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Left Ventricular Diastolic Dysfunction as a Predictor of the First Diagnosed Nonvalvular Atrial Fibrillation in 840 Elderly Men and Women

Teresa S. M. Tsang, MD, FACC,* Bernard J. Gersh, MB, ChB, DPhil, FACC,* Christopher P. Appleton, MD,§ A. Jamil Tajik, MD, FACC,* Marion E. Barnes, MS,* Kent R. Bailey, PhD,† Jae K. Oh, MD, FACC,* Cynthia Leibson, PhD,‡ Samantha C. Montgomery, MS,† James B. Seward, MD, FACC*

Rochester, Minnesota; and Scottsdale, Arizona

OBJECTIVES The objective of this study was to determine whether diastolic dysfunction is associated with increased risk of nonvalvular atrial fibrillation (NVAF) in older adults with no history of atrial arrhythmia.

BACKGROUND Few data exist regarding the relationship between diastolic function and NVAF.

METHODS The clinical and echocardiographic characteristics of patients age ≥65 years who had an echocardiogram performed between 1990 and 1998 were reviewed. Exclusion criteria were history of atrial arrhythmia, stroke, valvular or congenital heart disease, or pacemaker implantation. Patients were followed up in their medical records to the last clinical visit or death for documentation of first AF.

RESULTS Of 840 patients (39% men; mean [± SD] age, 75 ± 7 years), 80 (9.5%) developed NVAF over a mean (± SD) follow-up of 4.1 ± 2.7 years. Abnormal relaxation, pseudonormal, and restrictive left ventricular diastolic filling were associated with hazard ratios of 3.33 (95% confidence interval [CI], 1.5 to 7.4; $p = 0.003$), 4.84 (95% CI, 2.05 to 11.4; $p < 0.001$), and 5.26 (95% CI, 2.3 to 12.03; $p < 0.001$), respectively, when compared with normal diastolic function. After a number of adjustments, diastolic function profile remained incremental to history of congestive heart failure and previous myocardial infarction for prediction of NVAF. Age-adjusted Kaplan-Meier five-year risks of NVAF were 1%, 12%, 14%, and 21% for normal, abnormal relaxation, pseudonormal, and restrictive diastolic filling, respectively.

CONCLUSIONS The presence and severity of diastolic dysfunction are independently predictive of first documented NVAF in the elderly. (J Am Coll Cardiol 2002;40:1636–44) © 2002 by the American College of Cardiology Foundation

In the face of a burgeoning older population, the prevalence of atrial fibrillation (AF), which is associated with marked morbidity, mortality, and socioeconomic burden (1–4), is rapidly increasing. Together with congestive heart failure (CHF) and type 2 diabetes mellitus, AF constitutes one of the three growing epidemics in the twenty-first century (5,6). Demographically, the decline in rheumatic heart disease in the developed world has shifted the etiology toward a preponderance of nonvalvular AF (NVAF) (7), which is one of the most powerful independent risk factors for stroke (8,9) and is responsible for 75,000 strokes annually in the U.S. Although diastolic dysfunction (10) and AF (3) are both age-related conditions, the relationship between diastolic function and the development of NVAF has not been defined. The objective of this study was to determine whether diastolic dysfunction is associated with increased risk of NVAF in elderly subjects with no prior history of atrial arrhythmias.

From the *Division of Cardiovascular Diseases and Internal Medicine, †Section of Biostatistics, and ‡Section of Clinical Epidemiology, Mayo Clinic, Rochester, Minnesota; and the §Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale, Arizona. Grant support provided by the American Heart Association and the American Society of Echocardiography.

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METHODS

Study design and population. A cohort design was used in this study. After the study was approved by the Mayo Foundation Institutional Review Board, a list of potential subjects was identified from the computerized echocardiography database. This list included all residents of Olmsted County, Minnesota, who underwent at least one transthoracic echocardiogram at Mayo Clinic (Rochester, Minnesota), Olmsted Medical Center (Rochester, Minnesota), or their affiliated hospitals between January 1, 1990, and December 31, 1998, and who were at least 65 years old on the day of the procedure. Mayo Clinic and its two affiliated hospitals, together with Olmsted Medical Center and its affiliated hospital, provide >95% of the medical care delivered to Olmsted County residents (11). Consequently, the population from which the sample was drawn included nearly all elderly Olmsted County residents referred for a transthoracic echocardiogram during the period of interest.

A total of 6,078 Olmsted County residents, age ≥65 years, underwent transthoracic echocardiography during the period studied. For patients who had more than one echocardiogram performed, the earliest examination within the study period was designated as the baseline study. The list of patients was cross-referenced with the computerized

Abbreviations and Acronyms

AF = atrial fibrillation
CAD = coronary artery disease
CHF = congestive heart failure
DT = deceleration time
LA = left atrium or left atrial
LV = left ventricle or left ventricular
MI = myocardial infarction
NVAF = nonvalvular atrial fibrillation

Mayo Clinic registration file, medical index (containing diagnostic codes), surgical database, and electrocardiographic database. Excluded were 1,772 patients who, on or before the date of the baseline echocardiogram, had a diagnosis of AF or other atrial arrhythmia, stroke (any type), congenital heart anomaly, or had undergone cardiac valve surgery or permanent pacemaker implantation. Also excluded were 182 patients who denied access to their medical records for research purposes. From the remaining 4,124 potential subjects, a random sample of 2,200 (53%) was drawn by SAS random number selection. Retrospective comprehensive review of the Mayo Clinic medical records of these 2,200 patients was undertaken. During this review, an additional 1,360 patients were excluded because they were found to have exclusion criteria (124 patients), more than mild valvular disease by echocardiographic criteria (929 patients), or had not (or could not) have assessments of transmitral flow velocities, left atrial (LA) volume, or body surface area for indexing LA volume (307 patients). The remaining 840 patients constituted the study population.

Clinical and echocardiographic data. The medical records of each of the 840 patients were reviewed for data on age, gender, weight, height, and clinical risk factors. The definition of coronary artery disease (CAD) included a history of treated angina, a clinical diagnosis of myocardial infarction (MI), any coronary revascularization procedure, or the presence of ≥50% stenoses in any of the three major coronary arteries or their larger branches by angiography. Valvular heart disease was defined by the presence of more than mild stenosis or regurgitation of any valve. Smoking status was classified as never, past (quit smoking ≥6 months earlier), or current. Hyperlipidemia was defined by documentation of the diagnosis in the history, current or past use of a lipid-modifying agent, a fasting total cholesterol level of ≥200 mg/dl, or a low-density lipoprotein cholesterol level of ≥130 mg/dl on at least two occasions. Hypertension was defined as documentation of the clinical diagnosis and/or use of antihypertensive medications. Diabetes mellitus was defined by the documented clinical diagnosis or treatment with oral hypoglycemic agents or insulin. Family history of CAD referred to the reported presence in first-degree relatives of CAD or angina requiring treatment, MI, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty. Chronic obstructive pulmonary disease was defined by the clinical diagnosis documented in the medical record.

Maximal LA volume was measured offline using the biplane area-length method (12–14) and also was indexed by body surface area (indexed LA volume). The cardiologists measuring LA volume were blinded to the outcome of the study, namely, the development of NVAF. All other echocardiographic data were retrieved electronically from the computerized echocardiographic database. These data included M-mode LA dimension, left ventricular (LV) end-systolic and end-diastolic dimensions, LV mass indexed to height, LV ejection fraction, LV fractional shortening, LV stroke volume, cardiac index, tricuspid regurgitation velocity, and transmitral flow profile, including peak E velocity, peak A velocity, E/A ratio, and mitral early deceleration time (DT). Unlike other transmitral flow parameters, isovolumic relaxation time was not routinely measured and, therefore, not used for analyses.

The transmitral Doppler flow profile is integral to the assessment of diastolic function (15). Early transmitral flow begins after the pressure in the LV falls below that in the LA and accelerates to a peak velocity, which is expressed as peak E. As the atrioventricular pressure gradient falls, mitral inflow decelerates, and the duration of the deceleration process is defined by DT. A period of diastasis follows, during which atrial and ventricular pressures remain approximately equal. Atrial contraction produces another forward pressure gradient, and the peak velocity achieved is expressed as peak A.

Conventionally, abnormal relaxation is considered the mildest form of diastolic dysfunction (grade I) (15). In our study the presence of mitral E/A <0.75 or DT >240 ms was considered evidence of abnormal relaxation. In a more severe stage of diastolic dysfunction with pseudonormal LV filling (grade II), the transmitral flow characteristics are similar to those in patients with normal diastolic function. However, patients with this abnormality generally have elevated LV filling pressures with an enlarged LA. In this study, both pseudonormal and normal LV filling were defined by the presence of mitral E/A of 0.75 to 1.50 and DT of 151 to 240 ms, but distinguished by whether LA volume was ≥28 ml/m^2 (pseudonormal) or <28 ml/m^2 (normal) (16). Restrictive diastolic filling (grade III, reversibly restrictive; grade IV, irreversibly restrictive) is associated with markedly elevated LV filling pressures and is the most severe form of diastolic dysfunction (14,15). In this study the presence of mitral E/A >1.5 or DT ≤150 ms were considered evidence of this abnormality. Due to the retrospective nature of the study, we were not able to reliably differentiate reversible versus irreversible restrictive physiology.

Outcome determination. The outcome of interest, namely, first documented NVAF, was defined by the first presentation of AF that was clinically documented by a physician. All cases of AF had to be confirmed by electrocardiogram (ECG). The ascertainment of AF was accomplished through review of the medical record of each patient

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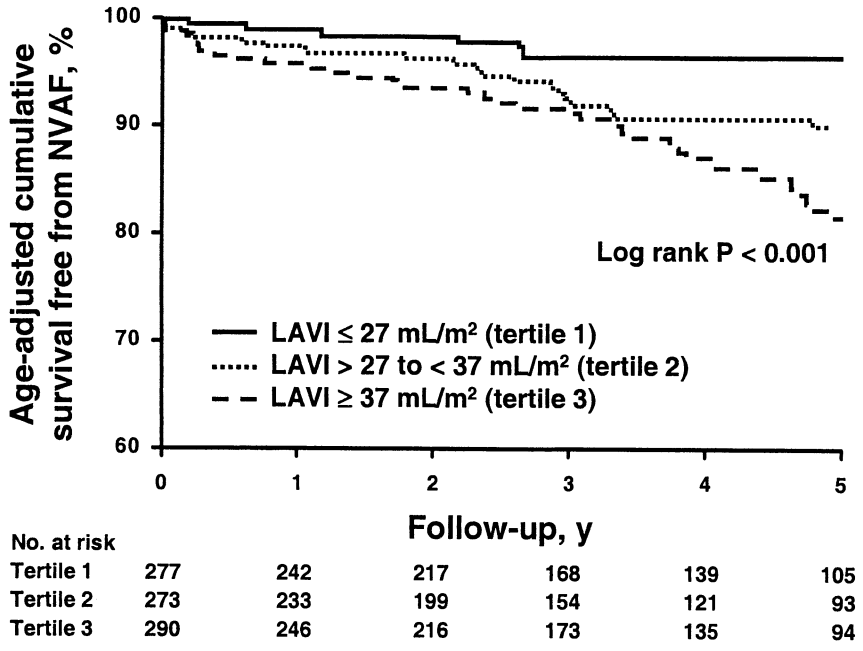


Figure 1. Age-adjusted cumulative survival without nonvalvular atrial fibrillation (NVAF) by left atrial volume indexed to body surface area (LAVI).

and examination of the ECGs accompanying the diagnosis. As part of quality assurance of the medical review, the list of patients with the outcome event based on clinical documentation was cross-referenced with medical index diagnostic code, International Classification of Diseases 9th revision (ICD-9) 427.31, and with the ECG database. The same ascertainment criteria were applied to all patients. Transient postoperative AF, occurring as an isolated episode within one month after surgery, was not counted as an outcome event. Because newly documented NVAF, not the duration or persistence of the arrhythmia, was the outcome event of interest, no distinction was made between paroxysmal and persistent NVAF.

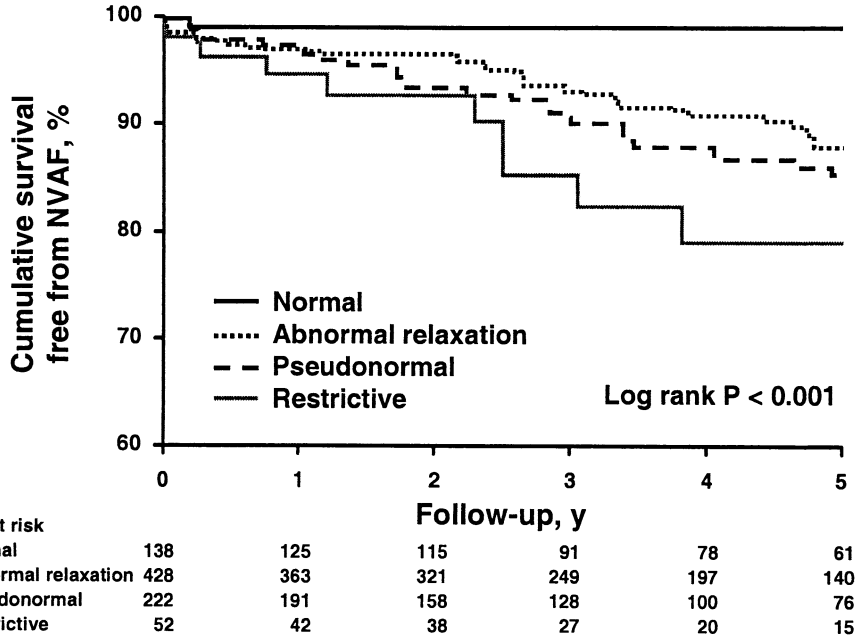
Statistical methods. Differences in baseline characteristics between patients who did and did not develop NVAF after baseline echocardiography were assessed using chi-square analyses for categorical variables and rank sum tests for continuous variables. Descriptive statistics for both groups were tabulated as means and SD or frequency percentages.

Simple and multiple Cox proportional hazards analyses were used to estimate the simple and joint associations among clinical variables, echocardiographic variables, and the risk of NVAF. The set of variables was reduced by forward stepwise algorithm until only those significant at $p < 0.05$ remained in the multivariate model. From these models, hazard ratios (HR), 95% confidence intervals (CI), and the associated p values were generated.

The age-adjusted effects of indexed LA volume tertiles and diastolic function categories on the risk of NVAF were also assessed by an age-stratified weighted Kaplan-Meier and log-rank procedure, with weights reflecting the age stratum proportions in the overall sample (Figs. 1 and 2). To evaluate the incremental prognostic value of LA volume and diastolic function profile, the global log likelihood ratio chi-square statistics for models developed using: 1) clinical risk factors alone; 2) clinical risk factors plus log (LA volume); 3) clinical risk factors plus diastolic function profile; and 4) clinical risk factors plus diastolic function profile and log (LA volume) were determined by Cox proportional hazards regression and depicted graphically (Fig. 3). Because LA volume had a highly skewed distribution, logarithmic transformation was performed, resulting in more normally distributed data for statistical modeling. In all cases, statistical significance was defined as two-tailed $p < 0.05$.

RESULTS

Baseline characteristics of the study population. A total of 840 residents of Olmsted County, whose mean age was 75 ± 7 years (range, 65 to 100 years), met all study criteria. Of these, 325 (39%) were men with a mean age of 73 ± 6 years, and 515 were women with a mean age of 76 ± 7 years ($p < 0.001$). The primary indications for echocardiographic assessment were dyspnea (30%), chest discomfort (22%), palpitations, light-headedness, presyncope or syncope (18%), cardiac function assessment (22%), murmurs (7%), and other reasons (1%). Patients who developed NVAF after baseline echocardiography were more likely to have had a history of prior hypertension, MI, CAD, CHF (Table 1), mitral annular calcification, larger LV end-diastolic dimension, greater posterior LV wall thickness, greater LV mass (indexed by height), lower LV ejection fraction, lower LV fractional shortening, larger LA dimension, and larger LA volume (Table 2). At baseline, 138 patients (16%) were considered to have a normal diastolic function profile, 428



No. at risk						
Normal	138	125	115	91	78	61
Abnormal relaxation	428	363	321	249	197	140
Pseudonormal	222	191	158	128	100	76
Restrictive	52	42	38	27	20	15

Figure 2. Age-adjusted cumulative survival without nonvalvular atrial fibrillation (NVAF) by diastolic function profile.

(51%) demonstrated abnormal relaxation, 222 (26%) fulfilled the criteria for pseudonormal LV filling, and 52 (6%; percentages add to <100 due to rounding) had restrictive diastolic physiology. The mean absolute (and indexed) LA volumes for patients with normal, abnormal relaxation, pseudonormal, and restrictive diastolic filling were 41 ± 8 ml (22 ± 4 ml/m^2), 60 ± 22 ml (33 ± 12 ml/m^2), 73 ± 20 ml (41 ± 10 ml/m^2), and 81 ± 38 ml (47 ± 22 ml/m^2), respectively.

Predictors of NVAF. A total of 80 patients (9.5%) developed newly diagnosed, electrocardiographically confirmed, NVAF during a mean follow-up of 4.1 ± 2.7 years for the cohort. The average time from echocardiogram to NVAF was 3.0 ± 2.4 years. The significant age- and gender-adjusted predictors of NVAF are shown in Table 3. In a multivariate clinical model, age, prior history of MI, and history of CHF were independent predictors of NVAF, while a prior history of hypertension or diabetes mellitus

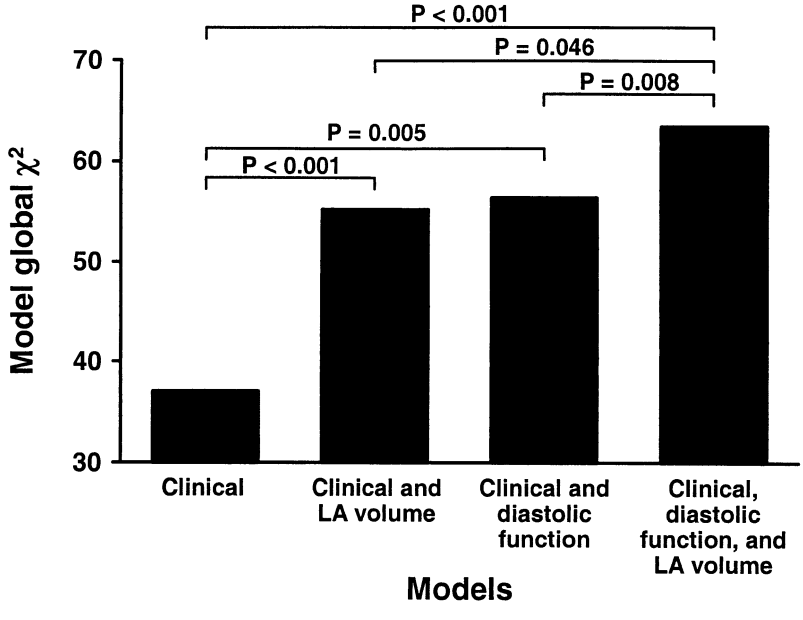


Figure 3. Predictive power of four models (clinical with only clinical risk factors, clinical and left atrial [LA] volume, clinical and diastolic function profile, and clinical with LA volume and diastolic function profile) for nonvalvular atrial fibrillation.

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Table 1. Baseline Clinical Characteristics of Study Population According to NVAF Status at Follow-Up

Characteristics	NVAF (n = 80)	No NVAF (n = 760)	p Value
Age, mean ± SD, yr	75.9 ± 7	74.5 ± 7	0.062
Men, %	39	33	0.232
Weight, mean ± SD, kg	76 ± 18	74 ± 16	0.600
Body surface area, mean ± SD, m^2	1.8 ± 0.2	1.8 ± 0.2	0.929
Body mass index, mean ± SD, kg/m^2	28 ± 6	27 ± 5	0.131
Pulse rate, mean ± SD, beats/min	71 ± 15	70 ± 12	0.724
SBP, mean ± SD, mm Hg	145 ± 27	141 ± 22	0.254
DBP, mean ± SD, mm Hg	76 ± 15	77 ± 12	0.854
Height, mean ± SD, cm	164 ± 10	165 ± 10	0.259
History of hypertension, %	67.5	54.3	0.024
History of CAD, %	22.5	13.6	0.030
History of myocardial infarction, %	30.0	14.9	< 0.001
History of congestive heart failure, %	23.8	8.2	< 0.001
History of carotid artery disease, %	6.3	8.3	0.525
History of peripheral vascular disease, %	16.3	15.7	0.890
History of hyperlipidemia, %	41.3	40.3	0.864
History of diabetes mellitus, %	15.0	10.7	0.239
History of present or past smoking, %	46.3	48.4	0.712
Family history of CAD, %	37.5	36.8	0.908
History of COPD, %	16.3	15.7	0.890
Left ventricular hypertrophy on ECG, %	8.8	4.2	0.087

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; ECG = electrocardiogram; NVAF = nonvalvular atrial fibrillation; SBP = systolic blood pressure.

was not (Table 4). Gender was not a significant predictor when adjusted for age alone (Table 3), or in any of the multivariate models (Table 4).

After adjusting for age, larger LA volume was associated with increased risk of NVAF (Fig. 1). After adjusting for multiple clinical risk factors, LA volume remained incremental to a prior history of CHF and MI for the prediction of NVAF (per log: HR, 3.51; 95% CI, 1.94 to 6.35; $p < 0.001$) (Table 4).

The presence and severity of diastolic dysfunction were independently associated with higher risk of NVAF. Abnormal relaxation, pseudonormal, and restrictive diastolic filling were associated with HRs of 3.33 (95% CI, 1.50 to 7.40; $p = 0.003$), 4.84 (95% CI, 2.05 to 11.40; $p < 0.001$), and 5.26 (95% CI, 2.30 to 12.03; $p < 0.001$), respectively, when compared with normal diastolic function in the same model, unadjusted for other factors. When adjusted for age and gender (Table 3), and after adjustments for clinical risk factors or LA volume (Table 4), diastolic dysfunction remained independently predictive of subsequent NVAF.

Table 2. Baseline Echocardiographic Characteristics of Study Population According to NVAF Status at Follow-Up*

Characteristics	NVAF (n = 80)	No NVAF (n = 760)	p Value
M-mode LA dimension, mm	44 ± 7	41 ± 6	< 0.001
LA volume, ml	75 ± 26	60 ± 24	< 0.001
Indexed LA volume, ml/m^2	41 ± 13	33 ± 13	< 0.001
Log LA volume, ml	4.3 ± 0.32	4.0 ± 0.36	< 0.001
LV end-systolic dimension, mm	31 ± 8	30 ± 7	0.187
LV end-diastolic dimension, mm	51 ± 7	48 ± 6	0.016
LV septal wall thickness, diastolic, mm	11.5 ± 1.8	11.2 ± 2.2	0.147
LV posterior wall thickness, diastolic, mm	10.9 ± 1.6	10.6 ± 1.9	0.019
Indexed LV mass by height, g/m	133 ± 30	117 ± 37	0.008
LV ejection fraction, %	57 ± 14	60 ± 11	0.039
LV fractional shortening, %	35 ± 10	38 ± 8	0.039
LV stroke volume, ml	76 ± 18	77 ± 18	0.960
Cardiac index, $l/min/m^2$	2.92 ± 0.72	2.95 ± 0.78	0.990
Mitral annular calcification, %	24	12	0.002
Mitral inflow peak E velocity, m/s	0.75 ± 0.23	0.71 ± 0.20	0.290
Mitral inflow peak A velocity, m/s	0.84 ± 0.25	0.84 ± 0.24	0.858
Mitral E/A	0.96 ± 0.46	0.89 ± 0.36	0.363
Mitral DT, ms	242 ± 68	231 ± 53	0.172
Tricuspid regurgitation velocity, m/s	2.60 ± 0.72	2.60 ± 0.36	0.920

*Values are mean ± SD unless otherwise indicated.
DT = deceleration time; LA = left atrial; LV = left ventricular; NVAF = nonvalvular atrial fibrillation.

Table 3. Predictors of NVAF, Adjusted for Age and Gender

Variables*	Hazard Ratio (95% CI)	p Value
Age, per year‡	1.03 (1.01–1.07)	0.050
Male gender†	0.90 (0.56–1.45)	0.662
Body mass index	1.04 (1.00–1.08)	0.044
History of hypertension	1.59 (0.99–2.56)	0.053
History of congestive heart failure	3.75 (2.19–6.40)	< 0.001
History of myocardial infarction	2.78 (1.71–4.51)	< 0.001
History of coronary artery disease	2.09 (1.21–3.59)	0.008
History of diabetes mellitus	1.90 (1.03–3.54)	0.042
LA dimension, per 5 mm	1.48 (1.24–1.78)	< 0.001
LA volume, per log	4.43 (2.55–7.67)	< 0.001
Indexed LA volume, per 10 ml/m^2	1.23 (1.12–1.36)	< 0.001
LV end-systolic dimension, per 5 mm	1.22 (1.02–1.46)	0.031
LV end-diastolic dimension, per 5 mm	1.41 (1.15–1.74)	0.001
LV ejection fraction, per 10%	0.76 (0.63–0.91)	0.003
LV fractional shortening, per 5%	0.83 (0.73–0.94)	0.004
LV mass indexed by height, g/m	1.01 (1.00–1.02)	0.014
Mitral peak E velocity, 0.2 m/s	6.69 (0.72–61.92)	0.094
Mitral E/A	1.53 (1.00–2.36)	0.053
Abnormal LV diastolic relaxation‡	2.89 (1.28–6.51)	0.010
Pseudonormal LV filling‡	4.60 (1.94–10.90)	< 0.001
Restrictive LV diastolic filling‡	4.50 (1.92–10.38)	< 0.001

*$p > 0.1$ for the following variables: systolic blood pressure, diastolic blood pressure, pulse rate, pulse pressure, body surface area, hyperlipidemia, carotid artery disease, smoking, chronic obstructive pulmonary disease, LV stroke volume, cardiac index, tricuspid regurgitation velocity, and mitral A velocity; †age was adjusted for gender only, and gender was adjusted for age only; ‡age- and gender-adjusted model with all three diastolic function categories in the model.

CI = confidence interval; LA = left atrial; LV = left ventricular; NVAF = nonvalvular atrial fibrillation.

Kaplan-Meier five-year age-adjusted cumulative risks of NVAF were 1%, 12%, 14%, and 21% for patients with normal, abnormal relaxation, pseudonormal, and restrictive LV diastolic filling, respectively (Fig. 2).

Systolic function, measured by ejection fraction as a continuous variable, was a significant predictor of NVAF when adjusted for age and gender (Table 3), but not after adjusting for multiple clinical risk factors (Table 4). The predictive power for NVAF, based on global model chi-square value, was improved significantly with the addition of the diastolic function profile to clinical risk factors alone. The predictive value increased further when LA volume was added to the model. The predictive power of the model containing only clinical risk factors and LA volume compared favorably with that containing clinical risk factors and diastolic function profile (Fig. 3).

Table 4. Multivariate Models for Prediction of NVAF

	Clinical Risk Factors, HR (95% CI); p	Clinical Risk Factors and EF, HR (95% CI); p	Clinical Risk Factors and LA Volume, HR (95% CI); p	Clinical Risk Factors and Diastolic Function, HR (95% CI); p	Clinical Risk Factors, Diastolic Function, and LA Volume, HR (95% CI); p
Age, per 10 yrs	1.42 (1.02–1.96); 0.036	1.26 (0.98–1.54); 0.195	1.31 (0.95–1.81); 0.106	1.36 (0.97–1.90); 0.076	1.30 (0.94–1.82); 0.118
Male gender	0.88 (0.54–1.43); 0.611	0.88 (0.52–1.45); 0.658	0.74 (0.45–1.22); 0.233	0.91 (0.55–1.48); 0.692	0.78 (0.47–1.30); 0.345
Myocardial infarction	2.11 (1.25–3.56); 0.005	1.37 (0.98–3.21); 0.332	2.16 (1.28–3.65); 0.004	2.23 (1.32–3.79); 0.003	2.20 (1.30–3.74); 0.003
Congestive heart failure	2.72 (1.54–4.79); <0.001	2.52 (1.48–4.62); 0.015	1.89 (1.04–3.47); 0.038	2.72 (1.51–4.89); <0.001	2.14 (1.15–3.99); 0.017
Hypertension	1.48 (0.92–2.38); 0.111	1.66 (0.99–2.39); 0.064	1.33 (0.82–2.16); 0.243	1.46 (0.90–2.37); 0.124	1.35 (0.83–2.19); 0.230
Diabetes mellitus	1.17 (0.60–2.27); 0.652	1.56 (0.84–2.32); 0.251	1.32 (0.68–2.56); 0.409	1.22 (0.63–2.36); 0.555	1.31 (0.68–2.54); 0.423
EF	NA	0.99 (0.68–1.30); 0.600	NA	NA	NA
Log LA volume, per log	NA	NA	3.51 (1.94–6.35); <0.001	NA	2.52 (1.29–4.95); 0.007
Abnormal relaxation	NA	NA	NA	3.41 (1.40–8.29); 0.007	2.99 (1.14–7.85); 0.026
Pseudonormal	NA	NA	NA	5.75 (2.24–14.77); <0.001	4.06 (1.44–11.47); 0.008
Restrictive	NA	NA	NA	4.35 (1.73–10.94); 0.002	3.11 (1.10–8.79); 0.032

CI = confidence interval; EF = ejection fraction; HR = hazard ratio; LA = left atrial; NA = not applicable; NVAF = nonvalvular atrial fibrillation.

DISCUSSION

Diastolic dysfunction as a predictor of first documented NVAF. This study demonstrated that the presence of diastolic dysfunction was associated with increased risk of NVAF in this elderly cohort referred for echocardiography. Furthermore, the gradient of risk appeared to be related to the severity of diastolic dysfunction. A decrease in diastolic performance with advancing age is well documented and has been regarded as part of "normative" aging (17,18). Our data challenges the concept that changes in diastolic function are "normal for age," as even a mild degree of diastolic

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dysfunction, such as abnormal relaxation, more than tripled the likelihood of developing the adverse outcome of AF. Moreover, this occurred over a relatively short follow-up period of approximately four years.

Diastolic dysfunction has also been shown to be largely responsible for approximately one-half of all new cases of CHF in the Framingham study (19) and in an Olmsted County study (20). The ability to detect diastolic abnormalities has been made possible by the introduction of Doppler echocardiography in the 1980s (21,22), and various sophisticated techniques for increasingly precise assessment of diastolic function have been developed since then. Simple transmitral flow characteristics, however, remain central to the evaluation of diastolic function and provide important prognostic information (23–25). In this study a simple diastolic function profile using only mitral DT, mitral E/A, and LA volume allowed a meaningful stratification of risk for subsequent NVAF. The diastolic function profile was incremental to clinical risk factors and LA volume for such prediction (Table 4, Fig. 3).

LA volume as a predictor of NVAF. As in the Framingham Heart study (26) and the Cardiovascular Health study (27), M-mode LA dimension was also found to predict the development of NVAF in this study. Each 5-mm-larger LA dimension was associated with an increase in risk of 48% (Table 3). Left atrial volume provides a more sensitive assessment of LA enlargement (28), and, as we have shown previously, it is an important independent predictor of AF, providing incremental information beyond that afforded by the clinical risk factors and conventional M-mode LA dimension (29). In our previous study, patients with valvular heart disease, a strong determinant of AF, were not excluded. In the current study, LA volume was confirmed to be independent of both clinical risk factors and diastolic function profile for the prediction of AF in the absence of valvular heart disease (Table 4). The data suggested that the larger the LA volume, the greater the risk of NVAF (Table 3, Fig. 1).

The importance of LA volume as a predictor of NVAF was underscored by the finding that the predictive value was enhanced further by the addition of LA volume to the model that already included clinical risk factors and the diastolic function profile (Fig. 3). The model based only on clinical risk factors and LA volume compared favorably with that containing clinical risk factors and diastolic function profile. These findings lend support to the contention that LA volume is a robust barometer of diastolic filling abnormalities (16). While transmitral flow indexes provide important information on diastolic function, they are known to be load-dependent (21). Although speculative at this point, it is possible that the relationship between transmitral inflow characteristics and LA volume may be analogous to that between serum glucose and glycosylated hemoglobin. Left atrial volume may provide a measure of chronicity, and not just severity of diastolic dysfunction, and the chronicity may, in turn, reflect the extent of alterations in the atrial substrate predisposing to electrophysiologic abnormalities and development of arrhythmia.

Clinical risk factors for predicting NVAF. The incidence of NVAF in this referral study population was 23.2 per 1,000 person-years. This was, as expected, higher than that identified in the Cardiovascular Health study of randomly selected community members who were 65 years or older and fulfilled Medicare eligibility (19.2 per 1,000 person-years) (27). In both studies there was a predominance of women (Olmsted referral study, 61%; Cardiovascular Health study, 57%). Like other investigators (26,27), we found certain clinical variables to be important predictors of NVAF (Tables 3 and 4). However, in contrast, we found that hypertension was not independently significant after adjusting for multiple factors. That hypertension did not retain independent significance could reflect the high prevalence of the condition in this cohort at baseline. In addition, unlike some studies, male gender was not an independent predictor. The reason for this finding is uncertain, although our cohort did include a greater proportion of women than some other populations that have been studied. Our study, however, demonstrated that the inclusion of LA volume and the diastolic function profile significantly augmented the predictive value of models based on clinical risk factors alone (Fig. 3).

Mechanism for diastolic dysfunction as a precursor for the development of NVAF. In this study of older adults, even a milder form of diastolic dysfunction, namely, abnormal relaxation, appeared to increase the propensity for NVAF, independent of the effects of age. Skubas et al. (30) reported that diastolic relaxation abnormalities were highly prevalent in patients presenting for the Maze procedure. It is conceivable that LV relaxation abnormalities lead to a reduction in passive LA emptying, with the development of higher atrial pressures during atrial diastole. This, in turn, may result in a larger LA volume at the onset of atrial systole, with enhanced atrial ejection occurring as a compensatory response (31). Over time, the LA and pulmonary veins dilate. The distention and stretching of these structures may potentiate electrical remodeling, with shortening of the atrial effective refractory period (32) or an increase in dispersion of refractoriness, resulting in vulnerability to AF (33,34).

Both passive atrial stretch and an increase in atrial pressure during atrial contraction have been found to stimulate the release of atrial natriuretic factor (35). In addition, Grandi et al. (36) demonstrated that diastolic impairment is the main influence on the levels of atrial natriuretic factor in patients with mild hypertension. In one study the level of atrial natriuretic factor was found to be a predictor of paroxysmal AF (37). Thus, the relationship between diastolic abnormalities and the development of NVAF may be mediated through an increase in atrial pressure, atrial stretch, and neurohormonal activation, including the release of atrial natriuretic factor.

Study limitations. The clinical data for this study were obtained by retrospective chart review; therefore, certain inherent biases are possible. The method of ascertainment of AF, based on clinical documentation with electrocardiographic confirmation, could have underestimated the actual number of incident AF cases. For instance, some patients with AF could have been asymptomatic, and if they did not present to the medical system for other reasons, the arrhythmia could have remained undetected for some time. However, it was previously established that 96% of Olmsted County residents aged 65 to 74 years had at least one encounter with the Mayo medical system within a three-year period (11). For simplicity, we used mitral inflow characteristics and LA volume in the construction of a diastolic function profile for prediction of the outcome event of NVAF. It is recognized that more refined discrimination of categories of diastolic dysfunction can be achieved if additional assessments, including pulmonary venous flow, color M-mode, and tissue Doppler imaging techniques, are also used. However, given the study period being 1990 to 1998, pulmonary venous flow measurements were not available in a considerable number of studies during the earlier half of the period, and tissue Doppler assessments did not become part of routine standard echocardiogram study until 1999. Color M-mode was used only selectively during this period of time. Because all subjects were patients referred for echocardiographic assessment at Mayo Clinic or Olmsted Medical Center, the extent to which the findings can be generalized to the rest of Olmsted County residents and to non-Olmsted residents is unknown. The population studied was predominantly white, and whether similar findings can be identified in other racial groups needs to be verified in future studies.

Conclusions. Diastolic dysfunction appears to be a potent precursor of NVAF in the elderly, with an independent, graded relationship between the severity of diastolic dysfunction and the development of NVAF. These findings provide a foundation for further investigation into the links between age, diseased atrial substrate, electrophysiologic remodeling, and subsequent AF, as well as a compelling rationale for search of effective approaches to prevent and reverse diastolic dysfunction, which may have far-reaching public health consequences.

Reprint requests and correspondence: Dr. Teresa S. M. Tsang, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: tsang.teresa@mayo.edu.

REFERENCES

1. Wolf PA, Mitchell JB, Baker CS, Kannel WB D', Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158:229–34.
2. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol 2001;37:371–8.
3. Feinberg WM, Kronmal RA, Newman AB, et al. Stroke risk in an elderly population with atrial fibrillation. J Gen Intern Med 1999;14:56–9.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. Circulation 1998;98:946–52.
5. Scheinman MM. Atrial fibrillation and congestive heart failure: the intersection of two common diseases. Circulation 1998;98:941–2.
6. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997;337:1360–9.
7. Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999;99:3028–35.
8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke 1991;22:983–8.
9. Go AS, Hylek EM, Phillips KA, et al. Implications of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Circulation 2000;102:11–3.
10. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. Mayo Clin Proc 1994;69:212–24.
11. Melton LJ III. History of the Rochester epidemiology project. Mayo Clin Proc 1996;71:266–74.
12. Arcilla RA, Thilenius OG, Chiemmongkoltip P, Ranniger K. Left atrial volume calculation by angiocardiography in children. Chest 1973;63:189–97.
13. Ren JF, Kotler MN, DePace NL, et al. Two-dimensional echocardiographic determination of left atrial emptying volume: a noninvasive index in quantifying the degree of nonrheumatic mitral regurgitation. J Am Coll Cardiol 1983;2:729–36.
14. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease: additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;22:1972–82.
15. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8–18.
16. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002. In press.
17. Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. Circulation 1977;56:273–8.
18. Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, Lakatta EG. Left ventricular diastolic filling performance in older male athletes. JAMA 1995;273:1371–5.
19. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
20. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.
21. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 1988;12:426–40.
22. Appleton CP, Hatle LK. The natural history of left ventricular filling abnormalities: assessment by two-dimensional and Doppler echocardiography. Echocardiography 1992;9:437–57.
23. Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiography study. Circulation 1991;83:808–16.
24. Rihal CS, Nishimura RA, Hatle LK, Bailey KR, Tajik AJ. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated

cardiomyopathy: relation to symptoms and prognosis. Circulation 1994;90:2772–9.
25. Hurrell DG, Oh JK, Mahoney DW, Miller FA Jr, Seward JB. Short deceleration time of mitral inflow E velocity: prognostic implication with atrial fibrillation versus sinus rhythm. J Am Soc Echocardiogr 1998;11:450–7.
26. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation: the Framingham Heart study. Circulation 1994;89:724–30.
27. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455–61.
28. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829–32.
29. Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1,655 older men and women. Mayo Clin Proc 2001;76:467–75.
30. Skubas NJ, Bakola AA, Apostolidou I, Sundt TM III, Cox JL, Lappas DG. Echocardiographic characterization of left ventricular diastolic properties in patients presenting for the maze procedure. Semin Thorac Cardiovasc Surg 1999;11:134–41.
31. Triposkiadis F, Tentolouris K, Androulakis A, et al. Left atrial mechanical function in the healthy elderly: new insights from a combined assessment of changes in atrial volume and transmitral flow velocity. J Am Soc Echocardiogr 1995;8:801–9.
32. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation 1997;96:1686–95.
33. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conductive to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996;7:833–42.
34. Jais P, Peng JT, Shah DC, et al. Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation. J Cardiovasc Electrophysiol 2000;11:623–5.
35. Christensen G, Leistad E. Atrial systolic pressure, as well as stretch, is a principal stimulus for release of ANF. Am J Physiol 1997;272: H820–6.
36. Grandi AM, Zanzi P, Ceriani L, et al. Relationship between left ventricular diastolic function and atrial natriuretic factor in never-treated mild hypertensives. Am J Hypertens 1997;10:946–50.
37. Yamada T, Fukunami M, Shimonagata T, et al. Prediction of paroxysmal atrial fibrillation in patients with congestive heart failure: a prospective study. J Am Coll Cardiol 2000;35:405–13.