ORIGINAL ARTICLE

Association of Parental Heart Failure with Risk of Heart Failure in Offspring

Douglas S. Lee, M.D., Ph.D., Michael J. Pencina, Ph.D., Emelia J. Benjamin, M.D., Thomas J. Wang, M.D., Daniel Levy, M.D., Christopher J. O'Donnell, M.D., M.P.H., Byung-Ho Nam, Ph.D., Martin G. Larson, Sc.D., Ralph B. D'Agostino, Ph.D., and Ramachandran S. Vasan, M.D.

ABSTRACT

BACKGROUND

The association between heart failure in parents and the prevalence of left ventricular systolic dysfunction and the risk of heart failure in their offspring has not been investigated in a community-based setting.

METHODS

We examined the cross-sectional association of heart failure in parents with the prevalence of left ventricular systolic dysfunction, as well as left ventricular mass, internal dimensions, and wall thickness, in 1497 participants of the Framingham Offspring Study (mean age, 57 years; 819 women) who underwent routine echocardiography. We also investigated prospectively whether heart failure in parents increased the risk of heart failure in 2214 offspring (mean age, 44 years; 1150 women).

RESULTS

As compared with the 1039 participants whose parents did not have heart failure, the 458 participants in the cross-sectional cohort who had at least one parent with heart failure were more likely to have increased left ventricular mass (17.0 percent vs. 26.9 percent), left ventricular internal dimensions (18.6 percent vs. 23.4 percent), and left ventricular systolic dysfunction (3.1 percent vs. 5.7 percent); the multivariable-adjusted odds ratios were 1.35 (95 percent confidence interval, 0.99 to 1.84), 1.29 (95 percent confidence interval, 0.96 to 1.72), and 2.37 (95 percent confidence interval, 1.22 to 4.61), respectively. In the longitudinal cohort, heart failure developed in 90 offspring during follow-up (mean length of follow-up, 20 years). The age- and sex-adjusted 10-year incidence rates of heart failure were 2.72 percent among offspring with a parent with heart failure, as compared with 1.62 percent among those without a parent with heart failure. This increase in risk persisted after multivariable adjustment (hazard ratio, 1.70; 95 percent confidence interval, 1.11 to 2.60).

CONCLUSIONS

Heart failure in parents is associated with an increased prevalence of left ventricular systolic dysfunction cross-sectionally and an elevated risk of heart failure longitudinally. Our data emphasize the contribution of familial factors to the heart-failure burden in the community.

From the Framingham Heart Study of the National Heart, Lung, and Blood Institute, Framingham, Mass. (D.S.L., M.J.P., E.J.B., T.J.W., D.L., C.J.O., B.-H.N., M.G.L., R.B.D., R.S.V.); the National Heart, Lung, and Blood Institute, Bethesda, Md. (D.L., C.J.O.); and the Cardiology Division, Massachusetts General Hospital and Harvard Medical School (T.J.W., C.J.O.); the Department of Mathematics, Boston University (M.J.P., R.B.D.); the Department of Preventive Medicine and Epidemiology (E.J.B., D.L., R.S.V.), and the Cardiology Section (E.J.B., R.S.V.), Boston University School of Medicine — all in Boston. Address reprint requests to Dr. Vasan at the Framingham Heart Study, 73 Mt. Wayte Ave., Suite 2, Framingham, MA 01702, or at vasan@bu.edu.

N Engl J Med 2006;355:138-47.

Heart failure is associated with high rates of morbidity and mortality.[1] National guidelines emphasize the importance of preventing heart failure by identifying and treating risk factors (stage A) and subclinical precursors (stage B).[2] In this context, it is noteworthy that cardiovascular disease in parents is a recognized risk factor for cardiovascular disease[3] and subclinical atherosclerosis.[4] In addition, the risk conferred by a family history has been well documented for dilated cardiomyopathy,[5] although the frequency of familial aggregation varies widely from 12.5 percent[6] to 35 percent.[7,8] Whether parental heart failure confers an increased risk of the condition in the offspring is less certain. If this is the case, the information could facilitate targeted preventive strategies.

Heart failure commonly encountered in the community is regarded as a complex trait,[9] with only a small proportion of cases attributable to monogenic disorders.[10,11] Likewise, echocardiographic precursors of heart failure (such as increased left ventricular mass and dimensions) are considered to be complex phenotypes that are influenced by environmental and genetic factors. Therefore, the relationship of parental heart failure to risk in the offspring would be expected to be similarly complex. The risk of heart failure and subclinical left ventricular dysfunction conferred by parental heart failure has not been well characterized in the community, however.

We hypothesized that heart failure in parents is associated with an increased prevalence of echocardiographic left ventricular systolic dysfunction in their offspring. We also postulated that parental heart failure would increase the risk of overt heart failure in the offspring incrementally over that associated with established risk factors. We tested these hypotheses in the Framingham Offspring Study cohort.

METHODS

STUDY COHORT

The Framingham Offspring Study began in 1971 with the enrollment of children of the original Framingham Heart Study cohort[12] and their spouses.[13] Members of the offspring cohort, who are examined approximately every four years, were eligible for our study if they were at least 30 years of age and if both parents were in the original cohort. The study protocol was approved by the institutional review board of Boston Medical Center, and all participants provided written informed consent.

DEFINITION OF HEART FAILURE

Members of the original cohort and of the offspring cohort are under continuous surveillance for the development of cardiovascular disease events, including heart failure. All heart-failure events were adjudicated by a physician panel according to the previously published Framingham criteria (Table 1).[14]

CROSS-SECTIONAL ECHOCARDIOGRAPHIC STUDY

We used results obtained at examination cycle 6 (1995 through 1998) to assess the association of parental heart failure with echocardiographic measures of left ventricular structure and function in the offspring. All participants underwent routine transthoracic echocardiographic examination with Doppler color-flow imaging. M-mode measurements of left ventricular dimensions were obtained by the leading-edge-to-leading-edge technique.[15] The reproducibility of echocardiographic measurements was excellent.[16] Valve disease was de-

Table 1. Framingham Heart Failure Criteria.*

Major criteria
Paroxysmal nocturnal dyspnea
Orthopnea
Jugular venous distention
Hepatojugular reflux
Pulmonary rales
Radiographic evidence of cardiomegaly
Acute pulmonary edema
Third heart sound
Central venous pressure >16 cm of water
Weight loss >4.5 kg during first 5 days of treatment for suspected heart failure
Minor criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Heart rate >120 beats per minute

* Heart failure was considered to be present if two major or one major plus two minor criteria were present in the absence of an alternative explanation for the symptoms and signs.

fined by the presence on Doppler echocardiography of either valvular regurgitation that was more than mild or mitral or aortic stenosis that was at least mild.

Echocardiographic measurements included left ventricular mass, left ventricular end-diastolic internal dimensions, left ventricular wall thickness, and fractional shortening. Left ventricular mass was assessed by means of a validated formula.[17] Left ventricular wall thickness was defined as the sum of the diastolic thicknesses of the septum and the posterior wall. Increased left ventricular mass, internal dimensions, and wall thickness were defined a priori as measurements that met or exceeded the sex-specific 80th percentiles.[15] Left ventricular systolic dysfunction was defined by a fractional shortening of less than 0.29, by evidence on two-dimensional echocardiography of mild or greater systolic dysfunction on visual assessment in multiple views, or by both criteria.[15] A fractional shortening of 0.29 corresponds to a left ventricular ejection fraction of approximately 50 percent or less and was the 1st percentile value in a reference sample.[15]

LONGITUDINAL STUDY

We examined whether the incidence of heart failure was increased among children whose parents had documented heart failure. The baseline examination was defined as the earliest examination attended by an offspring during cycles 2 (1978 through 1982), 4 (1987 through 1992), and 6 (1995 through 1998). These specific examination cycles were chosen because the participants underwent routine transthoracic two-dimensional guided M-mode echocardiography at each of these examinations, which provided an opportunity to adjust for left ventricular mass as a covariate in supplementary analyses. Offspring were eligible for the study if they were free of heart failure at the baseline examination. Heart-failure events were evaluated in the offspring from 1978 through 2004 and in the parents from 1948 through 2004, up to the last examination attended by their offspring while the offspring were free of heart failure. Offspring with parental heart failure were defined as those with at least one parent who had heart failure between 1948 and 2004.

STATISTICAL ANALYSIS

For both echocardiographic and longitudinal analyses, we confirmed that there was no interaction between parental heart-failure status and sex; therefore, data for men and women were pooled in the analyses. We used multiple logistic regression to examine the association of parental heart failure with echocardiographic measures in the offspring, with adjustment for age, sex, and height. Additional multivariable models were adjusted for age, sex, height, weight, systolic blood pressure, and the presence or absence of diabetes, hypertension treatment, prior myocardial infarction, and echocardiographic evidence of valve disease. The analyses initially included the full echocardiographic cohort; they were repeated after the exclusion of those with prevalent heart failure at examination 6.

We used time-dependent multivariable Cox regression to determine the risk of heart-failure events in the offspring according to parental heart-failure status, with adjustment for established risk factors for heart failure.[18] Parental heart-failure status and all covariates were updated approximately every four years (at examinations 3 through 7). We estimated the hazard ratios for heart failure in the offspring of parents with heart failure as compared with the offspring of parents without heart failure (the reference group). Cox models were constructed hierarchically with the following adjustments for covariates: age and sex; age, sex, systolic blood pressure, body-mass index, ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, and the presence or absence of diabetes, treatment for hypertension, clinical valve disease (defined as a systolic murmur of grade 3/6 or more or any diastolic murmur), and myocardial infarction; and all of these covariates plus log-transformed left ventricular mass (updated at examinations 2, 4, and 6).

We estimated the population attributable risk (PAR) for heart failure associated with parental occurrence of the condition as a function of the proportion of cases occurring in those with a parent with heart failure (pd) and the multivariable-adjusted relative risk (RR, equivalent to hazard ratio from models with clinical covariates), calculated[19] as

$$\mathrm{PAR} = \mathrm{pd}\,\frac{(\mathrm{RR}-1)}{\mathrm{RR}} \times 100.$$

Because genetic influences often result in premature onset of disease,[20] we performed additional analyses to investigate the relations between early-onset heart failure (before or at the

age of 75 years, the median age at the onset of heart failure) in parents and offspring. Supplementary analyses further restricted the sample to offspring without prior myocardial infarction and to offspring without prior myocardial infarction or valve disease. These analyses were performed to determine whether the risk of parental heart failure was observable in offspring without these key precursors of heart failure.

In secondary analyses, we evaluated the contribution of coronary heart disease to the risk of heart failure by classifying heart failure in parents and offspring as ischemic or nonischemic. Heart failure antedated by myocardial infarction (either clinically recognized or unrecognized) or coronary insufficiency was classified as ischemic; otherwise it was classified as nonischemic. To explore the relations of parental heart failure to systolic as compared with diastolic heart failure in the offspring, we extracted data on left ventricular ejection fraction from echocardiograms obtained within 30 days after the first hospitalization for heart failure. Systolic dysfunction (systolic heart failure) was defined as an estimated left ventricular ejection fraction of 50 percent or less and diastolic heart failure as a left ventricular ejection fraction of more than 50 percent.

All analyses were performed with SAS software, version 8. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The sample for cross-sectional echocardiographic analyses consisted of 1497 offspring (mean age, 57 years; 819 women; 83 percent of the eligible participants who attended examination 6). These included 458 offspring who had parents with heart failure and 1039 who had parents without heart failure. The sample for longitudinal analyses consisted of 2214 participants (mean age, 44 years; 1150 women), including 698 offspring with (31.5 percent) and 1516 without (68.5 percent) parents with heart failure. Most participants in the longitudinal analysis participated in examination cycle 2 (1768 participants), and the remainder entered the investigation at examination 4 (384 participants) or 6 (62 participants). The baseline characteristics of both samples are shown in Table 2. Participants who had parents with heart failure were older and had higher values for blood pressure and body-mass index than participants who had parents without heart failure.

Table 2. Baseline Characteristics According to the Presence or Absence of Parental Heart Failure.*

Characteristic	Echocardiographic Sample			Longitudinal Sample		
	No Parental Heart Failure (N=1039)	Parental Heart Failure† (N=458)	P Value	No Parental Heart Failure (N=1516)	Parental Heart Failure† (N=698)	P Value
Age — yr	56.0±9.3	58.1±9.0	<0.001	43.7±9.0	45.2±8.9	<0.001
Female sex — no. (%)	563 (54.2)	256 (55.9)	0.54	778 (51.3)	372 (53.3)	0.39
Systolic blood pressure — mm Hg	125±19	130±19	<0.001	120±16	124±17	<0.001
Body-mass index‡	27.1±4.5	28.2±5.2	<0.001	25.9±4.5	26.4±4.7	<0.01
Total cholesterol:HDL cholesterol	4.31±1.51	4.46±1.66	0.11	4.39±1.60	4.59±1.67	<0.01
Diabetes — no. (%)	73 (7.0)	51 (11.1)	<0.01	39 (2.6)	17 (2.4)	0.85
Myocardial infarction — no. (%)	26 (2.5)	15 (3.3)	0.40	16 (1.1)	11 (1.6)	0.30
Hypertension — no. (%)	348 (33.5)	202 (44.1)	<0.001	306 (20.2)	182 (26.1)	<0.01
Hypertension treatment — no. (%)	214 (20.6)	135 (29.5)	<0.001	134 (8.8)	89 (12.8)	<0.01
Valve disease — no. (%)§	39 (3.8)	18 (3.9)	0.86	11 (0.7)	5 (0.7)	0.98
Prevalent heart failure — no. (%)	9 (0.9)	3 (0.7)	1.0			

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein.
† Heart failure was present in either the mother or the father at or before the participant's baseline examination (or, for the longitudinal cohort, before the last examination attended).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Echocardiographic valve disease and clinical valve disease are reported for the echocardiographic and the clinical samples, respectively.

PREVALENCE OF ECHOCARDIOGRAPHIC FINDINGS ACCORDING TO PARENTAL HEART-FAILURE STATUS

The prevalence of increased left ventricular mass, left ventricular internal dimensions, and left ventricular systolic dysfunction was higher among offspring who had parents with heart failure than among offspring who had parents without heart failure (Table 3). Among women, 2.7 percent of those who had parents with heart failure and 1.1 percent of those who had parents without heart failure had ventricular systolic dysfunction. Among men, the corresponding figures were 9.4 percent and 5.5 percent. Parental heart failure was associated with increased odds of left ventricular systolic dysfunction as well as of increased left ventricular mass and internal dimensions in age-, sex-, and height-adjusted models (Table 4). After adjustment for other covariates, the association of parental heart failure with left ventricular systolic dysfunction in the offspring was maintained, but other relations were attenuated (Table 4); the association with left ventricular systolic dysfunction was maintained when the analyses were repeated with the exclusion of 12 offspring with prevalent heart failure.

INCIDENCE OF HEART FAILURE ACCORDING TO PARENTAL HEART-FAILURE STATUS

During a mean follow-up of 20 years, heart failure developed in 90 offspring who were members of 87 different nuclear families. As compared with the absence of parental heart failure, the presence of parental heart failure was associated with higher age- and sex-adjusted incidence rates of heart failure. After adjustment for significant covariates, the risk associated with parental heart failure as compared with no parental heart failure was increased by 70 percent (Table 5). Additional adjustment for left ventricular mass did not attenuate the association (Table 5). Further adjustment for the above variables and asymptomatic left ventricular dysfunction (defined as a fractional shortening of less than 0.29) did not alter our results significantly (hazard ratio for the presence of parental heart failure, 1.85; 95 percent confidence interval, 1.15 to 2.96; P=0.01). The risk associated with parental heart failure was maintained in analyses evaluating the onset of heart failure at or before the age of 75 years in both parents and offspring and in the subgroup of participants who were also free of myocardial infarction and valve

Table 3. Echocardiographic Measurements According to the Presence or Absence of Parental Heart Failure.*

Variable	No Parental Heart Failure (N=1039)	Parental Heart Failure† (N=458)	P Value‡
Echocardiographic measurements			
LV mass — g	167±48	173±48	<0.01
LV diastolic internal dimensions — cm	4.81±0.52	4.83±0.53	0.09
LV wall thickness — cm	1.90±0.26	1.94±0.27	0.02
LV fractional shortening	0.37±0.06	0.37±0.06	0.62
Echocardiographic abnormalities§			
Increased LV mass (LV hypertrophy) — no. (%)	177 (17.0)	123 (26.9)	<0.001
Increased LV diastolic internal dimensions (LV enlargement) — no. (%)	193 (18.6)	107 (23.4)	0.03
Increased LV wall thickness — no. (%)	196 (18.9)	105 (22.9)	0.49
LV systolic dysfunction — no. (%)	32 (3.1)	26 (5.7)	0.046
Women — no./total no. (%)	6/563 (1.1)	7/256 (2.7)	0.11
Men — no./total no. (%)	26/476 (5.5)	19/202 (9.4)	0.16

* Plus–minus values are means ±SD. LV denotes left ventricular.
† Heart failure was present in either the mother or the father at or before the participant's baseline examination (or, for the longitudinal cohort, before the last examination attended).
‡ P values for pooled analyses are adjusted for age, sex, and height; sex-specific subanalyses are adjusted for age and height.
§ Increased echocardiographic measures were defined as those at or above the sex-specific 80th percentile. In the case of left ventricular mass, diastolic internal dimensions, and wall thickness, the values for these percentiles were 233.1 g, 5.47 cm, and 2.19 cm, respectively, in men, and 166.4 g, 4.92 cm, and 1.97 cm in women.

Table 4. Association of Parental Heart Failure with the Prevalence of Echocardiographic Abnormalities in the Offspring.*

Echocardiographic Abnormality	Age-, Sex-, and Height-Adjusted Values		Multivariable-Adjusted Values†	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
All 1497 participants				
Increased LV mass (LV hypertrophy)	1.74 (1.32–2.29)	<0.001	1.35 (0.99–1.84)	0.06
Increased LV diastolic internal dimensions (LV enlargement)	1.36 (1.04–1.79)	0.03	1.29 (0.96–1.72)	0.09
Increased LV wall thickness	1.11 (0.83–1.46)	0.49	0.87 (0.64–1.19)	0.38
LV systolic dysfunction	1.75 (1.01–3.02)	0.046	2.37 (1.22–4.61)	0.01
1485 Participants without prevalent heart failure				
Increased LV mass (LV hypertrophy)	1.74 (1.32–2.29)	<0.001	1.30 (0.96–1.77)	0.09
Increased LV diastolic internal dimensions (LV enlargement)	1.42 (1.08–1.87)	0.01	1.31 (0.98–1.75)	0.07
Increased LV wall thickness	1.10 (0.83–1.46)	0.52	0.86 (0.63–1.17)	0.32
LV systolic dysfunction	1.69 (0.95–3.01)	0.08	2.12 (1.05–4.30)	0.036

* Participants who had parents without heart failure served as the reference group. CI denotes confidence interval, and LV left ventricular.

† The multivariable model was adjusted for age, sex, height, weight, systolic blood pressure, and the presence or absence of valve disease, diabetes, prior myocardial infarction, and treatment for hypertension.

disease (Table 5). The population-attributable risk of heart failure that was due to the presence of the condition in a parent was 17.8 percent.

INCIDENCE AND CAUSE OF HEART FAILURE

Among offspring with heart failure, 44 had ischemic and 46 had nonischemic heart failure. Among parents with heart failure, 327 had ischemic and 371 had nonischemic heart failure. Heart failure (ischemic or nonischemic) developed in approximately 3.4 percent of the offspring who had parents without heart failure, approximately 6.4 percent of those who had parents with ischemic heart failure, and 4.9 percent of those who had parents with nonischemic heart failure (Table 6). Ischemic heart failure developed in 1.7 percent of offspring who had parents without heart failure, 3.4 percent of those who had parents with ischemic heart failure, and 1.9 percent of those who had parents with nonischemic heart failure. Nonischemic heart failure developed in 1.6 percent of offspring who had parents without heart failure, 3.1 percent of those who had parents with ischemic heart failure, and 3.0 percent of those who had parents with nonischemic heart failure.

In secondary analyses, after adjustment for multiple covariates and left ventricular mass, parental ischemic heart failure was associated with an increased risk of any heart failure, ischemic heart failure, or nonischemic heart failure in the offspring (Table 6). Parental nonischemic heart failure was not associated with ischemic heart failure in offspring, but there was a trend, which was not statistically significant, toward an increased risk of nonischemic heart failure in offspring.

ADDITIONAL ANALYSES OF HEART FAILURE IN THE OFFSPRING COHORT

Heart failure occurred in 51 of 1516 offspring (3.4 percent) who had parents without heart failure, 34 of 625 offspring (5.4 percent) who had one parent with heart failure, and 5 of 73 offspring (6.8 percent) with both parents affected. In age- and sex-adjusted analyses, heart failure in one parent was associated with a relative risk of heart failure in the offspring of 1.69 (95 percent confidence interval, 1.09 to 2.61; P=0.02) and heart failure in both parents was associated with a relative risk of 1.92 (95 percent confidence interval, 0.77 to 4.84; P=0.16). Data on left ventricular ejection fraction were available for 87 offspring with heart failure. Of 38 offspring with heart failure and a validated parental occurrence of heart failure, 24 (63.2 percent) had a left ventricular ejection fraction of 50 percent or less. Of 49 offspring with heart failure who had parents without heart failure, 35 (71.4 percent) had a left ventricular ejection fraction of 50 percent or less.

Table 5. Association of Parental Heart Failure with the Risk of Heart Failure in the Offspring.*

Model	No Parental Heart Failure	Parental Heart Failure	P Value
All participants			
No. of cases/no. at risk	51/1516	39/698	
Age- and sex-adjusted 10-yr incidence rate — % (95% CI)	1.62 (1.10–2.39)	2.72 (1.80–4.11)	
	hazard ratio (95% CI)		
Age- and sex-adjusted	1.00†	1.72 (1.13–2.61)	0.01
Multivariable-adjusted‡§	1.00†	1.70 (1.11–2.60)	0.02
After additional adjustment for LV mass	1.00†	1.82 (1.14–2.91)	0.01
Age <75 yr (parents and offspring)			
No. of cases/no. at risk¶	43/1841	21/373	
Age- and sex-adjusted 10-yr incidence rate — % (95% CI)	1.14 (0.73–1.79)	2.83 (1.66–4.82)	
	hazard ratio (95% CI)		
Age- and sex-adjusted	1.00†	2.58 (1.53–4.35)	<0.001
Multivariable-adjusted‡	1.00†	2.19 (1.28–3.73)	<0.01
After additional adjustment for LV mass	1.00†	2.12 (1.19–3.79)	0.01
Age <75 yr (parents and offspring), offspring free of myocardial infarction			
No. of cases/no. at risk	22/1724	12/333	
Age- and sex-adjusted 10-yr incidence rate — % (95% CI)	0.62 (0.33–1.16)	1.82 (0.88–3.75)	
	hazard ratio (95% CI)		
Age- and sex-adjusted	1.00†	2.99 (1.48–6.04)	<0.01
Multivariable-adjusted‡	1.00†	2.56 (1.26–5.21)	<0.01
After additional adjustment for LV mass	1.00†	2.68 (1.20–5.98)	0.02
Age <75 yr (parents and offspring), offspring free of myocardial infarction and valve disease			
No. of cases/no. at risk	17/1680	11/321	
Age- and sex-adjusted 10-yr incidence rate — % (95% CI)	0.49 (0.25–0.99)	1.75 (0.81–3.79)	
	hazard ratio (95% CI)		
Age- and sex-adjusted	1.00†	3.63 (1.70–7.75)	<0.001
Multivariable-adjusted‡	1.00†	2.99 (1.39–6.45)	<0.01
After additional adjustment for LV mass	1.00†	4.52 (1.83–11.14)	0.001

* CI denotes confidence interval, LV left ventricular, and HDL high-density lipoprotein.
† This group served as the reference group.
‡ Multivariable models were adjusted for age, sex, systolic blood pressure, body-mass index, total cholesterol:HDL cholesterol ratio, and the presence or absence of diabetes and treatment for hypertension. In addition, the models that included all participants and those younger than 75 years of age were adjusted for the presence or absence of prior myocardial infarction. The models that included all participants, those younger than 75 years of age, and those younger than 75 years of age who, in the case of the offspring, had not had a myocardial infarction were also adjusted for the presence or absence of valve disease.
§ The adjusted hazard ratios of significant covariates in the multivariable model were as follows: age, 1.10 per year (95 percent confidence interval, 1.06 to 1.13); systolic blood pressure, 1.02 per 1 mm Hg increase (95 percent confidence interval, 1.01 to 1.03); total cholesterol:HDL cholesterol ratio, 1.13 per unit increase (95 percent confidence interval, 1.07 to 1.19); diabetes, 2.82 (95 percent confidence interval, 1.76 to 4.52); myocardial infarction, 4.86 (95 percent confidence interval, 2.90 to 8.15); and valve disease, 6.95 (95 percent confidence interval, 3.29 to 14.67).
¶ The number at risk was reclassified in analyses in which the onset of heart failure was before the age of 75 years, because parental heart failure occurred at or after 75 years of age in 325 offspring.

Table 6. Association of Parental Heart Failure with the Risk of Heart Failure in Offspring According to the Cause of Heart Failure in Parents and Offspring.*

Cause of Heart Failure in Offspring	No Parental Heart Failure		Parental Ischemic Heart Failure		Parental Nonischemic Heart Failure	
	No. of Cases/ No. at Risk (%)	HR (95% CI)†	No. of Cases/ No. at Risk (%)	HR (95% CI)†	No. of Cases/ No. at Risk (%)	HR (95% CI)†
Any cause	51/1516 (3.4)	1.00‡	21/327 (6.4)	2.63 (1.51–4.59)	18/371 (4.9)	1.26 (0.67–2.38)
P value				<0.001		0.47
Ischemic cause§	26/1516 (1.7)	1.00‡	11/327 (3.4)	2.46 (1.10–5.49)	7/371 (1.9)	0.69 (0.20–2.36)
P value				0.03		0.55
Nonischemic cause¶	25/1516 (1.6)	1.00‡	10/327 (3.1)	2.28 (1.02–5.10)	11/371 (3.0)	1.82 (0.84–3.94)
P value				0.046		0.13

* HR denotes hazard ratio, and CI confidence interval. Percentages may not sum to the totals because of rounding.
† Hazard ratios were determined from models adjusted for age, sex, systolic blood pressure, body-mass index, total cholesterol:high-density lipoprotein cholesterol ratio, left ventricular mass, and the presence or absence of hypertension treatment, diabetes, and valve disease.
‡ This group served as the reference group.
§ Data from offspring in whom nonischemic heart failure developed during the follow-up period were censored as nonevents at the time of the development of heart failure.
¶ Data from offspring in whom ischemic heart failure developed during the follow-up period were censored as nonevents at the time of the development of heart failure.

DISCUSSION

In a cross-sectional analysis, we found that heart failure in parents was associated with a significant increase by a factor of about 2 in the likelihood of left ventricular systolic dysfunction in their offspring; the finding was consistent in both men and women. Parental heart failure was associated prospectively with at least a 70 percent increase in the risk of heart failure in the offspring after adjustment for established risk factors, including left ventricular mass. The increased risk associated with parental heart failure remained when the analysis was restricted to those with onset of heart failure at or before the age of 75 years and to those without myocardial infarction or valve disease. Approximately 18 percent of the heart-failure burden in the offspring was attributable to parental heart failure. Our findings that heart failure in their parents predisposes people to both left ventricular systolic dysfunction and overt heart failure underscore the contribution of familial factors to development of the condition.

The results of secondary analyses suggested that parental ischemic heart failure was strongly related to the risk of heart failure from any cause in the offspring. Parental nonischemic heart failure was not related to the risk of ischemic heart failure in the offspring, but it was associated (albeit not significantly) with the risk of nonischemic heart failure in the offspring. Given the moderate size of the sample and the empirical adjudication of the cause of heart failure in both parents and offspring, these observations should be viewed as hypothesis-generating and as warranting study in larger samples.

Several mechanisms may explain the link between heart failure in parents and their offspring. First, there may be transmission of genetic factors that are associated with maladaptive responses to environmental or biologic stresses, as has been reported for a predisposition to carotid atherosclerosis,[21] blood-pressure response to angiotensin II,[22] and the development of cardiovascular disease in diabetes.[23] Second, there may be familial aggregation of known heart-failure risk factors, such as high blood pressure or body-mass index.[24,25] However, in our study parental heart failure remained associated with the offspring's risk of heart failure in risk factor–adjusted analyses. The occurrence of both systolic and diastolic heart failure in offspring suggests the possibility that altered diastolic function, increased vascular stiffness, and a propensity for sodium retention may be contributory mechanisms. Finally, there may be familial aggregation of unidentified genetic, environmental, behavioral, and lifestyle-related factors.

One hypothesis of particular interest is that there may be familial aggregation of left ventricu-

lar remodeling indexes.[26] Prior studies have suggested that left ventricular mass and dimensions are heritable traits.[27-29] In addition, familial aggregation of increased left ventricular dimensions has been observed in relatives of patients with dilated cardiomyopathy. Other investigators have demonstrated that increased left ventricular size and mass predispose people to heart-failure events, reduced ejection fraction, or both.[30,31] We demonstrated that both asymptomatic left ventricular systolic dysfunction and clinical heart failure occur more frequently in the offspring of parents with heart failure than in the offspring of parents without heart failure, an observation lending support to the familial-remodeling hypothesis. However, the risk of heart failure in the offspring remained after adjustment for the presence or absence of myocardial infarction and left ventricular mass. This observation raises the possibility that additional mechanisms may contribute to the familial aggregation of heart failure, such as familial risk of increased vascular stiffness or altered ventricular–vascular coupling.

The strengths of our study include the use of a community-based sample, the routine ascertainment of risk factors and collection of echocardiographic data, the integration of cross-sectional and longitudinal components, and the use of standardized methods of ascertainment of heart failure in both parents and offspring. The use of a prospective design averted potential recall bias and inaccuracies related to self-reported family history.[32,33]

Several limitations of our study merit attention. Echocardiographic data were not available for 23 percent of the 2344 offspring who were alive at examination cycle 6, because they did not attend the examination. Nonattendance of examinations after the baseline examination, however, would not affect our longitudinal analyses, because ascertainment of heart-failure events does not require attendance at Framingham Heart Study examinations. Because of the small numbers of affected offspring, the study did not have sufficient statistical power to evaluate the effects on the risk of heart failure of having one as compared with two affected parents or of having an affected mother as compared with an affected father. Because our sample was exclusively white, the generalizability of the findings to other races or ethnic groups is limited.

Our demonstration of an increased familial risk of heart failure suggests, but does not establish, a causal relation of genetic factors to the disease process. It also provides support for the need for studies to examine the genetic underpinnings of this complex disease.

Our findings lend support to suggestions that information should be collected on parental heart failure as part of the family history to help identify persons at risk for heart failure.[34] Current national guidelines suggest that persons with a strong family history of cardiomyopathy should undergo a noninvasive left ventricular function evaluation, and our observations strengthen these recommendations. Noninvasive screening strategies may identify high-risk persons with subclinical stage B heart failure[2] who could be targeted for prevention early in the disease process.

In our community-based sample, parental heart failure was associated with subclinical left ventricular echocardiographic alterations and an increased risk of clinical heart failure in the offspring. Provided that parental occurrence of heart failure can be ascertained reliably by a thorough history taking, this information may facilitate early identification of persons at risk for heart failure.

Supported by a Canadian Institutes of Health Research Clinician-Scientist award (to Dr. Lee) and by a contract (N01-HC-25195) with and research grants (K23 HL074077, K24HL04334, and U01 HL 66582) from the National Heart, Lung, and Blood Institute.

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Heart disease and stroke statistics — 2005 update. Dallas: American Heart Association, 2005.
2. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary — a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.
3. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA 2004;291:2204-11.
4. Wang TJ, Nam BH, D'Agostino RB, et al. Carotid intima-media thickness is associated with premature parental coronary heart disease: the Framingham Heart Study. Circulation 2003;108:572-6.
5. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardio-

myopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992;326:77-82.
6. Rakar S, Sinagra G, Di Lenarda A, et al. Epidemiology of dilated cardiomyopathy: a prospective post-mortem study of 5252 necropsies. Eur Heart J 1997;18:117-23.
7. Baig MK, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 1998;31:195-201.
8. Grunig E, Tasman JA, Kucherer H, Franz W, Kubler W, Katus HA. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 1998;31:186-94.
9. Pasotti M, Repetto A, Tavazzi L, Arbustini E. Genetic predisposition to heart failure. Med Clin North Am 2004;88:1173-92.
10. Kamisago M, Sharma SD, DePalma SR, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. N Engl J Med 2000;343:1688-96.
11. Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 1999;341:1715-24.
12. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. Ann N Y Acad Sci 1963;107:539-56.
13. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 1979;110:281-90.
14. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441-6.
15. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham Heart Study. JAMA 2002;288:1252-9.
16. Sundstrom J, Sullivan L, Selhub J, et al. Relations of plasma homocysteine to left ventricular structure and function: the Framingham Heart Study. Eur Heart J 2004;25:523-30.
17. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
18. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. Arch Intern Med 1999;159:1197-204.
19. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-9.
20. Thomas DC. Statistical methods in genetic epidemiology. New York: Oxford University Press, 2004.
21. Karvonen J, Kauma H, Kervinen K, et al. Apolipoprotein E polymorphism affects carotid artery atherosclerosis in smoking hypertensive men. J Hypertens 2002;20:2371-8.
22. Vuagnat A, Giacche M, Hopkins PN, et al. Blood pressure response to angiotensin II, low-density lipoprotein cholesterol and polymorphisms of the angiotensin II type 1 receptor gene in hypertensive sibling pairs. J Mol Med 2001;79:175-83.
23. Pettersson-Fernholm K, Forsblom C, Hudson BI, Perola M, Grant PJ, Groop PH. The functional –374 T/A RAGE gene polymorphism is associated with proteinuria and cardiovascular disease in type 1 diabetic patients. Diabetes 2003;52:891-4.
24. Bell CG, Benzinou M, Siddiq A, et al. Genome-wide linkage analysis for severe obesity in French caucasians finds significant susceptibility locus on chromosome 19q. Diabetes 2004;53:1857-65.
25. Levy D, DeStefano AL, Larson MG, et al. Evidence for a gene influencing blood pressure on chromosome 17: genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. Hypertension 2000;36:477-83.
26. Dong Y, Wang X, Zhu H, Treiber FA, Snieder H. Endothelin-1 gene and progression of blood pressure and left ventricular mass: longitudinal findings in youth. Hypertension 2004;44:884-90.
27. Post WS, Larson MG, Myers RH, Galderisi M, Levy D. Heritability of left ventricular mass: the Framingham Heart Study. Hypertension 1997;30:1025-8.
28. Arnett DK, Hong Y, Bella JN, Oberman A, et al. Sibling correlation of left ventricular mass and geometry in hypertensive African Americans and whites: the HyperGEN study. Am J Hypertens 2001;14:1226-30.
29. Swan L, Birnie DH, Padmanabhan S, Inglis G, Connell JM, Hillis WS. The genetic determination of left ventricular mass in healthy adults. Eur Heart J 2003;24:577-82.
30. Drazner MH, Rame JE, Marino EK, et al. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. J Am Coll Cardiol 2004;43:2207-15.
31. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 1997;336:1350-5.
32. Kee F, Tiret L, Robo JY, et al. Reliability of reported family history of myocardial infarction. BMJ 1993;307:1528-30.
33. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. Ann Intern Med 2004;140:434-40.
34. Awareness of family health history as a risk factor for disease — United States, 2004. MMWR Morb Mortal Wkly Rep 2004;53:1044-7.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.