CASE REPORT

Ischaemia as a cause of LVOT gradient reversal in HCM

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Summary

We present the case of a previously fit 84-year-old female with long-standing systemic hypertension and the echo phenotype of hypertrophic cardiomyopathy (HCM) – asymmetrical septal hypertrophy, significant resting left ventricular (LV) outflow obstruction and mitral regurgitation (MR) secondary to systolic anterior motion (SAM) of the mitral valve. Valsalva provocation caused an increase in LVOT dynamic gradient and MR severity. The patient presented with a progressive decrease in exercise capacity along with chest pain relieved by rest or sublingual GTN. Exercise stress echo demonstrated a paradoxical response with reduction of both LVOT gradient and severity of MR. There was evidence of inducible regional wall motion abnormalities associated with no change in LV cavity size. Coronary angiogram revealed significant triple vessel disease.

Learning points:

- 20% of adult HCM patients over the age of 45 years have been shown to have coexistent coronary artery disease (CAD) that is associated with a reduced overall survival. Diagnosis of CAD in patients with HCM is difficult to make based on clinical grounds because of the high incidence of angina in patients with HCM but no CAD.
- Reduction of LVOT gradient with stress in patients with HCM (in the absence of a vaso-vagal response) may indicate ischaemia due to significant multivessel epicardial CAD, including left mainstem stenosis. Hence, this finding during stress echocardiography suggests that further investigation of the coronaries should be considered.
- Exercise stress echocardiography has not been validated for the assessment of ischaemia secondary to epicardial coronary disease in patients with HCM because ischaemia in this group of patients is often caused by multiple mechanisms, including microvascular ischaemia and myocardial bridging.
- Comparative assessment of rest and peak exercise 2D strain may add incremental value in identifying regional wall motion abnormalities, which may be difficult to distinguish by eye in hypertrophied, dynamic myocardium.
- A paradoxical response to exercise with significant decrease in LVOT obstruction and MR has been reported in the literature. This is often associated with a trend toward increased exercise capacity and better prognostic outcomes. Our clinical case presents a significant decrease in LVOT obstruction and MR that was associated with a trend toward reduced exercise capacity and was caused by ischaemia.

Background

The majority of symptomatic HCM patients with mild-to-moderate resting LVOT obstruction demonstrate an increase in dynamic gradient with exercise, which is considered to be the main cause for clinical symptoms. However, a decrease in dynamic LVOT gradient during exercise may indicate significant coexistent CAD that has been proven to be associated with a reduced overall survival in this group. Regional wall motion abnormalities in the hypertrophied left ventricle may be difficult to appreciate visually both at rest and during exercise stress. Strain analysis may prove to be a useful tool for the assessment of regional abnormalities in this patient group.

Case presentation

An 84-year-old female presented to a rapid access chest pain clinic with a one-year history of central chest pain brought on by exertion and relieved by rest or GTN. The patient was in sinus rhythm at 77 bpm and resting blood pressure was well controlled on antihypertensive medication 148/67 mmHg. The patient's exercise tolerance has reduced over time and exertional shortness of breath was reported, which had been managed by lifestyle limitation. The patient had no orthopnoea, paroxysmal nocturnal dyspnoea, palpitations, dizzy spells or blackouts.

Cardiovascular risk factors included hypertension and hypercholesterolaemia. The patient had undergone previous vaginal hysterectomy and received steroid injections to an osteoarthritic left knee. The patient had previously suffered from peptic ulcer disease and depression and had presbycusis.

Medication included: lercanidipine 20 mg od, losartan 100 mg od, hydrochlorotiazide 25 mg od, venlafaxine 75 mg od and GTN spray as required.

Investigations

ECG

Sinus rhythm with LVH strain pattern.

Cardiac auscultation

Soft systolic murmur at the left parasternal edge accentuated by Valsalva manoeuvre.

Transthoracic echocardiography

Demonstrated resting morphology and haemodynamics suggestive of HCM with small LV cavity size, asymmetrical septal hypertrophy (maximum wall thickness 20 mm) and preserved radial systolic function. There was complete systolic anterior motion (SAM) of the mitral valve at rest with LVOT gradient of 57 mmHg increasing to 82 mmHg with Valsalva and associated with worsening of MR from moderate to severe. Systolic pulmonary artery pressure was estimated at 35 mmHg.

Exercise stress echo

Performed on a semi-supine bicycle using an extended protocol with acquisition of Doppler data in order to fully assess the LVOT, MR and regional LV function.

The patient exercised for 5 min to a maximal workload of only 25 W, achieved 85% of predicted heart rate (118 bpm) and demonstrated a significant hypertensive response: blood pressure (BP) increased from 148/67 mmHg at rest to 218/152 mmHg at peak exercise. The patient complained of shortness of breath but no chest pain.

All LV segments showed recruitment of contractile function with low stress. At peak stress, the inferolateral wall became hypokinetic with no change in LV cavity size. There was subclinical reduction in regional function of the inferior wall revealed by the reduction of global longitudinal strain. In addition, in
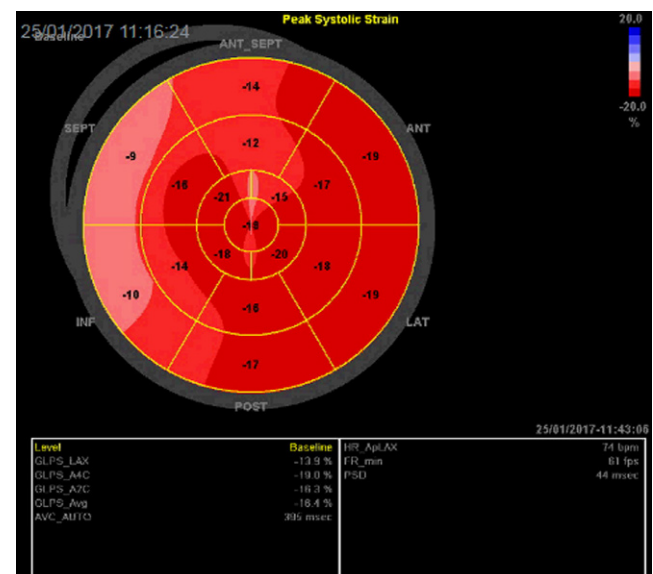
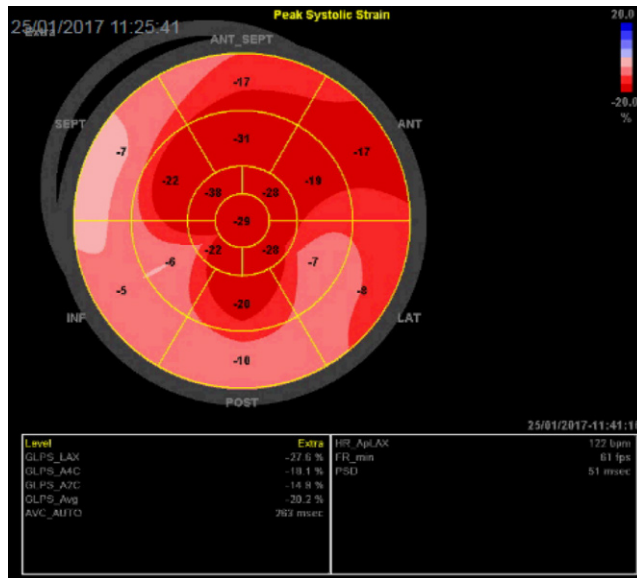

Figure 1
LV global longitudinal strain at rest.

Figure 2
LV global longitudinal strain at peak exercise: significant reduction in inferior wall strain on exercise.

the anterior and anteroseptal segments, there was an appropriate increase in strain toward the mid-apical segments, but in the basal segments, strain failed to increase significantly, suggesting potential ischaemia affecting the hypertrophied myocardium in proximal LAD territory (Figs 1 and 2). The SAM of the mitral valve became incomplete (Videos 1 and 2) leading to resolution of the LVOT obstruction (18 mmHg) (Figs 3 and 4) and significant reduction in MR from severe to mild (Videos 3 and 4).

The patient was referred for coronary angiography to assess the coronary arteries and MRI for detailed assessment of cardiac morphology.
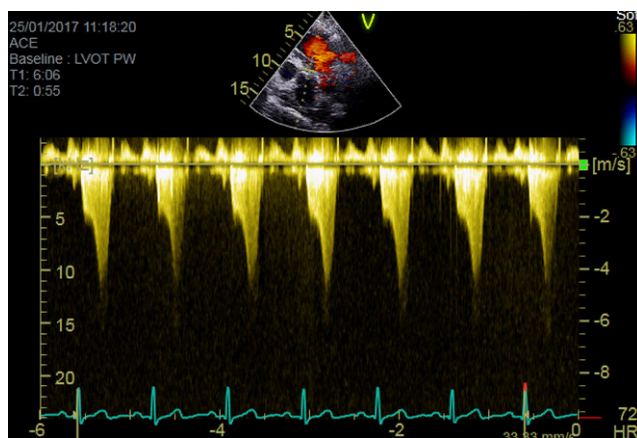

Figure 3
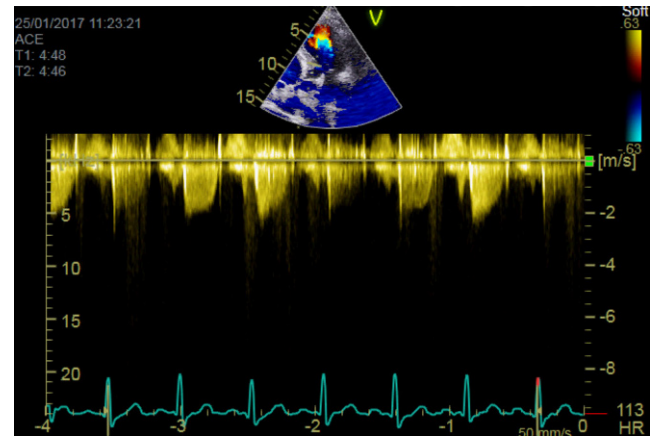Baseline: severe LVOT obstruction.

Figure 4
Peak exercise: significant reduction in LVOT obstruction.

Cardiac MRI

Acquired to assess the function and viability and 0.1 mol/Kg using Gadovist as contrast agent. The scan demonstrated small left ventricle volumes with dynamic ejection fraction (LV EF 74%) and a focal mid-ventricular inferior wall hypokinesia. Prominent asymmetrical increase in LV mid-ventricular septal thickness of maximum 19 mm and the lateral wall thickness of 4 mm. Prominent SAM of the anterior mitral valve leaflet with LVOT obstruction and MR was confirmed (Video 5). RV was small in volume with no
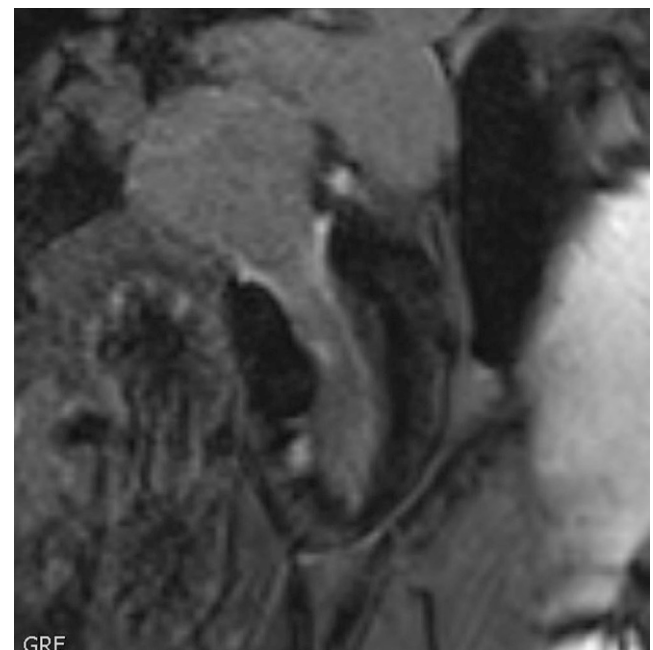

Figure 5
CMR: patchy and diffuse LV late gadolinium enhancement.

abnormalities to structure and function. On gadolinium contrast, there was no early enhancement. Prominent focal subendocardial patch of delayed enhancement was seen in the mid-ventricular inferior wall. Patchy and diffuse enhancement was also noted throughout the thickened LV myocardium (Fig. 5).

Coronary angiography

Demonstrated 70% left main stem distal stenosis caused by eccentric calcification (Video 6); 80% mid-LAD stenosis after bifurcation with diagonal (Video 6); 40% proximal obtuse marginal stenosis and tight 90% proximal RCA stenosis (Video 7).

Right heart catheterisation recorded a right atrial pressure of 15 mmHg, mean pulmonary artery pressure 35 mmHg and a pulmonary capillary wedge pressure of 16 mmHg.

Video 1

Apical 3-chamber view at rest: complete SAM of anterior MV leaflet. View Video 1 at http://movie-usa. glencoesoftware.com/video/10.1530/ERP-17-0030/video-1.

Video 2

Apical 3-chamber at peak stress: incomplete SAM of anterior MV leaflet. View Video 2 at http://movie-usa. glencoesoftware.com/video/10.1530/ERP-17-0030/video-2.

Video 3

Apical 3-chamber view at rest: markedly turbulent flow in LVOT and significant MR. View Video 3 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0030/video-3.

Video 4

Apical 3-chamber view at peak stress: mild flow turbulence in LVOT and reduction in MR. View Video 4 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0030/video-4.

Video 5

CMR: SAM with secondary LVOT obstruction. View Video 5 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0030/video-5.

Video 6

Coronary angiogram: left main stem and LAD stenosis. View Video 6 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0030/video-6.

Video 7

Coronary angiogram: RCA stenosis. View Video 7 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0030/video-7.

Treatment and outcome

Patient clinical and imaging data were reviewed and discussed in an MDT meeting.

The patient was consented for surgery including mitral valve replacement, myectomy and coronary bypass grafting on symptomatic and prognostic grounds with a mortality risk of 3–5%, stroke risk 1–2% and need for permanent pacemaker of 2%. Patient declined surgical treatment and opted for conservative medical management. As the patient was not taking any antianginal medication, the patient was started on bisoprolol 2.5 mg with a plan to increase antianginal medication as tolerated, and review in the outpatient clinic. The option to perform percutaneous coronary intervention to the left main, mid-LAD and proximal RCA – with the aim to relieve some of the symptoms and improve the quality of life – would be reconsidered as an outpatient if the patient continued to be symptomatic.

Discussion

This clinical case presented several interesting diagnostic and clinical challenges:

- Distinguishing the diagnosis between HCM and hypertensive heart disease in an 84-year-old patient with a long-standing history of hypertension
- Demonstrating ischaemia and appreciating its primary cause and prognostic significance
- Unusual haemodynamic response to exercise

Hypertrophic cardiomyopathy (HCM) is a common cardiac disorder with a prevalence of approximately one in 500 (1). In some individuals, it is difficult to differentiate HCM from LVH secondary to long-term hypertension: 4%–47% of patients with hypertensive LV hypertrophy manifest asymmetrical septal hypertrophy (2). Increased afterload in HTN promotes regional hypertrophy at the basal septum (3). Our 84-year-old patient had a well-documented, chronic history of systemic hypertension but had not been previously diagnosed with HCM. ECG was non-specific. Conventional echo features were strongly suggestive of HCM with asymmetrical septal hypertrophy associated with complete SAM, significant dynamic LVOT obstruction and MR. An MRI also confirmed HCM morphology with asymmetrical septal hypertrophy, complete SAM and typical features of myocardial fibrosis.

It is well recognised that HCM patients may develop myocardial ischaemia in the absence of coronary

atherosclerosis. This may be caused by multiple factors such as: increased wall thickness that causes supply/demand mismatch and increased compression of the microcirculation during systole; opposing proximal and distal coronary flow effects resulting from compression and deformation of the intramural blood vessels and impaired ventricular relaxation; LVOT obstruction that increases the intracavity pressures and generates an additional coronary flow deceleration wave during ventricular systole; organic histological abnormalities of the microcirculatory vessels (4, 5). A recent study has also shown that small vessel disease is a secondary phenomenon modified by factors such as LV mass, sex and perhaps local autocrine factors (6). However, adult patients with HCM may also have atherosclerotic coronary artery disease (CAD). Reports on the prevalence of CAD in HCM have varied, but up to 20% of adult HCM patients over the age of 45 years have been shown to have coexistent CAD (7). Severe epicardial CAD in patients with HCM is associated with increased morbidity and mortality including sudden cardiac death (8).

Our patient presented with typical angina and exertional dyspnoea, relieved by rest and GTN. This was unusual as in HCM a reduction of preload would normally exaggerate LVOT gradient. The patient also demonstrated a very limited exercise capacity as the patient was able to exercise for only 5 min. Exercise stress echo image analysis demonstrated an ischaemic response in the inferolateral wall and no change in LV cavity size in the absence of diagnostic ECG changes or chest pain. To improve our diagnostic accuracy, we performed a detailed comparative 2D strain analysis of the rest and peak stress data. We noticed a significant reduction in the inferior wall deformation by 50% at peak stress that suggested significant inferior wall ischaemia. This finding correlated well with 90% RCA stenosis demonstrated by angiogram and the prominent focal subendocardial patch of delayed enhancement seen in the mid-ventricular inferior wall on the MRI study. Further detailed analysis of LV septal segments 2D strain demonstrated an augmentation of mid-apical segments deformation in parallel with an unusual reduction of strain values in basal septal segments at peak stress. This may potentially explain the incomplete SAM with secondary reduction in LVOT obstruction during exercise. In addition, the analysis of the anterior wall segments deformation demonstrated no significant augmentation at peak stress. These findings were highly suggestive of ischaemia in proximal LAD territory and correlated well with the significant distal left main and proximal LAD stenosis. In view of these findings, significant reduction in LVOT obstruction and MR on exercise was felt to be more likely ischaemic rather than a paradoxical response to exercise.

The majority of HCM patients with resting obstruction have worsening symptoms with exertion that are believed to be in proportion to the degree of LVOT obstruction. However, some patients exhibit a paradoxical response to exercise with a significant decrease in SAM/LVOT obstruction and MR during exercise. This paradoxical response has been previously associated with specific characteristics of ventricular loading both at rest and during exertion. It has been suggested that larger LV volumes may predispose to a decrease in obstruction, possibly because tension in the submitral apparatus reduces SAM. Similarly, the increase in systolic volume may cause the reduction in the LVOT obstruction (9). This response was associated with a trend toward increased exertional capacity and functional class, fewer complications and a more physiological profile of LV structure and function.

In our clinical case, the paradoxical response to exercise was most likely caused by ischaemia and clinical symptoms were very helpful in differentiating the ischaemic aetiology from other specific LV loading characteristics. This has important clinical significance because it has been shown that significant CAD is associated with reduced overall survival (10). Under these circumstances, we recommended coronary angiography. This confirmed severe, complex CAD.

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