Determinants and Prognostic Value of Left Atrial Volume in Patients With Dilated Cardiomyopathy

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OBJECTIVES	We aimed to investigate the determinants of left atrial (LA) volume and its prognostic value in patients with dilated cardiomyopathy (DCM).
BACKGROUND	Enlargement of the LA is a marker of mortality in the general population. Patients with DCM are characterized by a wide range of LA sizes, but the clinical role of this observation has been played down.
METHODS	A complete echocardiographic Doppler examination was performed in 337 patients (age 60 ± 13 years; 84% male) with the diagnosis of DCM. Left atrial maximal volume (LA_{max}) was measured at left ventricular (LV) end systole (four-chamber view; area–length method). Left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) and ejection fraction (EF) were also measured. Mitral regurgitation (MR) was graded using a 5-point scale. Mitral E-wave (E) and A-wave (A) velocities, as well as their ratio (E/A), were measured off-line.
RESULTS	Determinants of LA_{max} were: atrial fibrillation (r = 0.34, p < 0.0001), LVEDV (r = 0.46, p < 0.0001), EF (r = 0.40, p < 0.0001), MR (r = 0.39, p < 0.0001), and E/A ratio (r = 0.36, p < 0.0001). During follow-up (41 ± 29 months), 77 patients died and 12 underwent heart transplantation. Univariate Cox analysis showed that LA_{max} (hazard ratio [HR] 1.01, 95% confidence interval [CI] 1.007–1.013, p < 0.0001), LVESV (HR 1.003, CI 1.001–1.005, p = 0.0003), E/A ratio (HR 1.6, CI 1.3–2.005, p < 0.0001), and MR (HR 1.21, CI 1.03–1.44, p = 0.02) were related to the outcome. On bivariate Cox analysis, LA_{max} predicted the prognosis independently of each determinant. Patients with a larger LA volume (LA_{max}/m^2 >68.5 ml/m²) had a risk ratio of 3.8 compared with those with a smaller LA volume.
CONCLUSIONS	In patients with DCM, LA volume is associated with LV remodeling, diastolic dysfunction, and the degree of MR. The maximal volume of the LA has an independent and incremental prognostic value, compared with all its determinants. (J Am Coll Cardiol 2002;40:1425–30) © 2002 by the American College of Cardiology Foundation

In patients with dilated cardiomyopathy (DCM), a wide range of left atrial (LA) sizes has been observed (1,2). The prognostic impact of this observation has recently been analyzed in the Studies Of Left Ventricular Dysfunction (SOLVD) population (3). Patients with a reduced left ventricular (LV) ejection fraction (EF) had an increased risk proportional to the increase in the size of the LA, which was independent of EF, age, or symptomatic status. However, it is unclear whether the prognostic power of the enlarged LA might be the result of LV diastolic dysfunction or the presence of mitral regurgitation (MR) or atrial fibrillation (AF). This is noteworthy because all of these pathophysiologic variables contribute to both enlarging the atrial chamber (4–6) and influencing the prognosis in patients with a reduced EF (1,2,7,8). Although atrial enlargement has long been known to be associated with an increased mortality rate in the general population (9), the pathophysiologic determinants of atrial size have rarely been investigated,

particularly in patients with ventricular diseases. It has recently been demonstrated that the size of the LA is better described by volume rather than diameter (10). However, unidimensional measurement is still the method used worldwide to quantify atrial size, so that the potential clinical information provided by atrial volume is largely hidden. The aims of the present study were to analyze the degree of LA remodeling and the pathophysiologic determinants of LA volume in patients with LV systolic dysfunction and to verify the prognostic power of atrial volume in relation to its determinants.

METHODS

Patients were recruited from those routinely referred to the Outpatient Clinic of Verona Hospital with a diagnosis of DCM. Consecutive patients who had a complete echocardiographic Doppler examination in the echocardiographic laboratory of our institution within one month of clinical evaluation (beginning of follow-up) formed the study population. The exclusion criteria were: 1) significant organic mitral or aortic valve disease; 2) the presence of clinical or echocardiographic features of amyloidosis or constrictive pericarditis; and 3) a recent myocardial infarction (<6

Abbreviations and Acronyms

AF	= atrial fibrillation
CI	= confidence interval
DCM	= dilated cardiomyopathy
EF	= ejection fraction
HR	= hazard ratio
LA	= left atrium/atrial
LV	= left ventricle/ventricular
LVEDV and LVESV	= left ventricular end-diastolic and end-systolic volume, respectively
MR	= mitral regurgitation
ROC	= receiver-operating characteristic

months). The duration of the disease was taken to be the number of years of awareness of cardiac impairment.

Twenty-six gender- and age-matched subjects in sinus rhythm, with no history of cardiac disease and with entirely normal echocardiographic findings, who had been referred to the echocardiographic laboratory to rule out pericardial disease or for systolic murmurs, were enrolled as a control group.

Follow-up information was obtained from clinical records, death certificates, and correspondence. The composite end point of follow-up was death or heart transplantation. Patients who died of noncardiac causes were censored at the time of death.

Echocardiography. Left atrial maximal volume (LA_{max}) was measured at LV end systole, and LA minimal volume (LA_{min}) at LV end diastole from the apical four-chamber view (area–length method). Left ventricular end-diastolic and end-systolic volumes (area–length method) and EF were measured off-line from the apical four-chamber view. Mitral E-wave (E) and A-wave (A) velocities, E/A ratio, and E-wave deceleration time (DT_E) were also measured off-line. This last variable was measured as the interval (in milliseconds) from peak early mitral filling to an extrapolation of the deceleration to 0 m/s. All measurements were obtained from the mean of 3 beats for patients in sinus rhythm and 5 beats for those with AF. A restrictive mitral inflow pattern was defined as an E/A >2 or between 1 and 2 and DT_E <140 ms in patients in sinus rhythm or a DT_E <140 ms in patients with AF. Mitral regurgitation was semiquantitatively assessed by color flow Doppler echocardiography. Five regurgitant grades were routinely determined and recorded directly in the study data base (0 = no regurgitation; 1 = mild; 2 = mild to moderate; 3 = moderate; 4 = moderate to severe; 5 = severe).

Statistical analysis. Continuous data are presented as the mean value ± SD. Comparisons of all measurements between normal subjects and patients with DCM were made using the unpaired t test. Determinants of LA_{max} were evaluated using linear regression analysis. Multivariate analysis was used to identify the independent relationship between each variable and LA volume. Ejection fraction was not used in the multivariate model, so as to avoid multicollinearity, because it is both statistically and pathophysi-

Table 1. Clinical and Echocardiographic Characteristics of 337 Patients With Dilated Cardiomyopathy

Variable	Mean ± SD
Age (yrs)	60 ± 13
AF (%)	12
NYHA functional class	2.3 ± 0.4
LA_{max} (ml)	131 ± 65
LA_{max}/m^2 (ml/m²)	70 ± 35
LVEDV (ml)	315 ± 120
LVESV (ml)	227 ± 112
EF (%)	31 ± 9
E (m/s)	0.6 ± 0.3
E/A ratio	1.2 ± 0.9
DT_E (ms)	200 ± 75
Restrictive mitral pattern (%)	22
MR grade	1.4 ± 1.3
LV mass (g)	386 ± 119

AF = atrial fibrillation; DT_E = E-wave deceleration time; E = mitral E-wave velocity; E/A = early mitral to atrial flow velocity ratio; EF = ejection fraction; LA_{max} = left atrial maximal volume; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association.

ologically related to left ventricular end-diastolic and end-systolic volume (LVEDV and LVESV). The E-wave DT and velocity were also not used in the model because of their strong relation to the E/A ratio. The relation of specific variables to mortality was investigated univariately using the Cox proportional hazards model. To assess the independence of the predictive value of LA_{max} from that of its determinants, bivariate models were used.

The prognostic power of LA parameters (LA_{max}, LA_{max}/m^2, LA_{min}, LA_{min}/m^2) significantly related to the outcome was compared using the log-likelihood ratio test.

Receiving-operator characteristics (ROC) curves were constructed to compare different predictive values at particular time points. Differences between curves were assessed with the z-statistic. The best prognostic cut-off value for survival status, defined as that which gave the highest product of sensitivity and specificity, was used to dichotomize patients for Kaplan-Meier survival analysis. To perform these analyses, two different statistical programs were employed: Statview 5.0 (Abacus Concepts, SAS Institute, Cary, North Carolina) and MedCalc 5.0 (Mariakerke, Belgium). A p value <0.05 was considered statistically significant.

RESULTS

A total of 337 patients (294 men and 43 women; age 60 ± 13 years) formed the study population. Table 1 shows the clinical and echocardiographic characteristics of the patients. The etiology of their cardiomyopathy was idiopathic in 25% and ischemic in the remaining 75%.

Left atrial remodeling and determinants of LA volume. Patients with DCM showed a larger LA_{max} (131 ± [SD] 65 ml, SEM 4.1; range 25 to 481) compared with normal control subjects (59 ± [SD] 19 ml, SEM 3.8; p < 0.0001); however, a wide range was observed. The frequency of LA remodeling was high: 75% of patients with DCM had a

Table 2. Echocardiographic Determinants of Left Atrial Maximal Volume in the Study Population (Univariate Analysis)

Variable	r	p Value
AF	0.34	< 0.0001
LVEDV (ml)	0.46	< 0.0001
LVESV (ml)	0.45	< 0.0001
EF (%)	0.40	< 0.0001
E (m/s)	0.30	< 0.0001
E/A ratio	0.36	< 0.0001
DT_E (ms)	0.32	< 0.0001
MR grade	0.39	< 0.0001
LV mass (g)	0.29	0.0002

Abbreviations as in Table 1.

LA_{max} higher (by >1 SD of the mean value) than that of control subjects. In contrast, no differences in the E-wave velocity (0.61 ± [SD] 0.2, SEM 0.015 vs. 0.64 ± [SD] 0.2, SEM 0.04; p = 0.6), A-wave velocity (0.59 ± [SD] 0.3, SEM 0.015 vs. 0.67 ± [SD] 0.2, SEM 0.039; p = 0.08), E/A ratio (1.19 ± [SD] 0.9, SEM 0.060 vs. 0.98 ± [SD] 0.3, SEM 0.058; p = 0.2), or DT_E (200 ± [SD] 75, SEM 4.86 vs. 215 ± [SD] 47, SEM 9.4; p = 0.3) were observed between patients and control subjects. The determinants of LA volume were defined by means of linear regression analysis (Table 2).

The LA_{max} increased with LV enlargement, increasing severity of MR, degree of diastolic dysfunction, and presence of AF. Multivariate analysis showed that LA_{max} was independently related to age and the degree of MR and more strongly related to the LVEDV and E/A ratio (Table 3).

In 102 patients for whom the duration of the disease was available, LA_{max} normalized by body surface area (LA_{max}/m^2) showed a positive relation to the duration of the disease (p = 0.007), independently of age (p = 0.0005), in a multivariate model.

Survival analysis. During follow-up (median 41 ± 29 months), 77 patients died and 12 underwent heart transplantation. Five patients died of noncardiac causes and, accordingly their follow-up, were censored at the time of death. Cox univariate analysis showed several clinical and echocardiographic markers of prognosis in our population (Table 4). The maximal volume of the LA was a strong predictor of mortality (hazard ratio [HR] 1.01, 95% confidence interval [CI] 1.007 to 1.013; p < 0.0001). However, most of the variables identified as determinants of LA_{max}—

Table 3. Echocardiographic Determinants of Left Atrial Maximal Volume in the Study Population (Multivariate Analysis)

Variable	p Value
Age (yrs)	0.02
AF	0.04
MR grade	0.003
E/A ratio	< 0.0001
LVEDV (ml)	0.0004
LVESV (ml)	0.9

Abbreviations as in Table 1.

Table 4. Predictors of Death in the Study Population (Cox Univariate Analysis)

Variable	p Value	HR (95% CI)
NYHA functional class	< 0.0001	2.05 (1.46–2.88)
Age (yrs)	0.005	1.03 (1.01–1.057)
AF	0.5	0.8 (0.5–1.42)
LA_{max} (ml)	< 0.0001	1.01 (1.007–1.013)
LA_{max}/m^2 (ml/m²)	< 0.0001	1.02 (1.015–1.026)
LA_{min} (ml)	< 0.0001	1.01 (1.006–1.013)
LA_{min}/m^2 (ml/m²)	< 0.0001	1.02 (1.01–1.03)
LVEDV (ml)	0.001	1.003 (1.001–1.005)
LVESV/m² (ml/m²)	0.0001	1.006 (1.003–1.009)
LVESV (ml)	0.0003	1.003 (1.001–1.005)
LVESV/m² (ml/m²)	< 0.0001	1.007 (1.003–1.010)
EF (%)	0.0006	0.96 (0.93–0.98)
E/A ratio	< 0.0001	1.6 (1.28–2.005)
Restrictive mitral pattern	< 0.0001	0.33 (0.20–0.55)
MR grade	0.02	1.21 (1.028–1.44)

CI = confidence interval; HR = hazard ratio; LA_{min} = left atrial minimal volume; other abbreviations as in Table 1.

namely, ventricular volumes, MR, and markers of diastolic function—showed clinically important predictive power, as well.

Bivariate Cox models were subsequently used to assess the independence of the prognostic value of LA_{max} from that of each of its determinants (Table 5). Bivariate analysis was preferred to avoid multi-collinearity, because most of the determinants of LA_{max} are strongly related to each other.

Although the presence of AF did not influence the prognosis in our population, we performed a subgroup analysis of patients with chronic AF. This group consisted of 39 patients (mean age 63 ± 8 years, mean EF 26 ± 9%) who were followed up for 51 ± 29 months; 14 patients died. In this group, LA_{max} maintained its predictive power (HR 1.01, CI 1.003 to 1.018; p = 0.008), but EF did not have any impact on the prognosis. Likewise, the predictive value of LA_{max} was confirmed in patients without MR (grade <1) (HR 1.01, CI 1.006 to 1.017; p < 0.0001) and with MR (HR 1.008, CI 1.004 to 1.013; p = 0.0008).

When the overall population was classified into two groups according to the presence or absence of a restrictive

Table 5. Predictors of Death in the Study Population (Cox Bivariate Models)

Model	Variable	p Value	HR
1	LA_{max} (ml)	< 0.0001	1.009 (1.006–1.013)
	Age (yrs)	0.02	1.03 (1.005–1.057)
2	LA_{max} (ml)	< 0.0001	1.008 (1.005–1.012)
	LVESV (ml)	0.1	1.002 (1.00–1.004)
3	LA_{max} (ml)	< 0.0001	1.008 (1.005–1.012)
	EF (%)	0.08	0.97 (0.95–1.003)
4	LA_{max} (ml)	< 0.0001	1.008 (1.004–1.012)
	Restrictive mitral pattern	0.3	0.7 (0.38–1.31)
5	LA_{max} (ml)	< 0.0001	1.010 (1.005–1.015)
	E/A ratio	0.3	1.20 (0.87–1.65)
6	LA_{max} (ml)	< 0.0001	1.009 (1.005–1.014)
	MR grade	0.8	1.029 (0.84–1.26)

Abbreviations as in Table 1.
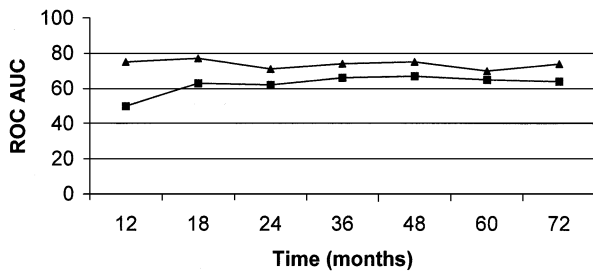
Figure 1. The receiver-operating characteristic (ROC) areas under the curve (AUC) of left atrial maximal volume/m^2 **(line with triangles)** and left ventricular end-systolic volume/m^2 **(line with squares)** of patients with dilated cardiomyopathy for prediction of death at 12 to 72 months.

mitral filling pattern, LA_{max} significantly predicted the outcome in both groups (HR 1.006, CI 1.001 to 1.012, p = 0.03 and HR 1.01, CI 1.005 to 1.017, p = 0.0003, respectively).

The log-likelihood ratio test showed that LA_{max}/m^2 was a more powerful predictor of survival than LA_{max} (p < 0.0001), LA_{min} (p < 0.0001), and LA_{min}/m^2 (p = 0.02).

The best cut-off value for LA_{max}/m^2 in the overall population, regardless of the duration of follow-up, was calculated using ROC analysis. The value of 68.5 ml/m^2 predicted survival with 65% sensitivity (95% CI 55.8 to 73.9) and 76% specificity (CI 65.6 to 88.4). Patients with a higher LA_{max}/m^2 value had a 3.8 times higher risk of an adverse outcome than patients with a smaller LA. The ROC area under the curve (AUC) for LA_{max}/m^2, as a continuous variable, was higher than that for LVESV/m^2 over the whole follow-up period, reaching statistical significance at 12 months (p = 0.009) (Fig. 1).

Kaplan-Meier curves were constructed using a cut-off value for LA_{max}/m^2 of 68.5 ml/m^2. Survival analysis was performed for the subgroup of patients with particularly severe systolic dysfunction (EF <30%). The presence of a
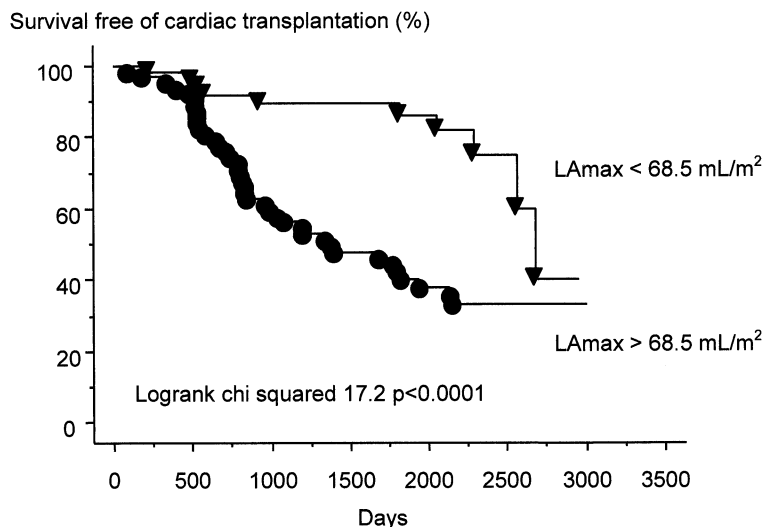
large LA volume predicted a worse outcome, compared with patients with a smaller LA (Fig. 2).

DISCUSSION

The present study showed that LA remodeling is frequent, in patients with DCM. Left atrial volume is mainly determined by the degree of LV dilation, diastolic dysfunction, and the extent of MR. On survival analysis, LA volume is found to be a powerful prognostic marker, adding important clinical information, independent of any of its determinants.

In patients with chronic heart failure due to DCM, diastolic dysfunction is an important hallmark of the severity of the disease. The degree of diastolic impairment correlates with symptoms and prognosis more closely than does EF (1,2,11–13). However, the predictive power of diastolic markers has been frequently but not uniformly confirmed (14). This is probably due to the strong load dependency of mitral parameters, which can dramatically change after blood volume depletion (15). It has been shown that the predictive power of mitral inflow can be enhanced when analyzed in relation to loading modification (16). The role of LA size as a diastolic marker is well known (17–19), and, accordingly, we found a strong relation between atrial volume and diastolic markers. Interestingly, the predictive value of atrial volume is stronger and independent of echocardiographic Doppler diastolic parameters. This might be related to a lower load dependency due to increased fibrosis and reduced elastic recoil in a chronically enlarged atrium (20–22). Furthermore, LA size has been shown to reflect prognosis in patients who have cardiac disease with prevalent diastolic function, such as aortic stenosis and restrictive cardiomyopathy (23–25).

Functional MR is a major confounding factor in the hemodynamic of patients with LV systolic dysfunction

Survival free of cardiac transplantation (%)

LA_{max} < 68.5 mL/m^2

LA_{max} > 68.5 mL/m^2

Logrank chi squared 17.2 p<0.0001

Figure 2. Kaplan-Meier survival curves of a subgroup of patients with severe systolic dysfunction (ejection fraction <30%), taken from the overall study population and classified into two groups according to the best cut-off value of left atrial maximal volume (LA_{max})/m^2 (68.5 ml/m^2), as obtained from the receiver-operating characteristic curves (see text for details).

(26,27). Mitral regurgitant volume is a key determinant of atrial volume (5), which may reflect the severity, duration, and prognosis of MR (28). However, in our study, the predictive role of LA volume proved to be more powerful than MR, independent of the degree of MR, and it was confirmed in both the group of patients with and the group without MR.

The relationship between atrial dilation, AF, and LV dysfunction is intriguing, and it may contribute to overshadowing of the predictive power of atrial size. However, in our study, AF had no prognostic power, and, more interestingly, the predictive value of LA volume was confirmed in the subgroup of patients with AF.

In our opinion, LA enlargement represents a strong predictive marker, because the atrial chamber is a window allowing comprehensive evaluation of several factors associated with a bad prognosis, which are often difficult to document separately. Atrial size might also reflect marked hemodynamic atrial overload in specific phases during the course of chronic heart disease, such as during exercise, giving evidence of temporal hemodynamic impairment (MR or diastolic dysfunction) which otherwise would remain silent (29). An appealing suggestion is that LA volume stores information on the history of the disease (30), highlighting its duration (31). Accordingly, in our study, LA volume correlated weakly but significantly with the duration of the disease.

These observations might help to explain the difference in AUCs between atrial and ventricular volumes in short-term follow-up (12 months). The low predictive value of $LVESV/m^2$ at this time point might depend on improvement of LV function, which, in some cases, occurs spontaneously (32) or after pharmacologic or surgical therapy in the early phase of the disease. The excellent prognosis associated with ventricular recovery (32) might confound the predictive power of the dysfunctional ventricle at baseline.

It is possible that in patients with DCM, atrial enlargement could also be due to concomitant atrial myopathic disease (33) caused by a more widespread primary pathologic process. Finally, the prognostic role of LA size might be partly related to natriuretic peptide levels (e.g., atrial natriuretic peptide) (34), which have been demonstrated to have diagnostic (35) and prognostic power (36) in patients with LV systolic dysfunction.

Others studies have included LA size in the survival analysis. In particular, two studies (1,2) showed that LA size predicted the outcome independent of the restrictive mitral pattern, New York Heart Association functional class and EF, but they confirmed that the restrictive pattern had a higher predictive power than did atrial size. A possible explanation might be the difference between their patient cohorts and ours. Both studies analyzed populations of patients with very severe diastolic dysfunction, with a prevalence of a restrictive pattern of 42% and 46%, respectively. The narrow range of these pathophysiologic variables

raises the question as to whether those cohorts can adequately represent the whole spectrum of the disease. In contrast, our population was characterized by a wider range of systolic dysfunction, and only a 22% prevalence rate of a restrictive pattern, indicating a less severe disease state.

Furthermore, in the study by Pinamonti et al. (2), the overall population had a relatively young mean age (39 ± 15 years). This casts doubt on the accuracy of mitral parameters in describing restrictive physiology, because of the strong age dependence of the mitral pattern.

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