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Age and the Effectiveness of Anti-Hypertensive Therapy on Improvement in Diastolic Function

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Abstract

Objective—Diastolic dysfunction is associated with adverse outcomes and is highly prevalent among older adults with hypertension. Lowering systolic blood pressure (SBP) with anti-hypertensive therapy has been shown to improve diastolic function, but whether or not age influences this effect is unknown.

Methods—In the Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction trial, 189 patients (age range, 45 to 93 years) with hypertension and diastolic dysfunction underwent echocardiography before and after 24 weeks of intensive versus standard anti-hypertensive therapy titrated to a goal SBP <135 versus <140 mmHg. We performed linear regression analyses to examine the association between age and improvement in diastolic function achieved with SBP reduction.

Results—Anti-hypertensive therapy reduced SBP by 28±19 mmHg overall, and this was not significantly different across age strata. However, percent improvement in diastolic relaxation velocity (lateral E' peak velocity) for every 10 mmHg reduction in SBP was lower in older compared to younger patients. In analyses adjusting for age stratum, sex, treatment arm, baseline relaxation velocity, and baseline blood pressure, older age was associated with reduced improvement in diastolic relaxation velocity per 10 mmHg of SBP reduction (β -1.64; $P=0.009$). In contrast, the degree of change in left ventricular mass index per 10 mmHg reduction in SBP was not influenced by age ($P=0.89$).

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Conclusions—In our sample of individuals with hypertension and diastolic dysfunction, older compared to younger adults experienced less improvement in diastolic function in response to similar reductions in SBP.

Keywords

aging; blood pressure; hypertension; diastolic dysfunction; antihypertensive agents

INTRODUCTION

Diastolic dysfunction is highly prevalent in the community and is associated with adverse outcomes, including incident heart failure (HF) and all-cause mortality.¹⁻⁶ Subclinical diastolic dysfunction is especially common in the setting of both advancing age and long-standing hypertension, potentially due to distinct yet overlapping mechanisms.^{7,8} Advanced age is associated with increased duration of exposure to elevated blood pressure and, in turn, greater prevalence of the end-organ effects of hypertension⁹ including concentric left ventricular (LV) remodeling and increased LV mass.¹⁰ In addition, aging is associated with vascular changes that include arterial stiffening, which can promote intrinsic stiffening of the LV^{11,12} and potentially lead to impaired myocardial relaxation.^{13,14}

Several therapies have been proposed for improving diastolic function, including blood pressure reduction with anti-hypertensive therapy. In multi-center randomized controlled trials, effectively lowering systolic blood pressure (SBP) in individuals with both hypertension and echocardiographic evidence of diastolic dysfunction has been shown to result in significant improvements in diastolic function, regardless of the anti-hypertensive agent used.^{15,16} Moreover, the degree of improvement in diastolic dysfunction was directly related to the degree of blood pressure lowering. These findings may be related to an anti-hypertensive induced reversal of cardiomyocyte hypertrophy and/or yet undetermined effects on myocardial fibrosis.^{17,18} Because diastolic dysfunction in older age may be due to the prolonged effects of hypertension in addition to aging-specific effects on cardiovascular structure and function, blood pressure reduction alone may have limited efficacy in treating diastolic dysfunction in older adults. The extent to which diastolic function may respond to BP lowering therapy differently across age groups has not been investigated previously, but has important implications for the development of interventions aimed at reducing the risks associated with diastolic dysfunction. Therefore, in a sample of adults with baseline hypertension and diastolic dysfunction, we examined the influence of age on change in diastolic function in response to SBP reduction with anti-hypertensive therapy.

METHODS

Study Sample

The study design and sampling strategy for the Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction (EXCEED) trial has been described previously.^{16,19} In brief, a total of 228 individuals with hypertension and diastolic dysfunction were enrolled in a trial to evaluate the relative effect of intensive versus standard anti-hypertensive therapy on improvement in diastolic function. Individuals were

included if the following criteria were met: 1) systolic blood pressure (SBP) 150 and 200 mmHg; 2) age greater than or equal to 45 years old; 3) echocardiographic presence of diastolic dysfunction (lateral E' <10 cm/s for individuals aged 45-54 years; <9 cm/s for individuals aged 55-65 years; and, <8 cm/s for individuals aged >65 years old); 4) LV ejection fraction (EF) >50%; and, 5) absence of HF symptoms. Individuals were excluded for any of the following reasons: diastolic blood pressure (DBP) >120 mmHg or use of at least 3 anti-hypertensive agents at baseline; history of secondary hypertension; history of heart failure; history of diabetes; serum creatinine >2.0 mg/dL or nephrotic syndrome; atrial fibrillation; a vascular event within the prior 6 months; or, intolerance to angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Anti-hypertensive therapy with valsartan and amlodipine was titrated to a goal SBP of <140 versus <135 mmHg in the intensive versus standard arms, respectively, and then continued over a period of 24 weeks. Of the patients enrolled at baseline, 32 had unavailable echocardiographic data at follow up and 7 patients had unavailable blood pressure at the time of the follow-up echocardiogram. Thus, a total of 189 individuals had 2D and Doppler echocardiography, in addition to concurrent BP measurements, performed at both baseline and follow-up examinations. Blood pressure was measured in the seated position and the mean of 3 consecutive BP measurements was used in analyses of baseline BP; the mean of 2 consecutive BP measurements was used for analyses of follow-up BP. Estimated glomerular filtration rate (eGFR) was calculated using the modified diet in renal disease (MDRD) formula.²⁰

Echocardiographic Measures

The echocardiographic image acquisition and analysis protocols have been described previously.¹⁶ In brief, echocardiograms recorded on videotape were digitized and all measurements made on digital studies were calibrated within each study. All echocardiographic measurements and analyses were performed in the same core laboratory by readers using an offline workstation while blinded to clinical data, including randomized treatment assignment. Diastolic function was assessed using standardized methods, including the peak E prime velocity measured at the lateral aspect of the mitral annulus on tissue Doppler imaging.⁶ LV mass was estimated using LV linear dimensions according to a validated method²¹ and indexed to body surface area as well as to height^{2,7}. LV volumes were derived according to the modified biplane Simpson's rule in the apical 4- and 2-chamber views, and EF was calculated in the standard fashion from LV end-diastolic volume and LV end-systolic volume. Major LV measures of structure and function included: LV wall thickness (LVWT), relative wall thickness (RWT), LV mass indexed to body surface area (LVMI), left atrial volume indexed to body surface area (LAVI), LV ejection fraction (EF), peak lateral E' velocity (E'), isovolumic relaxation time (IVRT), E-wave deceleration time (DT), and E-wave to a-wave ratio (E/a). All measurements of diastolic function were performed by a single observer blinded to clinical data. Reproducibility of diastolic measures was comparable to that reported in prior studies,²² with intra-observer coefficients of variation 5.8%.

Statistical Analyses

One-way ANOVA and Kruskal-Wallis tests were used to examine clinical and echocardiographic characteristics at baseline and at follow up (24 weeks), as well as change

in these characteristics from baseline to follow up, across age strata. In unadjusted multivariable linear regression analyses, we examined the association between age and percent change in each major LV measure per 10 mmHg reduction in SBP. We next used multivariable linear regression models to assess the relation of age to percent change in each major LV measure per 10 mmHg reduction in SBP (dependent variable) while adjusting for age stratum, treatment arm, sex, baseline SBP, baseline DBP, and baseline LV measure (independent variables). We included age stratum in every model in order to avoid residual confounding due to possible sampling bias, given that participants in EXCEED were enrolled based on age-based criterion for diastolic dysfunction (as determined by E').

In secondary analyses, analyses of percent change in E' per 10 mmHg SBP reduction included additional adjustment for eGFR, baseline RWT, baseline LVMI, and baseline LAVI. Analyses were repeated in models that included additional adjustment for race, body mass index (BMI), baseline heart rate, change in heart rate, baseline pulse pressure, and change in pulse pressure.

We also estimated power to detect significant associations between age and the primary outcome variable in our sample. We determined the minimum difference in R-squared (R^2) value for 1 predictor change that could be detected with 80% power and alpha threshold of 0.05, given the observed R^2 value, the number of predictors included, and the sample size from the fully-adjusted multivariable linear regression models.

A two-sided P value threshold of less than 0.05 was considered statistically significant. All analyses were performed using STATA v10.0 (StataCorp, College Station, TX).

RESULTS

Clinical and echocardiographic characteristics of the study sample are shown in Tables 1 and 2. The prevalence of baseline LV hypertrophy, defined according to previously reported cutpoints²³ for LV mass/height^{2.7}, was 8%. Of the total sample, 93% reported prior use of at least 2 classes of anti-hypertensive medications at baseline. From baseline to follow up, reduction in SBP was similar across all age strata (Table 1). Absolute changes from baseline to follow up in LV mass and diastolic indices were also not significantly different across increasing age strata (Table 2). In unadjusted linear regression analyses, older age was inversely related to percent change in E' ($P=0.046$) and E/a ($P=0.005$) per 10 mmHg reduction in SBP (Table 3).

In multivariable adjusted analyses, age was not significantly associated with percent change in any structural LV measures or in percent change in LVEF (Table 3). However, older age was associated with lesser improvements in diastolic function, as reflected by smaller increases in E'. The inverse association between advanced age and percent increase in E' per 10 mmHg reduction in SBP was significant (regression coefficient -1.64 per 1 year of age; $P=0.009$), even after adjustment for age stratum, treatment arm, sex, baseline SBP, baseline DBP, and baseline E'. This association remained significant in models additionally adjusting for eGFR, RWT, LVMI, and LAVI ($P=0.009$). This association was also unchanged in models adjusting for race, BMI, baseline heart rate, change in heart rate, baseline pulse

pressure, and change in pulse pressure ($P < 0.01$). Although age was not associated with percent change in LAVI in unadjusted analyses, older age was associated with less change in LAVI in multivariable analyses adjusting for age stratum, treatment arm, sex, baseline SBP, baseline DBP, and baseline LAVI ($P = 0.03$).

When analyses of LVMI were repeated with LV mass normalized to height^{2.7}, results were unchanged (data not shown). In multivariable analyses additionally adjusting for percent change in DBP or PP from baseline to follow up, the associations of age with percent increase in E' per 10 mmHg reduction in SBP remained significant ($P = 0.004$). In analyses testing for effect modification by treatment arm, we observed no significant interaction of intensive versus standard blood pressure lowering therapy of age on the primary outcome ($P = 0.06$). Although the main trial was designed to achieve targets for lowering SBP, we also repeated the main multivariable analyses above to assess in effect of age on change in E' per 5 mmHg reduction in DBP; in these analyses, the association of age was not significant ($P = 0.94$).

At a significance level of $\alpha = 0.05$, our sample had $>80\%$ power to detect a change in the model R^2 of 0.037 or smaller for age in multivariable linear regression model.

DISCUSSION

We observed that absolute improvement in diastolic function, in response to blood pressure reduction, occurred across the age spectrum. However, relative improvement in diastolic function, as reflected by change in myocardial tissue relaxation velocity per increment reduction in SBP, was significantly lower in older compared to younger patients. This age-based finding was consistently observed even after accounting for clinical and echocardiographic covariates.

There are several possible explanations for the attenuated effect of blood pressure lowering on diastolic function in older versus younger individuals. The cumulative effects of aging and hypertension likely jointly contribute to progression of diastolic dysfunction over the life course and, in the current study, older individuals likely had longer prior exposure to elevated arterial pressures than younger individuals.²⁴ Aging has been associated with more advanced hypertensive heart disease,¹⁰ which is characterized by cardiomyocyte hypertrophy and also extensive myocardial fibrosis.²⁵ Aging may also augment the development of hypertensive heart disease via age-related alterations in neurohormonal and related pathways.²⁶ Indeed, circulating levels of aldosterone relative to renin concentrations are detectably higher across increasing age groups of ambulatory individuals living in the community.²⁷ Age-related vascular changes may also directly or indirectly render the myocardium less amenable to the benefits of blood pressure reduction. Arterial stiffening, a hallmark of functional vascular aging, is known to be coupled pathophysiologically with myocardial stiffening^{11,12,28} and has also been associated with echocardiographic evidence of diastolic dysfunction.^{13,14}

Aging could also lead to the development of diastolic dysfunction through pathways that do not involve overt hypertension. Based on data collected from physiology studies^{29,30} and

cardiac magnetic resonance imaging,³¹⁻³³ in addition to echocardiography,^{7,8,34} subclinical decrements in cardiac function have been associated with older age, even in relatively healthy and normotensive adults. These alterations in LV function are typically accompanied by age-related changes in structure, such as increased LV wall thickness and mass, which can also manifest in the absence of overt hypertension.^{10,32,35,36} Interestingly, we observed that older compared to younger individuals had less improvement in diastolic function but no difference in reduction of LV mass following SBP lowering. The age-independence of change in structure is consistent with findings from prior blood pressure lowering trials.³⁷ The age-dependence of change in diastolic function could be related to cellular and molecular cardiac alterations associated with biologic aging, including cardiomyocyte dropout with replacement fibrosis,^{38,39} alterations in pro-collagen processing leading to increased fibrillar collagen content,⁴⁰ and changes in sarcoplasmic reticulum function.⁴¹ Risk factors for diastolic dysfunction, which are more prevalent in older compared to younger adults,¹ are also potential contributors. In our study, we excluded individuals with cardiovascular disease, diabetes, and chronic kidney disease; our analyses also adjusted for eGFR and several parameters of LV remodeling. However, it remains possible that the development of non-cardiac subclinical disease with aging, including metabolic abnormalities, could predispose to relatively 'resistant' diastolic dysfunction^{4,42} in older age.

Several limitations of this study merit consideration. Although we adjusted for age-based entry strata in our analyses, we cannot exclude the possibility that age-based entry criteria influenced our results. In our analyses, we were unable to account for duration of antecedent hypertension or use of non-intervention medications that may have had an effect on diastolic function, because this information was not available in our study sample. Markers of myocardial fibrosis and measures of acute versus chronic effects of alterations in afterload and preload were also not available for the current study. The lower prevalence of overt LV hypertrophy in our study sample may have been due to the effects of antecedent anti-hypertensive therapy and/or measurement bias; thus, further work is needed to assess the degree to which age is associated with changes in LV mass, particularly across the spectrum of hypertensive heart disease. We observed non-significant results for parameters of diastolic function other than E' , potentially because these analyses were subject to limited power due to sample size and study design. Importantly, the main EXCEED trial enrolled participants based on presence of abnormal E' value and was designed to assess change in E' as the primary endpoint. Nonetheless, E' is considered a robust marker of diastolic function⁶ and has been the focus of clinical trials involving individuals with hypertension.^{15,16} Additionally, we observed an age-related attenuation of decrease in LAVI, which is also considered a marker of diastolic dysfunction.⁶ The smaller sample size of our study precluded extensive effect modification or stratum-specific analyses, which may be subject of future investigations. The overall findings of our study may have been limited by smaller sample size, possible measurement imprecision, and/or misclassification; however, all such limitations would have biased our results to the null. The generalizability of our findings to unselected populations with a wider representation of age, race/ethnicity, and clinical characteristics (including cardiovascular risk factors and comorbidities) is not known.

In summary, we observed that older compared to younger individuals experienced less improvement in diastolic function in response to similar reductions in SBP, despite comparable reduction in LV hypertrophy. The relationship between structural and functional myocardial changes in the setting of diastolic dysfunction and hypertension may vary with increasing age. In particular, biologic aging processes may promote, either directly or in conjunction with chronic hypertension, cellular and extracellular myocardial changes that are less likely to be ameliorated by conventional anti-hypertensive therapy alone. Further research is needed to investigate potential therapies for the prevention and treatment of age-related myocardial fibrosis and diastolic dysfunction,⁴³⁻⁴⁵ which may be both blood pressure dependent and independent.

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ABBREVIATIONS

DT	E-wave deceleration time
E'	peak lateral E' velocity
E/a	E-wave to a-wave ratio
EF	left ventricular ejection fraction
IVRT	isovolumic relaxation time (IVRT)
LAVI	left atrial volume indexed to body surface area
LVMi	LV mass indexed to body surface area
LVWT	LV wall thickness
RWT	relative wall thickness

REFERENCES

1. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a doppler echocardiographic-based survey of a population sample. *Eur Heart J*. 2003; 24:320–328. [PubMed: 12581679]
2. Kuznetsova T, Herbots L, Lopez B, Jin Y, Richart T, Thijs L, et al. Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail*. 2009; 2:105–112. [PubMed: 19808325]
3. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr. et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011; 306:856–863. [PubMed: 21862747]
4. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation*. 2011; 124:24–30. [PubMed: 21670229]
5. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med*. 2011; 171:1082–1087. [PubMed: 21709107]

6. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009; 22:107–133. [PubMed: 19187853]
7. De Sutter J, De Backer J, Van de Veire N, Velghe A, De Buyzere M, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (e') and the ratio of transmitral early peak velocity to e' (e'/e'). *Am J Cardiol.* 2005; 95:1020–1023. [PubMed: 15820183]
8. Innelli P, Sanchez R, Marra F, Esposito R, Galderisi M. The impact of aging on left ventricular longitudinal function in healthy subjects: A pulsed tissue doppler study. *Eur J Echocardiogr.* 2008; 9:241–249. [PubMed: 17586096]
9. O'Sullivan C, Duggan J, Lyons S, Thornton J, Lee M, O'Brien E. Hypertensive target-organ damage in the very elderly. *Hypertension.* 2003; 42:130–135. [PubMed: 12860837]
10. Cheng S, Xanthakis V, Sullivan LM, Lieb W, Massaro J, Aragam J, et al. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: Longitudinal observations from the Framingham Heart Study. *Circulation.* 2010; 122:570–578. [PubMed: 20660804]
11. Chen CH, Nakayama M, Nevo E, Fetis BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: Implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol.* 1998; 32:1221–1227. [PubMed: 9809929]
12. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: A community-based study. *Circulation.* 2005; 112:2254–2262. [PubMed: 16203909]
13. Abhayaratna WP, Srikusalanukul W, Budge MM. Aortic stiffness for the detection of preclinical left ventricular diastolic dysfunction: Pulse wave velocity versus pulse pressure. *J Hypertens.* 2008; 26:758–764. [PubMed: 18327086]
14. Xu L, Jiang CQ, Lam TH, Yue XJ, Lin JM, Cheng KK, et al. Arterial stiffness and left-ventricular diastolic dysfunction: Guangzhou biobank cohort study-cvd. *J Hum Hypertens.* 2011; 25:152–158. [PubMed: 20428193]
15. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: A randomised trial. *Lancet.* 2007; 369:2079–2087. [PubMed: 17586303]
16. Solomon SD, Verma A, Desai A, Hassanein A, Izzo J, Oparil S, et al. Effect of intensive versus standard blood pressure lowering on diastolic function in patients with uncontrolled hypertension and diastolic dysfunction. *Hypertension.* 2010; 55:241–248. [PubMed: 19996069]
17. Tamura T, Said S, Harris J, Lu W, Gerdes AM. Reverse remodeling of cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system. *Circulation.* 2000; 102:253–259. [PubMed: 10889139]
18. Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. *Circulation.* 2002; 105:2512–2517. [PubMed: 12034658]
19. Hassanein A, Desai A, Verma A, Oparil S, Izzo J, Rocha R, et al. Exceed: Exforge-intensive control of hypertension to evaluate efficacy in diastolic dysfunction: Study rationale, design, and participant characteristics. *Ther Adv Cardiovasc Dis.* 2009; 3:429–439. [PubMed: 19638366]
20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med.* 1999; 130:461–470. [PubMed: 10075613]
21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, 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; 18:1440–1463. [PubMed: 16376782]
22. Galderisi M, Benjamin EJ, Evans JC, D'Agostino RB, Fuller DL, Lehman B, et al. Intra- and interobserver reproducibility of doppler-assessed indexes of left ventricular diastolic function in a

- population-based study (the Framingham Heart Study). *Am J Cardiol.* 1992; 70:1341–1346. [PubMed: 1442588]
23. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: Assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol.* 1995; 25:1056–1062. [PubMed: 7897116]
 24. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation.* 1997; 96:308–315. [PubMed: 9236450]
 25. Diez J, Gonzalez A, Lopez B, Querejeta R. Mechanisms of disease: Pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. *Nat Clin Pract Cardiovasc Med.* 2005; 2:209–216. [PubMed: 16265485]
 26. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol.* 2006; 7:589–600. [PubMed: 16936699]
 27. Newton-Cheh C, Guo CY, Gona P, Larson MG, Benjamin EJ, Wang TJ, et al. Clinical and genetic correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. *Hypertension.* 2007; 49:846–856. [PubMed: 17296870]
 28. Kass DA. Ventricular arterial stiffening: Integrating the pathophysiology. *Hypertension.* 2005; 46:185–193. [PubMed: 15911741]
 29. Schulman SP, Lakatta EG, Fleg JL, Lakatta L, Becker LC, Gerstenblith G. Age-related decline in left ventricular filling at rest and exercise. *Am J Physiol.* 1992; 263:H1932–1938. [PubMed: 1362335]
 30. Swinne CJ, Shapiro EP, Lima SD, Fleg JL. Age-associated changes in left ventricular diastolic performance during isometric exercise in normal subjects. *Am J Cardiol.* 1992; 69:823–826. [PubMed: 1546666]
 31. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, et al. Cardiovascular function in multi-ethnic study of atherosclerosis: Normal values by age, sex, and ethnicity. *AJR Am J Roentgenol.* 2006; 186:S357–365. [PubMed: 16714609]
 32. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: The Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging.* 2009; 2:191–198. [PubMed: 19808592]
 33. Fonseca CG, Oxenham HC, Cowan BR, Occleshaw CJ, Young AA. Aging alters patterns of regional nonuniformity in lv strain relaxation: A 3-d mr tissue tagging study. *Am J Physiol Heart Circ Physiol.* 2003; 285:H621–630. [PubMed: 12689861]
 34. Nakai H, Takeuchi M, Nishikage T, Kokumai M, Otani S, Lang RM. Effect of aging on twist-displacement loop by 2-dimensional speckle tracking imaging. *J Am Soc Echocardiogr.* 2006; 19:880–885. [PubMed: 16824997]
 35. Gardin JM, Siscovick D, Anton-Culver H, Lynch JC, Smith VE, Klopfenstein HS, et al. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The cardiovascular health study. *Circulation.* 1995; 91:1739–1748. [PubMed: 7882482]
 36. Lieb W, Xanthakis V, Sullivan LM, Aragam J, Pencina MJ, Larson MG, et al. Longitudinal tracking of left ventricular mass over the adult life course: Clinical correlates of short- and long-term change in the framingham offspring study. *Circulation.* 2009; 119:3085–3092. [PubMed: 19506113]
 37. Gerds E, Roman MJ, Palmieri V, Wachtell K, Smith G, Nieminen MS, et al. Impact of age on left ventricular hypertrophy regression during antihypertensive treatment with losartan or atenolol (the life study). *J Hum Hypertens.* 2004; 18:417–422. [PubMed: 15103312]
 38. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res.* 1991; 68:1560–1568. [PubMed: 2036710]
 39. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, Anversa P. Gender differences and aging: Effects on the human heart. *J Am Coll Cardiol.* 1995; 26:1068–1079. [PubMed: 7560601]

40. Bradshaw AD, Baicu CF, Rentz TJ, Van Laer AO, Bonnema DD, Zile MR. Age-dependent alterations in fibrillar collagen content and myocardial diastolic function: Role of sparc in post-synthetic procollagen processing. *Am J Physiol Heart Circ Physiol*. 2010; 298:H614–622. [PubMed: 20008277]
41. Kaufman TM, Horton JW, White DJ, Mahony L. Age-related changes in myocardial relaxation and sarcoplasmic reticulum function. *Am J Physiol*. 1990; 259:H309–316. [PubMed: 2386215]
42. de las Fuentes L, Brown AL, Mathews SJ, Waggoner AD, Soto PF, Gropler RJ, Davila-Roman VG. Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. *Eur Heart J*. 2007; 28:553–559. [PubMed: 17311827]
43. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation*. 2004; 110:1799–1805. [PubMed: 15364801]
44. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation*. 2010; 122:1797–1805. [PubMed: 20956204]
45. Liu J, Masurekar MR, Vatner DE, Jyothirmayi GN, Regan TJ, Vatner SF, et al. Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. *Am J Physiol Heart Circ Physiol*. 2003; 285:H2587–2591. [PubMed: 12946933]

Table 1

Clinical Characteristics

Characteristic	Age 45-54 years (N=49)	Age 55-65 years (N=89)	Age >65 years (N=51)	P value
Baseline				
Age, years	48.9±2.7	59.2±3.3	73.2±5.4	<0.001
Women, %	45	53	55	0.64
Non-white race, %	47	28	10	<0.001
Weight, kg	99.0±21.5	89.3±17.8	77.0±15	<0.0001
BMI, kg/m ²	34.2±7.4	32.3±5.4	27.7±4.1	<0.001
eGFR, mL/min	89.6±21.0	85.5±19.2	73.2±15.9	<0.001
Treatment Arm, %				
Intensive	49	52	51	0.91
Standard	51	48	49	
HR, bpm	74±12	71±10	69±10	0.03
SBP, mmHg	164±13	164±16	166±18	0.63
DBP, mmHg	97±11	95±11	85±10	<0.001
PP, mmHg	66±13	69±15	82±17	<0.0001
Follow Up (at 24 weeks)				
Weight, kg	100.0±21.9	89.0±17.8	76.6±16.3	<0.0001
BMI, kg/m ²	34.5±7.5	31.2±5.1	27.6±3.8	<0.0001
HR, bpm	75±11	68±10	67±12	0.0005
SBP, mmHg	134±14	136±15	138±13	0.36
DBP, mmHg	83±11	80±11	71±9	<0.001
PP, mmHg	53±17	56±11	67±11	<0.0001
Absolute change (baseline to 24 weeks)				
Weight, kg	0.9±2.7	-0.6±4.0	0.4±3.3	0.04
BMI, kg/m ²	0.3±1.0	-0.2±1.4	0.1±1.1	0.05
HR, bpm	0±12	-3±10	-2±11	0.17
SBP, mmHg	-30±15	-28±21	-28±19	0.81
DBP, mmHg	-14±8	-14±13	-13±10	0.58
PP, mmHg	-14±20	-13±15	-15±15	0.90
Percent change (baseline to 24 weeks)				
Weight, kg	0.9±3.1	-0.6±4.4	0.5±4.0	0.08
BMI, kg/m ²	0.9±3.1	-0.6±4.4	0.5±4.0	0.08
HR	2.0±15.6	-3.8±12.6	-2.5±15.6	0.09
SBP	-17.8±8.5	-16.2±11.7	-16.1±10.5	0.64
DBP	-16.1±13.5	-14.4±12.7	-15.2±11.8	0.74
PP, mmHg	-18.5±30.4	-16.8±19.4	-15.8±17.5	0.83

BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Values are shown as mean ± standard deviations or percentages.

Table 2

Echocardiographic Left Ventricular Characteristics

Characteristic	Age 45-54 y (N=49)	Age 55-65 y (N=89)	Age >65 y (N=51)	P value
<i>Baseline</i>				
LVWT, cm	1.75±0.21	1.73±0.23	1.74±0.27	0.88
RWT	0.36±0.04	0.36±0.05	0.37±0.05	0.88
LVMI, g/m ²	70.0±13.5	70.6±14.0	76.0±17.1	0.07
LV mass/height ^{2.7}	34.8±7.6	34.3±7.6	35.7±8.6	0.60
LAVI, mL/m ²	24.0±3.0	25.5±3.4	26.9±3.4	<0.001
LVEF, %	55.0±2.6	54.7±2.7	55.2±2.7	0.90
E', cm/s	8.1±1.3	7.6±1.1	7.0±1.0	0.13
E/a ratio	1.02±0.25	0.95±0.22	0.88±0.24	0.016
E/E' ratio	8.2±2.2	8.8±2.4	9.7±2.0	0.004
DT, msec	239.1±31.0	241.7±28.0	251.2±30.3	0.09
IVRT, msec	110.8±18.6	109.9±15.9	110.9±17.8	0.93
<i>Follow Up (at 24 weeks)</i>				
LVWT, cm	1.68±0.19	1.61±0.17	1.64±0.18	0.12
RWT	0.35±0.04	0.34±0.04	0.35±0.04	0.11
LVMI, g/m ²	65.1±11.7	64.3±9.6	68.1±11.2	0.14
LV mass/height ^{2.7}	32.5±6.6	31.1±5.3	31.9±6.0	0.39
LAVI, mL/m ²	22.6±3.3	24.2±3.5	25.5±4.3	<0.001
LVEF, %	58.3±4.0	58.1±4.4	59.1±3.7	0.37
E', cm/s	9.8±1.9	9.2±1.6	8.2±1.7	<0.001
E/a ratio	1.16±0.33	1.02±0.25	0.94±0.26	<0.001
E/E' ratio	7.4±2.1	8.0±2.5	8.9±2.2	0.006
DT, msec	209.6±26.8	220.3±25.6	235.8±27.3	<0.001
IVRT, msec	88.9±14.8	92.6±15.5	93.1±16.7	0.31
<i>Change (percent change from baseline to 24 weeks)</i>				
LVWT	-3.5±10.1	-5.9±9.8	-4.6±10.1	0.38
RWT	-2.8±11.2	-5.7±11.5	-2.8±10.5	0.21
LVMI	-5.1±17.8	-7.6±14.3	-7.7±17.0	0.62
LV mass/height ^{2.7}	-4.7±17.7	-7.5±14.0	-8.1±17.1	0.51
LAVI	-5.4±10.9	-4.6±8.9	-5.2±13.7	0.90
LVEF	3.4±4.0	3.3±4.3	3.8±4.1	0.80
E'	22.4±21.7	21.5±20.9	18.2±22.6	0.57
E/a ratio	1.6±3.8	1.1±2.8	0.9±3.2	0.56
E/E' ratio	-7.1±22.9	-8.0±22.4	-6.3±22.8	0.91
DT	-10.5±14.2	-8.1±12.0	-5.5±10.5	0.13
IVRT	-16.3±26.6	-14.5±14.3	-14.9±15.9	0.87

LVDD, left ventricular diameter at end-diastole; LVWT, left ventricular wall thickness; RWT, relative wall thickness; LVMI, left ventricular mass indexed to body surface area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E', E-prime; E/a, E-wave to a-wave; E/E', E-wave to E-prime ratio; DT, E-wave deceleration time; IVRT, isovolumic relaxation time.

Values are shown as means $\pm$ standard deviation.

Table 3

Relationship of Age with Change in Left Ventricular Structure and Function in Response to Lowering Systolic Blood Pressure

Dependent Variable	Unadjusted		Multivariable-Adjusted	
	β (SE)	P value	β (SE)	P value
<i>Change in Structural Measures</i>				
LVWT, cm	0.12 (0.14)	0.38	0.28 (0.36)	0.45
RWT, ratio	0.31 (0.18)	0.09	0.43 (0.49)	0.38
LVMI, g/m ²	−0.21 (0.18)	0.24	0.10 (0.46)	0.83
LAVI, mL/m ²	0.19 (0.12)	0.13	0.71 (0.33)	0.03
<i>Change in Functional Measures</i>				
LVEF, %	0.01 (0.06)	0.93	0.01 (0.17)	0.96
E', cm/s	−0.47 (0.23)	0.046	−1.64 (0.62)	0.009
E/A, ratio	−0.06 (0.02)	0.005	−0.06 (0.06)	0.30
E/E', ratio	−0.43 (0.31)	0.17	0.85 (0.82)	0.30
DT, msec	0.36 (0.25)	0.15	1.05 (0.69)	0.13
IVRT, msec	0.41 (0.28)	0.14	0.72 (0.77)	0.35

LVDD, left ventricular diameter at end-diastole; LVWT, left ventricular wall thickness; RWT, relative wall thickness; LVMI, left ventricular mass indexed to body surface area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E', E prime; E/A, E-wave to a-wave ratio; E-wave to E-prime ratio; DT, E-wave deceleration time; IVRT, isovolumic relaxation time.

* Regression coefficients represent the relationship of age (per 1 year) on change in the dependent variable per 10 mmHg reduction in SBP. Analyses are adjusted for sex, stratum, treatment arm, baseline SBP, baseline DBP, and baseline value of the dependent variable.