Indian Heart Journal xxx (xxxx) xxx

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Mitral valve remodeling in the development of obstructive hypertrophic cardiomyopathy

Francesco Moroni [a, b], Abhishek Chaturvedi [a], Ehsan Jafree [a], Zachary M. Gertz [a, *]

[a] VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA
[b] The Robert M Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA, USA

ARTICLE INFO

Article history:
Received 26 February 2023
Received in revised form
16 May 2023
Accepted 18 June 2023
Available online xxx

Keywords:
Hypertrophic cardiomyopathy
Left ventricular tract obstruction
Mitral valve
Systolic anterior motion

ABSTRACT

Approximately 2/3 of patients with hypertrophic cardiomyopathy (HCM) have significant left ventricular outflow tract obstruction (LVOTO), which is caused by the interaction mitral valve apparatus and the hypertrophied septum. The contribution of mitral valve remodeling to the development of obstruction over time has never been described. We analyzed retrospectively 40 patients with HCM and no baseline obstruction followed up for a median of 2179 days. At follow up, 13 patients developed significant LVOTO. Patients who developed LVOTO had longer posterior leaflets and longer anterior leaflet residual length.

Up to 2/3 hypertrophic cardiomyopathy (HCM) patients have significant obstruction of the left ventricular outflow tract (LVOT), which occurs when the septum contacts the mitral valve apparatus.[1] The purpose of our study was to evaluate the contribution of mitral valve remodeling to the development of LVOT obstruction among these patients. We also assessed progressive septal thickening, to determine the relative contributions of each.

We conducted a retrospective cohort study with approval from our institutional review board. We identified all subjects with a diagnosis of non-obstructive HCM [2] regularly followed at our institution between years 2000–2021, who had at least 2 transthoracic echocardiograms (TTE) at least 6 months apart.

TTEs were read by a single expert operator, blinded to patients' characteristics, in a random order. Key morphological parameters were measured as shown in Fig.1. Significant obstruction was defined as peak gradient >30 mmHg either at rest or during Valsalva [2] Morphological mitral valve anomalies were tracked, [3] and severity of mitral valve regurgitation was graded according to guidelines indications.[4]

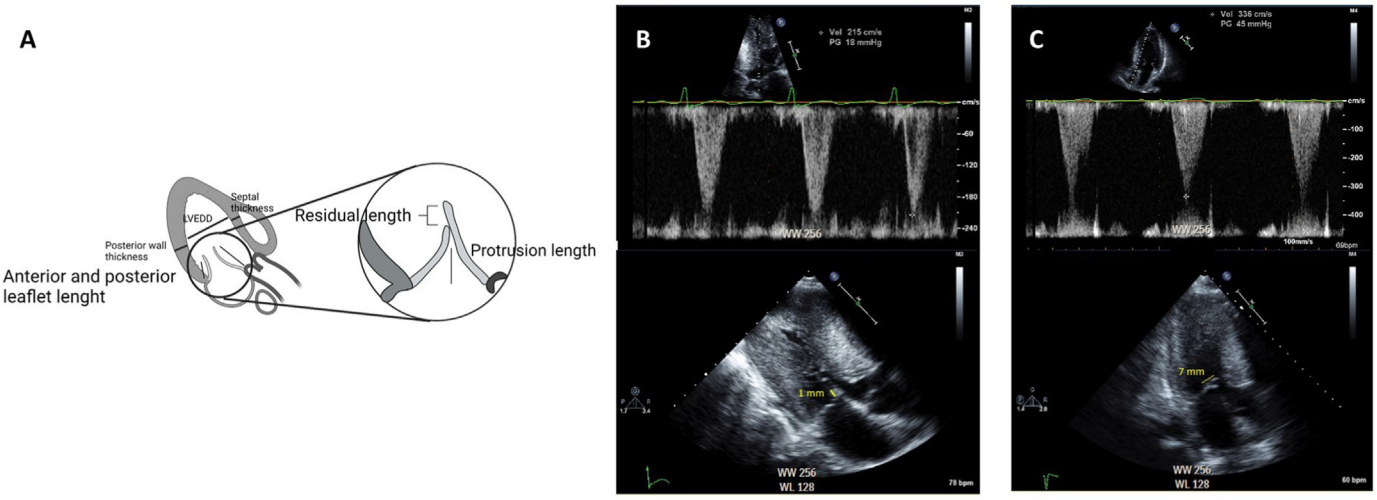
Categorical variables are expressed as number (percentage) and continuous variables as mean ± standard deviation or median (range). Association was tested using Chi-square test for nominal variables and Mann–Whitney test for continuous variables. All analyses were carried out using R v4.1.2 (CRAN, Vienna, Austria).

Forty of 187 patients with HCM identified through the electronic medical record search were found to be eligible for the study. Average age on first TTE was 50 ± 15 years, and 47% of patients were female. Twelve subjects had papillary muscle hypertrophy. Fifteen subjects had at least one anomaly in the mitral valve apparatus (Fig. 1). Three individuals had more-than-moderate mitral regurgitation on baseline TTE. After a median follow up of 2179 days (range 262–5376), 13 (32%) patients developed LVOT obstruction. No subject had significant midventricular obstruction at either baseline or follow up study. Patients who developed LVOT obstruction had a significantly higher baseline gradient (17 vs 9 mmHg, $p < 0.001$) and were more likely to have significant mitral regurgitation (23% vs 0%, $p < 0.001$). Residual length of the anterior mitral valve leaflet, was larger among patients who developed LVOT obstruction (4.3 vs 1.5 mm, $p = 0.003$ – Fig. 1).

The development of LVOT obstruction is common among patients with a baseline diagnosis of non-obstructive HCM. Remodeling of the mitral valve, with elongation of the leaflets and consequent shift of the coaptation point, may contribute to the development of obstruction. [5] Progressive left ventricular hypertrophy did not occur, suggesting that mitral valve remodeling may be the primary driver in the development of LVOT obstruction. The main limitation of this study is its retrospective design, leading to

* Corresponding author. VCU Pauley Heart Center, 1200 East Broad Street, Box 980036, Richmond, 23298, VA, USA.
E-mail address: zachary.gertz@vcuhealth.org (Z.M. Gertz).

https://doi.org/10.1016/j.ihj.2023.06.007



Variable	No LVOTO at FUp (n=27)	LVOTO at FUp (n=13)	p
Follow up duration	2,783±1,171	2,381±1,207	0.313
Baseline Echocardiogram			
Peak LVOT gradient (mmHg)	9 (2 – 23)	17 (6 – 28)	<0.001
LVEF (%)	63 (40 – 75)	64 (55 – 75)	0.746
LVEDD (mm)	41 (31 – 54)	40 (32 – 52)	0.409
Maximal wall thickness (mm)	19 (14 – 31)	18 (14 – 27)	0.981
Moderate or greater MR	0 (0%)	3 (23%)	0.009
Anterior mitral leaflet length (mm)	23 (15 – 29)	22 (16 – 28)	0.573
Posterior mitral leaflet length (mm)	11 (6 – 17)	12 (8 – 18)	0.259
Protrusion height (mm)	6 (0 – 17)	9 (3 – 30)	0.124
Residual length (mm)	2 (0 – 13)	3 (0 – 13)	0.348
Interpapillary distance (mm)	16 (8 – 22)	17 (9 – 28)	0.310
Follow up Echocardiogram			
Peak LVOT gradient (mmHg)	9 (3 – 12)	66 (34 – 130)	<0.001
LVEF (%)	63 (45 – 75)	67 (55 – 75)	0.115
LVEDD (mm)	44 (30 – 57)	42 (30 – 56)	0.387
Maximal wall thickness (mm)	18 (14 – 35)	20 (16 – 29)	0.235
Moderate or greater MR	0 (0%)	5 (39%)	<0.001
Anterior mitral leaflet length (mm)	24 (17 – 33)	23 (14 – 29)	0.518
Posterior mitral leaflet length (mm)	12 (6 – 25)	15 (11 – 20)	0.061
Protrusion height (mm)	7 (0 – 18)	9 (9 – 14)	0.114
Residual length (mm)	1.5 (0 – 8)	4.3 (0 – 9)	0.003
Interpapillary distance (mm)	16 (7 – 26)	15 (11 – 20)	0.546

Fig. 1. Mitral valve morphology and development of left ventricular outflow tract obstruction in non-obstructive hypertrophic cardiomyopathy, and characteristics of the patient population. Top panels display graphically mitral valve morphological changes in the setting of the development of obstruction. Panel A: Leaflet length was measured in apical 3 chamber view in mid-diastole. Protrusion length was measured as the distance between coaptation point and mitral annular plane. Residual length was measured as the length of the anterior mitral valve leaflet beyond the point of coaptation. Wall thickness and ventricular dimensions were measured in end-diastolic frames. Panel B and Panel C show residual length and peak left ventricular outflow tract gradient in a patient who developed significant obstruction at follow up. Note the increase in residual length from 1 mm to 7 mm and the significant increase in left ventricular outflow tract gradient between baseline and follow up echocardiogram approximately 4 years apart.
Bottom panel show baseline and follow up echocardiographic variables. LAVi, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; RVSP, right ventri.

heterogeneous follow up duration and non-standardized TTE acquisitions, all read by a single, blinded operator. Furthermore, sample size could be insufficient to achieve adequate statistical power.

In conclusion, remodeling of the mitral valve, with elongation of the leaflets and consequent shift of the coaptation point, may be a component of the development of obstruction in HCM. Mitral valve could potentially be itself a target for gradient reduction, especially in light of novel percutaneous technologies such as lampoon.[6] Further research is needed to further evaluate the role of mitral valve remodeling in the natural history of HOCM.

Ethics approval statement

The present study was granted approval by Virginia Commonwealth University Institutional Review Board. The requirement of written informed consent was waived given the retrospective nature of the study.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Funding

None.

Declaration of competing interest

The Authors report no conflict of interest relative to the present work.

References

1. Veselka J, Anavekar NS, Charron P. Hypertrophic obstructive cardiomyopathy. *Lancet*. 2017;389(10075):1253–1267.
2. Ommen SR, Mital S, Burke MA, et al. AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2020;142(25):e533–e557, 2020.
3. Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. *J Am Coll Cardiol*. 2016;67(15):1846–1858.
4. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr*. 2017;30(4):303–371.
5. Patel P, Dhillon A, Popovic ZB, et al. Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy patients without severe septal hypertrophy: implications of mitral valve and papillary muscle abnormalities assessed using cardiac magnetic resonance and echocardiography. *Circ Cardiovasc Imaging*. 2015;8(7), e003132.
6. Case BC, Lisko JC, Babaliaros VC, et al. LAMPOON techniques to prevent or manage left ventricular outflow tract obstruction in transcatheter mitral valve replacement. *Ann Cardiothorac Surg*. 2021;10(1):172–179.