Stress Echocardiography in Hypertrophic Cardiomyopathy

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34.1 Background

Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous but relatively common autosomal dominant genetic heart disease (1 in 500 of the general population for the disease phenotype recognized by echocardiography) that probably is the most frequently occurring cardiomyopathy [1]. HCM is characterized morphologically and defined by a nonhypertrophied, nondilated left ventricle in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident (e.g., systemic hypertension, aortic valve stenosis). Clinical diagnosis is customarily made with two-dimensional echocardiography by detection of otherwise unexplained LV wall thickening, usually in the presence of a small LV cavity, after suspicion is raised by the clinical profile or as a part of family screening. Most HCM patients have the propensity to developing dynamic obstruction to LV outflow under resting or physiologically provocable conditions, produced by systolic anterior motion of the mitral valve with ventricular septal contrast [1]. HCM is caused by a variety of mutations encoding contractile proteins of the cardiac sarcomeres, and – in a minority of cases – nonsarcomeric proteins. This genetic diversity is compromised by considerable intragenic heterogeneity, with more than 400 individual mutations now identified. The genetic heterogeneity only partially accounts for the clinical heterogeneity of the presentation, which may range anywhere from sudden death to progressive heart failure to a completely asymptomatic condition. The strongest risk factors are a family history of sudden death, a personal history of cardiac arrest or recurrent syncope, multiple-repetitive nonsustained ventricular tachycardia, and adverse genotype. Resting adds to clinical stratification by assessing massive left ventricular hypertrophy (>30 mm), intraventricular obstruction (>50 mmHg), and wall thinning in serial evaluations over time (Fig. 34.1). On the top of this established information, stress echocardiography is now increasingly used to offer a substantial contribution to risk stratification of these patients, which remains a formidable challenge for the clinician [2].

E. Picano, *Stress Echocardiography*,

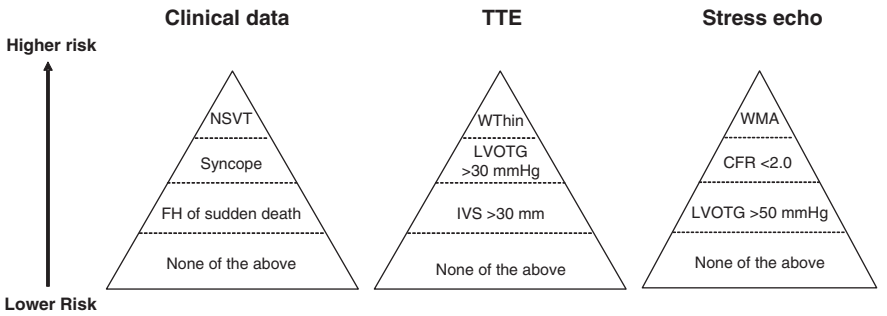


Fig. 34.1 The pyramid of risk in hypertrophic cardiomyopathy (HCM) according to simple clinical assessment (*left panel*), resting transthoracic echocardiography (*middle panel*), and stress echocardiography (*right panel*) parameters. For each pyramid, three main factors are identified. *CFR* coronary flow reserve, *IVS* interventricular septal thickness, *LVOTG* left ventricular outflow tract gradient, *WMA* wall motion abnormalities, *FH* Family history, *NSVT* non-sustained ventricular tchycardia, *Wthin* Wall thinning at serial resting echo evaluation

34.2 Pathophysiology

Symptoms and signs of myocardial ischemia are often found in patients with HCM, despite the presence of angiographically normal coronary arteries (Fig. 34.2). Myocardial ischemia can contribute to some of the severe complications of HCM including ventricular arrhythmias, sudden death, progressive left ventricular remodeling, and systolic dysfunction. Coronary flow reserve is severely blunted not only in the hypertrophied septum, but also in the less hypertrophied left ventricular free wall [3]. The severity of microvascular dysfunction is an independent prediction of long-term deterioration and death from cardiovascular causes [4]. As in other models of microvascular disease, such as cardiac syndrome X or arterial hypertension [5], ST-segment changes and perfusion abnormalities are frequently elicited during stress in the absence of inducible wall motion abnormalities (Fig. 34.3), which remain a specific hallmark of epicardial coronary artery disease [6].

However, stress-induced ST-segment depression and perfusion abnormalities are probably not innocent even with normal coronary arteries: they are associated with reduced flow reserve [7], subendocardial underperfusion, and, most importantly, an adverse prognosis. Myocardial malperfusion detected by stress scintigraphy is frequently related to cardiac arrest and syncope in young patients with HCM [8]. Stress-induced ischemic-like electrocardiographic changes, in the absence of wall motion abnormalities, are also frequently related to syncope and/or left ventricular dilatation in adult patients with HCM and normal coronary arteries [9] (Fig. 34.4).

Fig. 34.3 Two-dimensional end-diastolic (*E-D*, *upper row*) and end-systolic (*E-S*, *second row*) frames of a parasternal long-axis view following dipyridamole infusion, showing a normal/hyperkinetic motion of intraventricular septum and inferolateral wall. In the *lower row*, pulsed Doppler of mid-distal left anterior descending coronary artery shows a blunted increase in coronary artery flow velocity during stress (rest = 38, peak = 67, cm/s, CFR = 1.25)

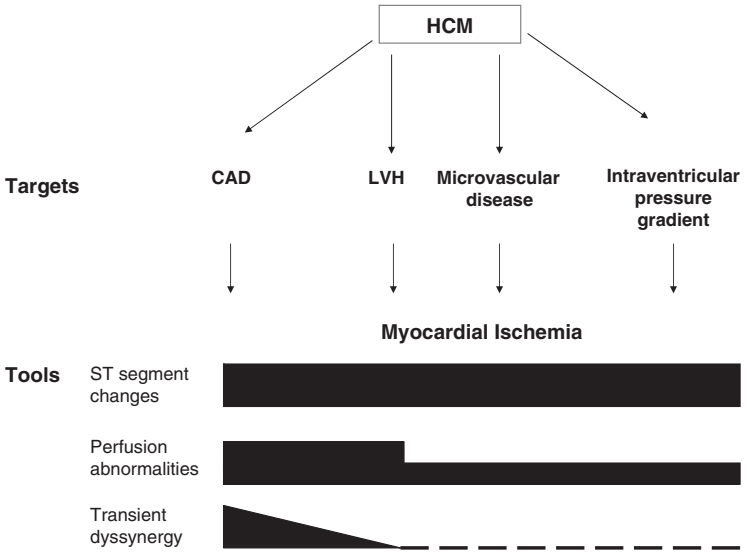
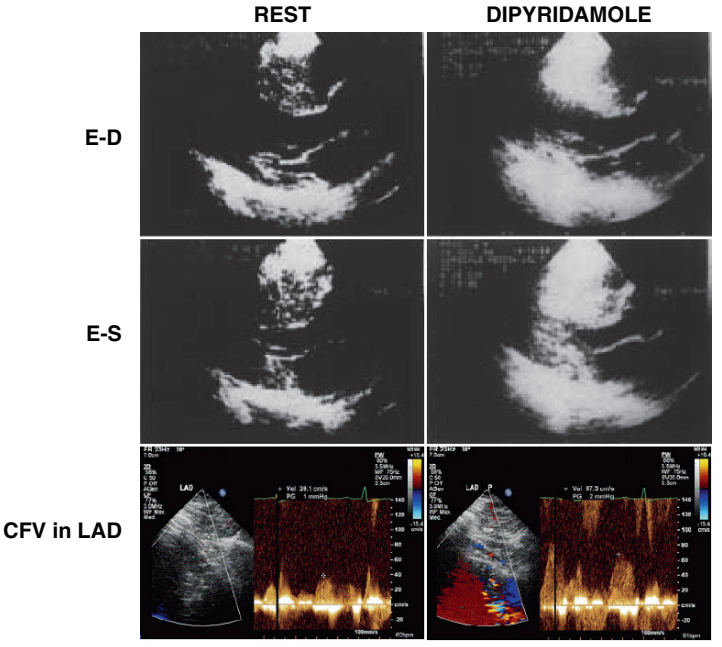


Fig. 34.2 The four main pathways to myocardial ischemia in hypertrophic cardiomyopathy (*HCM*): epicardial coronary artery disease (*CAD*); left ventricular hypertrophy; microvascular disease; intraventricular dynamic obstruction. Only CAD induces stress-induced wall motion abnormalities, but all four mechanisms may induce a reduction in coronary flow reserve



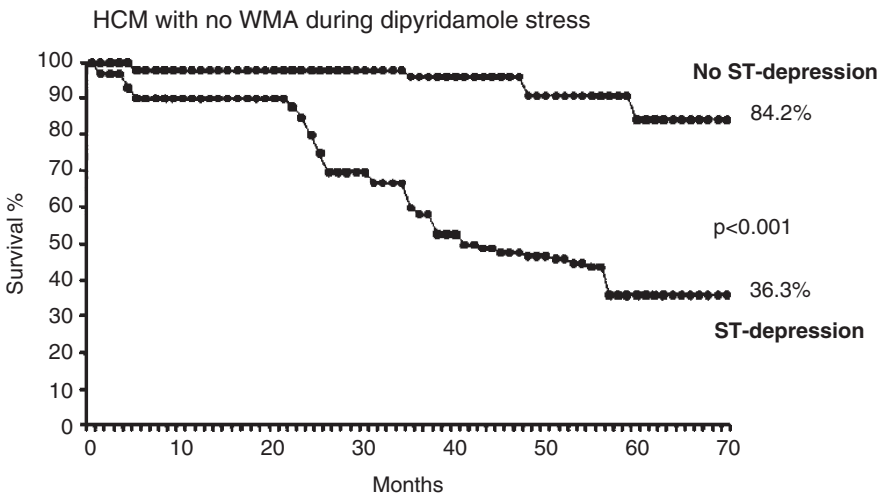


Fig. 34.4 Kaplan–Meier curve indicating the cumulative event-free survival rates in patients with a positive dipyridamole ECG test (*DET+*) and in patients with a negative dipyridamole ECG test (*DET−*). All these patients had angiographically normal coronary arteries and no wall motion abnormality during the dipyridamole test. FH, Family history; NSVT, non-sustained ventricular tchycardia; Within, wall thinning at serial resting echo evaluation (Modified from [9])

34.3 Stress Echocardiographic Findings in HCM

According to the pathophysiological background, stress echocardiography can recognize three important, distinct risk markers in HCM patients: the transient regional wall motion abnormality; the reduction in coronary flow reserve in absence of wall motion changes; and the dynamic intraventricular pressure gradient.

Angina and myocardial ischemia can occur in patients with HCM independently of angiographically assessed atherosclerotic coronary artery disease, which nevertheless can be present in 20–30% of HCM patients with a history of chest pain [10]. For the purposes of noninvasive identification of underlying coronary artery disease, wall motion abnormalities are equally sensitive and substantially more specific than perfusion abnormalities and ST-segment depression, as has been consistently observed in all models of primary or secondary coronary microvascular angina [10]. Stress echocardiography based on wall motion abnormalities is therefore the test of choice [11] and patients with inducible wall motion abnormalities will have the greatest benefit from an ischemia-driven revascularization. After ruling out wall motion abnormalities (and therefore functionally significant underlying coronary artery disease), stress echocardiography may offer invaluable information on coronary flow reserve and underlying microvascular disease. With a last-generation "two birds with one stone" protocol, both function and coronary flow reserve can be caught with a single stress (accelerated, fast high-dose dipyridamole). Even in absence of inducible

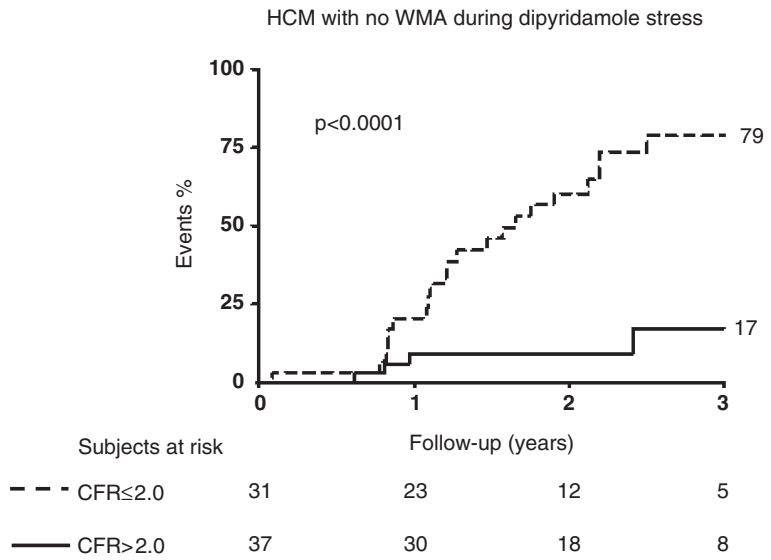


Fig. 34.5 Kaplan–Meier curve indicating the cumulative event-free survival rates in patients with reduced (*CFR*>2.0) and preserved (*CFR*>2.0) coronary flow reserve. All these patients had angiographically normal coronary arteries and no wall motion abnormality during dipyridamole test. (Modified from [12])

wall motion abnormalities, a reduced coronary flow reserve identifies a relatively higher risk subgroup (Fig. 34.5) [12]. In these patients, the absence of wall motion abnormalities does not necessarily contradict the ischemic nature of chest pain and ST-segment depression. In fact, the presence or absence of abnormal wall motion appears to relate to the account of ischemic subendocardial tissue, minor degrees of transmural involvement are less likely to reach the critical mass of ischemic tissue needed to determine wall motion and thickening abnormalities [6]. The third possible finding during stress is the development of a critical intraventricular pressure gradient (>50 mmHg) (Fig. 34.6), which identifies yet another mechanism – beyond coronary artery disease and microvascular dysfunction – possibly responsible for symptoms (chest pain and dyspnea) in HCM patients [13, 14]. An exercise-induced gradient greater than 50 mmHg may be responsible for ischemia (through increased extravascular compression forces) and dyspnea (with increased endoventricular diastolic pressure). These findings may have a potential, although not proven, therapeutic interest, possibly with "obstructions" more likely to benefit from β-blockade.

The stress for coronary artery disease detection can be exercise, dobutamine, or dipyridamole; the best stress for coronary flow reserve assessment is dipyridamole (or adenosine) [15], and the most suitable one to unmask a latent, albeit physiologically important, intraventricular gradient is exercise – even better if the echocardiography scan is performed in the more physiologic orthostatic position – rather than in left lateral decubitus [14]. Another approach of potential value in risk stratification in patients with HCM is the evaluation of the inotropic reserve after low-dose challenge with catecholamines, i.e., isoproterenol.

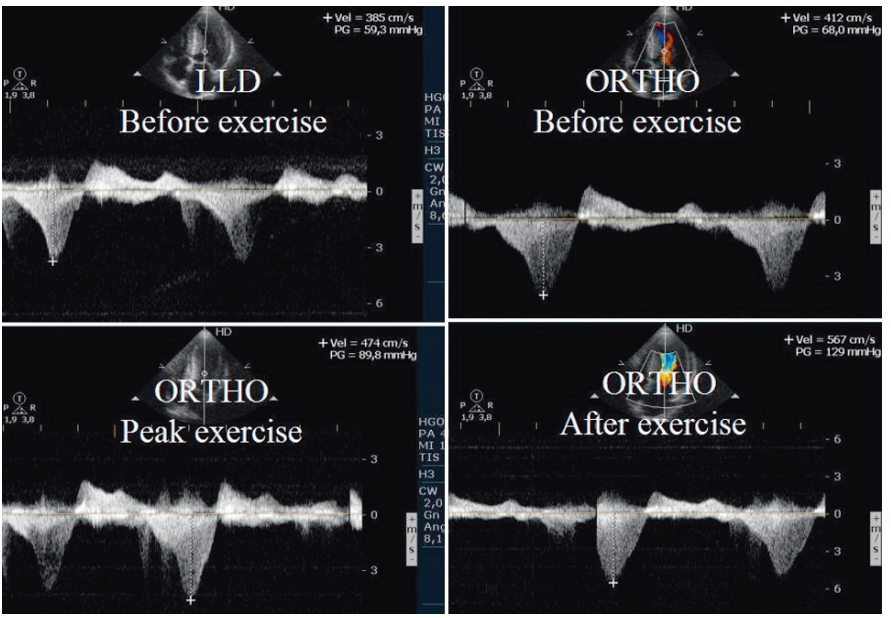


Fig. 34.6 Left ventricular outflow tract gradient during exercise in a patients with hypertrophic cardiomyopathy. (From [14])

A blunted increase in regional systolic thickening to low-dose adrenergic stimulation can predict a long-term adverse progression toward left ventricular dilatation [16].

34.4 Conclusion

Stress echocardiography can play a key role in the diagnostic and prognostic stratification of the HCM patient, identifying three distinct patterns: high-risk wall motion abnormalities, which dictate ischemia-driven revascularization; intermediate-risk reduction in coronary flow reserve warranting aggressive medical therapy; intermediate-risk patients with intraventricular gradients most likely to benefit from β-blockade; and low-risk patients with none of these features, in whom no specific intervention other than watchful waiting is warranted if the patient is asymptomatic (Fig. 34.7).

An additional advantage of stress echocardiography over alternative techniques is its low cost, wide availability, versatility, and radiation-free nature, most important in young patients often in need of several examinations over time. For instance, a thallium scan is associated with a radiological dose exposure of about 1,500 chest X-rays, with a risk of cancer of 1 in 400 in a 50-year-old man, and 1 in 200 in a 20-year-old woman [17–19]. Although more data are warranted at this point, stress echocardiography promises to offer an increasingly important contribution to the management of HCM patients.

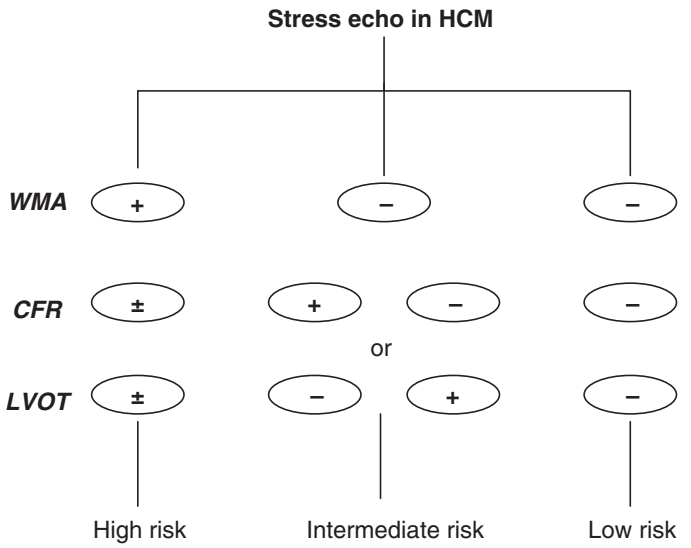


Fig. 34.7 The possible role of stress echocardiography in risk stratification of HCM patients with indeterminate risk. CFR, coronary flow reserve; HCM, hypertrophic cardiomyopathy; LVOT, left functional outflow tract obstruction

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