

Natural History of Asymptomatic Left Ventricular Systolic Dysfunction in the Community

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Background—Information is limited regarding the rates of progression to congestive heart failure (CHF) and death in individuals with asymptomatic left ventricular systolic dysfunction (ALVD). We sought to characterize the natural history of ALVD, by studying unselected individuals with this condition in the community.

Methods and Results—We studied 4257 participants (1860 men) from the Framingham Study who underwent routine echocardiography. The prevalence of ALVD (visually estimated ejection fraction [EF] ≤50% without a history of CHF) was 6.0% in men and 0.8% in women. During up to 12 years of follow-up, rates of CHF among subjects with normal left ventricular systolic function (EF >50%, n=4128) and ALVD (n=129) were 0.7 and 5.8 per 100 person-years, respectively. After adjustment for cardiovascular disease risk factors, ALVD was associated with a hazards ratio (HR) for CHF of 4.7 (95% CI 2.7 to 8.1), compared with individuals without ALVD. An elevated risk of CHF after ALVD was observed even in individuals without prior myocardial infarction or valvular disease, with an adjusted HR of 6.5 (CI 3.1 to 13.5). Mild ALVD (EF 40% to 50%, n=78) and moderate-to-severe ALVD (EF <40%, n=51) were associated with adjusted HRs for CHF of 3.3 (CI 1.7 to 6.6) and 7.8 (CI 3.9 to 15.6), respectively. ALVD was also associated with an increased mortality risk (adjusted HR 1.6, CI 1.1 to 2.4). The median survival of ALVD subjects was 7.1 years.

Conclusion—Individuals with ALVD in the community are at high risk of CHF and death, even when only mild impairment of EF is present. Additional studies are needed to define optimal therapy for mild ALVD. (*Circulation*. 2003;108:977-982.)

Key Words: heart failure ■ ventricular dysfunction ■ echocardiography

The mortality rate after the onset of congestive heart failure (CHF) remains high despite recent advances in the management of this condition.¹ Furthermore, two contemporary trends, the aging of industrialized populations and improvements in survival after myocardial infarction, are expected to cause a substantial increase in the prevalence of CHF. Thus, preventing CHF by targeting its preclinical stages and treating known risk factors may be the best strategies to reduce the overall societal burden of this disorder.

It is widely accepted that individuals may progress through an asymptomatic phase of left ventricular systolic dysfunction (ALVD) before the development of overt heart failure.²⁻⁴ Recent studies have demonstrated that ALVD is as prevalent as overt CHF in the general population.⁵⁻⁷ Moreover, treatment with angiotensin-converting enzyme (ACE) inhibitors may reduce the incidence of CHF in selected patients with this condition.^{8,9} The growing clinical interest in ALVD is evidenced by its inclusion in the new American College of Cardiology/American Heart

Association staging system for CHF¹⁰ and by proposals for community-wide screening for ALVD.⁴

Despite the contemporary interest in ALVD, information is limited regarding the natural history of this condition in unselected individuals.¹¹ Patients are frequently found to have reduced ejection fractions (EF) on echocardiograms performed for indications other than CHF. In order to define optimal therapeutic strategies for such individuals, it is critical to understand what proportion of such patients progress to CHF, the time course of such progression, and the factors that accompany the transition from preclinical to overt disease.³

The experience of participants in randomized-controlled trials provides one source of information regarding the prognosis associated with ALVD.^{8,9} However, clinical trials, particularly those involving an “asymptomatic” condition, have the potential for selection bias that limits their generalizability to a general population. For instance, participants in

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SOLVD Prevention and SAVE were predominantly postmyocardial infarction and middle-aged,^{8,9} in contrast to individuals with ALVD in the community, who are elderly and often do not have a history of myocardial infarction.^{5,7} Additionally, existing trials excluded subjects with mild left ventricular (LV) systolic dysfunction (EF between 40% and 50%), which is the predominant form of ALVD in the community.⁵⁻⁷

Accordingly, the prognosis of ALVD in the general population is best assessed by evaluating a community-based sample of asymptomatic individuals with varying degrees of LV systolic dysfunction, including people without clinically apparent heart disease.^{5,7} We sought to characterize the natural history of ALVD using observations from a large, community-based cohort in which echocardiography was performed routinely.

Methods

Subjects and Clinical Evaluation

The design and selection criteria of the original and offspring cohorts of the Framingham Heart Study have been detailed previously.^{12,13} Members of the original cohort have been examined biennially since 1948, while offspring cohort members have been examined approximately every 4 years since 1971. Participants attending the 20th examination of the original cohort (1987 to 1990, n=1401) or the 5th examination of the offspring cohort (1991 to 1995, n=3799) were eligible for the present investigation. We excluded subjects with inadequate echocardiograms (n=671), a history of CHF (n=69), or age <40 years (n=203). After these exclusions, 4257 participants (82% of attendees, 56% women) remained eligible. All subjects underwent a medical history, physical examination, ECG, and echocardiography at the baseline examination.

Echocardiography

Echocardiograms were read by a sonographer or cardiologist experienced in echocardiography and blinded to clinical information. LVEF was estimated based on the visual assessment of LV contractile performance and wall motion in multiple 2-dimensional views. Subjects were classified as having normal LV systolic function (EF >50%), mild systolic dysfunction (EF 40% to 50%), or moderate-to-severe systolic dysfunction (EF <40%). All studies with suspected LV systolic dysfunction were over-read by a cardiologist. The accuracy of visual assessments of EF has been validated previously.^{14,15}

Follow-Up

Framingham Study participants are under continuous surveillance for the development of cardiovascular disease events. Medical records were obtained for all hospitalizations and physician visits related to cardiovascular disease. A committee of 3 physicians adjudicated cardiovascular endpoints, including myocardial infarction and CHF.

The diagnosis of CHF was based on the presence of 2 major, or 1 major and 2 minor, clinical criteria, provided they could not be attributed to another diagnosis. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, distended neck veins, rales, radiographic cardiomegaly, pulmonary edema, a third heart sound, increased venous pressure, hepatojugular reflux, and weight loss on diuretic therapy. Minor criteria were bilateral ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, pulmonary vascular redistribution, decrease in vital capacity, and tachycardia. An onset date was assigned to all CHF cases using the earliest date of hospitalization, clinic visit, or symptoms as determined from review of the medical records and Framingham examination data.

Statistical Analyses

Subjects with LV systolic dysfunction on the echocardiogram but without a history of CHF were classified as having ALVD. We determined the prevalence of ALVD by sex and in 4 predefined age categories (40 to 59, 60 to 69, 70 to 79, and ≥80 years), according to the age at the time of the index echocardiogram. Rates of incident CHF and mortality were determined for ALVD (whole group, and separately for mild and moderate-to-severe ALVD categories) and for subjects with normal LVEF and no history of CHF. The occurrence of these outcomes was depicted graphically using Kaplan-Meier survival curves and compared using the log-rank test. Age- and sex-adjusted hazard ratios for these outcomes were estimated using Cox proportional hazards models, with non-ALVD subjects serving as the reference group. An additional comparison group, subjects with a history of CHF and EF ≤50% at the baseline examinations, was used in the assessment of mortality. We further characterized the clinical course of ALVD subjects by documenting the frequency of interim myocardial infarction in those who developed CHF.

Multivariable Cox models were used to evaluate the influence of ALVD on the risk of CHF and mortality after adjusting for established risk factors for CHF and mortality. Separate models were constructed for each outcome. All models were adjusted for age, sex, myocardial infarction, systolic blood pressure, antihypertensive medication use, diabetes, total-to-HDL cholesterol ratio, greater than mild valvular regurgitation or stenosis on echocardiography, smoking, and ECG left ventricular hypertrophy. We also estimated models for select subgroups: those with and without myocardial infarction at baseline; and subjects without myocardial infarction or valvular heart disease at baseline (individuals without an indication for routine echocardiography). We also performed analyses adjusting for cohort status (original versus offspring) and testing for the interaction between cohort status and ALVD, because of the different examination intervals in the 2 cohorts.

In further analyses, we evaluated predictors of CHF and death in subjects with ALVD using age-adjusted Cox models and entering other variables in stepwise fashion. The criterion for entry in this analysis was $P < 0.10$. Candidate predictors included sex, baseline myocardial infarction, interim myocardial infarction, hypertension, diabetes, total-to-HDL cholesterol ratio, greater than mild valvular regurgitation or stenosis, severity of ALVD (moderate-to-severe versus mild), atrial fibrillation, and smoking.

Results

Prevalence of ALVD

Characteristics of the 4257 eligible subjects attending the baseline examinations are shown in Table 1, according to the presence or absence of ALVD. The overall prevalence of ALVD was 3.0% (95% confidence interval [CI], 2.5% to 3.5%), increasing considerably with age (Table 2). Participants with ALVD were predominantly men (86%), and about half had a history of a myocardial infarction. The majority of ALVD subjects (n=78, 61%) were classified as having mild ALVD (EF 40% to 50%). Moderate (EF 30% to 39%) and severe (EF <30%) LV systolic dysfunction were present in 33% and 6% of ALVD subjects, respectively. About a third of subjects (n=45, 78% men) with ALVD did not have prior myocardial infarction or significant valve disease.

Incidence of CHF and Time to CHF Onset

During up to 12 years of follow-up (mean 5 years), overt CHF developed in 175 subjects overall (4%), including 34 of the 129 subjects (26%) with ALVD at baseline. The crude incidence rate of CHF among subjects with ALVD was 5.9 per 100 person-years (CI, 3.9 to 7.8), compared with 0.7 per 100 person-years (CI, 0.6 to 0.8) in those without ALVD. The

TABLE 1. Baseline Characteristics

	ALVD (n=129)	No ALVD (n=4128)
Mean age, y (range)	69 (42–90)	61 (40–95)
Male, n (%)	111 (86)	1749 (42)
Myocardial infarction, n (%)	63 (49)	93 (2)
Diabetes mellitus, n (%)	25 (19)	332 (8)
Mean systolic BP, mm Hg	139±22	131±22
Mean diastolic BP, mm Hg	76±11	75±10
Hypertension, n (%)*	84 (65)	1791 (43)
ECG-LVH, n (%)†	14 (11)	47 (1)
Valvular disease, n (%)‡	27 (21)	162 (4)
Atrial fibrillation, n (%)	16 (12)	83 (2)
Medication use, n (%)		
Antihypertensive therapy	58 (45)	1048 (25)
ACE inhibitor	16 (12)	310 (8)

Table excludes those with prior CHF. BP indicates blood pressure; ECG-LVH, electrocardiographic left ventricular hypertrophy.

*Systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 , or antihypertensive use.

†Increased voltage and lateral repolarization abnormalities.

‡At least moderate mitral or aortic regurgitation or stenosis on echocardiography.

incidence of CHF was nearly identical in men and women with ALVD.

As shown in Figure 1, there was a gradient of rising CHF risk with increasing degrees of LV systolic dysfunction. Unadjusted incidence rates for CHF were 3.9 per 100 person-years (CI, 1.9 to 5.8) in individuals with mild ALVD and 9.6 per 100 person-years (CI, 5.3 to 14.0) in participants with moderate-to-severe ALVD. The median survival free of CHF was 10.3 years for subjects with mild ALVD, and 5.9 years for those with moderate-to-severe ALVD (Figure 1, Kaplan-Meier estimates). The age- and sex-adjusted hazards ratios for CHF associated with mild ALVD and moderate-to-severe ALVD were 3.9 (CI, 2.2 to 6.7) and 8.5 (CI, 5.1 to 14.2), respectively, with the normal EF group as the reference.

Of ALVD subjects who developed CHF, 29% had an interim myocardial infarction (between baseline and CHF). Overall, 62% of ALVD subjects who developed CHF had a history of baseline or interim myocardial infarction.

Mortality Rates According to the Degree of ALVD

During follow-up, 52 (40%) subjects with ALVD and 484 (12%) participants without ALVD died. Corresponding crude

TABLE 2. Prevalence of ALVD

Age Group	Men (n=1860)	Women (n=2397)
40–59 years	2.1	0.5
60–69 years	7.2	0.8
70–79 years	11.3	1.0
80+ years	14.3	1.9
Pooled	6.0	0.8

Values are given as percent of patients. Denominator excludes those with prior CHF.

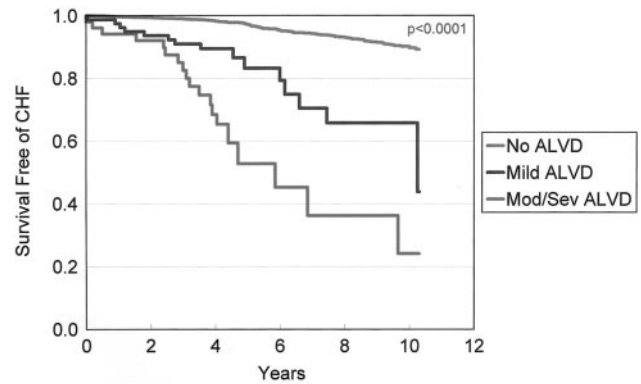


Figure 1. Kaplan-Meier curves for survival free of CHF. Referent group consists of subjects with normal left ventricular systolic function (EF $>50\%$). Mild ALVD indicates mild asymptomatic left ventricular systolic dysfunction (EF 40% to 50%); Mod/Sev ALVD, moderate-to-severe asymptomatic left ventricular systolic dysfunction (EF $<40\%$).

mortality rates were 8.1 per 100 person-years (CI, 5.9 to 10.3) and 2.1 per 100 person-years (CI, 1.9 to 2.3), respectively.

Figure 2 displays the Kaplan-Meier survival curves for subjects with ALVD, according to severity of LV systolic dysfunction, versus subjects without ALVD. Also shown, for comparison, is the survival curve for subjects with a history of CHF and EF $\leq 50\%$ at the baseline examination (n=26). The mortality rate for individuals with mild ALVD was 6.5 per 100 person-years (CI, 4.0 to 8.9), whereas that for persons with moderate-to-severe ALVD was 11.0 per 100 person-years (CI, 6.7 to 15.3). The median survival for subjects with ALVD was 7.1 years (7.9 years for those with mild ALVD and 5.4 years for those with moderate-to-severe ALVD; Kaplan-Meier estimates). The median survival for attendees with a history of overt CHF and LV systolic dysfunction was 4.6 years. The age- and sex-adjusted hazards ratios for mortality associated with mild ALVD, moderate-to-severe ALVD, and overt systolic CHF were 1.9 (CI, 1.3 to 2.8), 3.1 (CI, 2.0 to 4.7), and 5.0 (CI, 3.1 to 8.0), respectively (with non-ALVD as the referent).

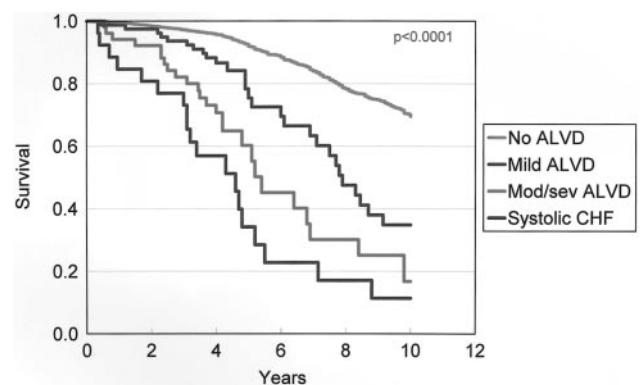


Figure 2. Kaplan-Meier curves for survival. Referent group consists of subjects with normal left ventricular systolic function (EF $>50\%$) and no history of CHF. Mild ALVD indicates mild asymptomatic left ventricular systolic dysfunction (EF 40% to 50%); Mod/Sev ALVD, moderate-to-severe asymptomatic left ventricular systolic dysfunction (EF $<40\%$); Systolic CHF, congestive heart failure with EF $\leq 50\%$.

TABLE 3. Rates of CHF (per 100 person-years) and Multivariable-Adjusted Hazards Ratios

Models	CHF Rate in Subjects With ALVD	CHF Rate in Subjects Without ALVD	Adjusted-Hazards Ratio (95% CI)
Overall	5.8	0.7	4.70 (2.72–8.14)*
Mild ALVD	3.9	0.7	3.32 (1.65–6.64)*
Moderate-to-severe ALVD	9.6	0.7	7.77 (3.86–15.63)*
Impact of ALVD in selected subgroups			
Those with a history of MI at baseline	5.9	2.2	3.31 (1.21–9.03)*
Those without a history of MI at baseline	5.8	0.6	4.88 (2.55–9.36)*
Subjects without MI or valvular disease	5.5	0.5	6.50 (3.13–13.50)*

Hazards ratios adjusted for age, sex, myocardial infarction, systolic blood pressure, antihypertensive therapy, diabetes, total-to-HDL cholesterol ratio, valvular disease, smoking, and ECG left ventricular hypertrophy. CI indicates confidence interval; MI, myocardial infarction.

* $P < 0.02$, subjects without ALVD as referent.

Deaths in ALVD subjects were attributed to coronary heart disease (40%), other cardiovascular disease (21%), noncardiovascular causes (35%), or unknown (4%). Forty-three percent of the coronary heart disease deaths were sudden (occurring within 1 hour of symptom onset). Subjects with ALVD did not invariably pass through a phase of overt CHF before death; 29 (56%) ALVD subjects who died did not develop antecedent CHF. The cause of death was known in 27 ALVD subjects who died without CHF, 11 (41%) of whom died from cardiovascular causes.

Impact of ALVD on Risk of CHF and Death: Multivariable Analyses

ALVD was associated with a nearly 5-fold increased risk of CHF in multivariable analyses (Table 3). The increased risk of CHF associated with ALVD was evident in those with and without a history of myocardial infarction at baseline. In individuals without either myocardial infarction or valve disease, there was a more than 6-fold increased risk of CHF associated with ALVD. Furthermore, absolute rates of CHF were very similar across different subgroups of ALVD subjects (Table 3). Results were similar in additional analyses adjusting for cohort status (original or offspring), and there was no significant interaction between cohort status and presence of ALVD. ALVD was also associated with an increased risk of mortality in multivariable analyses (adjusted-hazards ratio 1.6, CI, 1.1 to 2.4).

Predictors of CHF and Death Among Individuals With ALVD

Using stepwise regression analyses, we evaluated predictors of incident CHF and death in those with ALVD. Significant predictors of CHF in these subjects were occurrence of interim myocardial infarction ($P=0.0001$) and severity of ALVD ($P=0.0001$). Multivariable predictors of death were similar: age ($P=0.02$), interim myocardial infarction ($P=0.02$), and severity of ALVD ($P=0.02$). No other predictors were significant at $P < 0.05$.

Discussion

In this large, community-based cohort, the prevalence of ALVD was 3.0%, increasing with age and higher in men. The

majority of subjects with ALVD had only mild systolic impairment (EF 40% to 50%). Nonetheless, ALVD was associated with a high risk of progression to CHF and death, which was independent of baseline cardiovascular risk factors but was influenced by the degree of systolic dysfunction. The increased risk of CHF was seen across several clinical subgroups and was evident even in those without prior myocardial infarction or valvular heart disease, ie, individuals who would not normally undergo echocardiography. Our findings may have implications for the management of unselected patients with LV systolic dysfunction and for the evaluation of screening strategies for ALVD in the community.

Rates of Progression to CHF and Death: Comparison With Prior Studies

The present investigation extends present knowledge about the prognosis of ALVD, which is based primarily on the experience of participants in randomized-controlled trials.^{8,9} The annual incidence of CHF among Framingham subjects with moderate-to-severe ALVD was 9.6%, similar to the average annual CHF rate in the placebo arm of the SOLVD Prevention trial (9.7%).⁸ In contrast, the mortality rate among Framingham participants (11.0% per year for moderate-to-severe ALVD) was substantially higher than the average annual mortality rate in the SOLVD Prevention trial (5.1%). This disparity likely reflects the older age of individuals with ALVD in the community. Indeed, overall mortality rates associated with ALVD in 2 other community-based investigations are similar to those reported here.^{16,17}

Significance of Mild LV Systolic Dysfunction

There are few data regarding the natural history of mild LV systolic dysfunction in the community. Our findings indicate that mild ALVD is prognostically important, with rates of CHF and death that are 2- to 4-fold higher than those of individuals with normal LV systolic function. Importantly, the median survival free of CHF was about 10 years in those with mild ALVD, suggesting a window of opportunity during which these individuals could be identified and treated, provided optimal therapy could be determined.

The observational data presented in this study emphasize the need for studies to define optimal management of patients with mild ALVD. It is unclear if mild ALVD should be treated at all, in the absence of data from clinical trials. However, if risk reductions of 10% to 30% with treatment were possible, the 5-year numbers-needed-to-treat to prevent CHF would be relatively modest, ranging from 17 to 52 for those with mild ALVD. Although these numbers-needed-to-treat estimates are entirely speculative, they could form the basis for planning clinical trials.

Mechanisms of Progression to CHF and Death

The events that underlie the transition from ALVD to CHF are poorly understood.³ Our data suggest that an intercurrent myocardial infarction precipitates this transition in fewer than a third of CHF cases. Prior experimental and echocardiographic studies suggest that ventricular remodeling and dilatation may proceed in the absence of recurrent ischemic injury, due to activation of neurohormonal pathways accompanied by changes occurring at the cellular and molecular level in cardiac myocytes and the extracellular matrix.^{2,3,18} Thus, subjects with initially mild ventricular dysfunction may progress to moderate or severe ventricular dysfunction before developing symptomatic CHF.

Some ALVD subjects in our sample died of cardiovascular causes without passing through a symptomatic phase of CHF. A high rate of sudden death has been demonstrated in patients with severe systolic dysfunction after myocardial infarction, but similar data are not available from a more broadly-defined sample.¹⁹ Additional studies are needed to understand the mechanisms responsible for the increased mortality associated with ALVD.

Strengths and Limitations

We had the opportunity to study a large, well-characterized community-based cohort in which routine echocardiography was performed. Additional strengths of this investigation include the routine surveillance for cardiovascular endpoints, uniform criteria for diagnosing CHF, and the ability to use community-based controls with normal LV systolic function and individuals with prevalent CHF as comparison groups.

It should also be emphasized that the identification of ALVD in this study was based on an easily obtainable, visual estimate of EF by a cardiologist. This approach was taken because it mirrors what is routinely done in clinical practice in echocardiography laboratories.²⁰ Quantitative methods of assessment of LVEF (such as "Simpson's rule") are not routinely used because they are time-consuming and may not be applicable to all subjects because of the need for clear endocardial visualization.^{15,20} Furthermore, prior studies suggest that the reproducibility and accuracy of visual assessments are as good as those of quantitative methods.^{14,15} Our results demonstrate that a visual estimate of EF can distinguish normal from abnormal LV systolic function, and "mildly impaired" from "moderately reduced" EF, in a prognostically useful fashion. Any misclassification of LVEF introduced by this approach would likely be random and would lead to a conservative bias.

Several limitations of our investigation merit comment. We followed the convention of defining ALVD as a reduced EF in the absence of a history of CHF.⁸⁻¹⁰ Some subjects may have had symptoms but did not meet criteria for CHF. Additionally, some of our subjects were taking ACE inhibitors for hypertension or other indications, which could favorably impact the prognosis of ALVD. Our analyses of predictors of CHF and death among ALVD subjects were hampered by a modest sample size, and we did not investigate the impact of neurohormonal factors or progression of LV dysfunction.

We were limited in our ability to characterize the natural history of ALVD in women, because the condition was infrequent in women. A gender disparity in the prevalence of ALVD has been observed in other cohorts.^{5,6} However, symptomatic CHF is almost as common in women as in men, because of the greater burden of diastolic CHF in women.²¹ Pooled analyses of data on women with ALVD in different epidemiological investigations may be required to examine the natural history of this condition in women.

Conclusions

Individuals with ALVD in the community are at considerably increased risk of developing CHF and death. Although the magnitude of this risk varies according to the degree of LV systolic dysfunction, even mild LV systolic dysfunction is associated with a high rate of progression to overt CHF. These data suggest that it may be possible to reduce the incidence of CHF by targeting individuals with ALVD.¹⁰ Additional research is needed, however, to identify cost-effective strategies for detecting ALVD in the community, and to determine whether early treatment is warranted.

Acknowledgments

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