

Ventricular Structure and Function in Hypertensive Participants With Heart Failure and a Normal Ejection Fraction

The Cardiovascular Health Study

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- Objectives** The purpose of this study was to evaluate left ventricular (LV) size and structure in elderly subjects with hypertension (HTN) and heart failure who have a normal ejection fraction (HFNEF) in a large population-based sample.
- Background** The pathophysiology of HFNEF is incompletely understood but is generally attributed to LV diastolic dysfunction with normal or reduced LV diastolic chamber size despite greater than normal filling pressures.
- Methods** In the Cardiovascular Health Study (n = 5,888), demographic and clinical characteristics and ventricular structure and function were compared in healthy normal subjects (healthy; n = 499), subjects with HTN but not heart failure (HTN; n = 2,184), and subjects with HTN and HFNEF (HFNEF; n = 167).
- Results** Subjects with HFNEF were older, more obese, and more often African American than healthy and HTN subjects and had a higher prevalence of diabetes, coronary heart disease, and anemia than HTN subjects. Serum creatinine and cystatin-C were increased in HFNEF subjects. Average LV diastolic dimension was significantly increased in HFNEF subjects (5.2 ± 0.8 cm) compared with healthy (4.8 ± 0.6 cm) and HTN (4.9 ± 0.6 cm) subjects. As a result, average calculated stroke volume (89 ± 25 ml vs. 78 ± 20 ml and 80 ± 20 ml) and cardiac output (6.0 ± 2.0 l/min vs. 4.8 ± 1.3 l/min and 5.1 ± 1.4 l/min) were increased in HFNEF compared with healthy and HTN subjects, respectively.
- Conclusions** As a group, HFNEF subjects have increased LV diastolic diameter and increased calculated stroke volume. They also have increased prevalence of multiple comorbidities, including anemia, renal dysfunction, and obesity, that can cause volume overload. These data suggest that extracardiac factors, via volume overload, may contribute to the pathophysiology of HFNEF in the elderly. (J Am Coll Cardiol 2007;49:972-81) © 2007 by the American College of Cardiology Foundation



Multiple population-based studies have shown that among the elderly the majority with heart failure have a normal ejection fraction (HFNEF) and a history of hypertension (1-3). However, the pathophysiology of this disorder is poorly understood. It is usually attributed

primarily to left ventricular (LV) diastolic dysfunction, and has often been termed diastolic heart failure (4-7). In diastolic heart failure, LV diastolic chamber size is usually normal or reduced despite greater than normal filling

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pressures (6,8-10). However, LV diastolic chamber size has been reported in relatively modest numbers of patients with hypertensive HFNEF. Further, reports have been contradictory, with some indicating that LV volumes and cardiac output (CO) are indeed normal or reduced (1,7,11,12) and others indicating that LV volumes are increased (13-15), suggestive of a volume overload state.

The CHS (Cardiovascular Health Study) is a National Heart, Lung, and Blood Institute-sponsored multicenter population-based longitudinal cohort study of cardiovascular disease risk in

5,888 people ≥ 65 years of age. In the CHS population a substantial percentage of subjects had hypertension with or without heart failure and a normal ejection fraction (EF). Multiple physiologic measurements were performed, including echocardiography, by a standardized protocol (16). Thus, using CHS data, it was possible to examine LV size and function, renal function, and other relevant covariates as well as comorbidities that might affect ventricular volume in a population-based cohort of elderly subjects, including not only a group of subjects with HFNEF but also an "active" control group with chronic hypertension (HTN) but no heart failure and a healthy control group, to gain insight into the pathophysiology of HFNEF.

Methods

Study design and subjects. The overall design, objectives, and recruitment strategy of the CHS have been reported in detail (17). The CHS was designed to assess cardiovascular disease, cardiovascular disease outcomes, and risk factors among the elderly. Noninstitutionalized, independently living, community-dwelling participants 65 years of age or older were recruited from 4 geographically dispersed field centers: Forsyth County, North Carolina; Sacramento County, California; Allegheny County, Pennsylvania; and Washington County, Maryland. Persons were excluded from the CHS if they were receiving active treatment for cancer, were wheelchair bound or institutionalized, or were unable to participate in the examination. Prevalent coronary artery disease, stroke, and heart failure were not exclusion criteria. The original cohort (recruited in 1989 to 1990; $n = 5,201$) and those enrolled when the study was expanded to include more African Americans (in 1992 to 1993; $n = 687$) comprised 5,888 study participants (2,495 men and 3,393 women). The present study consisted of an analysis of echocardiographic data obtained at the baseline visit for the original cohort and at 2 years after the baseline visit for the second cohort.

Study groups. Three groups of participants with normal EF ($\geq 55\%$) were identified from the CHS study participants. Healthy control subjects ($n = 499$) were defined by a normal EF and the absence of prevalent or incident heart failure, significant valvular dysfunction, transient ischemic attack, stroke, myocardial infarction, angina or claudication, history of revascularization, HTN (defined by systolic blood pressure >140 mm Hg or diastolic >90 mm Hg or a reported history of HTN and use of antihypertensive medications), or diabetes (defined according to the American Diabetes Association criteria) and were not using beta-blockers, ACE inhibitors, digitalis, warfarin, or any other prescription medications up to the time of the first echocardiogram. Hypertensive participants without heart failure (HTN; $n = 2,184$) had a normal EF without any prevalent heart failure up to the time of the echocardiographic examination. Hypertensive participants with heart failure and normal EF (HFNEF; $n = 167$) included subjects with hypertension and prevalent heart failure with a normal EF at the time of the echocardiographic examination, in the absence of significant aortic or mitral valvular disease.

Definition of clinical parameters.

Details of the methods used to assess the presence of heart failure among participants in the CHS have been reported previously (18,19). In brief, an expert panel adjudicated the index event of heart failure by reviewing all pertinent data on the hospitalization or outpatient visit, including history, physical examination, report of chest radiography, and medication usage. Self-report of a physician diagnosis of heart failure was confirmed by documentation in the medical record of a constellation of symptoms (shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (edema, pulmonary rales, gallop rhythm, displaced LV apical impulse) or by supporting clinical findings, such as those from chest radiography. Diagnosis of heart failure was confirmed also if, in addition to having a previous physician diagnosis, the participant was receiving medical therapy for heart failure (a current prescription of a diuretic and digitalis or a vasodilator (nitroglycerin, hydralazine, or angiotensin-converting enzyme inhibitor). For the present study, any participant with at least 1 confirmed episode of heart failure before or at the time of their initial echocardiogram was considered to be prevalent for heart failure.

Comorbid conditions. Comorbid conditions were evaluated based on patient status available up to the time of the first echocardiogram and therefore include both prevalence and incidence data. Anemia was defined according to the World Health Organization criteria as hemoglobin <12 mg/dl in women and <13 mg/dl in men (20). Diabetes was defined according to American Diabetes Association criteria. Coronary heart disease was defined by the presence of previous myocardial infarction, angina pectoris, bypass surgery, or percutaneous coronary intervention. Renal function was assessed by serum creatinine measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York), a colorimetric method. Glomerular filtration rates were estimated from serum creatinine by standard formulas (21) and graded, as defined by national guidelines (22), as normal, mild, moderate, or severe failure. Cystatin-C, a novel serum measure of renal function, was measured from samples collected at the 1992 to 1993 visit and stored at -70°C , using a BNII nephelometer (Dade Behring, Deerfield, Illinois) and a particle-enhanced immunonephelometric assay (N Latex Cystatin-C, Dade Behring) (23).

Echocardiographic assessments. Echocardiography methods in the CHS have been published previously (16). In brief, M-mode 2-dimensional color Doppler and spectral Doppler standardized examinations with prespecified sequence, technique and priorities were performed at each field site with a Toshiba (Tustin, California) SSH-160A ultrasound machine fitted with standard 2.5-MHz transducers. Studies were recorded onto super-VHS videotapes

Abbreviations and Acronyms

| | |
|--------------|---|
| CHS | = Cardiovascular Health Study |
| CO | = cardiac output |
| EF | = ejection fraction |
| HFNEF | = heart failure with normal ejection fraction |
| HTN | = hypertension |
| LV | = left ventricle |
| SV | = stroke volume |

and batch-mailed to the echocardiography reading center where best images from each study were selected and digitized. Measurements were obtained on a digital image analysis system (Nova Microsonics, Allendale, New Jersey).

Two dimensional guided M-mode measurements of systolic and diastolic chamber dimensions and wall thickness were obtained according to the recommendations of the American Society of Echocardiography (24), and LV mass was derived from the formula described by Devereux et al. (25,26). Valvular regurgitation and stenosis were assessed as previously described (16). Of the 2,850 subjects in this study, 1,785 (63%) had M-mode echocardiographic data available for analysis of LV size and function and myocardial characteristics. Among the groups, data for LV size were available in 343 control (69%) subjects, 1,356 (62%) HTN subjects, and 86 (51%) HFNEF subjects. The major reason for data unavail-

ability was an inadequate acoustic window such that echocardiographic quantitative measurements were not possible. A smaller number were unavailable owing to inadequate Doppler tracings or to atrial fibrillation or mitral or aortic regurgitation that could alter the Doppler parameters.

Left ventricular end-diastolic and -systolic volumes (EDV and ESV, respectively) were calculated from M-mode echocardiographic dimensions by a previously validated technique (27):

$$EDV = 4.5 (LV \text{ diastolic dimension})^2 \quad [1]$$

$$ESV = 3.72 (LV \text{ systolic dimension})^2 \quad [2]$$

Because this technique has been shown to be reliable only in symmetrically contracting ventricles with normal ejection fraction, subjects with a regional wall motion abnormality were

Table 1 Demographic and Clinical Characteristics

| Parameters | Controls | HTN Without HF | HTN With HFNEF |
|---------------------------------|-------------|----------------|----------------|
| n | 499 | 2,184 | 167 |
| Age (yrs) | 71 ± 5 | 73 ± 6* | 76 ± 7*† |
| Gender (% female) | 57% | 63% | 57% |
| Race (%) | | | |
| European American | 93 | 77.8* | 64.5* |
| African American | 6.6 | 21.6 | 33.1 |
| American Indian/Alaskan Native | 0.2 | 0.1 | 1.2 |
| Asian/Pacific Islander | — | 0.1 | — |
| Other | 0.2 | 0.3 | 1.2 |
| Height (cm) | 166 ± 9 | 164 ± 9* | 164 ± 9 |
| Weight (kg) | 70 ± 13 | 74 ± 15* | 73 ± 17* |
| BSA (m ²) | 1.75 ± 0.19 | 1.78 ± 0.20* | 1.77 ± 0.20 |
| BMI (kg/m ²) | 25 ± 4 | 27 ± 5* | 27 ± 6* |
| Hemodynamics | | | |
| Heart rate (beats/min) | 63 ± 11 | 65 ± 11* | 68 ± 14*† |
| Systolic blood pressure (mm Hg) | 123 ± 10 | 148 ± 22* | 147 ± 25* |
| Diastolic (mm Hg) | 68 ± 8 | 73 ± 12* | 71 ± 13* |
| Renal function | | | |
| Serum creatinine (mg/dl) | 1.0 ± 0.2 | 1.1 ± 0.5* | 1.2 ± 0.5*† |
| Serum cystatin-C (mg/l) | 1.0 ± 0.2 | 1.1 ± 0.4* | 1.3 ± 0.4*† |
| Estimated GFR (ml/min) | 63 ± 16 | 61 ± 20 | 56 ± 22*† |
| Comorbidities (%) | | | |
| Diabetes mellitus | 0 | 20* | 30*† |
| Coronary heart disease | 0 | 20* | 58*† |
| Angina | 0 | 18* | 51*† |
| Myocardial infarction | 0 | 8* | 31*† |
| PTCA | 0 | 2* | 5*† |
| CABG | 0 | 3* | 12*† |
| Obesity‡ | 11 | 25* | 29* |
| Anemia§ | 7 | 8 | 19*† |
| Chronic renal disease | | | |
| Failure (<15 ml/min) | 0 | 0.1* | 4*† |
| Severe (15-30 ml/min) | 1 | 3 | 4 |
| Moderate (30-60 ml/min) | 48 | 47 | 53 |
| Mild (60-90 ml/min) | 46 | 41 | 32 |
| None (>90 ml/min) | 5 | 8 | 6 |

*p < 0.05 versus healthy control subjects; †p < 0.05 versus HTN by either ANOVA with Bonferroni post hoc correction for multiple comparisons of continuous variables or chi-squared analysis for dichotomous variables; ‡defined by body mass index (BMI) > 3 kg/m²; §defined by hemoglobin < 12 mg/dl in women and < 13 mg/dl in men.

ANOVA = analysis of variance; BSA = body surface area; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; HFNEF = heart failure with normal ejection fraction; HTN = hypertension; PTCA = percutaneous transluminal coronary angioplasty.

excluded from these calculations. From these volumes, stroke volume (SV) was estimated as: EDV – ESV. Cardiac output was calculated as: SV × heart rate.

Transmitral Doppler LV filling recordings were performed from the apical 4-chamber view and analyzed for diastolic filling indexes, including peak E- and A-wave velocities and their ratio.

Statistical analysis. Data are expressed as mean ± standard deviation. Chi-square test or analysis of variance was used for unadjusted analyses of the associations among groups and baseline variables. Differences in dichotomous variables were also corrected for multiple comparisons. Ventricular size was indexed to age, gender, body surface area, and race in the following manner. Measured LV internal diameter in diastole (LVIDd) was divided by LVID_{Predicted} (determined from the parameter estimates of multivariate linear regression analyses) and multiplied by 100. These data were analyzed with the Kolmogorov-Smirnov goodness-of-fit tests for normal distribution, which confirmed a normal distribution of the data. Differences in continuous variables between the HFNEF and control participants were compared using analysis of variance with a Bonferroni correction for multiple comparisons. Because ventricular diameter is known to vary with age, gender, and body size (28,29), these were also compared between groups with analysis of covariance with Bonferroni contrasts using age, gender, body size, and race as covariates. A p value of < 0.05 was considered to be significant. The SAS 9.0 program (SAS Institute, Cary, North Carolina) was used for all analyses.

Results

Clinical characteristics (Table 1). Subjects with HFNEF were older than either healthy normal control subjects or subjects with HTN alone. Compared with normal controls, subjects with HTN alone and subjects with HFNEF were more often African American and had higher body weights and body mass indexes. African Americans accounted for 16% of the overall CHS study population (924 of 5,888 subjects) but were over-represented in the groups with HTN (22%, 472 of 2,184) and HFNEF (33%, 55 of 167). The prevalence of several comorbid conditions, including diabetes, coronary heart disease, anemia, and chronic renal disease, was increased in subjects with HTN compared with healthy control subjects, and these were even more prevalent in subjects with HFNEF.

Heart rate was increased in subjects with hypertension compared with control subjects and greatest in subjects with HFNEF. By definition, blood pressure was increased in subjects with HTN and HFNEF compared with controls but did not differ between HTN and HFNEF subjects.

LV size and function. Of the 2,850 subjects in this study, 1,785 (63%) had M-mode echocardiographic data available for analysis of LV size and function and myocardial characteristics (Table 2). Among the groups, data for LV size was available in 343 (69%) control, 1,356 (62%) HTN, and 86 (51%) HFNEF subjects.

Table 2 Echocardiography

| Parameters | Control | HTN Without HF | HFNEF With HTN |
|--|-------------|----------------|----------------|
| LV size | | | |
| LVIDd (cm) | 4.8 ± 0.6 | 4.9 ± 0.6 | 5.1 ± 0.8*† |
| LVIDd/BSA (cm/m ²) | 2.8 ± 0.4 | 2.8 ± 0.4 | 2.9 ± 0.5† |
| LVIDs (cm) | 2.8 ± 0.5 | 2.7 ± 0.6 | 3.0 ± 0.7† |
| LVIDs/BSA (cm/m ²) | 1.6 ± 0.3 | 1.6 ± 0.3 | 1.7 ± 0.4† |
| EDV (ml) | 109 ± 27 | 110 ± 28 | 124 ± 38*† |
| EDV/BSA (ml/m ²) | 63 ± 14 | 62 ± 14 | 69 ± 22*† |
| ESV (ml) | 30 ± 12 | 29 ± 12 | 35 ± 16† |
| ESV/BSA (ml/m ²) | 18 ± 6 | 17 ± 6 | 20 ± 10*† |
| Myocardial characteristics | | | |
| PWT (cm) | 0.8 ± 0.1 | 0.9 ± 0.2* | 0.9 ± 0.2* |
| LV mass (g) | 134 ± 37 | 153 ± 48* | 176 ± 64*† |
| LV mass/BSA (g/m ²) | 78 ± 20 | 87 ± 24* | 98 ± 34*† |
| RWT (cm) | 0.34 ± 0.07 | 0.37 ± 0.09* | 0.36 ± 0.11 |
| EDV/LV mass (ml/g) | 0.83 ± 0.16 | 0.74 ± 0.17* | 0.75 ± 0.22* |
| CESS (g/cm ²) | 57 ± 21 | 60 ± 24 | 63 ± 26 |
| LV function | | | |
| Fractional shortening (%) | 42 ± 7 | 44 ± 8* | 42 ± 7 |
| Ejection fraction (%) | 72 ± 7 | 74 ± 7* | 72 ± 7 |
| Stroke volume (ml) | 78 ± 20 | 80 ± 20 | 89 ± 25*† |
| SV/BSA (m ³ /m ²) | 45 ± 11 | 46 ± 11 | 50 ± 14*† |
| Cardiac output (l/min) | 4.8 ± 1.3 | 5.1 ± 1.4* | 6.0 ± 2.0*† |
| Cardiac index (l/min/m ²) | 2.8 ± 0.8 | 2.9 ± 0.8 | 3.4 ± 1.2*† |
| Mitral Doppler flow | | | |
| E velocity (cm/s) | 70 ± 15 | 72 ± 19 | 79 ± 27*† |
| A velocity (cm/s) | 71 ± 18 | 84 ± 23* | 81 ± 31* |
| E/A ratio | 1.0 ± 0.3 | 0.9 ± 0.5* | 1.3 ± 1.2*† |

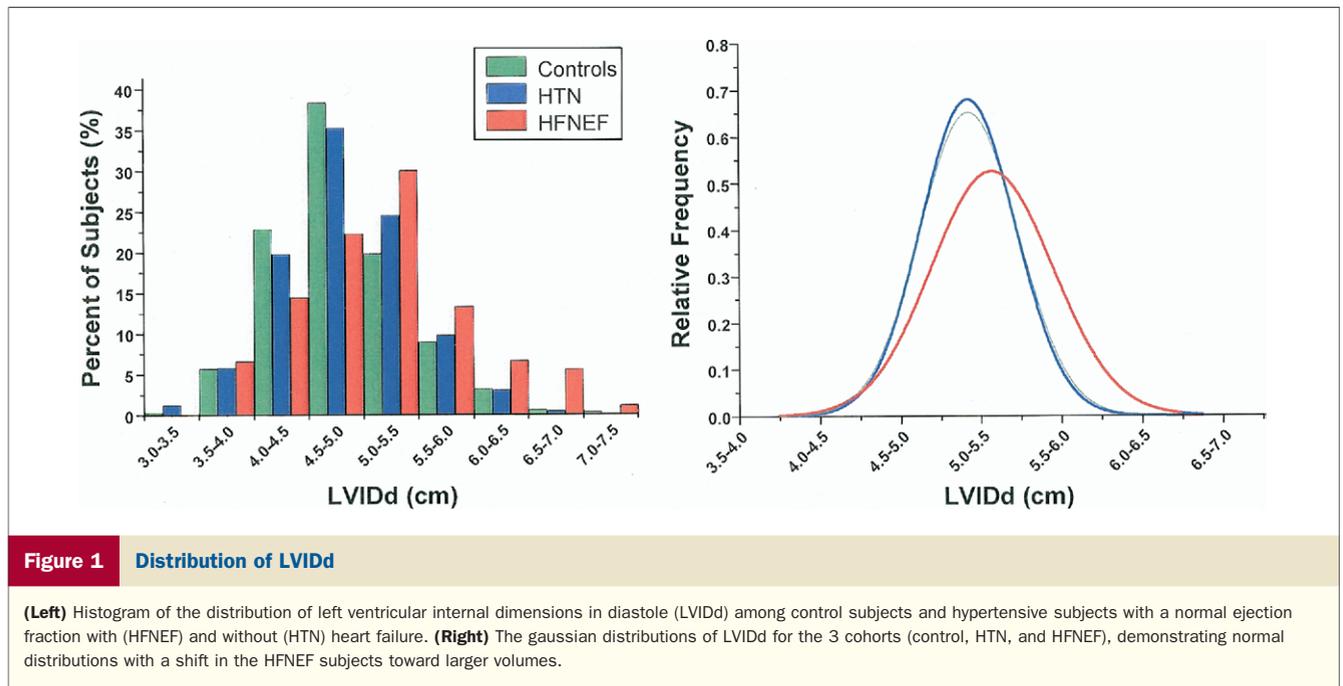
Data for LV size was available in 343 control, 1,356 HTN without HF, and 86 HFNEF subjects; *p < 0.05 versus healthy controls; †p < 0.05 versus HTN by ANOVA with Bonferroni post hoc correction for multiple comparisons.

CESS = circumferential end-systolic stress; EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; PWT = posterior wall thickness; RWT = relative wall thickness; other abbreviations as in Table 1.

Average LV systolic and diastolic dimensions did not differ between control subjects and those with HTN alone, but they were significantly larger in subjects with HFNEF. Accordingly, average calculated end-diastolic and end-systolic volumes were increased in HFNEF compared with the other groups (14% vs. 17%, respectively). Subjects with HFNEF demonstrated increased E-wave velocity compared with HTN and control subjects, and E/A ratios also were significantly higher.

Both HTN and HFNEF subjects had LV hypertrophy with increased posterior wall thickness and LV mass. In comparison with healthy normal control subjects, both HTN and HFNEF groups had evidence of concentric remodeling (increased relative wall thickness and lower EDV:mass ratio), but neither relative wall thickness nor the EDV:mass ratio differed between the HTN and HFNEF groups.

Functionally, fractional shortening and EF were slightly higher in the HTN group. Compared with healthy normal control subjects and HTN subjects, calculated SV, CO, and cardiac index were all increased in HFNEF. Notably, estimated CO at rest was on average more than 1 l/min greater in HFNEF subjects than in healthy control subjects and subjects with HTN alone.



The distribution of LV end-diastolic chamber diameter (Fig. 1), indexed to body surface area by gender (Fig. 2) and indexed to body surface area, gender, and race as a percentage of predicted indexed diameter (i.e., the LVID percentage) (Fig. 3) for the 3 study groups are shown. In this elderly cohort, age did not affect LV diastolic diameter. Chamber size indexed to known confounders was normally distributed in all groups, and all groups had subjects with LV internal dimensions that were below and above the predicted values. However, compared with healthy control and HTN subjects, the distribution for the HFNEF subjects was right shifted toward larger values and spanned a greater range. Similar rightward shifts were seen for the distributions of end-systolic volume, SV, and CO. The cumulative distribution of LV diastolic diameter indexed for age, gender, body size, and race (e.g., $LVID_{\text{Predicted}}$) (Fig. 3C) also shows a rightward shift in the curve, indicating that many of the HFNEF patients' LV size is increased compared with healthy control and HTN subjects.

Several baseline demographic factors known to affect LV size differed among the study groups (Table 1). Therefore, multivariate linear regression analysis was performed to determine the relative contribution of age, gender, body size, and race to the differences in ventricular dimensions. The analyses showed that LV end-diastolic dimension did not differ between HTN and control subjects but was, on average, increased 3.5 mm ($p < 0.0001$) in HFNEF subjects compared with healthy controls. In particular, the multiple linear regression analysis (Table 3) showed significant differences between men and women and between European and African Americans. In all subgroups, HFNEF subjects were older with a higher prevalence of diabetes, coronary heart disease, and chronic renal dysfunction than either control or HTN subjects, similar to the entire group of HFNEF subjects (Table 1).

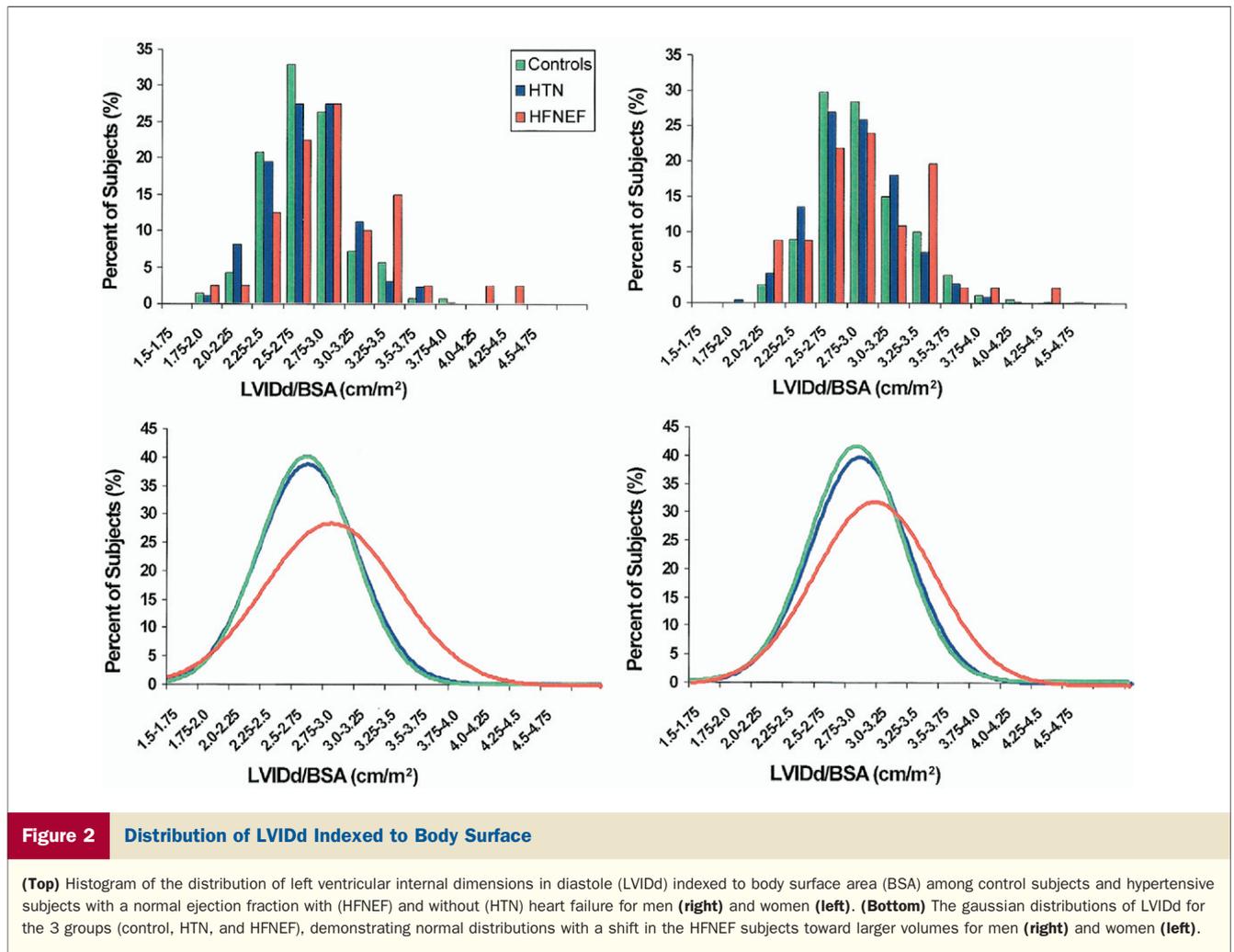
Cardiac volumes were generally smaller in women than in men and, for both genders, average volumes were smaller in African than in European Americans. Among various groups, including men and women and European and African Americans we found that subjects with HFNEF had consistently larger end-diastolic dimensions than healthy control and HTN subjects. The same was true for ESV index, SV index, and cardiac index (Fig. 4).

Although African Americans had smaller LV volumes than European Americans (Table 3), formal statistical testing using multivariate regression analysis did not demonstrate a significant interaction of race with the difference in heart size by group (control, HTN, or HFNEF) or gender. This suggests that in the current dataset, differences observed in ventricular size between groups are not significantly influenced by race.

In view of the increased prevalence of coronary artery disease and specifically history of myocardial infarction in the HFNEF group, we performed an analysis to determine if there was a correlation between myocardial infarction (MI) and increased heart size. Incorporation of a history of MI into the multivariate linear regression analysis of heart size yielded a statistically nonsignificant parameter estimate of 0.04 ($p = 0.43$). The lack of significance suggests that prior MI is not a major contributing factor to the increased heart size, but the study may be underpowered to detect such differences.

Discussion

These data from the CHS indicate that compared with healthy control subjects or subjects with HTN alone, HFNEF subjects are older with a higher prevalence of comorbid conditions, especially chronic renal disease, anemia, and obesity, and are more often African American. The HFNEF subjects have, on average, increased LV dimensions and calculated volumes



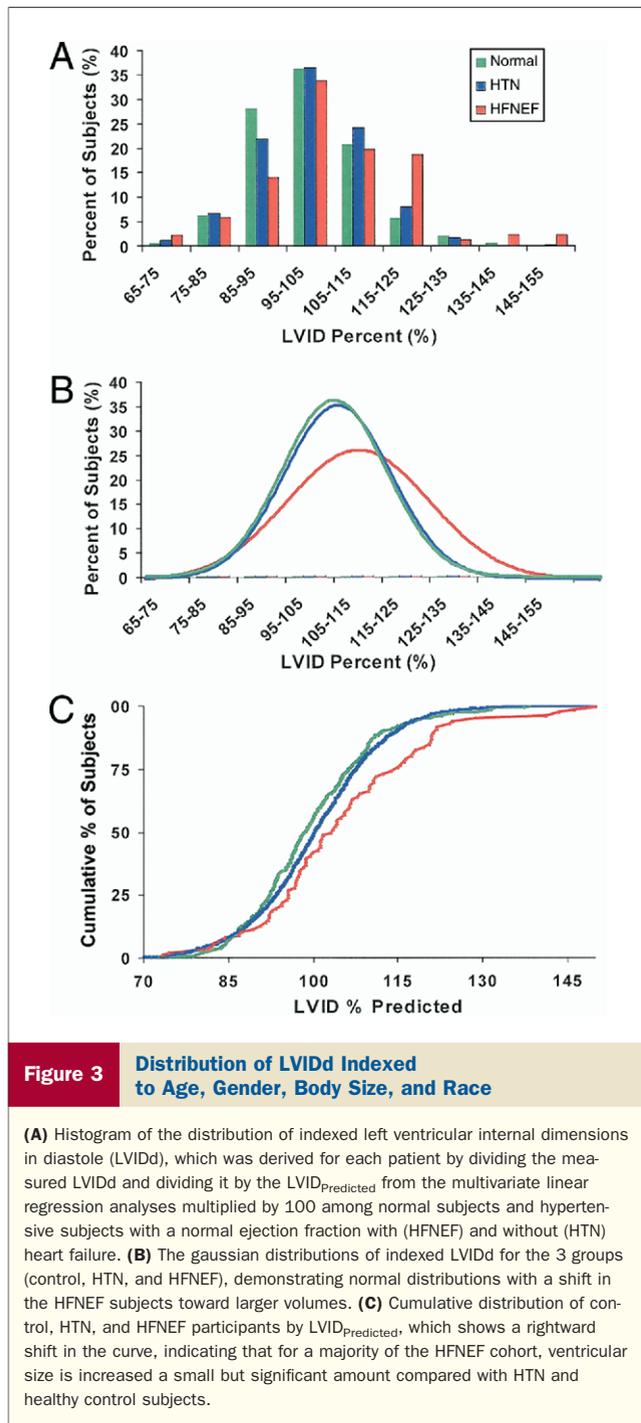
compared with both normal control subjects and subjects with HTN but no heart failure before and after adjustment for gender, body size, and race. These data have important implications for the understanding of the pathophysiology of HFNEF in the setting of HTN, as discussed subsequently.

Ventricular size in HFNEF. There have been 3 earlier reports from the CHS database of studies dealing with the topic of patients with HFNEF (1,30,31). There are slight variations in the characteristics of this population reported among the various studies. This is because of variations in criteria for patient selection. Despite differences in selection criteria and, therefore, differences in the group sample sizes as well as variation in selection of cases based on incident or prevalent heart failure, 1 study in which chamber size was reported demonstrated similar average increases in ventricular size in the cohort with HFNEF compared with control subjects (31).

The distributions of echocardiographic measurements of ventricular diameter, even when indexed for known covariates, are wide. Subjects from each of the 3 cohorts studied had ventricular dimensions that were both greater than and lower than the age, gender, body size, and race predicted means (Fig. 1). These wide distributions are due to normal

biologic variation and to technical variation of the measurement. As a result, when an individual subject's LV diameter is within the population normal range, one is precluded from determining whether it is increased, average, or decreased by a small amount for that particular individual. However, statistical analysis of a suitably large population can distinguish groups. The data from CHS demonstrate that ventricular size for individuals with HFNEF can be increased 10% to 15%, resulting in a shift in the distribution of ventricular dimension in the HFNEF cohort. This shift does not preclude a significant proportion of the values for LV diastolic diameter in the HFNEF population remaining within the normal or reduced range, even when adjusted for age, gender, body size, and race.

Increased ventricular diameter in the HFNEF group of subjects may also be explained by the presence of a few subjects with large ventricles not representative of the remainder of the HFNEF group. To evaluate this possibility each of the 3 groups was tested and found to have normal distribution of data rather than a bimodal distribution. Thus, the overall results are not merely due to a small subgroup of atypical patients with dilated ventricles within the HFNEF group. Additionally, the cumulative distribu-



tion of ventricular dimensions indexed to age, gender, body size, and race confirmed a rightward shift in the distribution, suggesting that many of the HFNEF patients had increased LV size compared with healthy control and HTN subjects (Fig. 3C).

Increased ventricular size in the HFNEF group may be caused by valvular regurgitation or subtle systolic dysfunction related to coronary artery disease. However, valvular regurgitation cannot account for ventricular enlargement in our HFNEF subjects, because subjects with significant valve regurgitation were excluded. Although subtle systolic dys-

function was not evident based on the presence of a normal EF in all groups, previous data in an animal model have demonstrated that a small amount of ischemic myocardial injury can lead to neurohormonal activation with intravascular volume expansion and elevation of LV end-diastolic pressure in the absence of reductions in maximal dP/dt or EF (32). However, although the HFNEF cohort had a higher prevalence of coronary artery disease (specifically myocardial infarction), statistical analysis demonstrated that this did not account for the observed difference in ventricular diameter in this dataset.

Indexing heart size. Normalizing indices of ventricular structure and function for covariates including age, gender, and body size permits appropriate comparisons (28,29,33) and has been recommended (24) but infrequently used. The present analysis accounted for age, gender, body size, and race in the evaluation of heart size and function and demonstrated that statistically significant increases in ventricular size without indexing were magnified with indexing. This is important when studying HFNEF, because of the disproportionate representation of African Americans and small elderly women compared with the control groups.

In the present dataset, there was no significant association of age with LV dimensions, possibly in part owing to the narrow age range of the population, which is a fundamental design characteristic of the CHS. Although earlier literature has emphasized that heart size varies with race (34-36), the magnitude of this effect in relation to other demographic features has not, to our knowledge, been evaluated or emphasized. The results of multivariate analysis in the CHS normal control subjects suggest that race exerts as potent an influence (if not a greater influence) on heart size as gender. However, to our knowledge, none of the previous echocardiographic studies that have characterized ventricular size and geometry in subjects with HFNEF controlled for race in the analyses of heart structure and function. This is particularly noteworthy, because many of these studies had a disproportionate representation of African Americans (7,10,12) compared with the respective control population. Although the results of multivariate regression analysis did not demonstrate a significant interaction of the primary results by race, because of the small number of African American subjects with HFNEF with evaluable echocardiographic data in the present dataset there is relatively low statistical power to detect such differences. Further study with larger datasets will be needed to adequately address the impact of race on the increased LV size observed in the HFNEF cohort.

Increased intravascular volume in HFNEF. The presence of increased end-diastolic dimension and, therefore, EDV, SV, and CO in the HFNEF subjects suggests that intravascular volume overload plays a role in the pathophysiology of HFNEF in some, if not many, patients. The CHS population with HTN and HFNEF exhibited a high prevalence of comorbid conditions which may contribute to fluid retention and subsequently a high output state. Excluding intracardiac shunts, all other high cardiac output

| Table 3 Multivariate Analysis of Determinants of Left Ventricular Internal Dimension in Diastole | | | |
|--|---------------------|-------------------------|---------|
| Covariates | Parameter Estimates | 95% CI of the Estimates | p Value |
| Age (per yr) | -0.00111 | 0.00714 to 0.00491 | 0.7176 |
| Gender (female vs. male) | -0.10875 | -0.18710 to -0.03040 | 0.0066 |
| Body surface area (per m ²) | 1.18638 | 0.98627 to 1.38649 | <0.0001 |
| Race (African vs. European American) | -0.29751 | -0.38076 to -0.21426 | <0.0001 |
| Group | | | |
| HFNEF vs. control | 0.35997 | 0.18609 to 0.53385 | <0.0001 |
| HFNEF vs. HTN | 0.21861 | 0.07949 to 0.35772 | 0.0021 |
| HTN vs. control | 0.10048 | 0.02035 to 0.18061 | 0.0140 |

Results of multivariate linear regression analysis delineating the effect of age, gender, body size, race, and group (control, HTN, HFNEF) on left ventricular dimension in diastole on the Cardiovascular Health Study.
 CI = confidence interval; other abbreviations as in Table 1.

states involve extracardiac mechanisms (37). Specifically, renal dysfunction (38), anemia (39), and obesity (40) were all more common individually and occurred more frequently in combination in the HFNEF subjects than in control or HTN subjects and are each known to lead to fluid retention. Indeed, 1 study found in hypertensive predominantly elderly women with HFNEF that total plasma volume was increased from normal despite the use of high-dose diuretics (14). Thus, the CHS data lead to the hypothesis that

extracardiac factors resulting in increased intravascular volume may contribute importantly to the pathophysiology of HFNEF. Other mechanisms resulting in peripheral vasoconstriction and central shift of blood volume could also play a role (41,42). However, the present study did not address these mechanisms.

Significance of LV hypertrophy. The presence of hypertrophy is usually observed in patients with HFNEF (2,3,43). Left ventricular wall thickness, mass, and relative wall

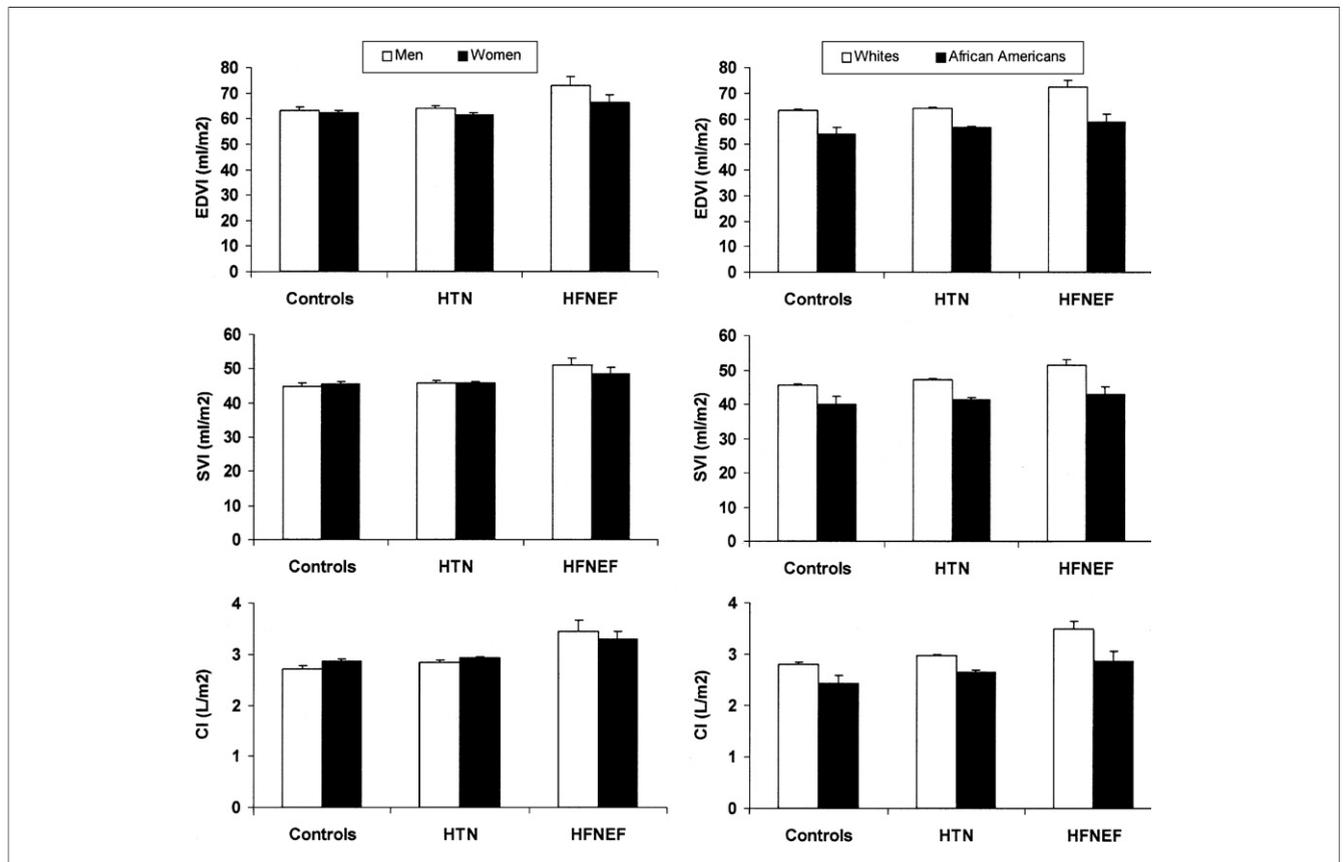


Figure 4 EDVI, SVI, and CI by Gender and Race in the Cohorts Studied

Calculated end-diastolic volume index (EDVI), stroke volume index (SVI), and cardiac index (CI) in healthy control subjects and hypertensive subjects with a normal ejection fraction with (HFNEF) and without (HTN) heart failure by gender and race (European [Whites] and African Americans). In all groups, average calculated left ventricular volumes and cardiac output were larger in HFNEF subjects than in control and HTN subjects.

thickness were increased and EDV/mass ratios were decreased in HFNEF, indicative of concentric hypertrophic LV remodeling. However, similar changes were found in the HTN group, and, as a result, indices of ventricular hypertrophic remodeling including relative wall thickness and volume/mass ratio did not differ between HFNEF and HTN subjects. Furthermore, the correlations between LV volume and mass were very similar between HTN subjects ($r = 0.59$; $p < 0.0001$) and HFNEF subjects ($r = 0.56$; $p < 0.0001$). Thus, the relationship between the degree of hypertrophy and the degree of chamber dilation did not differ based on the presence of heart failure. This finding suggests that LV hypertrophic remodeling may not necessarily be a primary pathophysiologic mechanism in patients with HFNEF. In many patients, increased mass may simply reflect ventricular dilation with a concomitant increase in myocardial volume, to maintain a normal wall stress, which was similar in all groups (Table 2).

Normal values of fractional shortening are considered to be in the range of 27% to 50% (24). The mean fractional shortening was on the higher side of normal in all cohorts of the present study. This is consistent with earlier reports of the CHS (1,31) suggesting that patients with HFNEF do not have a significant impairment in systolic properties (44). The relatively high values for the fractional shortening also are concordant with other data suggesting that endocardial shortening is increased in the elderly and subjects with LV hypertrophy (45,46).

Study limitations. The present study consisted of an analysis of echocardiographic data obtained at the baseline visit for the original cohort and 2 years after the baseline visit for the second cohort, which were read by 2 different core labs. However, echocardiographic examinations were performed on the same ultrasound machines, and the cardiac structures and functions that were measured were the same on both examinations. Comparison of the processing of a subset of baseline tapes at the University of California, Irvine, Reading Center and the Georgetown University Reading Center revealed no systematic differences in processing or interpretation of the echocardiograms. Additionally, none of the present conclusions were altered when the echocardiographic data were examined separately by reading center.

The patient population studied is subject to both participation and survivor bias and may not be representative of the characteristics of patients initially presenting with HFNEF. Indeed, the duration of heart failure before the performance of the initial echocardiogram may be an important factor influencing LV size. Unfortunately, such data are not available in the CHS database and therefore could not be controlled for in the present analyses. Additionally, although a majority (63%) of participants in CHS had echocardiographic measures of LV size, missing data could confound our results. Among the groups, data for LV size were available in 343 (69%) control, 1,356 (62%) HTN, and 86 (51%) HFNEF subjects. Participants with echocardiographic dimension measures were younger with smaller body size and less obesity and had less comorbid conditions.

This is typical of population-based studies. However, across the groups studied, there were no systematic differences between those who had LV size measured versus those who did not.

The present study did not directly measure LV volumes but rather used a previously validated technique to estimate ventricular volumes from echocardiographic diameter (27). This technique has been shown to be reliable in symmetrically contracting ventricles with normal EF, as was the case in the subjects studied. Although the EF derived from these data are higher than some other techniques, the volumetric data are similar to those derived from a population of elderly subjects with HFNEF studied with 3-dimensional echocardiography (14), and the ventricular volumes and CO obtained in the normal control subjects are nearly identical to other values reported in the literature using cardiac magnetic resonance imaging (28).

Another limitation of this and most studies of HFNEF is that all measurements were made at rest. Patients with HFNEF typically have chronic exercise intolerance and are prone to bouts of acute pulmonary edema-limited cardiopulmonary and vascular reserve. Therefore, it is possible that characterization of ventricular properties identified at rest, as in the present study, may not apply to conditions when exercise or other hemodynamic stress is present.

Conclusions

Participants in the population-based CHS with HTN and HFNEF had, on average, increased ventricular dimensions and therefore increased calculated volumes and CO compared with healthy control subjects and participants with HTN without heart failure. Furthermore, they had no greater concentric hypertrophic remodeling than hypertensive participants without heart failure, and they had considerably more frequent comorbidities, particularly ones that may cause volume overload, such as renal dysfunction and anemia. These data suggest that groups exist within the hypertensive HFNEF population and that volume overload states may contribute to the pathophysiology of this important syndrome.

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