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Ineffective and prolonged apical contraction is associated with chest pain and ischaemia in apical hypertrophic cardiomyopathy

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ABSTRACT

Objectives: To investigate the hypothesis that persistence of apical contraction into diastole is linked to reduced myocardial perfusion and chest pain.
Background: Apical hypertrophic cardiomyopathy (HCM) is defined by left ventricular (LV) hypertrophy predominantly of the apex. Hyperdynamic contractility resulting in obliteration of the apical cavity is often present. Apical HCM can lead to drug-refractory chest pain.
Methods: We retrospectively studied 126 subjects; 76 with apical HCM and 50 controls (31 with asymmetrical septal hypertrophy (ASH) and 19 with non-cardiac chest pain and culprit free angiograms and structurally normal hearts). Perfusion cardiac magnetic resonance imaging (CMR) scans were assessed for myocardial perfusion reserve index (MPRi), late gadolinium enhancement (LGE), LV volumes (muscle and cavity) and regional contractile persistence (apex, mid and basal LV).
Results: In apical HCM, apical MPRi was lower than in normal and ASH controls ($p < 0.05$). In apical HCM, duration of contractile persistence was associated with lower MPRi ($p < 0.01$) and chest pain ($p < 0.05$). In multivariate regression, contractile persistence was independently associated with chest pain ($p < 0.01$) and reduced MPRi ($p < 0.001$).
Conclusion: In apical HCM, regional contractile persistence is associated with impaired myocardial perfusion and chest pain. As apical myocardium makes limited contributions to stroke volume, apical contractility is also largely ineffective. Interventions to reduce apical contraction and/or muscle mass are potential therapies for improving symptoms without reducing cardiac output.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterised by marked left ventricular (LV) hypertrophy (LVH) [1]. Patients frequently experience troubling chest pain [2–5].

Several studies demonstrate myocardial perfusion abnormalities in HCM [6–10] and others describe biochemical evidence for myocardial ischaemia [11,12]. In the absence of coronary disease or LV outflow obstruction, microvascular disease is often assumed to be the cause of myocardial ischaemia. This assumption is based on a few studies that report structural abnormalities of the microvasculature [13–16]. Notably, limited data associates structural changes with perfusion abnormalities or chest pain [15,17].

Myocardial perfusion occurs almost exclusively in diastole and perfusion pressure is greatest in early diastole when suction force due to decompression of the myocardial microcirculation also augments flow [18]. We hypothesised that regional prolongation of systolic contractility into early diastole is associated with reduced myocardial perfusion in HCM.

The aim of this study was to examine associations between chest pain and myocardial perfusion with prolongation of contractility in

Abbreviations: ASH, asymmetrical septal hypertrophy; CMR, cardiac magnetic resonance; EF, ejection fraction; FWHM, full width half max; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; MPRi, myocardial perfusion reserve index; MWT, maximal wall thickness; PMT, papillary muscles and trabeculae; RV, right ventricular; SAX, short axis; SSFP, steady state free precession cine; SV, stroke volume; %CC, percentage of the cardiac cycle; %D, percentage of diastole.

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patients with apical HCM using cardiac magnetic resonance imaging (CMR).

2. Methods

2.1. Study design

This is a retrospective, cross-sectional, observational cohort study based at the London Chest Hospital, UK. Consecutive cases (age ≥16 years) of apical HCM (August 2008–February 2013) were identified from the registry of a regional CMR centre where adenosine stress perfusion imaging was routinely performed in HCM. We also studied control cohorts.

2.1.1. Apical HCM cohort

Morphologic criteria for apical HCM included a maximal end-diastolic LV wall thickness (MWT) ≥15 mm in the apical segments of the heart [1]. We excluded cases where basal septal exceeded apical wall thickness and individuals with left bundle branch block, atrial fibrillation or obstructive coronary disease (>50% narrowing in a major epicardial artery or previous revascularisation). Treated hypertension was not excluded [19].

2.1.2. Control cohorts

We identified two control groups:

a). Consecutive patients with the asymmetric septal hypertrophy (ASH) variant of HCM who had also undergone perfusion CMR imaging (control-HCM).
b). Normal controls identified through a low-intermediate risk chest pain pathway in whom coronary angiography and perfusion CMR were performed as part of a prospective research study comparing the diagnostic accuracies of these modalities (EVINCI: NCT00979199) [20]. All normal controls had angiographically normal coronary arteries and structurally normal hearts.

2.2. Collection of clinical data

Demographic and symptomatic data were collected from electronic records. Chest pain was recorded as present or absent from preceding outpatient clinic letters or scan indication information. Missing data are reported.

2.3. Consent and ethical approval

This study complies with the declaration of Helsinki and was conducted as audit (Clinical Management of the Inherited and Acquired Heart Muscle Diseases, Barts Health NHS Trust audit No. 5298). As per protocol, ethics committee approval and informed consent were not sought.

2.4. CMR image acquisitions and analysis

All studies were performed on a 1.5 T magnet (Achieva®, Philips Medical Systems) and images acquired using standard protocols, medication was not withheld prior to imaging. Briefly, balanced steady-state free precession cine (SSFP) images were acquired with 25–30 phases/cardiac cycle (8 mm slice thickness, 2 mm gap for short axis (SAX) images; typical voxel size 1.9 × 1.9 mm). For perfusion imaging, gadolinium based contrast bolus (Dotarem®) was followed by saline flush. SAX images at basal, mid and apical LV level were obtained at peak stress (adenosine 140 μg/kg/min, 4 min) and at rest. For late gadolinium enhancement (LGE), T1 weighted inversion-recovery gradient echo images were acquired approximately 10 min after gadolinium (typical voxel 2.07 × 2.16 mm, slice thickness 8 mm, FOV 300 mm).

2.4.1. LV dimensions and mass

Endocardial and epicardial borders, including papillary muscles and trabeculae (PMT) within blood pool, were manually traced on SAX images in all cardiac phases (Extended MR Workspace®, Philips Medical Systems). Ejection fraction (EF), stroke volume (SV) and LV mass were calculated. Regional (SAX) LV volume was calculated (epicardial – endocardial volume).

2.4.2. Measurement of contractile persistence

LV obliteration was measured by manually tracing endocardial and epicardial borders, including PMT within LV muscle volume, for each phase in the three SAX slices co-localizing with those for basal, mid-LV and apical perfusion (Fig. 1). To standardise the cardiac cycle, data were resampled at 30 phases/cycle if cines were obtained at any different frequency (typically 25–30 phases). LV cavity obliteration was defined as endocardial area ≤0.2 cm^2 (approximately 1/2 voxel). Diastolic obliteration was that present in any cardiac phase after end-systole. End systole was defined as the phase where total LV volume was lowest (Fig. 1A). Contractile persistence duration was expressed as either percentage of the cardiac cycle (%CC) or diastole (%D) during which obliteration was present.

2.4.3. Perfusion analysis

The myocardial perfusion reserve index (MPRi) was calculated in basal, mid and apical SAX slices that were not separated into American Heart Association (AHA) segments (without segmentation) [21,22]. Epicardial, endocardial and blood pool contours were manually traced. After baseline correction, stress and rest signal intensity (SI) time curves were constructed. Maximum upslope was measured using a 4-point window for the myocardium and a 2-point window for the blood pool and mean myocardial maximum upslope was obtained for basal, mid and apical SAX slices, and corrected for arterial input [23]. MPRi was calculated by dividing stress by rest values.

2.4.4. Late gadolinium enhancement

Quantity of LGE on T1 weighted images was determined using the full-width half max (FWHM) technique (CMR42, Circle Cardiovascular Imaging Inc., Canada) [24,25]. The FWHM method was applied to the three SAX slices co-localizing with basal, mid and apex perfusion images and LGE was expressed, without segmentation, as %myocardium.

2.4.5. Intra- and inter-observer error

For intra-observer error, MPRi was measured in a random sample of 10 apical HCM twice (with a gap of 1 week), in a random order. For inter-observer error, two independent measurements of MPRi were made in 5 scans, in a random order, by two observers. All patient-identifiable information was removed from the scans and the observers blinded to all other results.

2.5. Statistical analysis

Nominal and parametric baseline characteristics were compared with Chi-squared and paired or unpaired *t*-tests, respectively. Parametric and non-parametric intergroup differences were tested with one-way ANOVA and Kruskal–Wallis one-way ANOVA tests respectively. Multivariate regression was performed in apical HCM patients to find variables predicting apical MPRi (linear regression) and chest pain (logistic regression). The pre-specified, independent (predictor) variables included sex, age (years), apical LGE (%LV mass), apical MWT (mm), contractile persistence (%CC) and MPRi.

Unless stated, data are presented as mean (SD), p-values are two-tailed and a value of <0.05 was considered statistically significant. Where appropriate, Fisher's exact test corrected for small samples and post-hoc Bonferroni correction was used for differences between means. Analyses was performed using StatsDirect, (v2.7.9 (Cheshire, UK)) and STATA (v11).

3. Results

CMR images of sufficient quality were available from 126 subjects (76 apical HCM, 31 ASH-controls and 19 normal controls). The baseline characteristics of the cohort are shown in Table 1.

3.1. Global and regional LV morphological characteristics

Apical-HCM and control-HCM patients had similar LV end-diastolic and end-systolic volumes (EDV and ESV), LV mass and MWT. EF was marginally greater in apical HCM.

There were differences in regional morphology; apical and mid-LV end-diastolic cavity volumes were lower in apical than in control-HCM but similar at the base.

The myocardial volume in the apical SAX slices was greater in apical HCM than control-HCM, but similar in the basal and mid-LV. These data are shown in Table 1.

Resting LV outflow tract obstruction was present in 12 (39%) control-HCM patients. In the 28 HCM-control patients where symptom status was available 11 (39%) had resting LVOTO. In this small selected group, differences in the proportions with chest pain were no different between those with resting LVOTO and those without (9 of 11 vs. 11 of 17 respectively; X^2 $p = 0.33$).

3.2. LV cavity obliteration

No normal controls demonstrated LV obliteration; the threshold for cavity obliteration was lower than end-systolic apical endocardial area in normal controls (3.3 ± 1.4 cm^2) by 2.2 standard deviations (98th percentile).

In apical HCM, LV cavity obliteration was detected in the apex, mid and basal LV in 79%, 32% and 3% respectively, and in 39%, 13% and 0% of control-HCM (χ^2 $p < 0.001$ for apex, $p = 0.03$ for mid).

In apical HCM, LV cavity obliteration persisting into diastole was demonstrated in apical, mid and basal LV regions in 78%, 26% and 3% respectively, and in 26%, 13% and 0% of control-HCM (χ^2 $p < 0.001$ for apex).