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Research paper

Computed tomography imaging to quantify the area of the endocardial subvalvular apparatus in hypertrophic cardiomyopathy – Relationship to outflow tract obstruction and symptoms☆

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ABSTRACT

Background: Abnormalities of the endocardial subvalvular apparatus (SVA), which includes the papillary muscles directly attached to the mitral leaflet and left ventricular apical-basal muscle bundles, are occasionally identified in hypertrophic cardiomyopathy (HCM). Their associations with left ventricular outflow tract (LVOT) obstruction are unknown.

Methods: We retrospectively reviewed cardiac computed tomography image data sets of 107 consecutive patients with HCM [56 obstructive (HOCM) and 51 non-obstructive (HNOCM)] as well as 53 controls. We evaluated anomalies of the SVA, measured the cross-sectional area of the SVA at the level of the LVOT, and subsequently assessed its correlation with the LVOT pressure gradient with and without medication.

Results: The area of the SVA was greater in HOCM than in HNOCM patients and in the control group (2.5 ± 1.3 cm^2, 1.4 ± 0.8 cm^2, and 0.9 ± 0.6 cm^2, respectively; $p < 0.0001$). Anomalies in the SVA were more often observed in the HOCM group than in the HNOCM patients and controls (abnormal papillary muscles, 14%, 8%, and 0%, respectively; $P = 0.010$; LV apical–basal muscle bundles, 73%, 65%, and 45%, respectively; $P = 0.0094$). Among HOCM patients, logistic regression analysis demonstrated that an SVA area of 2.2 cm^2 was an independent risk factor of residual severe LVOT obstruction (≥50 mmHg) after medication (odds ratio, 10.1; 95% confidence interval, 2.05–49.80).

Conclusion: An increased area of the endocardial subvalvular apparatus could be an independent risk factor for clinically relevant LVOT obstruction refractory to medication.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder characterized by left ventricular (LV) hypertrophy. Recently, abnormalities in the endocardial structures under the mitral valve, termed "subvalvular apparatus", have been reported in HCM patients. They include an anomalous insertion of the anterolateral papillary muscle directly into the anterior mitral leaflet (abnormal papillary muscle),[1] LV apical–basal muscle bundles,[2] and complicated trabeculation.[3] These abnormalities could play a significant role in left ventricular outflow tract (LVOT) obstruction in HCM patients without severe septal hypertrophy.

Beta-blockers are the first-line drugs for the treatment of obstructive HCM (HOCM); if they are insufficient, it is reasonable to add calcium antagonists and class IA anti-arrhythmic drugs.[4,5] Cibenzoline, a class IA anti-arrhythmic drug, is more often used in Japan because of its low anticholinergic activity and ameliorating effect on LVOT obstruction compared with disopyramids.[6,7] HCM patients with an abnormal subvalvular apparatus tend to require surgical treatment to relieve LVOT obstruction because the effect of medication may be insufficient.[8] However, little is known about any association between the quantitative characteristics of the subvalvular apparatus and the effects of pharmacologic therapy.

Cardiac magnetic resonance (CMR) imaging has been the gold standard for morphologic evaluation in HCM patients, including

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quantitative assessment of wall thickness, chamber volumes, and LV systolic function.[9] However, the papillary muscles and endocardial trabeculae are difficult to accurately identify and quantify using CMR due to limited of spatial resolution.[10,11] Cardiac computed tomography (CT) imaging has higher spatial and temporal resolution than CMR, enabling detailed evaluation of the subvalvular apparatus.[4,5] However, the clinical utility of cardiac CT imaging in the management of HCM patients has not been investigated. Cardiac CT is sometimes performed before alcohol septal ablation (ASA) in patients with HOCM because it can identify septal branches that feed the hypertrophied myocardium. Cardiac CT imaging is also expected to provide useful information on the morphology of subvalvular apparatus, in the diastolic phase potentially more so than in systole.

The aims of our study were to retrospectively identify and quantify abnormal LV subvalvular apparatuses using cardiac CT in order to determine whether an abnormal subvalvular apparatus is associated with LVOT obstruction in HCM patients, and to investigate the efficacy of medication, mainly of beta-blockers, in patients with an abnormal subvalvular apparatus.

2. Methods

2.1. Patients

The study cohort included 107 consecutive HCM patients and 53 controls who underwent cardiac CT for assessment of coronary anatomy between September 2009 and May 2015. We retrospectively reviewed clinical and imaging findings as well as medical records. According to the 2011 American College of Cardiology Foundation/American Heart Association and the 2014 European Society of Cardiology (ESC) guidelines for HCM,[5,12] HCM was diagnosed when a hypertrophied left ventricle (maximal wall thickness $\geq$ 15 mm) was seen on two-dimensional echocardiography and CMR imaging, in the absence of another cardiac or systemic disease that could produce cardiac hypertrophy. Patients in the dilated phase of HCM or who had previously undergone alcohol septal ablation (ASA) or surgical myectomy were excluded. Controls were chosen from patients who underwent cardiac CT due to suspected coronary disease and who had normal LV systolic function with no coronary disease, cardiomyopathy, valve disease, severe hypertension, or family history of HCM.

The study was approved by the Research Ethics Board of Sakakibara Heart Institute and complied with the Declaration of Helsinki.

2.2. Identification of LVOT obstruction and definition of terms

The resting LVOT pressure gradient (LVOT-PG) was assessed by continuous-wave Doppler echocardiography, and at the time of diagnosis, LVOT obstruction was defined as peak LVOT-PG $\geq$ 30 mmHg under resting conditions. Obstructive HCM (HOCM) and non-obstructive HCM (HNOCM) were defined according to whether LVOT obstruction was found at diagnosis. LVOT-PG before medication was defined as the LVOT-PG measured at the time of diagnosis, and LVOT-PG after medication was defined as that assessed at least 1 month after initiation or intensification of drug therapy. Severe LVOT obstruction was defined as peak LVOT-PG $\geq$ 50 mmHg under resting conditions, usually considered the threshold at which LVOT obstruction is hemodynamically relevant.[5]

2.3. Cardiac CT

All HCM patients and controls underwent cardiac CT using a dual-source CT system (SOMATOM Definition Flash®; Siemens Healthcare, Forchheim, Germany). Each patient's electrocardiogram was prospectively monitored throughout the procedure. The appropriate time interval between contrast agent injection and scanning initiation was determined by test injection of 7 ml contrast agent. Scans were performed using spiral acquisition with retrospectively electrocardiogram-gated image reconstruction during injection of 23.8–28.0 mg I/kg/s iopamidol (370 mg I/mL) (Iopamiron 370; Bayer, Osaka, Japan), with a gantry rotation time of 280 ms, a reference tube current of 375 ± 72 mAs/rotation, and a tube voltage of 80–120 kVp. Transaxial images were reconstructed using filtered back projection with 0.75 mm section thickness. The reconstructed images were transferred to an image server and analyzed using dedicated three-dimensional software (Ziostation2®; Ziosoft, Tokyo, Japan).

2.4. CT image analysis

Cardiac images reconstructed in end-diastole were collected for analysis and transferred to the workstation for processing. First, the presence of abnormal papillary muscles (papillary muscles directly attached to the anterior mitral leaflet, Fig. 1a) and LV apical–basal muscle bundles (Fig. 1b) was identified in three-dimensionally

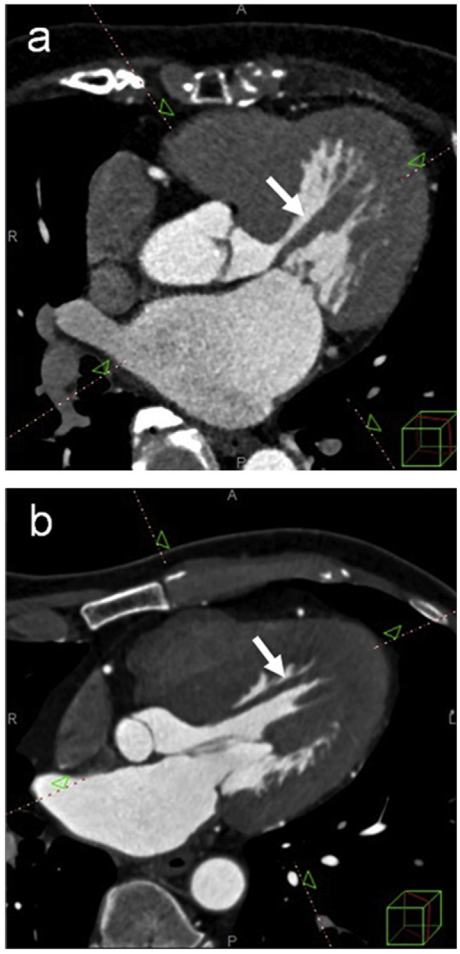

Fig. 1. Cardiac computed tomography images of abnormal papillary muscles and apical–basal muscle bundles. (a) Abnormal papillary muscle (arrow) directly attached to the anterior mitral leaflet in a 76-year-old female obstructive hypertrophic cardiomyopathy (HOCM) patient, with resting left ventricular outflow tract pressure gradients of 139 and 121 mmHg before and after medication, respectively. (b) Accessory left ventricular apical muscle bundle (arrow) in a 53-year-old male HOCM patient, with resting gradients of 99 and 48 mmHg before and after medication.