LEFT VENTRICULAR DILATATION AND THE RISK OF CONGESTIVE HEART FAILURE IN PEOPLE WITHOUT MYOCARDIAL INFARCTION

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ABSTRACT

Background Left ventricular dilatation is a well-recognized precursor of ventricular dysfunction and congestive heart failure after myocardial infarction. The effect of left ventricular dilatation on the risk of heart failure in people initially free of myocardial infarction is not known.

Methods We examined the relation of the left ventricular end-diastolic and end-systolic internal dimensions, as measured by M-mode echocardiography, to the risk of congestive heart failure in 4744 subjects (2661 women and 2083 men) who had not sustained a myocardial infarction and who were free of congestive heart failure. We used sex-stratified proportional-hazards regression to assess the association between base-line left ventricular internal dimensions and the subsequent risk of congestive heart failure, after adjusting for age, blood pressure, hypertension treatment, body-mass index, diabetes, valve disease, and interim myocardial infarction.

Results Over an 11-year follow-up period, congestive heart failure developed in 74 subjects (38 men and 36 women). The risk-factor–adjusted hazard ratio for congestive heart failure was 1.47 (95 percent confidence interval, 1.25 to 1.73) for an increment of 1 SD in the left ventricular end-diastolic dimension, indexed for height. We obtained similar results using the left ventricular end-systolic dimension (hazard ratio, 1.43; 95 percent confidence interval, 1.24 to 1.65).

Conclusions An increase in left ventricular internal dimension is a risk factor for congestive heart failure in men and women who have not had a myocardial infarction. Knowledge of the left ventricular dimension improves predictions of the risk of congestive heart failure made on the basis of traditional risk factors, perhaps by aiding in the identification of subjects with subclinical left ventricular dysfunction. (N Engl J Med 1997;336:1350-5.)

CARDIAC enlargement is associated with increased morbidity and mortality among healthy middle-aged and elderly people.[1-3] Increased cardiac size is also an important determinant of clinical outcome in patients with coronary heart disease[4-8] and in subjects with mild[9] or severe[10-12] heart failure. Several recent investigations have emphasized that cardiac dilatation is a precursor both of left ventricular dysfunction and of clinical heart failure in asymptomatic people who have had myocardial infarction.[13,14] The influence of increased cardiac dimensions on the risk of heart failure in people free of myocardial infarction or heart failure at base line has not been carefully investigated. We undertook the present investigation to examine prospectively the relation of echocardiographic left ventricular dimensions to the risk of congestive heart failure in a community-based sample of subjects free of myocardial infarction and congestive heart failure at base line.

METHODS

Study Sample

The selection criteria and study design of the Framingham Heart Study and the Framingham Offspring Study have been described previously.[15,16] Subjects in the Framingham Heart Study who participated in the 16th biennial examination (1979 to 1981) and subjects in the Framingham Offspring Study who participated in the 2nd study examination (1979 to 1983) constituted the study sample used in this investigation. At these base-line examinations, a detailed assessment of cardiovascular risk factors, anthropometric measurements, blood-pressure measurements at rest, 12-lead electrocardiography at rest, and echocardiography were routinely performed.

Of the 6216 subjects who attended the base-line examinations, 1259 were excluded from the study because of inadequate echocardiograms and 3 were lost to follow-up. Of the remaining 4954 subjects who were eligible for the present investigation, 210 were excluded for one of the following reasons: a diagnosis of preexisting heart failure (44 subjects), evidence of previous myocardial infarction (149), and incomplete information on the covariates used for the analyses (17). After the above exclusions, 4744 subjects (2661 women and 2083 men) remained eligible for the present investigation.

Echocardiographic Methods

All eligible subjects underwent M-mode echocardiography by methods previously described.[17] Left ventricular internal dimensions at end diastole and end systole were measured according to American Society of Echocardiography guidelines.[18] Three measurements were averaged for each value. Since height and sex are important determinants of left ventricular internal dimensions, sex-specific, height-indexed left ventricular internal dimensions were used for the primary sex-stratified analyses.[19] Left ventricular mass was calculated from measurements of left ventricular internal dimensions and left-ventricular-wall thickness made in accord-

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ance with the Penn convention in conjunction with the formula of Devereux and Reichek.[20] Left-ventricular-wall thickness was calculated as the sum of the end-diastolic thicknesses of the interventricular septum and left ventricular posterior wall.

Follow-up

All study subjects were periodically monitored for the development of congestive heart failure and other cardiovascular events. Information about such events was obtained with the aid of medical histories, physical examinations, and hospitalization records and by communication with personal physicians. All suspected new events were reviewed by a panel of three experienced investigators, who evaluated all pertinent medical and hospital records and pathology reports. A diagnosis of congestive heart failure was made if at least two major criteria, or one major and two minor criteria, were met.[21] Criteria for other cardiovascular events have been described elsewhere.[22]

Statistical Analysis

We used multivariable, sex-stratified Cox proportional-hazards regression models[23] to evaluate the association between height-indexed end-diastolic and end-systolic left ventricular internal dimensions and the risk of congestive heart failure among subjects during follow-up. Risk factors for heart failure that were considered in the multivariable analyses were defined at the base-line examination and included the following: age, hypertension status, systolic and diastolic blood pressure, body-mass index (as a measure of obesity), and the presence of diabetes mellitus and valve disease. Since myocardial infarction is a well-recognized cause of congestive heart failure, myocardial infarction during follow-up (interim myocardial infarction) was modeled as a time-dependent covariate. Hypertension was defined in accordance with the criteria of the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[24] Valve disease was defined as the presence of a systolic murmur (grade 3/6 or higher) or any diastolic murmur on precordial auscultation at the base-line examination. Criteria for the other risk factors have been published previously.[22] Separate analyses were performed for height-indexed left ventricular end-diastolic and end-systolic dimensions. Hazard ratios for congestive heart failure and their 95 percent confidence intervals were calculated for an increment of 1 SD in height-indexed left ventricular dimensions.

Several echocardiographic variables have previously been shown to predict the risk of congestive heart failure.[6-8,25-27] Therefore, we also used proportional-hazards stepwise forward analyses to assess which echocardiographic variables contributed most to the prediction of congestive heart failure. The echocardiographic variables evaluated in these analyses included height-indexed left ventricular end-diastolic and end-systolic dimensions, fractional shortening, and height-indexed left ventricular mass and left-ventricular-wall thickness. In these multivariable regression models (adjusted for age, sex, and clinical covariates), echocardiographic variables were assessed both one at a time and simultaneously. The criterion for entry into the model was a significance level of 0.05.

To explore the potential effect of wall thickness, sex, fractional shortening, and heart rate on the risk of congestive heart failure associated with left ventricular internal dimensions, secondary analyses including interaction terms (e.g., wall thickness with left ventricular internal dimensions) were performed. All the analyses were performed with the SAS System (SAS Institute, Cary, N.C.) procedures REG,[28] LOGISTIC, and PHREG[29] on a SUN Sparc 2 workstation. All P values reported are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the Study Sample

The clinical and echocardiographic features of the study sample are shown in Table 1. About one third of the subjects in this sample had hypertension. At base line, approximately 5.5 percent of the subjects had preexisting cardiovascular disease (other than myocardial infarction), 3.4 percent had diabetes mellitus, and 2.6 percent had clinical evidence of valve disease. Left ventricular end-diastolic and end-systolic dimensions were highly correlated ($r = 0.86$ in both men and women).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY SAMPLE.*

CHARACTERISTIC	SUBJECTS	
	MEN (N = 2083)	WOMEN (N = 2661)
Clinical		
Age (yr)	49±0.3	51±0.3
Body-mass index†	27±0.1	25±0.1
Blood pressure (mm Hg)		
Systolic	129±0.3	124±0.3
Diastolic	80±0.2	76±0.2
Alcohol intake (oz/wk)‡	5.2±0.1	2.2±0.1
Hypertension (% of subjects)	35.6	28.7
Angina (% of subjects)	3.1	3.2
Diabetes mellitus (% of subjects)	4.6	2.6
Valve disease (% of subjects)	3.1	2.3
Smoking (% of subjects)	35.0	33.1
Echocardiographic§		
Reduced fractional shortening (% of subjects)¶	5.2	1.9
LV internal dimension (mm)		
End-diastolic	50.9±0.09	45.8±0.08
End-systolic	32.6±0.08	28.3±0.07
Septal plus LV posterior-wall thickness (mm)	19.8±0.06	17.2±0.05
LV mass (g/m)	61.6±0.37	54.5±0.33

*Plus–minus values are means ±SE. All values are adjusted for age.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡To convert values to milliliters per week, multiply by 30.

§LV denotes left ventricular.

¶Reduced fractional shortening was defined as a value of ≤0.30.

Relation of Left Ventricular Internal Dimensions to the Risk of Congestive Heart Failure

During up to 11 years of follow-up (mean, 7.7), congestive heart failure developed in 74 of 4744 subjects (36 women and 38 men, 1.6 percent). Nineteen of these 74 subjects (13 men and 6 women, 26 percent) had a myocardial infarction between base line and the onset of congestive heart failure.

The results of multivariable proportional-hazards regression models that incorporated known risk factors for congestive heart failure are shown in Table 2. The risk-factor–adjusted hazard ratios for congestive heart failure were 1.47 (95 percent confidence interval, 1.25 to 1.73) and 1.43 (95 percent confidence interval, 1.24 to 1.65) per increment of 1 SD in the height-indexed left ventricular end-diastolic and end-systolic dimensions, respectively (Table 2,

TABLE 2. SEX-STRATIFIED MULTIVARIABLE COX PROPORTIONAL-HAZARDS REGRESSION MODELS EXAMINING THE RELATION OF LEFT VENTRICULAR INTERNAL DIMENSIONS TO THE RISK OF CONGESTIVE HEART FAILURE.*

MODEL AND ECHOCARDIOGRAPHIC VARIABLES	HAZARD RATIO (95% CI)†	CHI-SQUARE	P VALUE
Model 1A: with LV end-diastolic dimension and clinical risk factors			
Height-indexed LV end-diastolic dimension	1.47 (1.25–1.73)	21.86	<0.001
Model 1B: with LV end-diastolic dimension and fractional shortening together			
Fractional shortening	0.87 (0.71–1.05)	2.04	0.15
Height-indexed LV end-diastolic dimension	1.38 (1.15–1.66)	12.10	<0.001
Model 2A: with LV end-systolic dimension and clinical risk factors			
Height-indexed LV end-systolic dimension	1.43 (1.24–1.65)	24.55	<0.001
Model 2B: with LV end-systolic dimension and fractional shortening together			
Fractional shortening	1.11 (0.82–1.49)	0.46	0.50
Height-indexed LV end-systolic dimension	1.54 (1.20–1.98)	11.29	<0.001

*LV denotes left ventricular, and CI confidence interval. All models are adjusted for clinical risk factors including age, sex, hypertension, systolic and diastolic blood pressure, valve disease at base line, body-mass index, diabetes mellitus, and interim myocardial infarction (as a time-dependent covariate).

†Hazard ratios are per increment of 1 SD in the echocardiographic variables, defined as follows: LV end-diastolic dimension ÷ $(\text{height})^k$, 2.96 in men and women; LV end-systolic dimension ÷ $(\text{height})^k$, 2.64 in men and 2.50 in women; and fractional shortening, 3.8 in men and 4.1 in women — with k for LV end-diastolic dimension 0.57 in men and 0.50 in women and k for LV end-systolic dimension 0.60 in men and 0.68 in women.

Models 1A and 2A). Multivariable models incorporating fractional shortening first were also considered (Table 2, Models 1B and 2B); whereas left ventricular internal dimensions contributed significantly to the risk of congestive heart failure, base-line fractional shortening did not.

We used multivariable stepwise models to examine how several height-indexed echocardiographic variables and fractional shortening contributed to the risk of congestive heart failure. All except left-ventricular-wall thickness were significant individually ($P<0.001$ for each). When the variables were considered jointly, height-indexed left ventricular end-systolic dimension entered the stepwise model first, after which none of the remaining echocardiographic variables (left ventricular end-diastolic dimension, left ventricular mass, and fractional shortening) met the 0.05 criterion for significance.

Additional Analyses

To determine whether the relation of left ventricular internal dimensions to the risk of congestive heart failure was linear on the logarithmic scale, we considered multivariable models comparing the risk of congestive heart failure across (trend models) and among (multicategory models) quintiles of height-indexed left ventricular end-diastolic and end-systolic dimensions. These results (Fig. 1) indicate a log-linear relation between left ventricular internal dimensions and the risk of congestive heart failure.

We also studied multivariable models incorporating unindexed left ventricular internal dimensions and dimensions adjusted for body-surface area, with nearly identical results (e.g., the hazard ratio for congestive heart failure per increment of 1 SD in the left ventricular end-diastolic dimension indexed for body-surface area was 1.46 [95 percent confidence interval, 1.22 to 1.75]).

We performed secondary analyses evaluating several interaction terms. Sex, wall thickness, fractional shortening, and heart rate had no significant interaction with left ventricular end-diastolic or end-systolic dimensions (all P values exceeded 0.39).

Although the primary analyses modeled interim myocardial infarction as a time-dependent covariate, models ignoring interim myocardial infarction, models excluding subjects with an interim myocardial infarction, and models censoring data on subjects at the time of the interim myocardial infarction were also considered. Hazard ratios for congestive heart failure associated with height-indexed left ventricular internal dimensions increased in these analyses. For example, the hazard ratio per increment of 1 SD in the height-indexed left ventricular end-diastolic

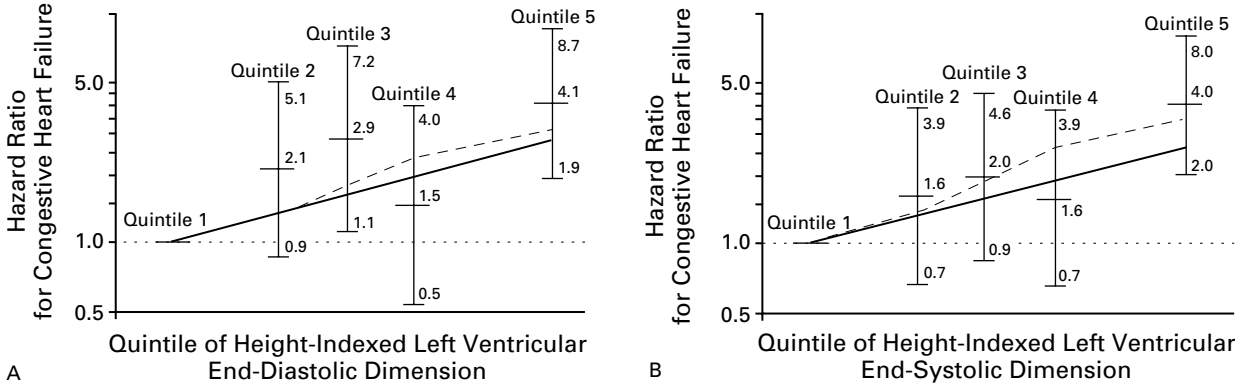

Figure 1. Relation of Height-Indexed Left Ventricular End-Diastolic (Panel A) and End-Systolic (Panel B) Internal Dimensions to the Risk of Heart Failure in Sex-Stratified Multivariable Proportional-Hazards Regression Models.

Hazard ratios for congestive heart failure are plotted on a logarithmic scale. The results of clinical-covariate–adjusted, sex-stratified statistical models incorporating height-indexed left ventricular internal dimensions as a continuous variable (solid lines), multicategory models evaluating risks among quintiles of height-indexed left ventricular internal dimensions (with the lowest quintile as the reference category; error bars and 95 percent confidence intervals), and models assessing trends in the risk of congestive heart failure according to quintile of height-indexed left ventricular internal dimensions (dashed lines) were consistent. The figure indicates that there is a log-linear relation of left ventricular internal dimensions to the risk of congestive heart failure. The spacing between quintiles reflects values for men; the quintile spacing for women was similar.

dimension increased to 1.64 (95 percent confidence interval, 1.36 to 1.97) in the model excluding subjects with an interim myocardial infarction.

DISCUSSION

Over three decades ago, the German pathologist A.J. Linzbach described structural dilatation of the left ventricle as the morphologic substrate of congestive heart failure.[30] More recent investigations of ventricular remodeling after myocardial infarction have substantiated this concept. Serial observations of left ventricular dimensions and measures of systolic function after myocardial infarction suggest that dilatation of the left ventricle is implicated in the development of progressive cardiac dysfunction and congestive heart failure.[13,14] However, the effect of increased ventricular dimensions on the risk of congestive heart failure in people who are free of myocardial infarction and congestive heart failure at base line is not known. In a previous investigation, we reported that the presence of left ventricular dilatation in asymptomatic, otherwise healthy men was associated with an increased risk of adverse outcomes.[3] That study was based on shorter follow-up than the current study, did not include women, used unindexed left ventricular internal dimensions, and did not examine congestive heart failure as an end point.[3]

Principal Findings

In the present investigation we examined prospectively the relation of left ventricular internal dimensions to the risk of congestive heart failure in men and women who are free of myocardial infarction or congestive heart failure at base line. In both sexes, increased left ventricular internal dimensions were associated with an increased incidence of congestive heart failure on follow-up. This relation was consistent regardless of the measure of left ventricular dimension used (end-diastolic or end-systolic and unindexed or indexed according to height or body-surface area) and persisted whether or not we included interim myocardial infarction in the multivariable models. Left ventricular dimensions emerged as the most important echocardiographic predictor of congestive heart failure among several echocardiographic variables evaluated. Fractional shortening, left ventricular mass, and left-ventricular-wall thickness were somewhat less informative. It is noteworthy that of 950 subjects in the highest quintile of height-indexed left ventricular end-diastolic dimension, only 72 (7.6 percent) had reduced fractional shortening. Our investigation extends previous observations underscoring the increased risk of congestive heart failure associated with ventricular dilatation after myocardial infarction[13,14] to people without myocardial infarction at the time of echocardiographic evaluation.

Possible Mechanisms

Whereas traditionally it has been believed that ventricular systolic dysfunction leads to chamber dilatation, a more contemporary hypothesis is that overt systolic dysfunction is preceded by an increase in chamber volume.[31] Ventricular dilatation is the initial compensatory response of the failing heart that

restores stroke volume; the dilated ventricle is thereby capable of ejecting the same stroke volume, but with a lesser degree of circumferential fiber shortening.[32] Nonetheless, the mechanical advantage conferred by ventricular dilatation is offset by a concomitant increase in myocardial oxygen consumption and diastolic and systolic ventricular-wall stress (according to Laplace's law).[33] Increased wall stress in the dilated ventricle creates afterload mismatch.[34] We speculate that some asymptomatic subjects with left ventricular dilatation have subclinical ventricular dysfunction, for which the increased chamber volume initially compensates; these patients may be at risk for overt congestive heart failure when the ventricular preload reserve is exceeded. In this context it is relevant to note that in clinical studies of patients with asymptomatic left ventricular systolic dysfunction, a reduction in cardiac-chamber dimensions is associated with a reduction in the risk of overt congestive heart failure.[8,35]

In the present investigation, only 19 of 74 subjects in whom congestive heart failure developed (26 percent) had a myocardial infarction between base line and the onset of heart failure. The mechanisms by which congestive heart failure developed in the majority of subjects with increased left ventricular dimensions are not known and merit further investigation.

Strengths and Limitations

The strengths of the present investigation include its prospective design, the large community-based sample, and the long duration of follow-up. The use of risk factors defined at base line (with the exception of interim myocardial infarction, which was treated as a time-dependent covariate) and the use of relatively insensitive clinical criteria for identifying valve disease are limitations. In addition, the use of M-mode echocardiography is associated with a potential for misclassification of subjects in whom left ventricular dilatation is localized to regions not seen from the parasternal window; however, this limitation is minimal in subjects without a previous myocardial infarction. Furthermore, the population studied was ambulatory and overwhelmingly white; the results may not be generalizable to hospitalized patients or to people of other races.

Clinical Implications

An increase in echocardiographic left ventricular internal dimensions is a risk factor for the development of congestive heart failure in people free of myocardial infarction at base line. Knowledge of left ventricular dimensions improves predictions of the risk of congestive heart failure made on the basis of traditional risk factors, perhaps by aiding in the identification of people with subclinical left ventricular dysfunction.

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