Prognostic Significance of Left Atrial Volume Dilatation in Patients with Hypertrophic Cardiomyopathy

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To evaluate the prognostic role of left atrial (LA) volume in hypertrophic cardiomyopathy (HCM), LA volume was measured at baseline and during follow-up in 140 patients with HCM. Unfavorable outcome, defined as occurrence of sudden death, heart transplantation, or invasive reduction of obstruction, developed in 16 patients. In patients with enlarged LA volume (>27 mL/m^2), there was an increased risk for unfavorable outcome (P = .0152). Patients with normal LA volume at baseline in whom volume increased more than 3 mL per year (fast dilating LA volume) had a worse prognosis than patients with normal and stable volume ($P < .001$) and similar to patients with dilated LA volume at baseline (P = not significant). LA volume dilated at baseline, fast dilating LA volume, and New York Heart Association functional class were independent predictors of unfavorable outcome development (odds ratio: 11.453; P = .021, P = 2.019, P = .020, respectively). The assessment of LA volume at baseline and during follow-up adds information regarding prognosis in patients with HCM. (J Am Soc Echocardiogr 2009;22:76-81.)

Keywords: Hypertrophic cardiomyopathy, Left atrial volume, Prognosis

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by left ventricular hypertrophy in the absence of causes capable of inducing hypertrophy.[1–4] The presentation and clinical course of the disease are extremely variable: patients can be asymptomatic throughout life, die suddenly, or develop an array of symptoms, ultimately leading to atrial fibrillation (AF), stroke, or heart failure.[1–5] The identification of patients at risk of unfavorable outcome is one of the most important issues of the disease.[6–9]

Left atrial (LA) volume, measured by 2-dimensional echocardiography, is the most accurate measure of LA size[10,11] because little variations in the linear dimension are often associated with large variation in volume as the result of asymmetric LA remodeling.[10–13] In HCM, increased LA linear dimension is a strong predictor of poor outcome,[14] moreover, increased LA volume predicts the development of AF[15,16] and it is related to exercise capacity[17] even in patients without obstruction at rest or during provocation.[18] There is evidence of increased LA volume in patients with a history of cardiovascular morbidity.[19] However, the prognostic role of LA volume in patients with HCM is not known. Thus, this study was undertaken to investigate the prognostic role of LA volume in patients with HCM.

MATERIALS AND METHODS

We considered 262 patients with HCM who were consecutively enrolled and followed up at the Federico II University School of Medicine. The diagnosis of HCM was made on the basis of M-mode and 2-dimensional echocardiographic evidence of a hypertrophied, nondilated left ventricle without any cardiac or systemic cause capable of inducing hypertrophy.[1–4] The initial evaluation was defined as the first visit to the Federico II University School of Medicine. Patients were excluded from the study if they **1**) had been followed up less than 1 year (66 patients); **2**) had no high-quality echocardiograms (14 patients); **3**) had end-stage HCM (6 patients); **4**) had previous myotomy-myectomy (4 patients); **5**) were in AF or had history of AF at the time of the enrollment (20 patients); or **6**) were aged less than 18 years at the time of enrollment (12 patients). This exclusion was done to attenuate the influence of body size variations during growth on the measure of LA volume indexed to body surface area (see below). Thus, the final population consisted of 140 patients, 87 men (mean age 40 ± 15 years, range 18–83 years). Follow-up was 5 ± 3 years (range 1–15 years). Symptoms were assessed at the time of enrollment in each patient and eventually during follow-up.

Echocardiography

Echocardiography was performed using Hewlett Packard imaging systems (Sonos 1000 from 1990 to 2000 and Sonos 5500 thereafter, Andover, MA) with 2.5 and harmonic 3.5 MHz variables frequency transducers. Left ventricular end-diastolic diameter was measured just below the mitral valve leaflets and indexed to the body surface

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Table 1 Demographic characteristics of patients divided into 2 subgroups according to LAVi values at baseline

Clinical and echocardiographic findings at baseline	LAVi ≤ 27 mL/m^2 (72)	LAVi > 27 mL/m^2 (68)	*P*
Age (y)	34.1 ± 14.4	45.7 ± 13.6	<.001
NHYA functional class	1.32 ± 0.55	1.71 ± 0.69	<.001
LA diameter (mm)	38.2 ± 4.1	47.2 ± 4.8	<.001
LAVi (mL/m^2)	20.5 ± 3.5	38.3 ± 10.4	<.001
LV end-diastolic diameter index (mm/m^2)	24.5 ± 2.9	25.1 ± 3.2	NS
LV fractional shortening (%)	44.8 ± 8.5	46.6 ± 9.0	NS
Maximal wall thickness (mm)	20.2 ± 5.5	22.2 ± 5.1	.033
LV outflow tract obstruction (mm Hg)	9.4 ± 22.4	25.7 ± 30.7	<.001
Significant LV outflow tract obstruction (≥30 mm Hg)	5	25	<.001
Mitral regurgitation (score)	0.43 ± 0.75	0.93 ± 1.03	.001

LA, Left atrial; *LAVi*, left atrial volume index; *LV*, left ventricular; *NYHA*, New York Heart Association.

area.[20] LA volume was computed from the apical 4-chamber view by tracing the outline of atrial endocardium at end systole.[12] The volume was computed by using the method of discs[12,18] and normalized to body surface area, defined as LA volume index (LAVi). LAVi greater than 27 mL/m^2 was considered dilated.[21] LAVi was also measured at the end of follow-up, defined as the last recorded value in patients who did not develop events or the last recorded value before events developed. Dilatation rate was thus based on the first and last echocardiographic studies. As an estimate of the degree of left ventricular hypertrophy, maximal wall thickness measured at any level in the left ventricular walls was obtained.[3]

Color Doppler flow imaging was used for semiquantitative assessment of mitral regurgitation.[22] Left ventricular outflow tract obstruction (LVOTG) was recorded at rest by a 1.9 MHz nonimaging transducer using the simplified Bernoulli equation ($P = 4v^2$, where P is pressure and v is flow velocity). Particular care was taken to avoid contamination of the left ventricular outflow waveform by the mitral regurgitation jet.[23] All echocardiographic measurements were obtained by averaging 3 consecutive cardiac cycles.

Clinical End Points and Definitions

Clinical information was gathered during return visits. The clinical end point considered in this study was a combined end point that included sudden and unexpected death, including resuscitated cardiac arrest, the development of severe symptoms (ie, New York Heart Association [NYHA] functional class III or IV) requiring invasive correction of LVOTG (septal ablation or myotomy-myectomy), or heart transplantation. AF was not considered as an end point because the impact of LA dilatation on the development of such arrhythmias has been already demonstrated.[15,16] Patients were treated as clinically indicated during follow-up; as a consequence, treatment was not standardized and the present study does not address the effects of treatment on the natural history of the disease.

Statistics

All statistical calculations were performed using SPSS for Windows, release 12 (SPSS, Chicago, IL). Paired and unpaired *t* test were used when appropriate. Chi-square analysis was used to test differences in categoric variables. The cumulative risk of development of events was assessed with the Kaplan–Meier method. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated by using univariate and multivariate Cox proportional-hazard regression models; all variables but LA dilation at baseline or during follow-up were continuous; LA dilation at baseline or during follow-up was coded 0 for patients with normal LAVi who did not dilate and 1 for all the others. The repeatability coefficient was determined as 1.96 × standard deviation of the absolute value of the differences.[24] A value of $P < .05$ was considered to be significant.

RESULTS

Patient Population

Baseline mean LAVi was 29.2 ± 11.8 mL/m^2. Patients were then divided into 2 subgroups according to their LAVi: ≤ 27 mL/m^2 in 72 patients and dilated at baseline (ie, > 27 mL/m^2) in 68 patients. The demographic characteristics of the 2 subgroups are reported in Table 1. During follow-up, there were 16 events: seven patients died suddenly, of whom 1 had a resuscitated cardiac arrest; 1 patient developed heart failure requiring heart transplantation; and 8 patients underwent invasive treatment of LVOTG because of refractory severe symptoms (myotomy-myectomy in 6 and septal ablation in 2).

LA Volume Measurement Reproducibility

Intraobserver variability. Test–retest variability (ie, 1 blinded observer measured LA volume on 2 sets of recorded images acquired independently and at different times) was tested in 19 consecutive subjects not included in the patient population (4 with valvular heart disease, 10 with coronary artery disease, and 5 without heart disease). Two echocardiograms were performed in each patient; the time elapsed between them was 24 to 36 hours. Patients' identities were blinded for the observer to measure both studies independently. The repeatability coefficient was 2.8 mL. Thus, in our population, a dilating LA volume was considered when volume increased ≥ 3 mL per year.

Prognostic Role of LA Volume at Baseline

The risk of unfavorable outcome was significantly greater in the group with a dilated LAVi (Figure 1). Accordingly, the negative predictive value of LA dilatation was 93%. In contrast, its positive predictive value was low (16%).

Outcome and Obstruction

We further analyzed outcome by excluding patients with significant obstruction at rest and found that a LAVi greater than 27 mL/m^2 in patients without obstruction still differentiated patients with and without events ($P = .0054$) (Figure 3). A similar analysis was not performed in the subgroup of patients with obstruction at rest because of the small number of such patients, preventing us from gaining significant information on survival. Survival was still signifi-

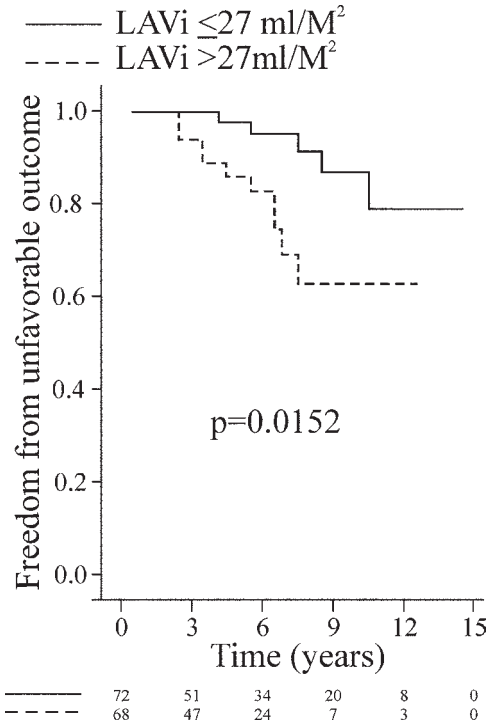

Figure 1 Probability of freedom from unfavorable outcome according to LAVi values at baseline (cut point: 27 mL/m^2). *LAVi*, Left atrial volume index.

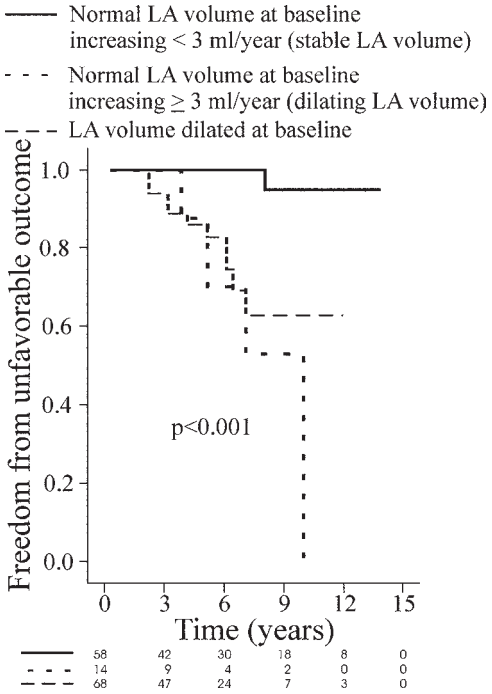

Figure 2 Probability of freedom from unfavorable outcome of patients with dilated LAVi at baseline (>27 mL/m^2) and of patients with LAVi ≤ 27 mL/m^2, with stable (ie, LA volume increase <3 mL/y) or fast dilating LA volume throughout follow-up (ie, LA volume increase ≥ 3 mL/y). Prognosis was significantly poorer in patients with dilated LAVi at baseline (>27 mL/m^2) and in patients with nondilated, fast dilating LAVi, as opposed to patients with nondilated, stable LAVi ($P < .001$ for both). *LA*, Left atrial.

cantly different when patients with normal LAVi without enlargement during follow-up were compared with patients with enlargement during follow-up or at entry, and the end point included was only heart transplantation and sudden death ($P = .008$) (Figure 4).

Prognostic Role of LA Dilatation Development

We tested the hypothesis that patients with a normal LAVi (ie, ≤27 mL/m^2) at entry who showed an increase in volume per year equal to or greater than our coefficient of reproducibility (ie, 3 mL) had a worse prognosis than patients with normal and stable LA volume throughout follow-up. There were 72 patients with normal LAVi at baseline (45 men with a mean age 34 ± 14 years, range 18–79 years). There was a decrease, no change, or an increase in volume less than 3 mL per year (stable LA volume group) in 58 of these patients, whereas the change in volume was ≥ 3 mL per year in 14 of these patients (fast dilating LA volume group).

Patients in the dilating group had a worse outcome than patients in the stable group ($P < .001$) and similar to that of patients with a dilated LAVi at baseline (P = not significant) (Figure 2). The negative predictive value for unfavorable outcome of a normal and stable LA volume was 98%; however, the positive predictive value was 18%.

By Cox regression univariate analysis, we identified predictors of unfavorable outcome (Table 2). Cox regression multivariate analysis was performed using variables that were significant by univariate Cox regression analysis, with in turn one of the LA variables (LAVi or the categoric variable LA dilation at baseline or during follow-up). When LAVi at baseline was used, NYHA functional class was the only predictor of unfavorable outcome (OR 2.812; 95% CI, 1.614–4.899); when the categoric variable LA dilation at baseline or during follow-up was used, NYHA functional class and this variable were independent predictors of unfavorable outcome (NYHA functional class: OR: 2.019; 95% CI, 1.115–3.656, $P = .020$; LA dilation at baseline or during follow-up: OR: 11.453; 95% CI, 1.444–90.848, $P = .021$). In the multivariate approach, neither mitral regurgitation nor LVOTG were predictors of unfavorable outcome.

DISCUSSION

Our study demonstrates that an enlarged left atrium or a fast dilating LA volume represent risk factors of unfavorable outcome in patients with HCM (Figures 1 and 2). Moreover, our data show that NYHA class and an LA volume dilated at baseline or with a fast dilation during follow-up are independent strong predictors of unfavorable outcome in patients with HCM. Patients with nondilated LA volume, who do not dilate during follow-up, are expected to have a good prognosis in view of the high negative predictive power, and can be reassured.

Outcome and HCM

HCM is a complex primary myocardial disease with a diverse clinical presentation that includes a benign or stable clinical course over many years, sudden death, and progressive, invalidating symptoms requiring therapeutic intervention. Sudden death often occurs in younger patients, although it is present in all decades of life.[25] In the present study, which was performed in an adult population with HCM, the annual incidence of sudden death was 1%, and the incidence of development of severe symptoms requiring invasive treatment (reduction of LVOTG or heart transplantation) was 1.2%. Thus, the

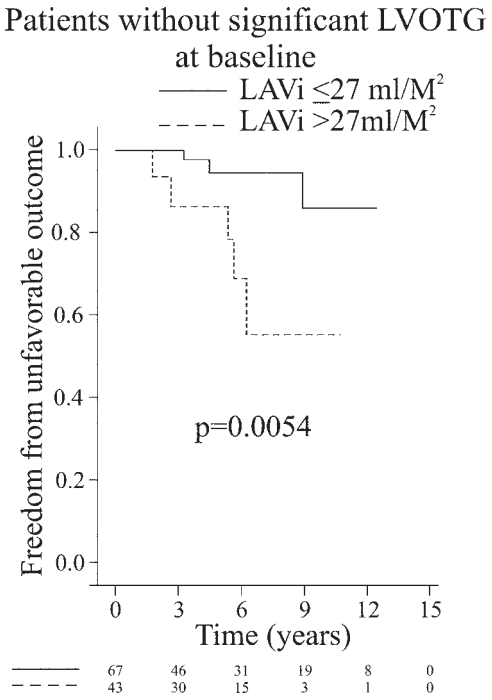

Figure 3 Probability of freedom from unfavorable outcome according to LAVi values at baseline (cut point: 27 mL/m^2) in patients without a significant (ie, ≥30 mm Hg) LVOTG at baseline. *LVOTG*, Left ventricular outflow tract obstruction; *LAVi*, left atrial volume index.

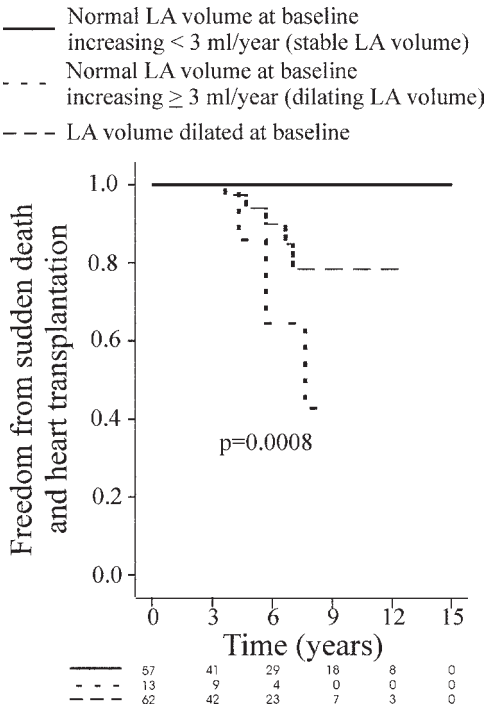

Figure 4 Probability of freedom from unfavorable outcome by excluding as an end point the invasive or surgical reduction of obstruction throughout follow-up. Prognosis was significantly poorer in patients with dilated LAVi at baseline (>27 mlL/m^2) and in patients with nondilated, fast dilating LAVi, as opposed to patients with nondilated, stable LAVi (P = .0008). *LA*, Left atrial.

incidence of the combined end point considered in the present study was 2.2% per year; these results are similar to those of previous reports[7,25] performed in larger populations with HCM. The identification of patients at risk of sudden death and progressive symptoms requiring therapeutic intervention is still a challenge.[6–9]

Outcome and LA Dilatation

In a study by Nistri and coworkers,[14] a marked increase in LA linear dimension was predictive of long-term outcome independently of coexistent AF or LVOTG, whereas there was no relationship between the occurrence of sudden death and LA linear dimensions. Our data complement Nistri et al's in that LA size is a determinant of prognosis in HCM. In contrast with their study, our study showed that LA linear dimension was not a predictor of unfavorable outcome by Cox univariate analysis (Table 2), perhaps because their population was taken from a Register and thus larger. This implies that the prognostic power of LA linear dimension is lower than that of LA volume and suggests that LA volume may be a more reliable predictor of prognosis in the individual patient.

It has been shown that LA volume provides a more accurate measure of LA size than conventional M-mode LA dimension in that little variation in diameter may result in large variation of LA volume.[10–13] In patients with HCM, 2 studies, one from our group[15] and one from Tani et al,[16] demonstrated that LA volume predicts the development of AF. In the present study, patients with LAVi dilation at baseline were older, had a higher degree of LVOTG and mitral regurgitation, and were more symptomatic in terms of NYHA class (Table 1). In the majority of patients with obstructive HCM, mitral valve regurgitation is a consequence of LVOTG.[26] Moreover, diastolic dysfunction is common in HCM regardless of obstruction[27,28] and influences LAVi. Thus, in HCM LA volume may serve as a marker of the severity and duration of LVOTG and diastolic dysfunction.[17–19,29] This is confirmed in our population, in that patients with a dilated LAVi at baseline had different clinical and echocardiographic characteristics (Table 1). Furthermore, this concept may explain why patients with a dilated LAVi have a worse prognosis in our study (Figure 1). In patients with HCM, LAVi is increased in patients with a history of cardiovascular morbidity[19] and is related to exercise capacity;[17] this holds true in patients without obstruction at rest or during provocation.[18] Thus, LA volume represents a marker of the disease severity and may help in the stratification of risk in patients with HCM.

Moreover, our study is the first to demonstrate the importance of LA volume measurement throughout follow-up. We found that in patients with a normal LA volume at baseline and an increase in volume of at least 3 mL per year, prognosis was worse than in patients with stable LA volume throughout follow-up and similar to that of patients with dilated LAVi at baseline (Figure 2). The negative predictive values for unfavorable outcome of a normal and stable LA volume was high: 98%. Although this result is of interest, it must be underscored that for other clinical risk factors in patients with HCM, our findings also show a low positive predictive value for events: 18%.

Outcome and Obstruction

We performed a Kaplan–Meier analysis that showed no statistical differences between patients with and without obstruction (P = .1). We acknowledge that the number of patients with obstruction in our population (30) is too small to affirm the negative impact of obstruc-

Table 2 Predictors of unfavorable outcome development by Cox regression univariate analysis

Variable	OR	CI 95%	*P*
Age (y)	1.016	0.980–1.053	NS
NYHA functional class	2.812	1.614–4.899	<.001
LA diameter (mm)	1.057	0.982–1.137	NS
LAVi (mL/m^2)	1.047	1.011–1.084	.011
LA dilatation, at baseline or during follow-up (categoric)	16.656	2.171–126.080	.007
LV end-diastolic dimension index (mm/m^2)	1.052	0.901–1.228	NS
LV fractional shortening (%)	1.007	0.956–1.062	NS
Maximal wall thickness (mm)	1.053	0.968–1.146	NS
LV outflow tract obstruction (mm Hg)	1.016	1.005–1.028	.006
Mitral regurgitation (score)	1.804	1.151–2.827	.010

LA, Left atrial; *LAVi*, left atrial volume index; *LV*, left ventricular; *NYHA*, New York Heart Association; *NS*, not significant; *OR*, odds ratio; *CI*, confidence interval.

tion on outcome, which has been strongly demonstrated in a large series of patients (>1000).[7] Nevertheless, we further analyzed outcome by excluding patients with significant obstruction at rest and found that in patients without obstruction a LAVi greater than 27 mL/m^2 still differentiated patients with and without events (P = .0054) (Figure 3); however, 3 patients without significant obstruction (gradients of 14, 23 and 25 mm Hg at entry) developed significant obstruction during follow-up and required myotomy-myectomy surgery. Finally, to exclude any potential influence of obstruction, we evaluated outcome by excluding as an end point the invasive or surgical reduction of obstruction throughout follow-up (ie, only heart transplantation and sudden death were considered unfavorable outcomes). We found that survival was still significantly different when patients with normal LAVi without enlargement during follow-up were compared with patients with enlarged LAVi during follow-up or at entry (P = .008) (Figure 4).

LIMITATIONS

Although the biplanar measurement of LA volume is recommended because of the retrospective nature of our work, we used the single plane method. We acknowledge that this is a limitation; however, the reproducibility of our measurement was excellent, indicating that this measure may be used in large population of patients. Moreover, Lester et al[10] demonstrated that the single and biplanar methods are closely correlated over a wide range of LA sizes.

Moreover, we calculated an annualized rate of LA dilation from first to last echocardiogram; to exclude fluctuations in measurement, we selected a cutoff value of LAVi increase larger than the intrinsic error. We do not imply, however, that this dilatation rate was consistent throughout follow-up.

CONCLUSIONS

We demonstrated that a dilated LA volume at baseline and a fast dilating LA volume during follow-up, together with NYHA functional class, have an independent predictive value for unfavorable outcome development; in other words, asymptomatic patients in whom LA volume is not dilated at baseline and does not dilate during follow-up are expected to have a good prognosis. Thus, both NYHA functional class and LA volume are robust clinical markers of disease severity. We suggest that asymptomatic patients with LAVi less than 27 mL/m^2 at baseline and an increase in volume less than 3 mL per year throughout follow-up may be reassured about their risk of developing events; in contrast, because of the low positive predictive value, patients with a dilated or dilating left atrium should be clinically monitored.

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