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Diastolic Dysfunction and Left Atrial Volume

A Population-Based Study

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OBJECTIVES We examined the association between diastolic function and left atrial volume indexed to body surface area (LAVi) in a population-based study.

BACKGROUND Atrial enlargement has been suggested as a marker of the severity and duration of diastolic dysfunction (DD). However, the association between DD and atrial enlargement and their individual prognostic implications in the population is poorly defined.

METHODS A cross-sectional sample of Olmsted County, Minnesota, residents ≥45 years of age (n = 2,042) underwent comprehensive Doppler echocardiography and medical record review.

RESULTS The LAVi increased with worsening DD: 23 ± 6 ml/m^2 (normal), 25 ± 8 ml/m^2 (grade I DD), 31 ± 8 ml/m^2 (grade II DD), 48 ± 12 ml/m^2 (grades III to IV DD). In bivariate analyses, age, left ventricular mass index, and DD grade were positively associated, whereas female gender and ejection fraction (EF) were inversely associated with LAVi ($p < 0.001$ for all). When controlling for age, gender, cardiovascular (CV) disease, EF, and left ventricular mass, grade II DD was associated with a 24%, and grade III to IV DD was associated with a 62% larger LA volume ($p < 0.0001$ for both). The area under the receiver-operator characteristic curve for LAVi to detect grade I, grade II, or grade III to IV DD was 0.57, 0.81, and 0.98, respectively. Both DD and LAVi were predictive of all-cause mortality, but when controlling for DD, LAVi was not an independent predictor of mortality.

CONCLUSIONS These data suggest that DD contributes to LA remodeling. Indeed, DD is a stronger predictor of mortality; presumably it better reflects the impact of CV disease within the general population. (J Am Coll Cardiol 2005;45:87–92) © 2005 by the American College of Cardiology Foundation

Left atrial (LA) enlargement is predictive of future stroke, atrial fibrillation, and death (1–3). The factors leading to atrial remodeling in the absence of mitral valve disease are not well established. Previous studies have reported an association between blood pressure and ventricular hypertrophy and atrial dimension (4). Hypertension, ventricular hypertrophy, and other cardiovascular (CV) diseases could potentially lead to diastolic dysfunction (DD), elevation of filling pressures, and atrial remodeling from chronic pressure overload. Indeed, LA volume has been suggested as a marker of the severity and duration of DD, perhaps obviating the need for more complex characterization of diastolic function and filling pressures with Doppler echocardiography (5,6). Doppler indexes reflect filling pressures at one point in time, whereas increased LA size may better reflect the cumulative effect of filling pressures over time. Additionally, other factors unrelated to diastolic pressure overload may affect LA size. Thus, the correlation between Doppler indexes of diastolic function/filling pressures and atrial size may not be strong.

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We sought to examine the relationship between atrial volume indexed to body surface area (LAVi) and clinical and Doppler echocardiographic parameters in randomly selected residents of Olmsted County, Minnesota, ≥45 years old. Further, we examined the predictive characteristics for use of LAVi to detect DD as defined by Doppler. Lastly, we examined the relative prognostic implications of DD and LA remodeling in the population.

METHODS

This study was approved by the Mayo Institutional Review Board, and subjects gave written informed consent.

Study setting. Olmsted County, Minnesota, is located in southern Minnesota. The characteristics of this population and the unique resources for population-based epidemiological research in Olmsted County have been previously described (7).

Population sampling, subject recruitment, and enrollment. Using the resources of the Rochester Epidemiology Project, residents of Olmsted County ≥45 years of age were invited to participate. The methods used to sample and characterize the population have been previously described (8–10). Of the 4,203 subjects invited, 2,042 (47%) participated.

Medical record review. Each subject's medical record was reviewed by trained nurse abstractors using established

Abbreviations and Acronyms

CV = cardiovascular
DD = diastolic dysfunction
EF = ejection fraction
LA = left atrium/atrial
LAVi = left atrial volume index
LV = left ventricular
LVMi = left ventricular mass index

criteria for hypertension (11), myocardial infarction (12), and congestive heart failure (13). In addition, a clinical diagnosis of coronary artery disease, diabetes mellitus, and history of atrial dysrhythmias were recorded. All six of these diagnoses are combined and used as a single variable: CV disease.

Doppler and two-dimensional echocardiography. All echocardiograms were performed by one of three registered diagnostic cardiac sonographers with the same echocardiographic instrument (HP Sonos-2500, Philips, Andover, Massachusetts) according to a standardized protocol and interpreted by a single echocardiologist (M.M.R.).

Assessment for valvular disease. Two-dimensional and color Doppler imaging were performed to screen for valvular stenosis or regurgitation. Participants were labeled as having valve disease if they had more than moderate regurgitation or stenosis.

Assessment of cardiac structure. Left ventricular (LV) mass (M-mode) was calculated according to the American Society of Echocardiography guidelines (14). The LA dimension was measured by two-dimensional guided M-mode echocardiography obtained in the parasternal short-axis view at the base of the heart according to American Society of Echocardiography recommendations (15). Three LA dimensions were used to calculate LA volume as an ellipse using the formula:

$$\text{LA volume} = \pi / 6\,[SA_1 \cdot SA_2 \cdot LA]$$

where SA_1 = the M-mode LA dimension as described previously, and SA_2 and LA are measurements of short- and long-axis dimensions in the apical four-chamber view at ventricular end-systole as previously described (10,16).

Assessment of diastolic function. Pulsed-wave Doppler examination of mitral (before and with Valsalva maneuver) and pulmonary venous inflow as well as Doppler tissue imaging of the mitral annulus was performed in each subject as previously described and validated (9,17–19). These variables were used to categorize diastolic function as normal, impaired relaxation with normal or near-normal filling pressures (grade I); impaired relaxation with moderate elevation of filling pressures, "pseudonormal filling" (grade II); and impaired relaxation with marked elevation of filling pressures, "restrictive filling" (grades III and IV) as previously described (9,17).

The mitral inflow early filling velocity (E) to atrial filling velocity (A) ratio was used for initial categorization. If the E/A was <0.75, grade I DD was present. If the E/A ratio was in the normal range (0.75 to 1.5) and the deceleration time was >140 ms, then the other Doppler indexes were used to determine if filling was normal (normal diastolic function) or "pseudonormal" (grade II DD). If there were two other Doppler indexes suggestive of elevated filling pressures (change in E/A with Valsalva of >0.5; pulmonary venous systolic [S] velocity less than diastolic [D] velocity; pulmonary venous atrial reversal duration greater than mitral A duration >30 ms; or ratio of E to the velocity of early mitral annular ascent [e′] of >10), then grade II DD was considered to be present. If the E/A ratio was >1.5 and the deceleration time was <140 ms, and at least one other Doppler index suggestive of elevated filling pressures was present, the subject was considered to have grade III DD (if the change in E/A with Valsalva was >0.50) or grade IV DD (if the change in E/A with Valsalva was <0.50). Here, a deceleration time of <140 ms was considered one index of elevated filling pressures, and another index was required for confirmation. These groups (grades III and IV) are combined for the purposes of this analysis. For subjects in atrial fibrillation, diastolic function was classified as indeterminate unless restrictive physiology (mitral inflow early velocity <140 ms) was present.

Subjects with a "normal" mitral inflow pattern and with one criterion for moderate DD, whose other Doppler parameters were borderline and suggestive of DD but did not quite meet the cutoff values, were classified as indeterminate rather than as normal. Subjects were also classified as indeterminate if sufficient Doppler parameters were not obtained for technical reasons or if E–A fusion was present.

Assessment of ejection fraction (EF). In each subject, measurements of EF by M-mode (Modified Quinones formula), quantitative two-dimensional (Biplane Simpson method of disks), and semiquantitative two-dimensional (visual estimate) methods were performed as previously described (9). As EFs by these methods were highly correlated and because the visual estimate method was available in >99% of participants, the visual estimate method was used for this analysis.

Definition of LA enlargement. Of the 2,042 participants, 1,020 had no history of CV, renal, or pulmonary disease and were taking no CV medications. Of these, 767 subjects had normal EF (>50%), no wall motion abnormalities, normal diastolic function, no valve disease, and normal sinus rhythm and comprised the normal reference subgroup. Reference ranges for ratio of LAV to body surface area were derived from this subgroup as previously described with LAVi >95th percentile used to define LA enlargement ($\geq$30 ml/m^2 for women and $\geq$33 ml/m^2 for men) (10).

Survival data. As part of the Rochester Epidemiology Project, mortality data on Olmsted County residents are collected by reviewing community medical records, death certificates, and obituary notices. Participants were followed up until death or April 30, 2003, at which time they were censored.

Statistical methods. Continuous variables are summarized as mean values ± SD and categorical data as a percent of the

Table 1. Predictive Characteristics of LAVi for Detection of DD (as Defined by Doppler) in the Study Population

	AUC (CI)	Partition LAVi (ml/m^2)	Sensitivity	Specificity
Versus all other classes of diastolic function within the entire study population				
Any DD (grades I–IV)	0.64 (0.61–0.67)	24.5	0.55	0.66
Moderate to severe DD (grade II, III, or IV)	0.81 (0.77–0.85)	27.1	0.69	0.77
Severe DD (grade III or IV)	0.97 (0.94–0.99)	33.8	0.92	0.92
Versus those with normal diastolic function				
Mild DD (grade I)	0.57 (0.53–0.61)	22.3	0.61	0.51
Moderate DD (grade II)	0.81 (0.77–0.85)	25.5	0.73	0.72
Severe DD (grade III or IV)	0.98 (0.96–1.0)	31.4	1.00	0.91

AUC = area under the receiver-operating characteristic curve; CI = 95% confidence interval; DD = diastolic dysfunction; LAVi = left atrial volume index.

group total. The association of natural log LAVi with clinical and echocardiographic variables was examined in stages using linear regression. The log transformation of LAVi was used to satisfy the assumptions necessary for the modeling. The first model consisted of just age and gender followed incrementally by the addition of CV disease, EF, and finally DD. This modeling approach was used to understand the added value of each variable relative to previous information and is summarized as a change in the model R^2 (percent of explained variance). The effect of each variable on LAVi was summarized as a mean percent change in raw LAVi relative to a one standard deviation change in the predictor. Receiver-operator characteristic curve analysis was used to evaluate the predictive accuracy of LAVi for the detection of various groupings of DD grade and is summarized by the area under the curve. We also reported the sensitivity and specificity of the LAVi at the "optimal point" on the receiver-operator characteristic curve as the point nearest the corner of the receiver-operator characteristic curve where sensitivity and specificity would be 100%. The value of LAVi at that point (the partition LAVi) is also reported (Table 1). Kaplan-Meier curves were used to evaluate the bivariate association of DD grade and quartile grouping of LAVi with all-cause mortality. The association of LAVi with all-cause mortality while adjusting for age, gender, EF, and DD grade was done using Cox proportional hazards regression.

Table 2. Participant Demographics (n = 1,657)

Male gender (%)	47
Age, yrs (mean ± SD)	61 ± 10
Height, cm (mean ± SD)	168 ± 10
Weight, kg (mean ± SD)	80 ± 17
BSA, m^2 (mean ± SD)	1.89 ± 0.23
LV mass/BSA, g/m^2 (mean ± SD)	97 ± 22
Ejection fraction, % (mean ± SD)	63 ± 7
Hypertension, n (%)	463 (28)
Coronary artery disease, n (%)	171 (10)
Diabetes, n (%)	117 (7)
Myocardial infarction, n (%)	68 (4)
History of atrial fibrillation, n (%)	49 (3)
Atrial fibrillation at echo, n (%)	4 (0.2)
Valve disease, n (%)	36 (2)
Congestive heart failure, n (%)	18 (1)

BSA = body surface area; LV = left ventricular.

RESULTS

Feasibility of Doppler echocardiographic assessment. From the overall cohort (n = 2,042), LA volume could not be measured in 154 subjects, and in 262 subjects the diastolic assessment was inconclusive. This left a total of 1,657 subjects with data for LAVi and in whom diastolic function was able to be graded.

Participant demographics. The characteristics of these 1,657 participants are presented in Table 2.

Mean LAVi and the prevalence of LA enlargement increase with worsening diastolic function grade. Table 3 demonstrates the distribution of diastolic function and the associated mean LAVi. Atrial size, as measured by LAVi, increases progressively with increasing DD ($r = 0.20$; $p < 0.0001$). The prevalence of LA enlargement also increases with increasing severity of DD.

The association of DD and LAVi. We defined the strength of the association between LAVi and DD before and after controlling for pertinent covariates (Table 4). Age, LV mass index (LVMi), and grades I, II, and III to IV DD all had a positive association with LAVi, whereas female gender and higher EF were inversely related to LAVi. In multivariate models, age, gender, LVMi, and DD grade were independently associated with LAVi.

We constructed specific models to examine the additive contribution of variables to a model predicting atrial size. Figure 1 demonstrates the change in explained variance (R^2) with stepwise addition of CV disease, EF, and LVM, or DD to a base model of age and gender (Fig. 1, left panel). When CV disease is added to the base model, adding LVMi and EF or DD grade improves the predictive value of the model (Fig. 1, middle panel). When LVMi and EF are added to the base model, DD grade still significantly

Table 3. LAVi According to Diastolic Function Grade

Diastolic Grade	n	% of Cohort	LAVi, ml/m^2 (Mean ± SD)	% Meeting Criteria for LAE
Normal	1,212	73	23 ± 6	9
Grade I	315	19	25 ± 8	17
Grade II	118	7	31 ± 8	48
Grade III to IV	12	1	48 ± 12	100

*≥30 ml/m^2 in women or ≥33 ml/m^2 in men.
LAE = left atrial enlargement; LAVi = left atrial volume index.

Table 4. Determinates of LAVi

	Bivariate Analysis		Adjusted Analysis	
	Effect	p Value	Effect	p Value
Age (yrs)	+8%	< 0.001	+5%	< 0.001
Female	−6%	< 0.001	−7%	< 0.001
Ejection fraction (%)	−3%	< 0.001	−0.3%	0.723
LV mass index (g/m^2)	+11%	< 0.001	+7%	< 0.001
Grade I DD	+7%	< 0.001	−0.5%	0.225
Grade II DD	+36%	< 0.001	+24%	< 0.001
Grade III to IV DD	+95%	< 0.001	+62%	< 0.001

Effect size indicates the percent change in LAVi for females vs. males, per 1-SD change in age (10 yrs), ejection fraction (7%), or LV mass index (22 g/m^2), or with grade I, II, or III to IV DD as compared with normal diastolic function.

DD = diastolic dysfunction; LAVi = left atrial volume index; LV = left ventricular.

increases the predictive value of the model (Fig. 1, right panel). Accounting for these variables explains 43% (R^2 = 0.43) of the variability in LAVi in the population.

Value of LAVi for the detection of DD. We examined the sensitivity and specificity of LAVi for the detection of DD at different LAVi values to develop a receiver-operator characteristic curve examining the ability of LAVi to detect increasing grades of DD as compared with all other subjects in the population or as compared with subjects with normal diastolic function (Table 1). Whereas LAVi provided excellent sensitivity and specificity for the detection of severe (grade III or IV) DD, sensitivity and specificity for detection of mild or moderate DD were less robust.

Mortality, LAVi, and DD. We have previously reported that Doppler-defined diastolic function grade was predictive of all-cause mortality in this population even when controlling for age, gender, and EF (deaths as of October 1, 2002: n = 48 deaths) (9). In this updated analysis (52 deaths as of April 30, 2003), both DD grade and LAVi were predictive of all-cause mortality in the population (Fig. 2). After controlling for age, gender, EF, and LAVi, diastolic function grade was associated with all-cause mortality. Adjusting for age, gender, EF, and diastolic function grade, LAVi was not associated with all-cause mortality (Table 5).

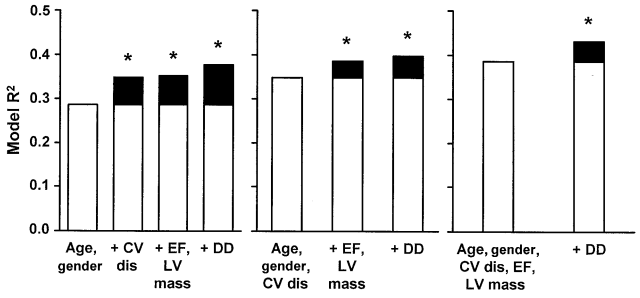

Figure 1. Stepwise multivariate analysis demonstrating the cumulative effect of age, gender, cardiovascular (CV) disease (dis), ejection fraction (EF), left ventricular mass index (LVMi), and diastolic dysfunction (DD) on left atrial volume index (LAVi) in the population. In the **left panel**, CV, EF and LVMi, and DD all add to the base model of age and gender for prediction of LAVi. In the **middle panel**, the addition of EF and LVMi as well as DD add to the base model of age, gender, and CV disease. In the **right panel**, the addition of DD adds to the base model incorporating age, gender, CV disease, EF and LVMi. *p < 0.001 compared with the base model.

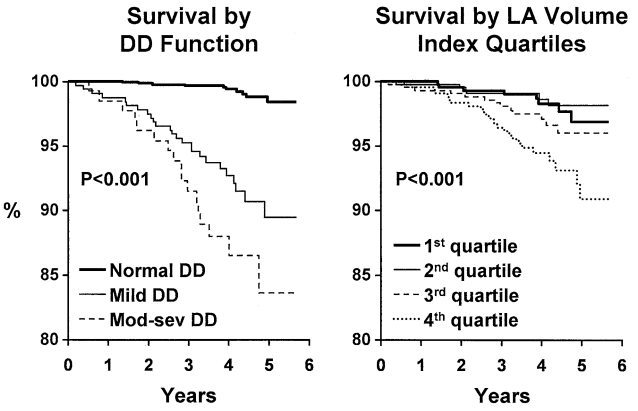

Figure 2. Kaplan-Meier survival curves demonstrating the relationships between severity of diastolic dysfunction (DD) **(left)** and left atrial (LA) volume index **(right)** and survival. Mod-sev = moderate to severe.

DISCUSSION

In this cross-sectional sample of a population ≥45 years old, atrial size as assessed by LAVi was correlated with severity of DD, and this association was still apparent after controlling for pertinent covariates including age, gender, presence of CV disease, EF, and LVMi. These cross-sectional data confirm the previously described association between atrial remodeling and CV disease or LV remodeling. They also lend support to the concept that DD mediates, at least in part, this association. Although LAVi was associated with the severity of DD, it was a poor marker of mild or moderate DD in the general population, and the severity of DD but not LAVi was independently associated with all-cause mortality.

LA volume as an index of atrial remodeling. Studies using LA dimension measured by M-mode echocardiography to assess LA remodeling have demonstrated that LA enlargement occurs in persons with CV disease and that LA remodeling predicts CV events (1–3). Because the LA may become less spherical as it remodels, LA volume is proposed as a better index of LA remodeling, and indeed we have

Table 5. Multivariate Analysis of Predictors of All-Cause Mortality

	Chi-Square	Hazard Ratio	p Value
Age (per yr)	22.5	1.08	< 0.0001
Female gender	0.09	1.09	0.77
Ejection fraction (per 1%)	9.76	0.96	0.0018
Mild DD (grade I DD vs. normal diastolic function)	10.31	3.74	0.0013
Moderate DD (grade II DD vs. normal diastolic function)	9.06	4.32	0.0026
Severe DD (grade III or IV DD vs. normal diastolic function)	8.15	7.39	0.0043
LAVi (quartile 2 vs. quartile 1)	1.03	0.58	0.31
LAVi (quartile 3 vs. quartile 1)	0.03	1.08	0.87
LAVi (quartile 4 vs. quartile 1)	0.02	0.93	0.87

Abbreviations as in Table 4.

previously reported that LA volume displays a somewhat stronger association with the presence of CV disease in the general population (10). Tsang et al. (3,20) reported that LA volume was more predictive of future atrial fibrillation and other CV events than LA dimension in variable clinical populations. Thus, LA volume may be a more sensitive index of LA remodeling than LA dimension and may provide superior prognostic information.

Atrial remodeling and DD. Although previous studies have established the association of CV disease and LV remodeling with LA enlargement, the mechanism whereby CV disease and LV remodeling results in LA remodeling has not been conclusively defined. Atrial myopathy independent of ventricular dysfunction could lead to LA remodeling independent of hemodynamic load. Volume overload secondary to mitral regurgitation and elevated LV filling pressures in patients with reduced EF are well recognized to be associated with LA enlargement. However, in patients with normal systolic function and without mitral regurgitation, those factors mediating LA remodeling are less clear. Previously, Nishimura et al. (21) demonstrated that increasing LA pressure positively correlated with Doppler evidence of DD in a group of patients with cardiomyopathy and EFs $\leq$40%. Similarly, Matsuda and Matsuda (22) demonstrated that LA maximal volume increased with increasing severity of DD as defined by invasive hemodynamic study. Thus, it has been hypothesized that CV disease leads to DD, which results in chronic diastolic atrial pressure overload and subsequent LA enlargement. The current findings are supportive of that concept as DD was independently associated with LAVi even when controlling for the presence of CV disease, LV systolic dysfunction, and LV hypertrophy. The LA volume was not a reliable indicator of mild to moderate (grade I or II) DD.

Is LAVi an adequate surrogate marker of DD? The Doppler echocardiographic assessment of diastolic function reflects the combined influence of impairment in LV relaxation (grade I DD) and impairment in LV relaxation with elevation in filling pressures (grade II DD). When filling pressures are very high, restrictive physiology (grades III and IV DD) is present either because of a decrease in operant compliance (upward shift on the same LV end-diastolic pressure-volume relationship) or as a result of a true decrease in LV compliance (upward and leftward shift of the LV end-diastolic pressure-volume relationship). Although these Doppler patterns have been validated with invasive hemodynamic measurements and have been demonstrated to have prognostic value, like any diagnostic test, sensitivity and specificity are imperfect. Further, the comprehensive assessment needed to optimally define diastolic function and filling pressures is technician dependent, requires informed interpretation, and is not routinely performed in all laboratories. Finally, such an assessment provides information about a single point in time and may not reflect the severity of DD over time. Thus, it has been suggested that LAVi may provide a superior and more easily measured index of CV risk (23). However, here we find that although LAVi is highly sensitive and specific for the detection of severe (grade III or IV) DD, it is not a robust marker of mild or moderate DD. Mild, moderate, and severe DD all have prognostic importance within the population as a whole, whereas LAVi adds no incremental prognostic value beyond that provided by DD. These findings suggest that, at least in a population-based setting, LAVi is not an adequate surrogate for comprehensive Doppler assessment of DD. We speculate that chronic and severe elevation of filling pressures is needed to induce significant atrial remodeling and that the minimal or milder degree of atrial pressure elevation likely associated with grade I or II DD is insufficient to induce clearly abnormal LA volume. In contrast, severe elevation of atrial pressures indicated by advanced (grade III or IV) DD is more likely to have induced significant atrial remodeling making LA volume relatively sensitive for the detection of advanced DD.

In contrast, Moller et al. (24) reported that LAVi was the most potent predictor of mortality in patients with acute myocardial infarction. Indeed, when added to a model that included LAVi, conventional predictors of survival such as EF, reperfusion therapy, and age were no longer predictive, although the presence of severe DD added independent prognostic information. Several factors may explain the disparities between this clinical study and our findings in the general population. There are differences in the extent and quality of diastolic assessment in retrospective studies using clinical databases versus prospective studies performed with no knowledge of clinical data. More importantly, however, these differences likely reflect comparison of the relative value of two indexes at very different stages in disease progression. It may be that in the population as a whole, changes in LAVi are most closely related to diastolic function abnormalities, and thus, LAVi provides no incremental predictive value. In contrast, in clinical cohorts confined to those with often advanced CV disease, atrial remodeling may be influenced by mitral regurgitation and nonhemodynamic remodeling associated with humoral activation (25,26) and arrhythmias (27), whereas Doppler patterns may be acutely influenced by ongoing treatment. Thus, LAVi may provide a better reflection of global impairment in cardiac function and systemic adaptations. Clinical populations have more likely had CV disease longer, as reflected in the much higher mean age present in the myocardial infarction study than the population-based study here. In support of this concept, Tsang et al. (20) examined clinical and echocardiographic predictors of CV events (heart failure, myocardial infarction, revascularization, stroke, or CV death) in elderly patients who had been referred for an echocardiogram and had known CV disease but who had not had the index CV events. In this population, lying somewhere between the myocardial infarction population and the general population, both LAVi and DD were predictive of future CV events. Thus, we view the current data as complementary to these and other clinical studies demonstrating the relationship between CV

disease, DD, and atrial remodeling across the spectrum of disease progression as assessed in the general and different clinical populations. Although inclusion of atrial volume in population-based studies seeking novel and more sensitive CV risk factors has been suggested (23), the current data suggest that in the general population, assessment of DD may hold more promise as an early marker of risk. We speculate that Doppler assessment of DD may be a sensitive marker of disease severity, whereas LA volume reflects only one aspect of disease impact (elevation of filling pressures). It is remarkable that a substantial increment in risk occurs in the presence of even Grade I DD, even controlling for association of this pattern with age and impaired systolic function. Further studies are needed to understand this potent association.

Potential limitations. These data are cross-sectional and cannot establish causal relationships between clinical and echocardiographic variables and LA size. As with all prospective epidemiologic studies, bias can be introduced by incomplete participation within the population. As Olmsted County, Minnesota, is not ethnically diverse, these data may not be pertinent to all populations.

Conclusions. In the general population, atrial remodeling as assessed by LAVi is closely associated with the severity of DD, a relationship that persists after adjustment for pertinent clinical and echocardiographic covariates. However, LAVi does not reliably predict milder but prognostically important degrees of DD, and the severity of DD is most predictive of future death.

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