Prognostic Significance of Left Atrial Size in Patients With Hypertrophic Cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy)†

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This study assessed left atrial (LA) dimension as a potential predictor of outcome in hypertrophic cardiomyopathy (HC). From the Italian Registry for Hypertrophic Cardiomyopathy, 1,491 patients (mean age 47 ± 17 years; 61% men; 19% obstructive), followed for 9.4 ± 7.4 years after the initial echocardiographic evaluation, constituted the study group. The mean LA transverse dimension was 43 ± 9 mm and was larger in patients with severe symptoms (48 ± 9 mm for New York Heart Association classes III and IV vs 42 ± 9 mm for classes I and II, p <0.001), atrial fibrillation (47 ± 9 vs 42 ± 8 mm in sinus rhythm, p <0.001), and left ventricular outflow obstruction (46 ± 9 mm for ≥30 mm Hg at rest vs 42 ± 9 mm for <30 mm Hg at rest, p <0.001). On univariate analysis, each 5-mm increase in LA size was associated with a hazard ratio (HR) of 1.2 for all-cause mortality (p <0.0001). On multivariate analysis, a LA dimension >48 mm (the 75th percentile) had a HR of 1.9 for all-cause mortality (p = 0.008), 2.0 for cardiovascular death (p = 0.014), and 3.1 for death related to heart failure (p = 0.008) but was unassociated with sudden death (p = 0.81). Similar results were obtained after the exclusion of patients with atrial fibrillation (HR 1.7, p = 0.008) or outflow obstruction (HR 1.8, p = 0.003). The predictive power of LA dimension >48 mm was also validated in an independent HC cohort from the United States, with similar HRs (1.8 for all-cause mortality, p = 0.019). In conclusion, in a large cohort of patients with HC from a nationwide registry, a marked increase in LA dimension were predictive of long-term outcome, independent of co-existent atrial fibrillation or outflow obstruction. LA dimension is a novel and independent marker of prognosis in HC, particularly relevant to the identification of patients at risk for death related to heart failure. **(Am J Cardiol 2006;98:960–965)**

Hypertrophic cardiomyopathy (HC) is a genetic form of heart disease with a diverse clinical expression and often unpredictable natural history.[1–5] The prediction of clinical outcome in HC remains incomplete, and therefore, the pursuit of additional prognostic markers continues to be important.[6–8] In HC, enlargement of the left atrium is common, is associated with several adverse pathophysiologic consequences such as left ventricular outflow obstruction,[9] and is predictive of atrial fibrillation, a major determinant of outcome.[10] Despite growing recognition of the left atrium as a marker of disease severity,[11] left atrial (LA) dimension has not been specifically analyzed as a predictor of outcome in a large HC cohort. Therefore, in the present study, we targeted LA dimension as a potential risk marker for an adverse clinical course and mortality in our multicenter HC cohort assembled throughout Italy.

Methods

The Italian Registry for Hypertrophic Cardiomyopathy: The Italian Registry for Hypertrophic Cardiomyopathy is a research initiative funded by the Italian Ministry of Health and the National Institute of Health (Istituto Superiore di Sanità), in the context of a large epidemiologic survey aimed at cardiovascular prevention called Il Progetto Cuore (http://www.cuore.iss.it/eng/index_en.htm). The enrollment period was May 2000 to May 2002. A direct invitation to participate was made to cardiology centers nationwide, ranging from tertiary referral institutions and transplantation units to community hospitals and outpatient clinics. In addition, the registry was advertised in newsletters and at the scientific sessions of national cardiology meetings.

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Table 1
General baseline features of the 1,491 patients with hypertrophic cardiomyopathy, based on initial left atrial dimensions

Variable	All (n = 1,491)	Percentile of LA Size				Overall p Value
		0–25th <36 mm (n = 363; 24%)	26th–50th 36–42 mm (n = 397; 27%)	51st–75th 43–48 mm (n = 374; 25%)	76th–100th >48 mm (n = 357; 24%)	
Age at initial evaluation (yrs)	47 ± 17	42 ± 8	45 ± 17	49 ± 17	49 ± 16	<0.001
Men	917 (61%)	217 (60%)	254 (64%)	212 (57%)	234 (66%)	NS
Follow-up (yrs)	9.7 ± 7.7	9.4 ± 6.8	9.6 ± 7.6	9.3 ± 7.7	9.8 ± 7.7	NS
Family history of HC and/or sudden cardiac death	516 (35%)	138 (38%)	167 (42%)	93 (25%)	118 (33%)	<0.01
With symptoms	1,077 (72%)	212 (58%)	247 (62%)	291 (78%)	327 (92%)	<0.001
Average NYHA functional class at initial evaluation	1.6 ± 0.7	1.4 ± 0.6	1.5 ± 0.7	1.7 ± 0.7	1.9 ± 0.8	<0.001
NYHA functional class III/IV	174 (12%)	19 (5%)	29 (7%)	50 (13%)	76 (21%)	<0.001
Angina	288 (19%)	77 (21%)	74 (19%)	79 (21%)	58 (16%)	NS
Syncope	134 (9%)	32 (9%)	35 (9%)	32 (9%)	35 (10%)	NS
Atrial fibrillation (paroxysmal or chronic)	252 (17%)	29 (8%)	50 (13%)	65 (17%)	108 (30%)	<0.001
Receiving medical therapy	1,004 (67%)	200 (55%)	261 (66%)	252 (67%)	291 (82%)	<0.001
LV obstruction at rest (≥30 mm Hg)	338 (23%)	54 (15%)	65 (16%)	94 (25%)	125 (35%)	<0.001
LA size (mm)	43 ± 9	32 ± 3	40 ± 2	45 ± 2	54 ± 6	N/A
LV end-diastolic dimension (mm)	44 ± 7	43 ± 6	44 ± 6	45 ± 7	46 ± 8	<0.001
LV end-systolic dimension (mm)	26 ± 7	25 ± 6	26 ± 6	27 ± 7	28 ± 8	<0.001
Maximum LV wall thickness (mm)	21 ± 5	20 ± 5	20 ± 5	21 ± 5	22 ± 5	<0.001

Information regarding the registry, detailed instructions for patient recruitment, and data collection forms were sent by mail to all centers that accepted the initial invitation and made available on a dedicated Web site (http://www.cardiomiopatiaipertrofica.it). A centralized database was established in Florence for data storage, retrieval, and analysis. Of >100 institutions directly contacted, the final number of participating centers was 40. The general features of the registry population have been described elsewhere.[12]

Diagnosis of HC and patient selection: Participating centers included all patients with diagnoses of HC followed at those institutions at the present time or in the past, including those already deceased at the time of this study. The diagnosis of HC was based on 2-dimensional echocardiographic evidence of a hypertrophied and nondilated left ventricle (wall thickness ≥15 mm), in the absence of any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident, such as systemic hypertension or aortic stenosis.[1,13]

Of the 1,677 patients constituting the overall registry population, 132 children (aged <16 years) were excluded because the relatively smaller LA size in this subgroup might have biased the overall study analysis. In addition, 54 other patients were excluded because of severe mitral regurgitation in the clinical context of associated primary mitral valve disease (i.e., myxomatous or calcific degeneration), because LA enlargement could not be attributed solely to HC.[14] Conversely, patients with mild-to-moderate mitral regurgitation secondary to mitral valve systolic anterior motion in the context of outflow obstruction were included in the study.[9] Therefore, the final study group was composed of 1,491 patients with HC.

Study end points: The primary clinical end points used in this study were (1) all-cause mortality; (2) cardiovascular mortality; (3) death related to heart failure, occurring in the context of cardiac decompensation and progressive disease course, and including stroke-related death (patients with heart transplantation were censored at the time of the operations and considered as equivalents to death related to heart failure)[2,12]; and (4) sudden cardiac death, defined as unexpected sudden collapse occurring <1 hour from the onset of symptoms in patients who had previously experienced relatively stable or uneventful clinical courses. In addition, potentially lethal cardiovascular events in which patients were either successfully resuscitated from cardiac arrest or received appropriate defibrillation shocks from implanted cardioverter-defibrillators were regarded as equivalents of sudden cardiac death in the present data analysis.[2,12]

Echocardiography: LA dimension was measured at end-systole as the anteroposterior linear diameter from the parasternal long-axis view, using 2-dimensional echocardiographic guidance to position the cursor as recommended.[15] The magnitude and distribution of left ventricular (LV) hypertrophy was assessed as previously described.[16] Obstruction of LV outflow was considered present when a peak instantaneous outflow gradient of ≥30 mm Hg was estimated with continuous-wave Doppler echocardiography under basal (resting) conditions. Participating centers were prospectively provided with detailed instructions regarding the standard echocardiographic measurements required for patient enrollment in the registry.[12]

Statistical analysis: Data are expressed as mean ± SD. The unpaired Student's *t* test or 1-way analysis of variance

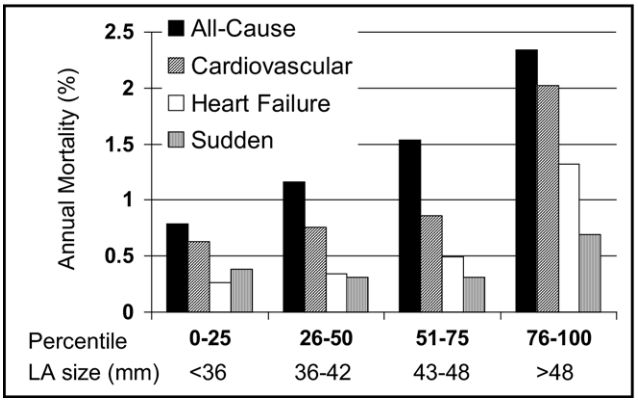

Figure 1. Annual mortality rates for the study patients according to LA size. For the overall group comparisons, p <0.05 for all end points except sudden death (p = 0.22).

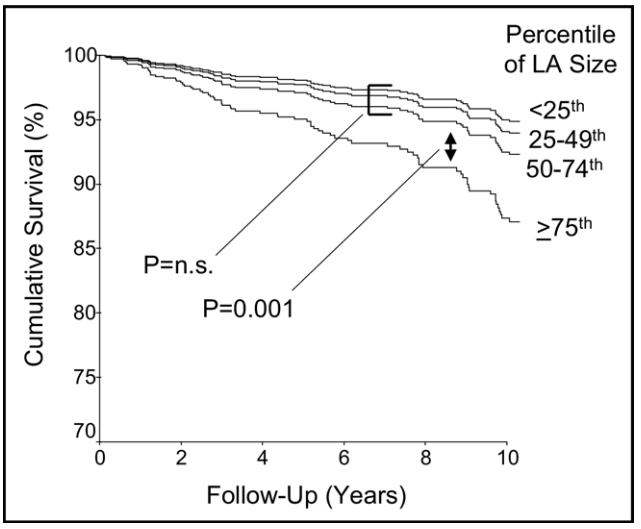

Figure 2. Relation of LA size to long-term survival (free of all-cause mortality). Hazard plot based on multivariate Cox regression analysis, including age, gender, the presence of outflow obstruction, and NYHA class at initial evaluation as covariates.

was used for the comparison of normally distributed data. The chi-square or Fisher's exact test was used to compare noncontinuous variables expressed as proportions. Relative risks and 95% confidence intervals (CIs) were calculated using univariate and multivariate Cox proportional-hazards regression models. Multivariate analyses were performed with a stepwise forward regression model, in which each variable with a p value ≤0.05 (on the basis of univariate analysis) was entered into the model; all multivariate models included age, gender, the presence of outflow obstruction, and New York Heart Association (NYHA) class at initial evaluation as covariates. All p values were 2 sided and were considered significant when <0.05. LA size was prospectively evaluated with regard to outcome as a continuous variable using the 25th, 50th, and 75th percentiles for the cohort distribution. Moreover, a receiver-operating characteristic curve analysis was constructed for the retrospective identification of the optimal LA size threshold.

Validation of study results on an independent cohort: The study results were compared with an independent cohort of 537 consecutive patients with HC[6] followed for 4.8 ± 3.9 years at the Hypertrophic Cardiomyopathy Center at the Minneapolis Heart Institute Foundation for the purpose of validation. Mean age was 42 ± 22 years, 317 patients (59%) were men, 36 (7%) were in NYHA classes III and IV, 152 (28%) had LV outflow obstructions >30 mm Hg, and 38 (16%) had paroxysmal or chronic atrial fibrillation. The study was approved by the institutional review board at each of the participating centers.

Results

Baseline echocardiographic features: The clinical and demographic characteristics of the 1,491 study patients are listed in Table 1. Overall, the average LA dimension was 43 ± 9 mm; the 25th, 50th, and 75th percentiles of the cohort distribution were 36, 42, and 48 mm, respectively (Table 1). Eight hundred twenty-seven patients (55%) had LA sizes >40 mm.

LA dimensions varied with respect to age (<25 years: 39 ± 8 mm; 26 to 40 years: 43 ± 9 mm; 41 to 60 years: 44 ± 9 mm; >60 years: 44 ± 9 mm; overall p <0.001) and gender (43 ± 9 mm in men vs 42 ± 8 mm in women, p = 0.009). Moreover, substantial LA enlargement was observed in those patients with severe symptoms (48 ± 9 mm for NYHA classes III and IV at baseline vs 42 ± 9 mm for NYHA classes I and II, p <0.001), paroxysmal or chronic atrial fibrillation (47 ± 9 vs 42 ± 8 mm in sinus rhythm, p <0.001), and LV outflow obstruction at rest (46 ± 9 mm for ≥30 mm Hg vs 41 ± 8 mm for <30 mm Hg, p <0.001).

Outcomes: The mean follow-up was 9.4 ± 7.7 years. During this time, 193 of the 1,491 patients died (13%), including 142 from cardiovascular causes and 51 from noncardiac causes. Of the 142 cardiovascular deaths, 130 were related to HC, including 58 sudden events and 72 due to congestive heart failure or stroke; the remaining 12 patients died of non-HC–related cardiac causes due to co-existent atherosclerotic coronary artery disease.

Relation of LA size to outcome: Annual all-cause, cardiovascular, and heart failure related mortality increased significantly with increasing LA dimensions (Figure 1). On univariate Cox regression analysis, each 5-mm increase in LA size was associated with a 1.2 hazard ratio (HR) for all-cause mortality (p <0.0001).

After adjustment for age, gender, the presence of outflow obstruction, atrial fibrillation, and NYHA class at initial evaluation, a LA dimension >75th percentile (i.e., >48 mm) was associated with an independent twofold increase in the risk for all-cause mortality and cardiovascular death compared with patients with LA dimensions ≤48 mm and a threefold increase in the risk for death related to heart failure (Figure 2), whereas no association was found be-

Table 2
Long-term risk associated with a left atrial size >48 mm at initial evaluation in 2 independent hypertrophic cardiomyopathy cohorts*

Cohort	Death from Any Cause		Cardiovascular Death		Heart Failure Related		Sudden Death	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Italian Hypertrophic Cardiomyopathy Registry (n = 1,491)	1.9 (1.2–3.2)	0.008	2.0 (1.1–3.5)	0.014	3.1 (1.3–7.2)	0.008	—	0.81
United States cohort (n = 537)	1.8 (1.1–2.9)	0.019	2.7 (1.4–5.3)	0.003	3.8 (1.1–12.8)	0.034	—	0.22

* Both models obtained by multivariate Cox proportional-hazards analysis, including age as a stratification factor (<20, 20 to 39, 40 to 60, and >60 years); other covariates included in the model were gender, the presence of LV outflow obstruction ≥30 mm Hg, atrial fibrillation, and NYHA class at initial evaluation. Patients with HC with LA sizes ≤48 mm constituted the reference category for this analysis.

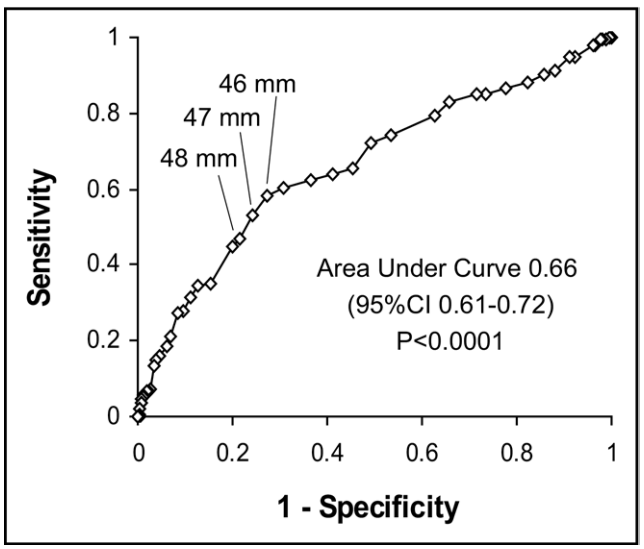

Figure 3. Receiver-operating characteristic curve of LA size values with respect to all-cause mortality. A LA size of 47 mm was identified as the optimal cut-off value.

tween LA size and the likelihood of sudden, unexpected death (Table 2).

Independent predictors of all-cause mortality, other than LA size, were LV outflow obstruction at rest (≥30 mm Hg) and atrial fibrillation (HRs 1.57 and 1.79, respectively; $p < 0.01$). The multivariate model including these 3 variables accounted for 87% of the all-cause mortality, whereas the remaining 13% was attributable to unmeasured confounders. Of note, LA dimensions >48 mm retained their predictive value after the exclusion of patients with chronic or paroxysmal atrial fibrillation (HR 1.7, 95% CI 1.1 to 2.5, $p = 0.0078$) or LV obstruction at rest (HR 1.8, 95% CI 1.2 to 2.6, $p = 0.0029$). In the subgroup of 338 patients with LV obstructions, LA dimension >48 mm strongly predicted death related to heart failure (independent HR 4.2, 95% CI 1.4 to 12.1, $p < 0.017$) but none of the other end points ($p > 0.1$ for all).

Receiver-operating characteristic curve analysis identified LA sizes of 46 to 48 mm as most accurate for the identification of patients at risk in our cohort (Figure 3). A cut-off value of 48 mm had 75% accuracy, 90% negative predictive value, and 23% positive predictive value for all-cause mortality. Negative predictive accuracy specifically for heart failure death increased to 94%.

Validation analysis in an independent cohort: The relation of LA size to outcome was also assessed independently in a cohort of 537 patients with HC from the United States.[6] The average LA size was 42 ± 9 mm, and the 25th, 50th, and 75th percentiles were 36, 41, and 46 mm, respectively. On multivariate analysis, a LA size >48 mm was associated with independent risk for all-cause mortality, cardiovascular death, and death related to heart failure, with HR values that were very similar to those of the Italian cohort (Table 2). Moreover, as for the Italian patients, there was no association of LA size with the likelihood of sudden, unexpected death (Table 2).

Discussion

The present study establishes a strong relation between LA dimension and adverse long-term outcomes in a large population of patients with HC from a nationwide Italian registry. During a follow-up of >9 years, each 5-mm increase in LA dimension at initial evaluation was associated with a 20% increase in all-cause mortality. LA diameter >75th percentile of the study group (48 mm) predicted an almost twofold independent increase in all-cause mortality and a threefold increase in death related to heart failure.

This association of LA diameter with outcome retained its statistical power even after the exclusion of specific patient subgroups known to be at risk for disease progression, such as those with atrial fibrillation or LV outflow obstruction at rest. Accordingly, a LA size <48 mm had a very large negative predictive value for all-cause mortality (90%) and for death related to heart failure (94%). In the subset of patients with LV outflow obstruction at rest, a LA size >48 mm showed a particularly strong association with death related to heart failure (HR 4.2).

Overall, the present data show that the standard echocardiographic measurement of LA diameter is a simple and powerful predictor of long-term disease progression and mortality related to heart failure in patients with HC. Conversely, LA dimension showed no association specifically with the likelihood of sudden cardiac death.

Of note, most of our 1,491 study patients had a LA dimension exceeding commonly used reference values

(55% >40 mm).[17] Therefore, a modest degree of LA remodeling represents a common feature of the HC disease process and cannot be considered, per se, a marker of increased risk. As a consequence, only severe LA dilation (>48 mm) was predictive of outcome in our cohort.

It is noteworthy that the LA dimensions in subgroups of patients with established clinical predictors of outcome, such as severe symptoms (NYHA class III or IV), paroxysmal or chronic atrial fibrillation, and LV outflow obstruction, averaged 46 to 48 mm. Our findings are consistent with those of a recent study reporting a LA diameter ≥46 mm as the single echocardiographic variable able to predict outcome after surgical myectomy in obstructive HC.[18]

In the present study, by virtue of a particularly large patient population and an extended follow-up period, we were able to establish LA dimension as a major predictor of outcome in HC. This concept agrees with previous studies showing the importance of LA dimension as a clinical marker of cardiovascular risk in the general population as well as in patients with hypertensive heart disease or dilated cardiomyopathy.[19–22] Furthermore, we validated our principal findings in an independent cohort of consecutive patients with HC from the United States, in which very similar results were achieved with regard to the prognostic significance of marked LA dilation. Therefore, LA dimension represents a clinically useful and practical marker with general applicability to different populations of patients with HC.

We acknowledge that the large number of operators involved in echocardiographic measurements in this large multicenter study represents an unavoidable limitation. However, care was taken to standardize measurements of LA and other cardiac dimensions by prospectively providing detailed technical instructions to all participating centers. Moreover, the present results are based on a conventional and easily obtained measurement, the anteroposterior LA diameter, which is a customary component of any clinical echocardiographic study. Finally, we believe that the substantial numeric strength of the study cohort (among the largest ever reported in this disease) offers a large measure of compensation for this methodologic issue.

Our findings have potential implications for clinical management. Patients with HC with marked LA dilation who are potentially at risk for disease progression and complications related to heart failure can be followed longitudinally to assess the progression of LA dimension and anticipate changes in clinical course. This may lead to a consideration for the more aggressive management of potentially treatable clinical features, such as atrial fibrillation and resting (or provoked) outflow tract obstruction.[9,18,23,24] In contrast, by virtue of a large negative predictive value, patients with normal or only mildly enlarged LA dimensions can be cautiously reassured with regard to disease progression and heart failure.

We found no relation between LA diameter and the occurrence of sudden, unexpected death occurring largely in asymptomatic or mildly symptomatic patients. Therefore, these data do not support LA dilation as a risk factor for sudden death, nor can LA dimensions within normal limits be used to reassure patients with HC regarding this specific risk.

Appendix

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