Abstract

In patients affected by hypertrophic cardiomyopathy (HCM), left atrial volume index (LAVi) is associated with an increased risk of tachyarrhythmias and major clinical events. To date, the clinical meaning of LAVi measured during exercise (stress LAVI, sLAVI) has not yet been investigated in HCM. This study sought to evaluate the correlation between LAVi / sLAVi and clinical outcome (risk of arrhythmias and heart failure) in patients with HCM. We enrolled a total of 51 consecutive patients with HCM (39 men; mean age 39.41±17.9), who underwent standard and stress echocardiography, following a common protocol. During follow up (median follow-up was 1.82 years), these composite end-points were collected: ARRHYT endpoint (atrial fibrillation, paroxysmal supraventricular tachycardia, nonsustained ventricular tachycardia, sustained ventricular tachycardia, ventricular fibrillation, syncope of likely cardiogenic nature, sudden cardiac death), and heart failure (HF) endpoint (worsening of functional class and left ventricular ejection fraction; hospitalization and death for end-stage HF). Eight patients were lost at follow-up.

ARRHYT end-point occurred in 13 (30.2%) patients (8, 18.6%, supraventricular and 10, 23.2%, ventricular arrhythmias), while HF end-point occurred in 5 (11.6%) patients.

sLAVi (mean value 31.16 ± 10.15 mL/m2) performed better than rLAVi as predictor of ARRHYT end-point (AIC:48.37 vs 50.37, if dichotomized according to the median values). A sLAVI value of 30 ml/m2 showed a predictive accuracy of 72.1% (c statistics of 0.7346), with a high negative predictive value (87.5%). These findings encourage future studies on sLAVI, as a potential predictor of arrhythmias and adverse outcome in patients with HCM.

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disorder defined by left ventricular hypertrophy in absence of abnormal loading conditions [1].

The presentation and clinical course of the disease are extremely variable: patients can be asymptomatic throughout life or develop complications as heart failure, sudden cardiac death and arrhythmias [1-3]. Thus it is important to identify at an early stage patients at risk of unfavorable outcomes [4-6].

Left ventricular outflow tract (LVOT) obstruction is present in about one third of patients at rest, and another 40% develop LVOT obstruction during exercise [7]. Obstructive HCM (OHCM) patients have major risk of developing clinical symptoms, arrhythmias and clinical events [8]. Moreover, patients with OHCM present generally with enlarged left atrium, which is "per se" a predictor of arrhythmias and clinical events [9]. Although most published studies use anteroposterior LA diameter [10], comparable findings using left atrial (LA) volume indexed to body surface area are reported [11,12].

LA volume, measured by 2-dimensional echocardiography, is the most accurate measure of LA size [13,14] because little variations in the linear dimension are often associated with large variation in volume as the result of asymmetric LA remodeling [15].

Indeed, it is well known that left atrial volume index (LAVi) is associated with a major risk of atrial fibrillation and supraventricular arrhythmias, and it is also a marker of diastolic dysfunction, diastolic heart failure, and major clinical events [16].

To date, the clinical meaning of LAVi, measured during stress echocardiography, in HCM patients has not yet been investigated. This study sought to evaluate the correlation between LAVi, measured rest (rLAVi) and stress (sLAVi) and arrhythmias in HCM patients.

Material and Methods

Study Population

In this observational, prospective study, we collected data from a cohort of 51 consecutive patients affected by HCM, followed from July 2014 to March 2017 at Cardiomyopathy Clinic, Monaldi Hospital, Naples, Italy.

HCM was diagnosed by two-dimensional echocardiography, in presence of unexplained maximal wall thickness ≥ 15mm in index cases or ≥ 13 mm in their family members [1].

We performed complete clinical evaluation, electrocardiogram (ECG), standard and stress echocardiography in all patients, following a common protocol.

Echocardiographic Analysis

Echocardiographic measurements at rest and during exercise were carried out using a Vivid E9 ultrasound system. Data were stored digitally for review and analysis using a dedicated software (Echo-PAC).

Bicycle exercise echocardiography was performed during upright posture. The patient pedals against an increasing workload at a constant cadence. The workload is escalated in a stepwise fashion while imaging is performed. Although imaging can be done throughout the exercise protocol, in most cases, interpretation is based on a comparison of resting and peak exercise images, including chamber dimensions (atria and ventricles), systolic and diastolic function, tissue doppler parameters. According to international recommendation, LAVi was determined using the area-length method [14]. rLAVi was considered as the mean value of three different measures, calculated at rest, in accordance with the American Society of Echocardiography guidelines [14].

In the same way, sLAVi was considered as the mean value of three different measures calculated at the peak of bicycle exercise.

Follow-up data

Patients were followed periodically, every 6-12 month, according to the decision of physicians. Patients who refused follow-up visits were not considered in the analysis of endpoints. Follow-up was programmed until the visit closest to 18 months. At each visit, Holter monitor report or implantable cardioverter defibrillator (ICD) interrogation, were recorded.

At follow-up, the following composite end-points were considered: arrhythmias (ARRHYT) end-

point (atrial fibrillation, AF; supraventricular tachycardia, SVT; nonsustained ventricular tachycardia, ns-VT; sustained ventricular tachycardia, s-VT; ventricular fibrillation, VF; sudden cardiac death, SCD), and heart failure (HF) endpoint (significant worsening of NYHA class and left ventricular ejection fraction, LVEF; hospitalization and death for end-stage HF).

Thus, we analyzed the correlation between rLAVi and sLAVi and the composite ARRHYT endpoint.

Statistical Analysis

Normally distributed and skewed continuous data are presented as mean ± SD and median ± interquartile range, respectively, whereas percentages are used for categorical data. Comparison between groups was based on Student t (for paired and unpaired data), Mann-Whitney U, Fisher exact, or x^2 tests, when appropriate.

Thereafter, given current lack of generally accepted cut-offs for LA volume in these patients, the study population was also stratified, first in quartiles, and than dichotomized in two groups, according to the median value of LAVi (≤ or > of the median value). This stratification was performed both for sLAVi and rLAVi. Intra-observer variability was good for both sLVAI and rLAVI (intraclass correlation coefficient= 0.60, CI 0.3.0.89; 0.87, CI 0.7-.0.93).

In addition, univariate logistic regression analyses were performed to identify association between LAVi (at rest and stress) and the ARRHYT endpoint. We tested 4 models, were the dependent variable was the ARRHYT endpoint, and the independent variable was sLAVi or rLAVi as continuous variables or as dichotomic variables (in model A: sLAVI as dichotomic variables, in model B: sLAVI as continuous variables, in model C: rLAVI as dichotomic variables, in model D: rLAVI as continuous variables) We compared this 4 model using AIC as major criteria.

For the best model, a receiver operating curve (ROC) estimation was used to calculate C-statistics for composite endpoint. Thus, sensitivity, specificity, negative and positive predictive value of the model were calculated.

We did not consider multivariable analysis owing to the exiguity of our sample size.

R software (version 3.2.1) was used for statistical analysis. *P values* < 0.05 were considered statistically significant, all tests being 2 sided.

Results

Study population

We studied 51 consecutive patients (mean age 39.41 ± 17.9 years; M=39 F=12). Mean follow-up was 1.71 years and median follow-up was 1.82 years. Clinical characteristics of the study population are reported in Table 1.

Stress Echo results

Stress echocardiography findings are reported in Table 2. At the peak of exercise, we observed a significant increase of LAVi, left ventricular outflow tract gradient, tricuspid S wave, and tricuspid annular plane systolic excursion (TAPSE).

sLAVi was significantly increased in 46 patients (90.2 %) compared to rest (mean values: 31.16 ± 10.15 ml/m^2 vs 28.05 ± 9.89 ml/m^2 , respectively, *p value*<0.001).

Follow-up

The follow up was completed in 43 patients (84%). The composite HF endpoint occurred in 5 (11.6%) patients. Eight patients (18.6%) showed supraventricular arrhythmias, while 10 patients (23.2%) had ventricular arrhythmias, and 13 patients (30.2%) presented atrial and ventricular arrhythmias (ARRHYT endpoint).

The comparison of rLAVi (A) and sLAVi (B) in patients with and without ARRHYT end-point is

reported in Figure 1.

Among groups in different rLAVI and sLAVI quartiles, patients in the 3rd and 4th ones had a significant higher occurrence of ARRHYT endpoint, particularly for sLAVI (Figure 2).

At the analysis of the 4 models (A, B, C, D) AIC were, respectively: 48.37, 52.78, 50.37, and 50.76. Hence, the model A (sLAVI as independent variable, dichotomized according to values > or ≤ of the median value, 30 ml/m2) was proved to be the most accurate.

Patients with sLAVI > 30ml/m2 had a significantly increased incidence of ARRHYT endpoint compared with patients with sLAVI ≤ 30ml/m^2 (10 out of 19, 52.6% vs 3 out of 24, 12.5%, p value=0.00768), being the odd ratio 7.78 (confidence interval, CI = [1.88, 41.37]) and the relative risk 4.2 (CI = [1.34, 13]) as showed Figure 3. The distribution of ARRHYT endpoint between patients with sLAVI ≤ and > 30ml/m^2 is summarized in Table 4

C-statistics, sensitivity, specificity, positive predictive value, negative predictive value and predictive accuracy of this cut-off are reported in Table 5.

Discussion

Left atrial size increases in response to two main pathophysiologic conditions: pressure overload (e.g. mitral stenosis, increased left ventricular filling pressure due to diastolic and/or systolic dysfunction) and volume overload (e.g. mitral regurgitation, left to right shunts) [17]. Thus, increased of left atrial volume may be considered as an adaptive response in order to maintain left ventricular stroke volume and cardiac output. However, continued left atrial enlargement may result in decreased left atrial compliance, reduced reservoir and contractile pump functions, and eventually increased incidence of atrial arrhythmias [18].

In patients with HCM the cause of LA enlargement is commonly related to systolic anterior movement related mitral regurgitation, and elevated left ventricular filling pressure [19].

By a clinical point of view left atrial antero-posterior diameter is a well-known marker of HCM severity and a close monitoring, due to the risk of arrhythmias and adverse events, is recommended

[20]. In recent years, much more attention has been concentrated around left atrial volume, which is a more precise marker of hemodynamic load, disease progression and unfavorable outcome [21,22]. An increased left atrial volume in HCM is associated with greater hypertrophy, more diastolic dysfunction, and higher filling pressures [23].

Compared with LA diameter, both LA volume and LA strain represent more powerful markers of new-onset atrial fibrillation [24]. Particularly, in those patients with normal LA diameter, a LA volume ≥37 mL/m^2 and LA strain ≤23.4% improve prediction of new-onset atrial fibrillation in HCM patients (C-statistics 73% and 83%, respectively).

However, the role of sLAVi in patients with HCM is still unknown. There is increasing interest for atrial size/function during exercise in physiology and different disease conditions. It has been previously investigated the dynamic of LA size in normal individuals and athletes heart [25,26]. During physical exercise, the increase of cardiac output, despite a reduction in filling time (due to higher heart rate), seems to be related to a progressive atrial remodeling, an increase in reservoir function, and a consequent increased ventricular preload [27].These phenomena can be exacerbated in a peculiar disease model such as HCM, where dynamic mitral regurgitation, LVOT obstruction and even diastolic dysfunction may play crucial role during exercise.

To our knowledge, this is the first report of the value of sLAVi, measured at peak of exercise, as a simple and non-invasive parameter to improve risk stratification of arrhythmias in patients with HCM. In this study, we enrolled 51 consecutive HCM patients who underwent stress echocardiography following a common protocol. The main finding of this study was the correlation between sLAVi and arrhythmic events (both atrial and ventricular) in patients with HCM, with an incremental risk in the population with sLAVi $\geq$ 30ml/m^2 (predictive accuracy 72.1%, C-statistics 0.7346, negative predictive value 87.5%). Furthermore, in our study, LAVI at stress performed better than LAVi at rest as predictor of arrhytmias (AIC:48.37 vs 50.37, if dichotomized according to the median values).

In a recent meta-analysis, Liu et al. demonstrated that AF and NSVT were independent predictors

of cardiovascular death [28]. The independent role of sLAVI as predictor of arrhythmias, but also of unfavorable outcome, should be further reinvestigated in prospective, large scale, collaborative studies [29].

Study limitations

Our findings are based on a single-center study with a relatively small sample size. Multivariate models on a significant number of HCM patients, and considering rest/stress parameters (i.e. LAVI; MR, LVOT obstruction), are warranted to define the independent prognostic role of LAVI.

Conclusions

Our study is the first study suggesting the feasibility and potential utility of sLAVi in HCM. We showed that patients with LAVi $\geq$ 30ml/m^2 had an increased risk of arrhythmias in patients with HCM. This suggests that sLAVi could be a potential and additional useful marker of arrhythmias in patients with HCM. Further studies are needed to verify the direct relation between sLAVI and arrhythmias and his possible role as independent predictor of prognosis.

Figures legend

Figure 1. Rest LAVi (rLAVi) in patients with (right) and without (left) ARRHYT endpoint (A). Stress LAVi (sLAVi) in patients with (right) and without (left) ARRHYT endpoint (B).

Figure 2. Rest LAVi (rLAVi) in patients with and without ARRHYT endpoint (A). Stress LAVI (sLAVi) in patients with and without ARRHYT endpoint (B). LAVi data are devided in

quartiles. Dark gray (0): absence of ARRHYT endpoint. Light gray (1): occurrence of ARRHYT endpoint

Figure 3. ARRHYT endpoint: comparison between patients with Stress LAVi (sLAVi) ≤Land > of 30ml/m^2. Dark gray (0): absence of ARRHYT endpoint. Light gray (1): occurrence of ARRHYT endpoint

References

1. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 201414;35:2733-2779

2. Maron BJ, Bonow RO, Cannon RO III, Leon MB, Epstein SE. Hypertrophic cardiomyopathy; interrelation of clinical manifestations, pathophysiology, and therapy. N Engl J Med 1987;316:780-9, 844-52

3. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy:clinical spectrum and treatment. Circulation 1995;92:1680-9.

4. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy.Circulation 2001;104:2517-24

5. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303

6. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J 2006;27:1933-41

7. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009 14;54:191-200

8. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol. 2014 8;64:83-99

9. Yang WI, Shim CY, Kim YJ, Kim SA, Rhee SJ, Choi EY, et al. Left atrial volume index: a predictor of adverse outcome in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr, 2009 22;5: 1338-1343

10. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006;98:960–965

11. Losi MA, Betocchi S, Barbati G, Parisi V, Tocchetti CG, Pastore F, et al. Prognostic significance of left atrial volume dilatation in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2009;22:76–81.

12. Tani T, Yagi T, Kitai T, Kim K, Nakamura H, Konda T, et al. Left atrial volume predicts adverse cardiac and cerebrovascular events in patients with hypertrophic cardiomyopathy. Cardiovasc Ultrasound 2011;9:34.

13. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829-32.

14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.

15. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR,et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018-23

16. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM et al. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. Cardiovasc Diagn Ther. 2017 7:36-44

17. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J. 2008;156:1056-1064

18. Pagel PS, Kehl F, Gare M, Hettrick DA, Kersten JR, Warltier DC. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography. Anesthesiology 2003;98:975-994.

19. Sen-Chowdhry S, Jacoby D, Moon JC, McKenna WJ. Update on hypertrophic cardiomyopathy and a guide to the guidelines. Nat Rev Cardiol. 2016;13:651-675

20. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, et al; Predictors of atrial fibrillation hypertrophic cardiomyopathy. Heart.2017;103(9):672-678.

21. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol. 2002;90:1284-1289.

22. Losi MA, Betocchi S, Barbati G, Parisi V, Tocchetti CG, Pastore F, et al. Prognostic Significance of Left Atrial Volume Dilatation in Patients with Hypertrophic Cardiomyopathy. J Am Soc Echocardiogr. 2009 Jan;22(1):76-81.

23. Tani T, Yagi T, Kitai T, Kim K, Nakamura H, Konda T, et al. Left atrial volume predicts adverse cardiac and cerebrovascular events in patients with hypertrophic cardiomyopathy. Cardiovasc Ultrasound 2011;9:34-45.

24. Debonnaire P, Joyce E, Hiemstra Y, Mertens BJ, Atsma DE, Schalij MJ, et al. Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation. Circ Arrhythm Electrophysiol. 2017;10:22-34.

25. Gabrielli L, Bijnens BH, Brambila C, Duchateau N, Marin J, Sitges-Serra I, et al.. Differential atrial performance at rest and exercise in athletes: potential trigger for developing atrial dysfunction? Scand J Med Sci Sports. 2016;26:1444–54.

26. Schnell F, Claessen G, La Gerche A, Claus P, Bogaert J, Delcroix M, et al. Atrial volume and function during exercise in health and disease. Journal of Cardiovascular Magnetic Resonance2017; 19:104.

27. Prior DL, La Gerche A. The athlete's heart. Heart. 2012;98:947–55.

28. Liu Q, Li D, Berger AE,Johns RA & Gao L. Survival and prognostic factors in hypertrophic cardiomyopathy: a meta-analysis. Sci Rep. 2017;7:11957.

29. Picano E, Ciampi Q, Citro R, D'Andrea A, Scali MC, Cortigiani L, et al. Stress echo 2020: the international stress echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound. 2017;15:3

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