER INDEXES OF DIASTOLIC FUNCTION: The univariate correlations between age and Doppler transmitral indexes in this population are similar in magnitude to those previously reported.[12-20] In the current multivariate analyses, there was little attenuation of the age-diastolic function relation even after adjusting for several clinical parameters that modulate LV inflow. The mechanisms of change in diastolic function with advancing age remain largely unexplained. The alterations in LV inflow observed with age resemble those seen with pathologic processes that become increasingly prevalent in the elderly, such as cardiac ischemia, hypertension and diabetes mellitus.[21] Furthermore, cardiac anatomy changes with age; LV wall thickness and left atrial diameter are increased in the elderly.[22,23] Hence, a variety of clinical and echocardiographic parameters were examined to clarify the age-diastolic function relation. This study extends the findings of a small study by Kitzman et al[20] who reported that in normal male subjects, age-related changes in Doppler diastolic function parameters are independent of clinical variables such as LV mass, heart rate and LV systolic function.

SEX AND BODY MASS INDEX: In the multivariate model, sex was significantly associated with peak velocity E, but accounted for <5% of the variance of peak velocity E. Other investigators[12,14,16-18] have not noted sex differences in LV inflow. In healthy subjects, obesity was not an important determinant of Doppler diastolic function. Although a few studies have examined the impact of body surface area on Doppler LV inflow with conflicting results,[12,14,18,20] no other study has analyzed the influence of obesity.

HEART RATE AND PR INTERVAL: In healthy subjects, heart rate was positively and significantly associated with peak velocity A and atrial filling fraction and inversely with peak velocities E and E/A, and time velocity integral E/A. Although some investigators have not found this association,[14,18,20] the present investigation confirms the findings of Zoghbi et al[17] and Harrison et al[24] that heart rate is an important determinant of LV filling in normal subjects. Investigators[24] have suggested that increasing heart rate may alter diastolic function by several mechanisms including a loss of diastolic filling time leading to an increased reliance on atrial contraction for atrial emptying, and an atrial Starling mechanism by which greater end-diastolic atrial volume augments atrial systole.

Multivariate analyses in the present investigation demonstrated that even in normal subjects, PR interval had a modest association with LV inflow; PR interval had a weak positive association with atrial filling fraction, and an inverse association with peak velocities E and E/A, and time velocity integral E/A. Although an investigation of subjects with pacemakers demonstrated that altering atrioventricular delay changes LV filling,[25] PR interval was not previously associated with Doppler transmitral flow in normal subjects.[18]

BLOOD PRESSURE: This study concurs with previous investigators[14,17] in demonstrating an absence of association between diastolic blood pressure and Doppler transmitral flow in normal adults. Controversy exists as to whether there is an association between systolic blood pressure and LV inflow.[14,17] The current study suggests that in normal subjects, systolic blood pressure accounts for at most a small proportion of the variance of LV inflow parameters; in multivariate analyses, systolic blood pressure remained significantly associated only with peak velocity A and accounted for only 2% of the variance.

LEFT VENTRICULAR SIZE AND SYSTOLIC FUNCTION, AND LEFT ATRIAL SIZE: It is plausible that age-associated decreases in LV diastolic function are secondary to alterations in myocardial size and function. Multivariate analyses did not demonstrate a significant impact of LV wall thickness, internal dimension and mass, and left atrial size on Doppler indexes of diastolic function. LV systolic function was associated with peak velocities E and E/A in the multivariate models. However, <5% of the variance in the Doppler indexes was explained by LV systolic function. Prior investigators have not noted an association between Doppler diastolic function in normal subjects and measures of LV wall thickness or mass in either univariate[13,19] or multivariate[18] analyses. A previous investigation examined the relation between LV filling and systolic function in normal subjects, and did not find any association; however, the study's sample size was small.[20] The only prior investigation to examine left atrial size found a similar absence of association with Doppler indexes of diastolic function.[20]

Mechanisms of age-related alterations of diastolic function: The pathogenesis of age-related alterations in the diastolic properties of the heart are complex, incompletely understood and reviewed elsewhere.[26,27] Briefly, published reports on animals suggest that an intricate combination of cellular hyperplasia,[28,29] cell death,[28] fibrosis,[29] decreased calcium sequestration[26,30] and increased passive stiffness[31] may underlie changes in LV diastolic function with aging in humans. The complex interaction between these microscopic and biochemical mechanisms may explain why clinical variables that can be assessed in the current epidemiologic setting or can be measured at cardiac catheterization[20] do not explain the aging changes in Doppler-assessed diastolic function.

Study limitations and advantages: The Framingham sample was rigorously screened to study healthy

subjects. Hence, the described determinants of diastolic function may not be relevant to subjects with co-morbidity, altered loading conditions[32,33] or extremes of heart rate. In addition, because subjects with hypertension and valvular disease were excluded from the reference sample, LV wall thickness and left atrial size were narrowly distributed; the findings should not be construed to mean that LV hypertrophy and left atrial enlargement are not determinants of diastolic function in other patient populations. Furthermore, a larger sample may have revealed minor statistical associations between LV inflow and body mass index, left atrial diameter, LV wall thickness, internal dimension and mass; however, the magnitude of these associations would be unlikely to be clinically important. Finally, subjects selected from an epidemiologic setting may lead to an overestimation of the impact of aging on LV inflow, because the sample may have included subjects with occult coronary disease.

Technical considerations may limit the use of the normative values. LV inflow was sampled at the mitral leaflet tips; therefore, the peak velocity measurements may be higher than values obtained at the annulus.[34] However, Gardin et al[34] have noted that the ratio of peak late to early transmitral flow is not significantly affected by the position of the Doppler sample volume. Furthermore, the number of subjects with technically inadequate Doppler echocardiograms (29%) was high; the study was performed early in the Framingham Study Doppler experience. Currently, only 4% of Framingham Study echocardiograms have technically inadequate Doppler LV inflows (Galderisi MG, unpublished data). However, the exclusion of subjects with technically inadequate echocardiograms would further bias the data set toward "super" normal subjects. Because the objective was to describe the determinants of Doppler diastolic function in healthy subjects, the exclusion of those with technically inadequate studies should not be a major limitation.

The Framingham Heart Study has several advantages over previous investigations. No other study of Doppler diastolic function has been reported from a population-based cohort. Subjects have been followed clinically for up to 38 years and have been systematically studied by echocardiography since the late 1970s. The prospective design of the study enables a more definitive characterization of a normal subset of subjects; the study has available longitudinal blood pressure and historical information to rigorously exclude subjects with prior hypertension or cardiac disease. Furthermore, previous investigations of the age-Doppler diastolic function relation were limited by an absence of multivariate analyses,[12-15,19] small sample sizes,[12-15,17,19,20] few subjects aged >70 years[12-15,19,20] and methodologic limitations, such as the inability to comment on Doppler reproducibility.[12,14,18,20]

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APPENDIX

Reproducibility: Interobserver variability of Doppler LV inflow was assessed by measuring a 10% random sample of subjects. The Pearson correlation coefficients of the 2 physicians' measurements were peak velocity E 0.97, peak velocity A 0.97, peak velocity E/A 0.99, time velocity integral E 0.91, time velocity integral A 0.84, time velocity integral E/A 0.90 and atrial filling fraction 0.93. The percent difference in the means was computed as $100[(\bar{x}_1 - \bar{x}_2)/(\bar{x}_1 + \bar{x}_2)/2]$, with x_1 being the first physician's measurement, and x_2 being the second one's measurement. The percent precision was computed as $100[1/n\ \Sigma(|x_1 - x_2|/(x_1 + x_2)/2)]$, with n being the number of subjects. The percent difference in the means and percent precision were, respectively: peak velocity E −0.6 and 5.0%; peak velocity A 2.0 and 5.6%; peak velocity E/A −2.2 and 4.1%; time velocity integral E −1.5 and 7.8%; time velocity integral A −4.4 and 11.0%; time velocity integral E/A 1.5 and 7.0%; and atrial filling fraction −5.1 and 7.2%.

REFERENCES

1. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: Background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. *Mayo Clin Proc* 1989;64:71-81.
2. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: The Framingham Study. *Am J Public Health* 1951;41:279-286.
3. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol* 1979;110:281-290.
4. Shurtleff D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study 18-year follow-up. In: Kannel WB, Gordon T, eds. The Framingham Study: An Epidemiologic Investigation of Cardiovascular Disease. Section 30. Washington, D.C.: US Government Printing Office, 1974; DHEW publication no. [NIH]:74-599.
5. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;59:956-960.
6. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-1083.
7. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension; its use in determining ejection fraction and stroke volume. *Chest* 1978;74:59-65.
8. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450-458.
9. SAS Institute Inc. SAS/STAT User's Guide: Release 6.03 ed. Cary, North Carolina: SAS Institute, 1990.
10. S-PLUS. S-PLUS User's Manual (Version 2.3). Seattle, Washington: Statistical Sciences, 1990.
11. Savage DD, Garrison RJ, Kannel WB, Anderson SJ, Feinleib M, Castelli WP. Considerations in the use of echocardiography in epidemiology; the Framingham Study. *Hypertension* 1987;9(suppl II):40-44.
12. Miyatake K, Okamoto M, Kinoshita N, Owa M, Nakasone I, Sakakibara H, Nimura Y. Augmentation of atrial contribution to left ventricular inflow with aging as assessed by intracardiac Doppler flowmetry. *Am J Cardiol* 1984;53: 586-589.
13. Sartori MP, Quinones MA, Kuo LC. Relation of Doppler-derived left ventricular filling parameters to age and radius/thickness ratio in normal and pathologic states. *Am J Cardiol* 1987;59:1179-1182.
14. Gardin JM, Rohan MK, Davidson DM, Dabestani A, Sklansky M, Garcia R, Knoll ML, White DB, Gardin SK, Henry WL. Doppler transmitral flow velocity parameters: relationship between age, body surface area, blood pressure and gender in normal subjects. *Am J Noninvas Cardiol* 1987;1:3-10.
15. Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA. Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. *Am J Cardiol* 1987;59:1174-1178.
16. Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;59:672-679.
17. Zoghbi WA, Habib GB, Quinones MA. Doppler assessment of right ventricu-

lar filling in a normal population: comparison with left ventricular filling dynamics. *Circulation* 1990;82:1316–1324.
18. Van Dam I, Fast J, De Boo T, Hopman J, Van Oort A, Heringa A, Alsters J, Van Der Werf T, Daniels O. Normal diastolic filling patterns of the left ventricle. *Eur Heart J* 1988;9:165–171.
19. Pearson AC, Labovitz AJ, Mrosek D, Williams GA, Kennedy HL. Assessment of diastolic function in normal and hypertrophied hearts: comparison of Doppler echocardiography and M-mode echocardiography. *Am Heart J* 1987; 113:1417–1425.
20. Kitzman DW, Sheikh KH, Beere PA, Philips JL, Higginbotham MB. Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. *J Am Coll Cardiol* 1991;18:1243–1250.
21. Spirito P, Maron BJ. Doppler echocardiography for assessing left ventricular diastolic function. *Ann Intern Med* 1988;109:122–126.
22. Gerstenblith G, Frederiksen J, Yin FCP, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273–278.
23. Gardin JM, Henry WL, Savage DD, Ware JH, Burn C, Borer JS. Echocardiographic measurements in normal subjects: evaluation of an adult population without clinically apparent heart disease. *JCU J Clin Ultrasound* 1979;7:439–447.
24. Harrison MR, Clifton GD, Pennell AT, DeMaria AN, Cater A. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol* 1991;67: 622–627.
25. Pearson AC, Janosik DL, Redd RR, Buckingham TA, Blum RI, Labovitz AJ, Mrosek D. Doppler echocardiographic assessment of the effect of varying atrioventricular delay and pacemaker mode on left ventricular filling. *Am Heart J* 1988;115:611–621.
26. Lakatta EG, Yin FCP. Myocardial aging: functional alterations and related cellular mechanisms. *Am J Physiol* 1982;242:H927–H941.
27. Lakatta EG. Do hypertension and aging have a similar effect on the myocardium? *Circulation* 1987;75(suppl I):I-69–I-77.
28. Anversa P, Hiler B, Ricci R, Guideri G, Olivetti G. Myocyte cell loss and myocyte hypertrophy in the aging rat heart. *J Am Coll Cardiol* 1986;8: 1441–1448.
29. Anversa P, Palackal T, Sonnenblick EH, Olivetti G, Meggs LG, Capasso JM. Myocyte cell loss and myocyte cellular hyperplasia in the hypertrophied aging rat heart. *Circ Res* 1990;67:871–885.
30. Froehlich JP, Lakatta EG, Beard E, Spurgeon HA, Weisfeldt ML, Gerstenblith G. Studies of sarcoplasmic reticulum function and contraction duration in young adult and aged rat myocardium. *J Mol Cell Cardiol* 1978;10:427–438.
31. Urthaler F, Walker AA, James TN. The effect of aging on ventricular contractile performance. *Am Heart J* 1978;96:481–485.
32. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. *Circulation* 1989;79: 1226–1236.
33. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;10:800–808.
34. Gardin JM, Dabestani A, Takenaka K, Rohan MK, Knoll M, Russell D, Henry WL. Effect of imaging view and sample volume location on evaluation of mitral flow velocity by pulsed Doppler echocardiography. *Am J Cardiol* 1986;57:1335–1339.