Journal of Cardiology 63 (2014) 89–94

Contents lists available at ScienceDirect

Journal of Cardiology

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

Review

# Subendocardial ischemia in hypertrophic cardiomyopathy

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ARTICLE INFO

*Article history:*
Received 9 June 2013
Received in revised form 5 September 2013
Accepted 4 October 2013
Available online 20 November 2013

*Keywords:*
Cardiomyopathies
Hypertrophic
Ischemia
Subendocardium

ABSTRACT

Hypertrophic cardiomyopathy (HCM) patients often develop subendocardial ischemia in the left ventricle without atherosclerotic coronary stenosis. Myocardial ischemia plays an important role in the pathophysiology of HCM, but diagnostic techniques for the detection of subendocardial ischemia have not been widely available. We developed specific techniques to quantify subendocardial ischemia on stress scintigraphy, and have compared the results with various clinical features in patients with HCM. This article reviews our understanding of subendocardial ischemia in HCM based on more than 20 years of experience.



**Contents**



## Case presentation

A 61-year-old man presents with chest pain on exertion. On examination, physical signs are normal without heart murmur. An electrocardiogram shows marked left ventricular (LV) hypertrophy in the absence of a history of hypertension. Imaging modalities show asymmetric septal hypertrophy on magnetic resonance imaging, no provokable LV outflow tract obstruction on echocardiography, no atherosclerotic stenosis on coronary computed tomography angiography, and unique findings on myocardial perfusion scintigraphy (Fig. 1). How should this case be managed?

## Background

HCM is an entity first described clinically in 1957 by Brock [1], followed pathologically the next year by Teare [2]. In the mid-1970s, the assessment of myocardial perfusion with thallium-201 was introduced to patients with HCM, showing regional myocardial hypoperfusion in the absence of epicardial coronary artery disease [3,4]. In 1987, O'Gara et al. [5] demonstrated transient LV cavity dilation on thallium-201 obtained immediately after cessation of maximal treadmill exercise in HCM patients with normal coronary arteries. This scintigraphic abnormality was reported by Udelson

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http://dx.doi.org/10.1016/j.jjcc.2013.10.005

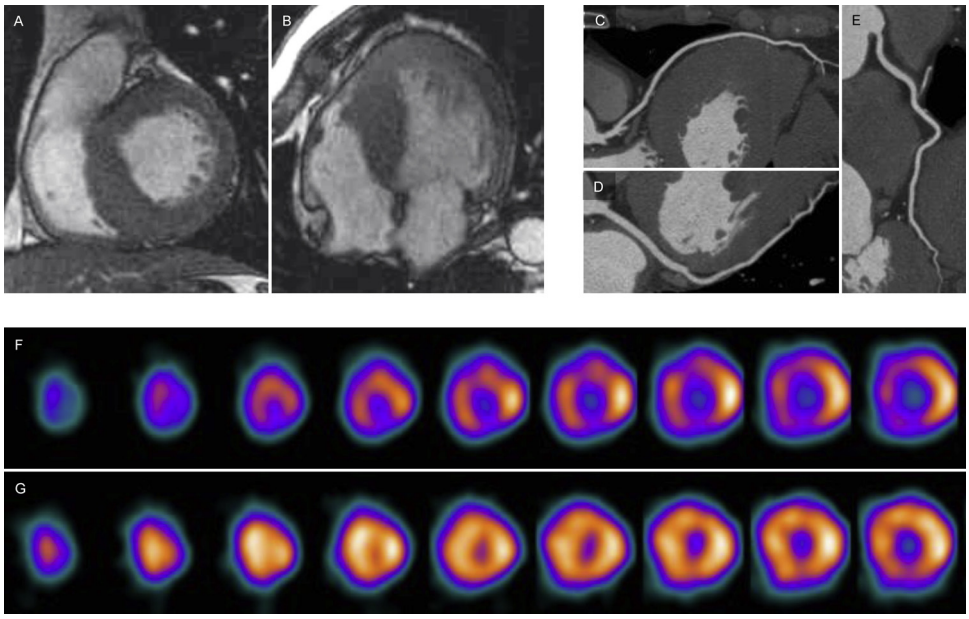


**Fig. 1.** Representative case of subendocardial ischemia in hypertrophic cardiomyopathy. Cardiac magnetic resonance shows asymmetric septal hypertrophy (Panel A, short-axis; Panel B, long-axis) in a 61-year-old man with chest pain on exertion. Coronary computed tomography angiography shows no atherosclerotic stenosis in the left descending coronary artery (Panel C), the left circumflex coronary artery (Panel D), and the right coronary artery (Panel E). Notably, exercise-induced transient cavity dilation is apparent on short-axis slices of thallium-201 scintigraphy after exercise (Panel F), compared with at rest (Panel G), features consistent with left ventricular subendocardial ischemia.

et al. in 1989 to occur without any significant changes in the LV cavity volume before and after exercise [6]. Moreover, in 1991, Cannon et al. [7] showed the association of the unique scintigraphic findings with myocardial lactate abnormalities. Thus, transient LV cavity dilation on stress scintigraphy in HCM patients without coronary stenosis, for example, as shown in Fig. 1, has been considered to reflect subendocardial ischemia in the LV. Myocardial ischemia plays an important role in the pathophysiology of HCM [8,9], but quantitative diagnostic techniques for the detection of subendocardial ischemia have not been fully understood in clinical practice.

In 1990, we developed specific software to quantify transient LV cavity dilation or subendocardial ischemia based on stress scintigraphy in patients with HCM [10]. Briefly, in a thallium-201 short-axis slice of the mid-LV, 36 radii were generated at 10-degree intervals from the center of the image. An area surrounded by 36 points, each displaying the maximum count on each radius, was calculated automatically in the stress and rest images, and subendocardial ischemia was assessed on the basis of the ratio of the surface area during stress to that at rest. The ratio that we calculated was not based on a genuine LV cavity during stress to that at rest, but the ratio could be an index of subendocardial ischemia because subendocardial ischemia causes the maximum count on the radius to move outward. This speculation is supported by our findings that LV end-diastolic volume did not change 10 min after exercise and at rest as assessed by radionuclide ventriculography [10]. We had applied this technique to HCM patients in the clinical setting for almost 10 years [11]. In 2000, we modified our method for a more accurate analysis; the LV was divided into 15 short-axis slices and 100 radii were generated at 3.6-degree intervals from the center of each image, as shown in Fig. 2. An area surrounded by 100 points each displaying the maximum count on each radius was calculated automatically in the stress and rest images. Subendocardial ischemia was considered present if the stress to rest ratio in the sum of the 15 surface areas was greater than the mean plus 2 standard deviations in normal subjects (i.e. 1.07) [12]. These programs that we previously developed and appropriately modified have enabled us to compare subendocardial ischemia with various clinical features in patients with HCM. This article reviews our understanding of subendocardial ischemia in HCM based on more than 20 years of experience.

## Epidemiology

Approximately one-third to one-half of patients with HCM developed subendocardial ischemia during stress testing without atherosclerotic coronary stenosis in our cohorts [10–12] and other populations [5,7]. In our different groups of patients with HCM, chest symptoms were more frequently observed in HCM patients with subendocardial ischemia than in patients without subendocardial ischemia (67% versus 31%, $p = 0.01$ [10] and 65% versus 25%, $p = 0.01$ [13]), but subendocardial ischemia was not associated with age, gender, body mass index, a previous history of syncope, or family history of HCM, or of unexpected sudden death [12].

## Electrocardiography

We examined the details of electrocardiographic findings during exercise testing with scintigraphy in 48 HCM patients, and found that resting ST-segment depression, defined as >0.1 mV in depth except for aVR, as shown in Fig. 3A, was an independent predictor for the presence of subendocardial ischemia [12]. In brief, the incidence of resting ST-segment depression was 11 patients of 17 with subendocardial ischemia and 9 of 31 patients without subendocardial ischemia ($p = 0.02$). The diagnostic performance of the total number of leads with resting ST-segment depression $\geq 3$ was a sensitivity of 65%, a specificity of 90%, an accuracy of 81%, a positive predictive value of 79%, and a negative predictive value of 82%. On the other hand, ST-segment depression during exercise was not a reliable marker of subendocardial ischemia, findings consistent with previous reports [5,7]. Repetitive ischemia in the subendocardium is a possible cause of resting ST-segment depression in HCM patients with subendocardial ischemia, as in patients with chronic ischemic heart disease [14].

Moreover, in 29 HCM patients with asymmetric septal hypertrophy, we found that 5 of 15 patients with diffuse subendocardial ischemia had small q waves in leads V5 and V6 (i.e. septal q waves)