Left Atrial Dysfunction as a Correlate of Heart Failure Symptoms in Hypertrophic Cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) represents a generalized myopathic process affecting both ventricular and atrial myocardium. We aimed to assess left atrial (LA) function by two-dimensional speckle tracking echocardiography and its relation with left ventricular (LV) function and clinical status in patients with HCM.

Methods: We prospectively enrolled 37 consecutive patients with HCM and 37 normal subjects with similar age and gender distribution. Longitudinal LV strain (ϵ) and LA ϵ and strain rate (Sr) parameters (systolic, early diastolic, and late diastolic during atrial contraction) were assessed.

Results: Peak LAϵ and LA Sr parameters were significantly lower in patients compared with controls ($P \leq .001$ for all). In patients, all LA function parameters correlated with LVϵ ($P < .003$ for all). Indexed LA volume, LA function parameters, and mitral regurgitation degree were the main correlates of New York Heart Association class; late diastolic strain rate during atrial contraction was the only independent predictor of symptomatic status.

Conclusion: In patients with HCM, LA function is significantly reduced and related to LV dysfunction. Moreover, LA booster pump function emerged as an independent correlate of heart failure symptoms in this setting. (J Am Soc Echocardiogr 2010;23:1090-8.)

Keywords: Deformation imaging, Hypertrophic cardiomyopathy, Left atrium, Left ventricle, Speckle tracking echocardiography

Hypertrophic cardiomyopathy (HCM) is characterized by a generalized myopathic process affecting both ventricular and atrial myocardium.[1,2] Left ventricular (LV) dysfunction and remodeling of the left atrium (LA) are common features of HCM. Moreover, LA dilation has proved to be a powerful determinant of exercise capacity[3] and adverse outcome[4] in this setting.

In patients with symptomatic HCM, exertional dyspnea is a common symptom. LA function plays a central role in maintaining optimal cardiac output despite impaired LV relaxation and reduced LV compliance.[5] It has been demonstrated that the Frank-Starling mechanism is also operative in the LA and that LA output increases as atrial diameter increases, which contributes to maintaining a normal stroke volume.[6] LV diastolic dysfunction, elevated filling pressure, LV hypertrophy, LV outflow tract obstruction, mitral regurgitation, and intrinsic atrial myopathy are all potential contributors to ongoing LA remodeling.[7] Increased LA volume may be accompanied by a progressive impairment in LA function, and both may precede symptom development and adversely affect prognosis. The role of LA dysfunction in the symptomatic status of patients with HCM has not been addressed.

There is a close interdependence between LV and LA function. LA reservoir function is influenced by LV contraction through the descent of LV base during systole, LA relaxation, and stiffness;[8] LA conduit function is dependent on LV relaxation and preload; and LA booster pump function is influenced by LV compliance, LV filling pressures, and intrinsic LA contractility.[9] Moreover, despite the existing theory of a generalized myopathic process affecting both ventricular and atrial myocardium, the relationship between LA myocardial function and the degree of LV dysfunction in patients with HCM has not been examined.

Both LV function and LA function (reservoir, conduit, and active contractile functions) can be adequately examined by two-dimensional speckle-tracking echocardiography (STE).[10] Strain imaging overcomes the main drawbacks of tissue Doppler-derived

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Abbreviations

ASr = Late diastolic strain rate during atrial contraction

ESr = Early diastolic strain rate

HCM = Hypertrophic cardiomyopathy

LA = Left atrial

LAVi = LA volume indexed to body surface area

LV = Left ventricular

NYHA = New York Heart Association

Sr = Strain rate

SSr = Systolic strain rate

STE = Speckle-tracking echocardiography

myocardial velocities and thus provides more accurate quantification of regional myocardial function.[11]

In the present study, we hypothesized that 1) LV longitudinal dysfunction is accompanied by an impairment of LA longitudinal function and that 2) heart failure symptoms are related in part to LA dysfunction in patients with HCM.

MATERIALS AND METHODS

Study Population

For enrollment, we prospectively screened consecutive patients who had been referred to our echocardiography laboratory and who met the diagnostic criteria for HCM: M-mode and two-dimensional echocardiographic evidence of a hypertrophied (diastolic wall thickness ≥ 15 mm), nondilated LV in the absence of exercise training history and cardiac or systemic conditions capable of inducing that magnitude of hypertrophy.[12] Patients with a poor acoustic window, patients who were technically unsuitable for STE analysis, and patients with non-sinus rhythm were excluded. The final study population consisted of 37 patients. The following clinical data were collected: age, gender, history of smoking, hypertension (defined as history of hypertension requiring medical therapy), diabetes mellitus, and hypercholesterolemia. The clinical status was defined according to the New York Heart Association (NYHA) classification. Information regarding current medication was also obtained. Thirty-seven healthy volunteers with similar age and gender distribution served as a control group. They had no evidence of heart disease by physical examination, 12-lead electrocardiogram, and echocardiography and were taking no medication. All subjects gave their informed consent to participate in the study.

Echocardiographic Study

A commercially available ultrasound machine (Vivid 7, General Electric Medical Systems, Horten, Norway) equipped with an M4S probe was used for all echocardiographic examinations. Standard echocardiographic views were obtained using second-harmonic imaging with frequency, depth, and sector width adjusted for frame-rate optimization (between 60-100 fps). Image settings and frame-rates were kept similar for LV four-chamber, two-chamber, and long-axis apical views, which were recorded immediately one after another.[13] For LA size measurements (area and volume) and deformation analysis, a conventional apical four-chamber view was recorded with attention to LA cavity optimization and wall definition. The LA appendage and the confluence of the pulmonary veins were excluded from the measurements. From the apical four-chamber view, the pre-atrial contraction LA volume and the minimal and maximal LA volumes were measured using the area-length method. LA active emptying fraction, LA expansion index, and LA passive emptying fraction were calculated as previously described.[14] LV volumes and ejection fraction were calculated using Simpson's biplane method.[15] LV mass was calculated by the equation of Devereux.[16] All volumes and LV mass were normalized to body surface area. The maximal LA volume indexed to body surface area (LAVi) was used in further statistical analyses. Peak systolic (S) and peak early diastolic (E′) mitral annular velocities were obtained by pulse-wave tissue Doppler imaging from the apical four-chamber view using both the septal and the lateral sites. The average E′ was used to calculate the ratio of peak early-diastolic transmitral flow velocity E to E′, to estimate LV filling pressures.[17] LV diastolic dysfunction was graded according to the American Society of Echocardiography/European Association of Echocardiography recommendations: grade I (impaired relaxation), grade II (pseudonormal filling pattern), and grade III (restrictive filling pattern).[16,18,19] LV outflow tract gradient was measured by continuous-wave Doppler from the apical 5-chamber view. LV outflow tract obstruction was defined as a peak gradient > 30 mm Hg at rest or during Valsalva maneuver.[12] Color Doppler echocardiography was used for the semiquantitative assessment of mitral regurgitation severity, as recommended.[17]

Both two-dimensional and Doppler images were digitally stored as three consecutive cycles recorded during end-expiratory apnea. Data were analyzed offline using a commercially available software package (EchoPac PC version BT08; General Electric Medical Systems) by a single observer experienced in two-dimensional strain quantitation by STE.

Measurement of Left Ventricular Strain and Left Atrial Strain and Strain Rate Parameters

Analysis of LV strain by STE was performed on the four-chamber, two-chamber, and long-axis apical views, as previously described.[20] Briefly, after manually tracing the LV endocardium, an automatically generated region of interest divided into six segments was provided for each view, which could be adjusted by contour position refinements and width tuning to fit the LV wall. LV segments with inadequate image quality were rejected by the software, leading to subject exclusion from further study. LV longitudinal strain was measurable from the apical four-chamber view in all patients. Global longitudinal peak systolic LV strain values, calculated using a 17-segmental model, were validated by the software in 30 patients. LV longitudinal strain rate (Sr) parameters (systolic Sr, early diastolic Sr, and late diastolic Sr) were also measured from the apical four-chamber view.

Analysis of LA strain and strain rate parameters by STE was performed on the same four-chamber view in which LA area and volume measurements were performed. Similar to STE-derived LV analysis, longitudinal global LA strain and strain rate parameters were assessed as the average of six segmental values. Peak LA strain (ε) and Sr (systolic [SSr], early diastolic [ESr], and late diastolic strain rate during atrial contraction [ASr]) were measured as LA function parameters: SSr for reservoir function, ESr for conduit function, and ASr for booster pump function.

Statistical Analysis

Measurements are presented as mean ± standard deviation. Variables were compared using Student *t* test, analysis of variance, or chi-square test when appropriate. The relationships between different parameters were assessed by correlation analysis: Pearson's method for continuous, normally distributed variables and Spearman's rho method for ordinal or continuous but skewed variables.

To assess the comparative accuracy of different echocardiography variables in identifying symptomatic patients with HCM, receiver operating characteristic curves and the respective area under the

Table 1 Clinical and echocardiographic characteristics in control subjects and patients with hypertrophic cardiomyopathy with or without symptoms of heart failure

	Controls (n = 37)	Asymptomatic patients (n = 12)	Symptomatic patients (n = 25)	*P* value
Age (y)	48 ± 12	46 ± 16	53 ± 15	.30
Men, n (%)	16 (43)	6 (50)	12 (48)	.81
Body mass index (kg/m^2)	25 ± 3	25 ± 5	28 ± 5*	.04
LV parameters				
LV mass index (g/m^2)	87 ± 13	176 ± 42*	193 ± 73*	<.001
LV EDVi (mL/m^2)	49 ± 10	47 ± 18	47 ± 15	.84
LV ESVi (mL/m^2)	19 ± 4	16 ± 8	16 ± 6	.31
LV ejection fraction (%)	62 ± 3	66 ± 8	65 ± 7*	.02
Mitral E velocity (cm/s)	79 ± 12	79 ± 16	78 ± 26	.97
Mitral A velocity (cm/s)	56 ± 11	78 ± 24*	72 ± 30*	.003
Mitral E deceleration time (ms)	168 ± 38	203 ± 63	213 ± 90*	.02
Peak septal S velocity (cm/s)	7.6 ± 1	6.2 ± 1.6*	5.5 ± 1.4*	<.001
Peak lateral S velocity (cm/s)	9.9 ± 2.4	6.2 ± 1.7	6.2 ± 2.0	<.001
Peak septal E' velocity (cm/s)	11.0 ± 2.5	5.1 ± 1.8*	4.9 ± 2.1*	<.001
Peak lateral E' velocity (cm/s)	15.5 ± 4	5.6 ± 1.4*	6.3 ± 2.2*	<.001
Peak septal A' velocity (cm/s)	7.6 ± 1.6	7.1 ± 1.7	5.8 ± 2,2*	.002
Peak lateral A' velocity (cm/s)	7.8 ± 1.9	8.8 ± 4.0	6.5 ± 2.9	.05
E/E' ratio	6.3 ± 1.5	14.9 ± 3.5*	15.6 ± 6.6*	<.001
LV ϵ (%)	−20.5 ± 2.7	−13.8 ± 2.9*	−11.6 ± 3.8*	<.001
LA parameters				
LAVi (mL/m^2)	33 ± 8	49 ± 13*	77 ± 39*†	<.001
LA ϵ (%)	32.0 ± 8.5	20.2 ± 5.1*	13.3 ± 5.6*†	<.001
LA SSr (s^{-1})	1.3 ± 0.2	0.9 ± 0.2*	0.6 ± 0.2*†	<.001
LA ESr (s^{-1})	−1.6 ± 0.5	−0.7 ± 0.2*	−0.5 ± 0.1*	<.001
LA ASr (s^{-1})	−1.6 ± 0.6	−1.3 ± 0.4*	−0.7 ± 0.4*†	<.001
LV outflow tract obstruction, n (%)	-	5 (42)	15 (60)	.3
Mitral regurgitation (1/2/3/4 degree)	-	8/2/1/1	3/10/11/0	.05

LV, Left ventricle; *EDVi,* left ventricular end-diastolic volume indexed to body surface area; *ESVi,* left ventricular end-systolic volume indexed to body surface area; *LV* ϵ, left ventricular global longitudinal strain; *LAVi,* maximal left atrial volume indexed to body surface area; *LA* ϵ, left atrial longitudinal strain; *SSr,* left atrial systolic strain rate; *ESr,* left atrial early diastolic strain rate; *ASr,* left atrial late diastolic strain rate.
*P < .05 patients with HCM vs controls.
†P < .05 symptomatic vs asymptomatic patients with HCM.

curve were calculated for every parameter related to NYHA class. Predictors of symptomatic status in patients with HCM were assessed using binary logistic analysis. Variables with a $P < .15$ in univariate analyses were included in the multivariable model. All statistical analyses were performed using SPSS 14.0 software for Windows (SPSS, Inc, Chicago, IL). A two-sided P value of .05 was considered significant. Measurement variability was assessed for LAϵ and Sr parameters in a randomly selected group of 15 patients with HCM. For interobserver variability, measurements were carried out by a second operator on previously acquired images. For intraobserver variability, two sets of measurements were carried out by the same operator, 1 month apart. Variability was calculated as the absolute differences between two measurements divided by the mean of the two measurements.

RESULTS

Study Participants

Table 1 lists demographic and echocardiographic characteristics of the study population. There were no significant differences between patients and control subjects with respect to age, gender, body surface area, or heart rate ($P > .05$ for all). LV outflow tract obstruction was present in 20 patients. Thirty-six patients had mitral regurgitation (grade 1 in 11 ; grade 2 in 12; grade 3 in 12; and grade 4 in 1). As expected, patients with HCM had higher indexed LV mass, LAVi, E/E' ratio, and lower S-wave velocities at both lateral and septal sites compared with control subjects ($P < .001$, for all). LV global longitudinal function (LVϵ) was severely reduced in patients with HCM, despite the slightly higher LV ejection fraction. Twelve patients were asymptomatic (NYHA class I), and 25 patients were symptomatic (NYHA class II in 15, class III in 7, and class IV in 3).

Left Atrial Function Parameters in Patients with Hypertrophic Cardiomyopathy

Left atrial strain and LA Sr (SSr, ESr, ASr) parameters were severely decreased in patients with HCM (Table 1). LA function parameters (except for ESr) were significantly lower (LAϵ, 13.3 ± 5.6 vs. 20.2 ± 5.1%; SSr, 0.6 ± 0.2 vs. 0.9 ± 0.2 s^{-1}; ASr, −0.7 ± 0.4 vs. −1.3 ± 0.4 s^{-1}, $P < .02$ for all), and LAVi was significantly higher (77 ± 39 vs. 49 ± 13 mL/m^2, $P = .006$) in symptomatic compared with asymptomatic patients with HCM (Figure 1). There were no significant differences between asymptomatic and symptomatic patients with HCM with respect to age, gender, E/E' ratio, S, E', A'-wave velocities at both lateral and septal sites, LV ejection fraction, or LVϵ (Table 1).

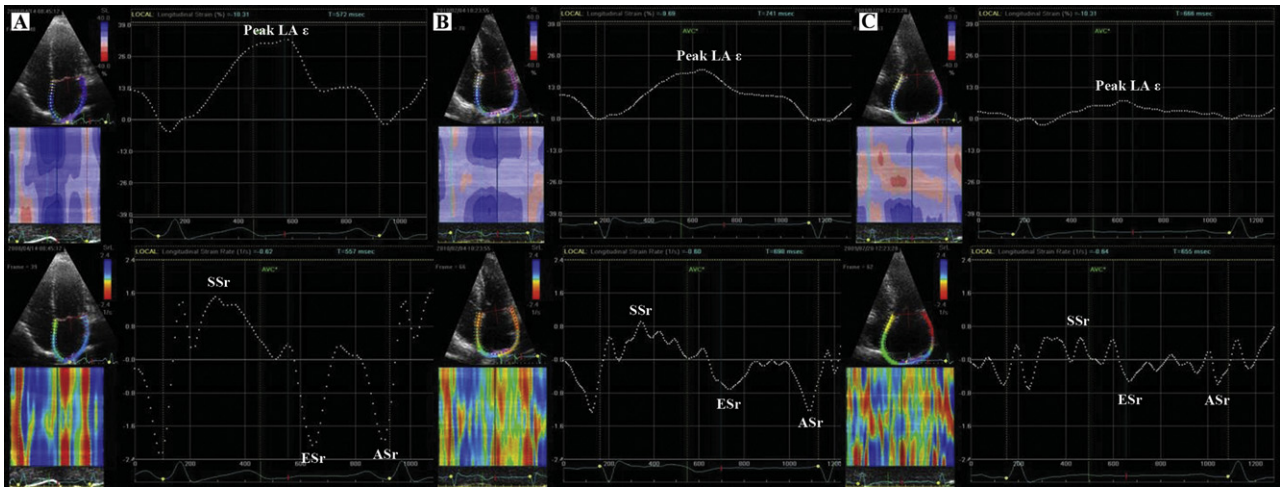

Figure 1 Comparative display of LA deformation parameters in a control subject **(A)** and asymptomatic **(B)** and symptomatic **(C)** patients with HCM. *Upper panels:* mean LA longitudinal strain curves (ϵ). *Lower panels:* mean values of LA SSr, ESr, and ASr. When compared with the control subject **(A)**, the asymptomatic **(B)** and symptomatic **(C)** patients with HCM have progressively lower longitudinal LA ϵ, SSr, ESr, and ASr.

Table 2 Correlates of left atrial function parameters in patients with hypertrophic cardiomyopathy

	LA ϵ		SSr		ESr		ASr	
	P	r	*P*	r	*P*	r	*P*	r
Age	.70		.47		.03	0.36	.48	
LVMi	.001	−0.53	.007	−0.45	.13		.01	0.40
Mitral E velocity	.16		.23		.67		.05	
Mitral A velocity	.58		.75		.04	0.35	.22	
Mitral E deceleration time	.47		.87		.04	0.34	.51	
Peak septal S velocity	<.001	0.56	.004	0.47	.01	−0.40	.01	−0.43
Peak lateral S velocity	.31		.15		.81		.21	
Peak septal E' velocity	.25		.51		.005	−0.46	.49	
Peak lateral E' velocity	.78		.61		.36		.79	
Peak septal A' velocity	<.001	0.72	<.001	0.68	.01	−0.41	<.001	−0.77
Peak lateral A' velocity	<.001	0.66	<.001	0.65	.01	−0.45	<.001	−0.82
E/E' ratio	.02	−0.41	.02	−0.40	.007	0.49	.06	
LV EF	.17		.12		.41		.81	
LV ϵ	<.001	−0.79	<.001	−0.71	.007	0.48	.003	0.53
LAVi	.002	−0.51	.008	−0.44	.17		.003	0.48
MR degree	.04	−0.33	.16		.07		.02	0.36

LVMi, Left ventricular mass indexed to body surface area; *LVϵ,* left ventricular global longitudinal strain; *LVEF,* left ventricular ejection fraction; *LA ϵ,* left atrial longitudinal strain; *SSr,* left atrial systolic strain rate; *ESr,* left atrial early diastolic strain rate; *ASr,* left atrial late diastolic strain rate; *E/E',* the ratio of peak early-diastolic transmitral flow velocity E to average E'; *LAVi,* maximal left atrial volume indexed to body surface area; *MR,* mitral regurgitation.

Left atrial strain (LA ϵ), systolic Sr (SSr), and late diastolic Sr (ASr) were significantly related to LAVi and to LV mass in patients with HCM. Early diastolic LA Sr (ESr) decreased with increasing age (Table 2). There was a significant correlation between LA functional indices derived from volumetric changes and LA-derived strain parameters. LA expansion index correlated significantly with LA ϵ (r = 0.57, $P < .001$) and SSr (r = 0.48, $P = .003$), LA passive emptying fraction correlated with ESr (r = −0.34, $P = .04$), and LA active emptying fraction correlated with ASr (r = −0.62, $P < .001$).

Intraobserver variability was 4.1% ± 3.4% for LAϵ, 7.5% ± 6.4% for SSr, 8.1% ± 6.0% for ESr, and 6.4% ± 5.7% for ASr. Interobserver variability for the same parameters was 5.9% ± 4.5%, 8.1% ± 3.2%, 12.9% ± 8.4%, and 9.5% ± 7.8%, respectively.

Relationship of Left Atrial Function with Left Ventricular Systolic and Diastolic Function in Patients with Hypertrophic Cardiomyopathy

All atrial function parameters (LAϵ, SSr, ESr, and ASr) were significantly related to LV global longitudinal strain (Figure 2). A similarly close correlation was found between LV longitudinal strain measured from the apical four-chamber view and LA function parameters (r = −0.72, $P < .001$ for LAϵ; r = −0.62, $P < .001$ for SSr; r = 0.45, $P = .005$ for ESr; and r = 0.48, $P = .003$ for ASr). Significant correlations were also found between LA function parameters and septal S, but not with lateral S. LV ejection fraction was not related to LAϵ, SSr, ESr, or ASr. Left atrial conduit function (ESr) and LA reservoir

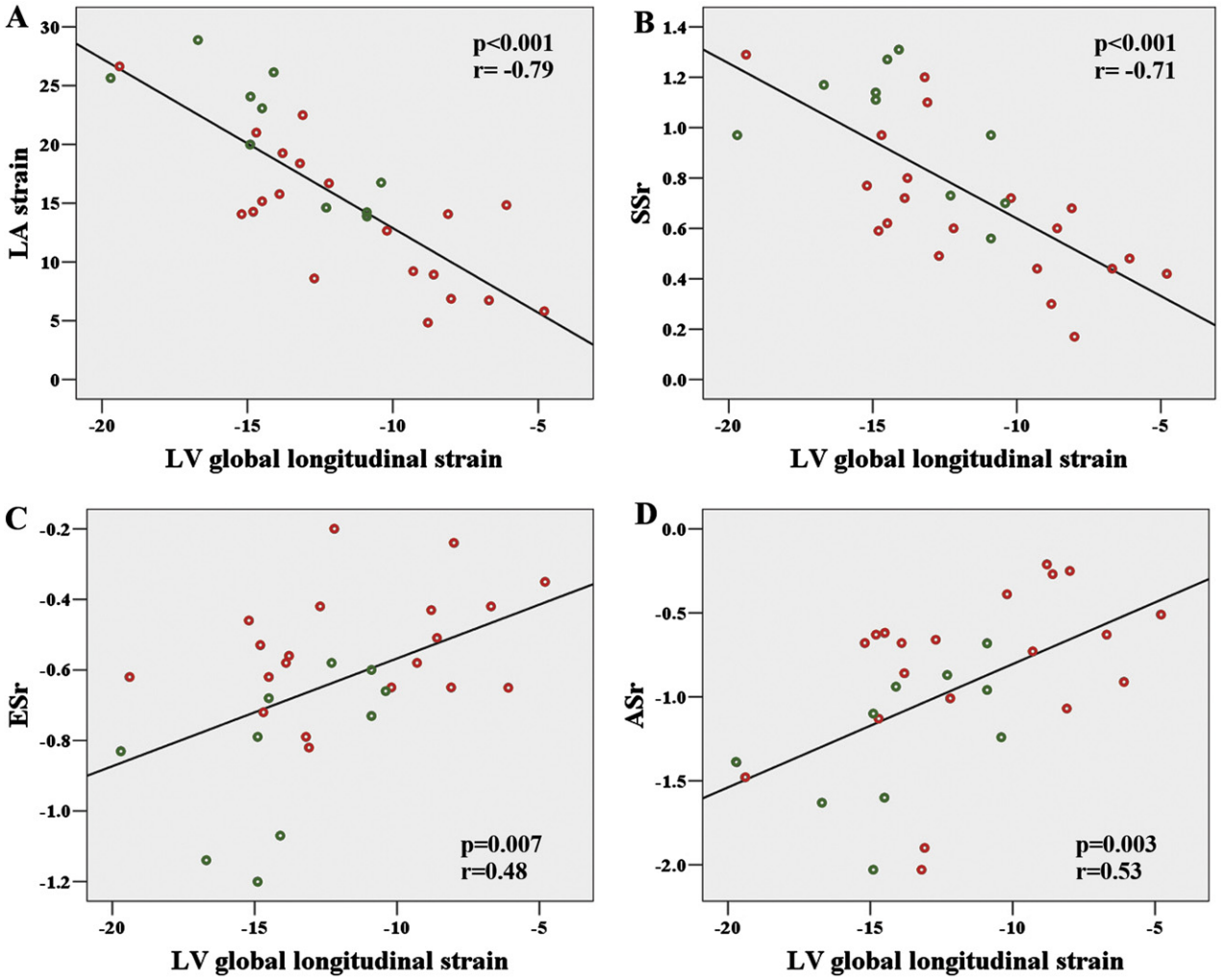

Figure 2 Linear regression analysis and Pearson correlation coefficients for the relationship of LV global longitudinal strain to each of LA deformation parameters: LA strain **(A)**, SSr **(B)**, ESr **(C)**, and ASr **(D)** (*red circles*, symptomatic patients; *green circles*, asymptomatic patients).

function (LAϵ and SSr), were related to E/E′ ratio, in contrast with LA booster pump function (ASr) (Table 2). Only LA conduit function was related to LV early diastolic longitudinal Sr (r = −0.43, P = .01), whereas LA reservoir and LA booster pump functions were not (P > .05 for both). LV late diastolic longitudinal Sr correlated with LAϵ (r = 0.46, P = .007), SSr (r = 0.42, P = .01), and ASr (r = −0.75, P < .001). There were no significant correlations between LV diastolic dysfunction degree and LA function parameters (P > .05 for all).

Indexed LA volume was related to indexed LV mass (r = 0.64, P < .001) and LV longitudinal strain (r = 0.56, P = .001). Neither E/E′ ratio nor LV outflow tract gradient was related to LAVi (P > .05 for both), whereas mitral regurgitation severity had only a weak correlation (r = 0.35, P = .03) with LA volume.

Correlates of New York Heart Association Class in Patients with Hypertrophic Cardiomyopathy

The main correlates of NYHA class in patients with HCM were LA function parameters (LAϵ, SSr, ESr and ASr), LAVi, and mitral regurgitation degree (Table 3). LA function parameters were the only significant correlates of NYHA class by analysis of variance. LV mass, LV ejection fraction, S, E′, A′-wave velocities at both lateral and septal sites, and E/E′ ratio were not related to NYHA class. LV outflow tract obstruction was not significantly different between asymptomatic and symptomatic patients and did not correlate with symptomatic status. Moreover, the resting peak LV outflow tract gradient was not significantly different between asymptomatic and symptomatic patients with HCM (69 ± 39 vs 81 ± 35 mm Hg, P = .51). To comparatively assess the accuracy of LAVi and LA function parameters (LAϵ, SSr, ESr, and ASr) in identifying symptomatic patients with HCM, receiver operating characteristic curves and the corresponding area under the curve were calculated. The best result has been obtained for ASr (area under the curve: 0.83) with a cutoff of −0.92 s^{-1} for identifying symptomatic patients with HCM (sensitivity: 75%, specificity: 83%) (Figure 3). The correlates of symptomatic status are displayed in Table 4. At multivariable logistic regression analysis, ASr emerged as the only independent correlate of heart failure symptoms in our study population (odds ratio = 2.63; 95% confidence interval, 1.015-6.922, P = .04).

Table 3 Correlates of New York Heart Association class in patients with hypertrophic cardiomyopathy

Variables	NYHA I (n = 12)	NYHA II (n = 15)	NYHA III–IV (n = 10)	*P* ANOVA	Spearman correlation coefficient	*P* Spearman
LAVi (mL/m^2)	49 ± 13	72 ± 45	83 ± 28	.06	0.55	<.001
LA ϵ (%)	20.2 ± 5.1	13.9 ± 4.9	12.6 ± 6.7	.005	−0.47	.003
LA SSr (s^{-1})	0.9 ± 0.2	0.6 ± 0.1	0.6 ± 0.4	.004	−0.47	.003
LA ESr (s^{-1})	−0.7 ± 0.2	−0.5 ± 0.1	−0.5 ± 0.2	.005	0.46	.005
LA ASr (s^{-1})	−1.3 ± 0.4	−0.7 ± 0.4	−0.7 ± 0.6	.01	0.48	.003
LV ϵ (%)	−13.9 ± 2.9	−12.2 ± 3.3	−10.3 ± 4.6	.14	0.36	.04
MR degree (1/2/3/4)	8/2/1/1	3/7/5/0	1/3/6/0	.02*	0.39	.01

ANOVA, Analysis of variance; *NYHA,* New York Heart Association; *LAVi,* maximal left atrial volume indexed to body surface area; *LA* ϵ, left atrial longitudinal strain; *LA SSr,* left atrial systolic strain rate; *LA ESr,* left atrial early diastolic strain rate; *LA ASr,* left atrial late diastolic strain rate; *MR,* mitral regurgitation; *LV* ϵ, left ventricular global longitudinal strain.
**P* value obtained by chi-square test.

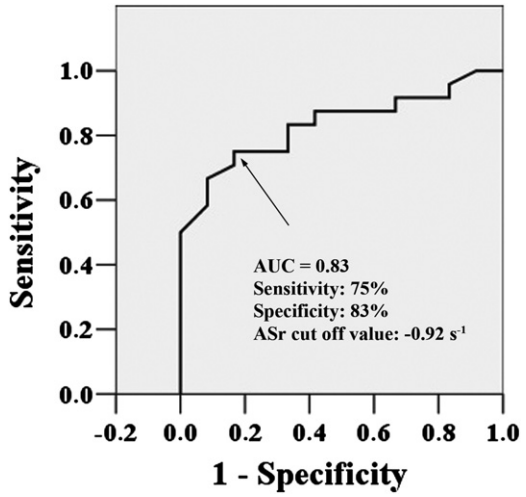

Figure 3 Receiver operating characteristic curve for late diastolic LA strain rate in identifying heart failure symptoms in patients with HCM. Best cutoff value for LA ASr in identifying heart failure symptoms was −0.92 s^{-1} (*arrow*), with an area under the receiver operating characteristic curve of 0.83.

Table 4 Correlates of symptomatic status in patients with hypertrophic cardiomyopathy

Variables	Univariate analysis OR	95% CI	*P*	Multivariable analysis *P*
Age	1.027	0.983-1.073	.23	-
LVϵ	1.215	0.954-1.549	.11	.49
LAVi	1.091	1.018-1.170	.01	.34
ASr	3.377*	1.349-8.616	.009	.04
MR degree	2.277	0.969-5.353	.056	.10
Presence of LV outflow tract obstruction (Y/N)	0.476	0.118-1.929	.29	-
Peak LV outflow tract gradient	1.010	0.981-1.041	.49	-

OR, Odds ratio; *CI,* confidence interval; *LV,* left ventricular; *LV*ϵ, left ventricular global longitudinal strain; *LAVi,* maximal left atrial volume indexed to body surface area; *ASr,* left atrial late diastolic strain rate; *MR,* mitral regurgitation; *Y/N,* YES or NO.
*OR is expressed per standard deviation increment in the variable.

DISCUSSION

The main findings of the present study in patients with HCM can be summarized as follows: LA and LV longitudinal deformation are mutually dependent and significantly impaired, despite preserved LV ejection fraction. Although the reduction in LA longitudinal function involves all three atrial phases, LA booster pump dysfunction represents the main correlate of functional disability.

Left Atrial Remodeling and Dysfunction in Patients with Hypertrophic Cardiomyopathy

The LA acts as a reservoir during LV systole, as a conduit during early diastole, and as a booster pump in late diastole, thus modulating LV filling.[21] The LA can act to increase LA pressure (in significant atrial disease) and can react to increased LV filling pressure (in significant ventricular disease). There is a growing body of evidence demonstrating that LA enlargement is a marker of significant atrial[22] or ventricular disease.[23,24]

In patients with HCM, the enlargement of the LA has proved to be inconsistently related to LV diastolic dysfunction, mitral regurgitation degree, or LV dynamic outflow tract obstruction.[25] Thus, the existence of an additional mechanism involved in atrial remodeling was postulated. The assessment of LA function using traditional parameters such as atrial fraction[25] or newer parameters derived from tissue Doppler or STE analysis[26] brought new insights into the pathophysiologic mechanisms involved in atrial remodeling in HCM. The poorer LA function was indeed attributed to a possible atrial myopathic process.[25,26] In our study, the three phases of LA function (reservoir, conduit, and booster pump) were significantly reduced. The passive stretching of the LA (reservoir function) and the active LA contraction (booster pump function) were inversely related to LA enlargement. This is in line with previous studies showing that the LA active emptying might decrease in the presence of severe LA dilation as the optimal Frank-Starling relationship is exceeded.[27] Neither diastolic parameters nor LV outflow tract gradient was related to LA enlargement, whereas mitral regurgitation severity had only a weak correlation. These data suggest that severe LA remodeling is not only a consequence of the hemodynamic abnormalities caused by LV dysfunction, mitral regurgitation, or LV outflow tract obstruction.

Relation of Left Atrial Function Parameters to Left Ventricular Dysfunction in Hypertrophic Cardiomyopathy

LV longitudinal function, as assessed by systolic annular velocities, strain, or Sr, is commonly reduced in patients with HCM despite preserved LV ejection fraction[28] and is related to the degree of hypertrophy, myocardial disarray, and fibrosis.[29] All these patients have LV diastolic dysfunction, even those with preclinical disease, without LV hypertrophy.[30]

The present study confirms and extends these data by showing that LV longitudinal function is strongly correlated to the three components of LA function. The greater the LV longitudinal dysfunction, the more severe the LA dysfunction. LA conduit function seems to be governed mainly by LV relaxation capacity, being the only LA function parameter correlated to LV early diastolic longitudinal Sr and to early diastolic septal velocity (E′). Whether the reduction in LA reservoir function in patients with HCM is more due to LV longitudinal dysfunction with a decrease in the systolic descent of LV base or to an impaired LA relaxation and stiffness (as a result of a myopathic process affecting both the ventricle and the atrium) needs further study. However, the E/E′ ratio and LV early diastolic longitudinal Sr were not related to LA booster pump function suggesting that in patients with HCM LA contraction is only partially modulated by LV diastolic performance and LV filling pressures.

Left Atrial Function and Heart Failure Symptoms in Hypertrophic Cardiomyopathy

The clinical course of HCM is characterized by an extreme heterogeneity with unpredictable development of heart failure symptoms in the presence of normal or supranormal LV ejection fraction and regardless of whether outflow tract obstruction is present or not.[7] The hemodynamic mechanisms for impaired exercise tolerance in patients with HCM are still poorly defined. However, increased LV chamber stiffness, impaired LV relaxation, and compromised LA function with elevated LV filling pressures have been postulated as the main mechanisms of heart failure symptoms in HCM. Myocardial ischemia and LV outflow tract obstruction associated with mitral regurgitation can further increase LV stiffness, leading to more severe LV diastolic dysfunction and more severe symptoms.

The LA plays an important role in maintaining LV filling and consequently LV stroke volume, especially when the LV is dysfunctional.[5] The enlargement of the LA and the increase in LA emptying fraction are adaptive responses to impaired LV diastolic function to maintain normal LV filling pressures.[31] LA remodeling predicts exercise capacity[3] and development of severe symptoms in patients with HCM.[32] LA fractional shortening is related to peak oxygen consumption in these patients.[33] Decreased LA compliance with reduced reservoir and contractile pump functions can counteract this adaptive mechanism and promote symptom occurrence. However, there are no data showing the relationship between LA function parameters, as assessed by STE, and symptoms in patients with HCM.

In the current study, LA reservoir, conduit, and booster pump functions correlated significantly with NYHA class. Specifically, the severity of heart failure symptoms increased with the severity of LA dysfunction. Left atrial enlargement and mitral regurgitation were also related to heart failure symptoms, whereas LV outflow tract obstruction was not significantly different between asymptomatic and symptomatic patients and did not correlate with symptomatic status. However, we cannot exclude the potential influence of exercise-induced increases in LV outflow tract gradient on heart failure symptoms in these patients.

LV filling pressures, assessed by the E/E′ ratio, failed to correlate with NYHA class in our patients. This may seem to contradict previous findings. However, the reported correlations between E/E′ ratio and exercise capacity in patients with HCM are relatively modest,[34,35] leading to the hypothesis that other factors also influence exercise capacity in this setting. Moreover, estimates of LV filling pressure based on the E/E′ ratio correlated weakly with direct measurements of LA pressure in symptomatic patients with HCM.[36,37]

Clinical Perspective

In patients with HCM, LA enlargement independently predicts long-term prognosis,[4,38] adverse cardiovascular events,[1] and post-myectomy survival.[39] In these patients, not only LA size but also myocardial fibrosis correlated with the presence of atrial fibrillation,[40] and the relationship of myocardial fibrosis burden with a more decreased LV longitudinal strain has recently been acknowledged.[29] Therefore, the noninvasive assessment of LA longitudinal deformation may add incremental information to LA size for predicting atrial fibrillation occurrence or response to therapy in HCM. Moreover, the potential prognostic implications of extensive LA structural and functional abnormalities and whether these alterations can be modified by treatment remain to be determined.

STUDY LIMITATIONS

Because this study was performed in a tertiary center, our study population may not reflect the typical patient seen in the community. However, one third of our patients were asymptomatic, allowing the identification of parameters related to symptoms. Because HCM is not a common disease, the study sample size was relatively small, particularly for the subanalyses of symptomatic versus asymptomatic patients. However, identifying factors associated with the symptomatic status is of clinical importance. Patients did not undergo mutation analysis for HCM diagnosis. Twenty-three of the 37 patients had asymmetric LV hypertrophy. In the remaining 14 patients with symmetric hypertrophy, wall thickness was $>$ 15 mm in the absence of exercise training history and of cardiac or systemic conditions capable of inducing such a degree of hypertrophy. LA deformation was assessed only in the apical four-chamber view, as previously performed by D'Andrea *et al.*[41] However, an average strain value for all LA segments in this view was assessed. Patients remained on their routine medication, which may have had some impact on their LA function or on the true extent of LV dysfunction. However, there was no significant difference in treatment between asymptomatic and symptomatic patients in this study.

CONCLUSIONS

In patients with HCM, LA reservoir, conduit, and booster pump functions were significantly reduced and closely related to LV longitudinal myocardial deformation. In this cohort, symptoms of heart failure were related to the severity of LA dilation and of LA dysfunction. The assessment of LA function can provide further insights into the pathophysiology and symptoms occurrence in HCM.

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