Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review

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Abstract

Risk stratification in hypertrophic cardiomyopathy (HCM) remains a challenge. Echocardiography is the cornerstone of diagnosis and part of the current algorithm for assessing the risk of sudden cardiac death (SCD). However, the algorithm does not utilize recent advances in echocardiography. The aim of this review was to summarize novel echocardiographic predictors with regard to unfavorable outcomes, focusing mainly on SCD. PubMed searches were performed by using the search string "hypertrophic cardiomyopathy" and "echocardiography." The records were independently screened for exclusion and inclusion criteria according to PRISMA guidelines; 841 articles were initially retrieved, of which 29 articles were finally included. Two studies on longitudinal strain (LS) and two studies on diastolic dysfunction by tissue Doppler imaging (TDI) found a correlation with late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR). LS and mechanical dispersion were found to be independent predictors of unfavorable outcome according to a total of 15 studies. Four studies showed that an increased E/é ratio was a significant predictor of cardiovascular death in patients with HCM. Right ventricular dysfunction was an independent predictor of death or heart transplantation according to two studies. Microvascular dysfunction and ischemia were detected by impaired coronary flow according to three studies and multivariate analysis in one of these studies predicted abnormal coronary flow reserve to be an independent predictor of poor outcome. Myocardial dysfunction assessed with speckle tracking strain analysis or with TDI as well as impaired coronary flow seem to be promising novel echocardiographic risk markers.

Keywords: Echocardiography; Hypertrophic Cardiomyopathy; Implantable Cardioverter Defibrillator; Risk Stratification; Sudden Cardiac Death

Abbreviations

ACC: American College of Cardiology; AHA: American Heart Association; CI: Confidence Interval; CMR: Cardiac Magnetic Resonance; CT: Computed Tomography; ESC: European Society of Cardiology; HCM: Hypertrophic Cardiomyopathy; HR: Hazard Ratio; ICD: Implantable Cardioverter Defibrillator; LAVi: Left Atrium Volume Index; LGE: Late Gadolinium Enhancement; LS: Longitudinal Strain; LV: Left Ventricular; LVOT: Left Ventricular Outflow Tract; LWWT: Left Ventricular Wall Thickness; NSVT: Non Sustained Ventricular Tachycardia; NYHA: New York Heart Association; OR: Odds Ratio; RS: Radial Strain; RV: Right Ventricular; SCD: Sudden Cardiac Death; TAPSE: Tricuspid Annular Plane Systolic Excursion; TDI: Tissue Doppler Imaging; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia

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Introduction

Hypertrophic cardiomyopathy (HCM) in adults is defined as maximal ventricular wall thickness ≥ 15 mm not solely explained by abnormal loading conditions such as hypertension and/or aortic stenosis [1]. Dyspnea, angina, dizziness, syncope, and palpitations are commonly encountered. The burden of symptoms varies substantially among patients. This heterogeneity is also expressed with regard to prognosis. While several HCM patients may experience a normal life expectancy, certain subgroups have an increased mortality [2,3]. The risk of embolic stroke, deterioration into end-stage heart failure, and sudden cardiac death (SCD) is well recognized. SCD is highly preventable by an implantable cardioverter defibrillator (ICD) [4]. Antitachycardia pacing and cardioversion may also constitute appropriate ICD therapy. However, inappropriate therapy does occur and complications requiring surgery are non-negligible. The justification for an ICD in HCM requires careful evaluation of the patient’s underlying risk factors for SCD [1].

Echocardiography is a cornerstone in the diagnosis and risk stratification of HCM. The 2011 American College of Cardiology (ACC) Foundation/American Heart Association (AHA) guideline recognizes severe left ventricular (LV) hypertrophy (≥ 30 mm) as a binary risk factor in addition to non-sustained ventricular tachycardia (NSVT), family history of SCD, unexplained syncope, and an abnormal blood pressure response to exercise [5]. In 2014, the European Society of Cardiology (ESC) launched a novel clinical risk prediction model for SCD in HCM based on a cohort study of 3,675 patients (HCM risk-SCD) [6]. This model included age, family history of SCD, NSVT, and unexplained syncope and also three echocardiography parameters: maximal left ventricular wall thickness (LVWT), left atrial diameter, and left-ventricular outflow tract (LVOT) gradient. Even though the current ESC guidelines have been validated, they have also been the subject of criticism [7-9]. There is still demand to improve both sensitivity and specificity in the discrimination of individuals at various risk. Notably, the more recent advances in echocardiography imaging are not part of the current algorithm. Therefore, we sought to elucidate non-established echocardiographic parameters in HCM patients with regard to outcome, especially SCD.

Objectives of the Study

The aim of this review was to summarize the recent echocardiographic advances in prognosis and risk stratification for SCD in patients with HCM.

Method

Literature search

The present systematic review was performed by searches in the database PubMed™. The database was searched by the search string "hypertrophic cardiomyopathy" and "echocardiography." Searches were limited to English language, human species, and time of publication (between January 2007 and February 2018). Studies evaluating the association between novel echocardiographic findings and outcome of patients with HCM were included. Studies based on children and adolescents were excluded. All reviews and case reports were excluded.

Selection of studies

The records identified by the search were independently screened by title or abstract, methodology, and exclusion and inclusion criteria. The full texts of the retrieved articles after the first screening were scrutinized to inspect whether data on the topic of interest were included. Any disagreement was resolved through discussion among the authors. The bibliographies of the selected studies were searched for sources of potentially relevant or supplemental information. The selection process and flow of papers through the search was summarized in a flow chart inspired by a PRISMA diagram (Figure 1).

**Report of outcomes**

The reported outcome measurements including comparisons and statistical hypothesis testing when appropriate: odds ratio (OR), hazard ratio (HR) with confidence interval (CI), and a two-sided p-value.

**Results and Discussion**

A total of 841 papers were originally retrieved by searching the databases, of which 726 papers were judged to be clearly irrelevant. The abstracts of the remaining 115 papers were retrieved and of these, 86 excluded, as they did not meet one or more of the inclusion criteria. The final extracted 29 papers are summarized below, with regard to the following echocardiographic subjects: Strain and mechanical dispersion, diastolic dysfunction, right ventricle and right atrium, and impaired coronary artery flow.

Speckle tracking strain and mechanical dispersion

Myocardial scarring is a substrate for electrical instability and subsequent ventricular tachycardia (VT) or ventricular fibrillation (VF) [10]. Fibrosis detected by the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) is a known risk factor for SCD in patients with HCM [11-13].

Recent studies have suggested that strain on echocardiography could be associated with fibrosis and could be an alternative to CMR. Myocardial fiber orientation results in four strain vectors: longitudinal, radial, circumferential, and rotational. Strain could be described as a measurement for myocardial deformation; lengthening and shortening (longitudinal strain) or myocardial thickening (radial, circumferential strain) [14]. Strain rate describes how fast the myocardium deforms (rate of deformation). Myocardial dispersion is defined as the standard deviation of time to peak negative strain in the LV segments and reflects myocardial dys-synchrony [15].

Strain can be assessed either by tissue Doppler imaging (TDI) or by speckle tracking. TDI is limited to movement relative to the sample volume, while speckle tracking is angle independent and permits assessment of strain in the axis of movement, rather than the axis of the ultrasound beam.

Strain correlates with fibrosis in myectomy specimens, but not with LGE on CMR

Almaas, et al. [16] studied 32 HCM patients with LVOT obstruction referred for myectomy. Echocardiography with strain analysis was performed prior to the myectomy for all and CMR with LGE was performed in 21 patients prior to myectomy. Preoperative longitudinal strain (LS) correlated with total (r = 0.50, p = 0.01) and interstitial fibrosis (r = 0.40, p = 0.03) in myectomy specimens, but neither with replacement fibrosis on myectomy specimens nor with LGE on CMR. Percentage LGE did not correlate with total, interstitial, or replacement fibrosis in myectomy specimens, indicating that strain correlates better than LGE to fibrosis in patients with HCM.

Multivariate analysis revealed that septal LS was an independent predictor of histological fibrosis ≥ 15%. In another analysis, presence of NSVT on Holter monitoring was studied with regard to strain. NSVT was associated with impaired septal LS (OR 1.52; 95% CI 1.52 to 2.21; p = 0.03), higher amount of total fibrosis (OR 1.04; 95% CI 1.00 to 1.08; p = 0.03), and interstitial fibrosis (OR 1.05; 95% CI 1.01 to 1.10; p = 0.03). No significant differences were demonstrated in the 13 patients with LGE present between patients with NSVT (n = 4) and without NSVT (n = 9) in the percentage of global or septal LGE (3.4% [1.7 to 7.6%] vs. 2.9% [0.8 to 7.7%]; p = 0.70 and 9.6% [5.2 to 10.3%] vs. 4.6% [1.5 to 13.0%]; p = 0.28, respectively).

Peak longitudinal strain correlates with LGE on CMR

Funabashi, et al. [17] found in 29 HCM patients, opposed to Almaas' findings, a significantly impaired peak LS in fibrotic lesions compared to non-fibrotic lesions detected with LGE on CMR (-8.9 ± 5.6% and -11.3 ± 5.9%, respectively, p = 0.001). There were no significant differences in regional peak radial strain (RS) between fibrotic and non-fibrotic lesions (-12.0 ± 10.1% and 12.2 ± 8.7%, respectively).

Peak longitudinal strain correlates with fibrosis detected on contrast-CT

Yajima, et al. [18] compared strain with fibrotic lesions detected by computed tomography (CT) in a case-control study with 10 HCM patients and 10 healthy controls. Fibrotic lesions in the LV were identified by CT as contrast defects in the early phase (25 seconds after contrast injection) and as abnormal enhancement in the late phase (6 minutes after contrast injection). In patients with HCM, the regional peak LS was significantly worse in fibrotic than non-fibrotic lesions in base-, mid-, and apical levels (p < 0.05). Absolute values of regional peak LS were significantly lower in both fibrotic and non-fibrotic lesions in HCM subjects compared to healthy controls (p < 0.01). Compared to controls, regional peak RS absolute values were significantly lower only at mid-level. Among HCM patients, no significant differences of peak RS were found in fibrotic compared to non-fibrotic lesions.
Strain and mechanical dispersion: a predictor of adverse outcome

Halrand, et al. [15] studied 150 HCM patients and 50 controls. Compared to controls, HCM patients had impaired global LS (-15.7 ± 3.6% vs. -21.1 ± 1.9%; p < 0.001) and more pronounced mechanical dispersion (64 ± 22 ms vs. 36 ± 13 ms; p < 0.001). Ventricular arrhythmias were defined as previously aborted cardiac arrest, documented sustained VT or VF, and NSVT during Holter or ICD monitoring. Patients with ventricular arrhythmias had worse global LS (-14.1 ± 3.6% vs. -16.3 ± 3.4%; p < 0.01), longer mechanical dispersion (79 ± 27 ms vs. 59 ± 16 ms; p < 0.001), and higher percentage of LGE on CMR (2% (0 to 23%; n = 19) vs. 0% (0 to 8%; n = 66); p < 0.001) compared to patients without ventricular arrhythmias. In multivariate analysis, (including the presence of LGE on CMR) mechanical dispersion was a strong independent predictor of ventricular arrhythmias (OR 1.57 for every 10 ms increase; 95% CI 1.09 to 2.28; p < 0.02) and was also correlated to LGE (r = 0.52, p < 0.001). Furthermore, mechanical dispersion significantly improved the risk stratification for ventricular arrhythmias when added to the conventional SCD risk stratification factor(s) ≥ 1 in a likelihood ratio test (chi-squared statistic; p = 0.01).

Jalanko, et al. [19] came to the same conclusion as Halrand, et al. [15] in a study comparing 31 HCM patients and 20 controls. Increased mechanical dispersion was significantly increased in HCM patients with NSVT compared to HCM patients without NSVT (93 ± 41 ms vs. 50 ± 18 ms; p = 0.012) and compared to controls (41 ± 16 ms; p < 0.001). Mechanical dispersion was the only variable independently associated with the presence of NSVT (HR 1.60; 95% CI 1.05 to 2.45; p = 0.013) at multivariate analysis.

Candan, et al. [20] studied 17 HCM patients with ICD therapy compared to 46 HCM patients without ICD therapy during a median follow-up period of 3 years (21.5 ± 6.9 months). Multivariate analysis determined longer mechanical dispersion (77.1 ± 21.8 vs. 62.4 ± 17.1; p = 0.007) and impaired global peak LS (-10.6 ± 2.8 vs. -12.7 ± 3.5; p = 0.03) to be independent predictors of appropriate ICD therapy.

Correia, et al. [21] found no difference in 32 HCM patients in the number of conventional SCD risk factors in those with NSVT (n = 9) compared to those without NSVT on 24-h Holter monitoring (n = 23). However, mid-septal LS (-7 ± 7 vs. -14 ± 6; p = 0.013), septal LS (-15 ± 7 vs. -24 ± 8; p = 0.006), apical lateral LS (-15 ± 7 vs. -24 ± 8; p = 0.006), and mean LS (-12 ± 4 vs. -17 ± 5; p = 0.013) were significantly worse in HCM patients with NSVT. Mid-septal LS > -10.5% had a sensitivity of 89% and a specificity of 74% (area under the curve 0.787; p < 0.013) for predicting NSVT independently of sex, age, or maximum wall thickness (p = 0.007). However, since it was not possible in most patients to acquire an appropriate image, peak systolic strain rate was not assessed, and the anterior and inferior wall LS was not evaluated.

Funabashi, et al. [22] retrospectively studied 44 HCM patients without coronary arterial stenosis on CT who underwent echocardiography within 12 months. Medical records were checked for occurrence of the composite end-point of cardiac death, heart failure, syncope, and appropriate ICD therapy. Median follow-up period was 18 months (572 ± 346 days). Global peak LS was significantly worse in HCM patients who reached the end-point than in those who did not (-8.2 ± 2.0% vs. -10.6 ± 2.5%; p < 0.001). The Cox proportional hazard model revealed that reduced global peak LS of at least -9.85% was a significant predictor of the composite end-point (HR 21.5; 95% CI 2.3 to 205.9, p = 0.008).

Ozawa, et al. [23] did a similar study with 41 HCM patients without obstructed coronary arteries on CT. Echocardiography was performed within 13 months of the cardiac CT. Mean follow-up period was 32.1 ± 23.2 months. Global LS was a significant predictor of the composite end-point of all-cause death, hospitalization due to heart failure, sustained VT, VF and appropriate ICD therapy (HR 1.89; 95% CI 1.11 to 3.21; p = 0.019 for univariate analysis and HR 2.14; 95% CI 1.2 to 3.9; p = 0.013 for multivariate analysis), but global circumferential strain was not (HR 1.07; 95% CI 0.98 to 1.17; p = 0.118).

Liu, et al. [24] examined 400 HCM patients and reported that worse global LS was independently associated with poor outcome (new-onset sustained VT/VF, heart failure, cardiac transplantation, and all-cause death) by univariate analysis. Patients with an impaired global

LS of > -10% had significantly higher event rates and four times the risk of events compared to global LS ≤-16% \((p = 0.006)\). However, 33 patients (8%) were initially excluded due to inadequate quality for strain analysis indicating that strain analysis is not always assessable.

Reant, \textit{et al.} [25] studied 115 HCM patients where the composite end-point was defined as death related to HCM (SCD, heart failure, or embolic stroke), sustained VT, appropriate ICD therapy or aborted SCD, and progression of symptoms to New York Heart Association (NYHA) functional class III or IV. Mean follow-up period was 19 ± 11 months. A Cox backward-entry selection model reported that impaired global LS of ≥ -15% at rest and LVOT gradient ≥ 50 mmHg at peak exercise were independently associated with an increased risk for the composite end-point in patients with HCM (HR 3.84; 95% CI 1.27 to 11.62; \(p = 0.017\) and HR 3.29; 95% CI 1.14 to 9.50; \(p = 0.028\), respectively).

Reant, \textit{et al.} [26] continued with a larger retrospective study with 472 HCM patients. Patients with atrial fibrillation were excluded. Median follow-up period was 4.3 years (interquartile range 0.1 to 7.8 years). Global LS was associated with the combined end-point of all-cause mortality, heart transplantation, aborted SCD, and appropriate ICD therapy after multivariate analysis, independently of age, LV end-systolic volume, and maximal provoked LVOT gradient. Thus, an increased absolute value of LS implies lower risk (HR 0.90; 95% CI 0.83 to 0.98; \(p = 0.018\)).

Hiemstra, \textit{et al.} [27] did a study of 427 HCM patients with a follow-up period of 6.7 years (interquartile range, 3.3 to 10.0), but included patients with atrial fibrillation. Global LS and left atrial volume index (LAVi) were independently associated with the end-point of all-cause mortality and appropriate ICD therapy on multivariable analysis (HR 1.10; 95% CI 1.03 to 1.19; \(p = 0.007\) and HR 4.27; 95% CI 2.35 to 7.74; \(p < 0.001\), respectively). The same cut-off value (-15%) for global LS, which was used in a study by Reant, \textit{et al.} [25] showed significant incremental value over clinical and standard echocardiographic parameters. The cumulative event-free survival at 6 years was 99% for global LS < -15% and LAVi < 34 mL/m\(^2\) versus 63% for patients with global LS ≥ -15% and LAVi ≥ 34 mL/m\(^2\) (log-rank, 49.3; \(p < 0.001\)).

Di Salvo, \textit{et al.} [28] studied 93 HCM patients and 30 patients with LV hypertrophy due to hypertension. In 24 HCM patients, NSVT was documented on 24-h Holter monitoring. Peak systolic basal and mid septal LS were worse in HCM patients with NSVT \((-10 ± 4 vs. -12 ± 4; \(p = 0.02\) and -12 ± 4 vs. -14 ± 3; \(p = 0.01\), respectively). However, LVOT-gradient, NYHA class, syncope, tissue synchronization imaging values, mean LS, medical therapy (antihypertensive medication), and LV mass were comparable between the groups. More than three LV segments with LS >-10% (sensitivity 81%; specificity 97.1%; area under the curve 0.944; \(p < 0.0001\)) were an independent predictor of NSVT. In total, 30 patients (24%) were excluded from the study because it was not possible to obtain all of the needed echocardiographic views.

Vergé, \textit{et al.} [29] studied 217 HCM patients with a recently developed speckle tracking method that enables layer-specific LS analysis (transmural, endocardial, and epicardial LS). Median follow-up period was 2.8 ± 1.5 years. Transmural global LS correlated well with the percentage of LGE on CMR \((r = - 0.32)\), and mean LS in the LV hypertrophic area correlated with maximal LVWT \((r = - 0.47)\). Univariate analysis revealed that mean transmural LS in the hypertrophic area was significantly predictive of SCD and appropriate ICD therapy \((10\) events, HR 0.83; 95% CI 0.72 to 0.95; \(p = 0.01\)). In total, 38 patients were excluded (18%) due to insufficient echocardiographic image quality.

**Summary**

The search generated a total of 15 articles that studied speckle tracking strain in patients with HCM. Ventricular arrythmias (tachycardia or fibrillation) appear to be the main cause of SCD in HCM patients. Myocardial fibrosis acts as an electrophysiological substrate for ventricular arrhythmias. The extent of myocardial fibrosis can be detected by LGE on CMR and is thought to be a novel risk marker for HCM-patients. In this review two studies found that peak LS and transmural global LS correlated well with the percentage of LGE on CMR, indicating that strain could be a useful method for detecting myocardial fibrosis.
One study found that regional peak LS correlated with fibrosis detected by contrast enhanced CT. However, peak RS did not correlate with either LGE on CMR or fibrosis on contrast-enhanced CT.

One study compared septal LS on echocardiography with LGE on CMR, NSVT on 24-h Holter monitoring and fibrosis in myectomy specimens. Septal LS correlated well with both total and interstitial fibrosis in myectomy specimens and with the presence of NSVT on 24-h Holter. However, in contrast to the previous mentioned studies, septal LS did not correlate with LGE on CMR. Interestingly, LGE on CMR did not correlate with fibrosis in myectomy specimens or with NSVT on 24-hour Holter. This question whether LGE on CMR or strain by echocardiography is the most reliable method to detect myocardial fibrosis.

The relationship between strain and outcome was studied in 12 articles; 10 articles found global LS to be an independent predictor of outcome. Two studies found a correlation between NSVT and regional LS (mid-septal, apical-septal, apical-lateral and basal-septal). Two studies found longer mechanical dispersion to be independently correlated with ventricular arrhythmias and one study found longer mechanical dispersion to be an independent predictor of appropriate ICD-therapy.

Even though myocardial fibrosis detected by LGE on CMR is thought to be a novel risk marker for HCM-patients, the routine use of CMR in clinical practice is limited because it is expensive and not widely available. Strain by echocardiography seems to correlate well with the extent of myocardial fibrosis and, more importantly, seems to provide valuable prognostic information.

However, strain evaluation demands good quality imaging of the LV in all three apical views and several studies excluded patients due to inadequate echocardiographic image quality. Thus, predicting risk for patients according to strain is not possible with impaired image quality.

**Diastolic dysfunction**

Diastolic dysfunction of the LV leads to impaired relaxation and altered diastolic pressure. The mitral inflow reflects the pressure difference between the left atrium and the LV and can be visualized by Doppler on echocardiography (mitral inflow signal). The early filling phase (E-wave) of the LV is passive, caused by the pressure difference that is created when the relaxation causes the pressure in the LV to drop below that of the left atrium. In a healthy heart, most of the blood fills the LV during the early passive phase. The time it takes for the early filling phase to start after the end of systole is referred to as the isovolumetric relaxation time. The late filling phase (A wave) is caused by the contraction of the atrium. The impaired relaxation of the LV affects the pressure difference and the relationship between the early and late filling phases (Mitral E/A-ratio). Higher LV pressure prolongs the isovolumetric relaxation time and delays ventricular filling by prolonging the time it takes for atrial pressure to exceed ventricular pressure. Higher LV pressure also alters how fast the early filling velocity declines (E-wave deceleration time).

The movement of the mitral valve annulus reflects both the systolic (movement towards the apex) and the diastolic functions (movement towards the atria). The velocity of the mitral valve annulus motion can be measured with pulsed wave TDI at both the septal and the lateral sides of the mitral valve in a four-chamber view on echocardiography. The maximum tissue velocity during the early filling phase is visualized by a wave called e-prime (e') and the late filling phase by a wave called a-prime (a'). The systolic maximum velocity of the mitral valve annulus motion is referred to as s-prime (s').

Mitral valve motion decreases when relaxation is impaired, thus, diastolic dysfunction will present a low e'. On the other hand, impaired relaxation causes increased filling pressures and a higher maximum mitral inflow velocity (E). In other words, the E/e' ratio will increase with decreased diastolic function.
Lower systolic and diastolic tissue velocities are associated with LGE on CMR

Moon, et al. [30] showed that LGE on CMR was associated with diastolic dysfunction parameters on echocardiography in 46 HCM patients. Changes in $e'$ and $s'$ during exercise were significantly lower in the group with LGE $\geq$ 6% (n = 23), compared to the group with LGE < 6% (n = 23). ($\Delta e'$: $2.8 \pm 1.8$ cm/s vs. $1.5 \pm 1.0$ cm/s, $p = 0.007$; $\Delta s'$: $2.2 \pm 1.2$ cm/s vs. $0.9 \pm 0.8$ cm/s, $p < 0.0001$).

Ghio, et al. [31] compared the diastolic and systolic velocities in 58 HCM patients and 15 controls. Systolic and diastolic velocities in controls were higher than in HCM patients ($p < 0.001$). CMR was also performed for 36 HCM patients. Peak systolic velocity and peak systolic strain on TDI were significantly lower in the segments with than in those without delayed enhancement on CMR ($4.3 \pm 2.0$ m/s vs. $3.7 \pm 1.7$ m/s; $p = 0.039$ and $-15.85 \pm 9.84\%$ vs. $-12.89 \pm 8.95\%$; $p = 0.007$, respectively). In contrast, diastolic velocities were not associated with LGE on CMR.

Tissue Doppler imaging as a prognostic marker for mortality

Biagini, et al. [32] studied 239 HCM patients with a median follow-up of 9.7 years (5th and 95th interquartile range 0.7 and 19.1, respectively). In a multivariate analysis, restrictive filling pattern defined as E/A ratio $\geq$ 2 and deceleration time $\leq$ 130 ms, was an independent marker of increased risk for cardiovascular death (HR for SCD 3.51; 95% CI 1.37 to 8.95; $p = 0.009$, HR for HCM-related death or heart transplantation 3.54; 95% CI 1.91 to 6.57; $p < 0.001$) compared to patients without a restrictive filling pattern.

Kitaoka, et al. [33] studied 130 HCM patients during a follow-up period of 3.7 $\pm$ 1.7 years. For 20 patients, the combined end-point of SCD, appropriate ICD therapy, heart failure, stroke or progression to NYHA class III, was reached. Multivariate analysis showed that septal E/e' ratio was an independent predictor of outcome (OR 1.43; 95% CI -0.67 to -0.12; $p = 0.008$).

Kitaoka, et al. [34] studied 85 HCM patients in a similar study with a follow-up period of 4.5 $\pm$ 1.7 years. Multivariate analysis revealed that the deceleration time of E (OR 0.97; 95% CI 0.099 to 0.053; $p = 0.008$) and the septal E/e' ratio (OR 1.43; 95% CI -0.67 to -0.12; $p = 0.008$) were independent predictors of cardiovascular events. For 11 patients the combined end-points consisting of HCM-related death, hospital admission for heart failure or stroke, new episode of atrial fibrillation, or progression to NYHA class III, was reached.

Moon, et al. [35] studied 454 patients with apical HCM and showed that reduced $s'$ (HR 0.83; 95% CI 0.72 to 0.96; $p = 0.014$) and greater E/e' ratio (HR 1.04; 95% CI 1.00 to 1.09; $p = 0.030$) on multivariate analysis were independent predictors of the combined end-point consisting of unplanned heart failure hospitalization, stroke, or cardiovascular mortality.

Pagourelias, et al. [36] studied the prognostic value of right ventricular (RV) filling pressures obtained by tissue Doppler imaging at the lateral tricuspid annulus in 386 HCM patients. Primary end-points were mortality due to heart failure (n = 13) and total cardiovascular mortality (heart failure and SCD, n = 35). Patients presenting with an increased RV E/e' ratio had a 1.6 times higher risk for heart failure mortality (HR 1.6; 95% CI 1.1 to 2.4; $p = 0.03$) and proved to be an independent predictor of heart failure mortality by multivariate analysis. Tricuspid E wave deceleration time was an independent predictor of the study’s composite end-point with a 1.1 higher risk for cardiovascular death (HR 1.1; 95% CI 1.0 to 1.2; $p = 0.03$).

Kalra, et al. [37] studied 274 non-obstructive HCM patients with a follow-up period of 4.0 $\pm$ 2.3 years. The study found that diastolic dysfunction evidenced by TDI-reduced lateral e’ mitral annular tissue velocity was an independent predictor for progression of heart failure (HR 0.77; 95% CI 0.65 to 0.91; $p = 0.003$) on multivariate regression analysis, but not for SCD or appropriate ICD interventions.

Summary

A total of eight studies focused on diastolic dysfunction in HCM patients. Two studies found that diastolic dysfunction measured by reduced velocities on TDI was associated with LGE on CMR. LGE on CMR in patients with HCM is known to be associated with a poor

prognosis. This leads to the hypothesis that the decreased myocardial function detected by TDI might be a useful prognostic factor in patients with HCM.

Increased filling pressures and higher maximum mitral inflow velocity measured with tissue Doppler imaging (E/e’ ratio) in patients with preserved ejection fraction is a marker for diastolic dysfunction and increased filling pressures. Four studies showed that an increased E/e’ ratio in patients with HCM was a significant predictor of cardiovascular death. One study found that increased right-ventricular filling pressure was an independent predictor for cardiovascular death. In contrast, one study showed an association between diastolic dysfunction and heart failure progression, but not with SCD or appropriate ICD therapy.

Echocardiography is a simple, repeatable, and inexpensive tool and in contrast to speckle tracking strain, tissue Doppler measurements do not require good quality images of the apical parts of the ventricle to be useful. Thus, tissue Doppler imaging seems more practical and assessable, providing important diagnostic and prognostic information. However, new reference values need to be established in order to incorporate tissue Doppler parameters in risk stratification analysis.

**Right ventricle and right atrium**

HCM mainly affects the LV and left atrium. However, recent studies have suggested that HCM can also be associated with RV dysfunction and right-atrial enlargement.

**Right ventricle**

Guo, et al. [38] studied a cohort of 2,413 HCM patients. The prevalence and clinical correlates of extreme RV hypertrophy (max RV wall thickness ≥ 10 mm) and extreme LV hypertrophy (max LVWT ≥ 30 mm) was 1.3% and 8.0%, respectively. The 31 patients with extreme RV hypertrophy tended to be younger (31.4 ± 16.1 years vs. 38.9 ± 15.0 years; p < 0.001) and female (51.6% vs. 24.2%; p < 0.002). Multivariate analysis revealed three independent predictors for cardiovascular mortality: extreme RV hypertrophy, LV end-diastolic dimension ≥ 50 mm (HR 2.9; 95% CI 1.61 to 7.45; p = 0.023), and age ≤ 18 years at baseline (HR 4.3; 95% CI 1.72 to 10.85; p = 0.002). Cardiovascular-related 10-year mortality and morbidity rates were significantly higher for patients with extreme RV hypertrophy (HR 4.2; 95% CI 1.48 to 11.84; p = 0.007, and HR 1.9; 95% CI 1.14 to 3.03; p = 0.014, respectively) compared to extreme LV hypertrophy.

Finocchiaro, et al. [39] studied the prevalence and clinical characterization of RV dysfunction in 324 HCM patients compared to 99 age- and gender-matched healthy controls. The mean follow-up period was 3.7 ± 2.3 years, during which 17 patients died and four underwent cardiac transplantation. At univariate analysis, LV ejection fraction < 50% and tricuspid annular plane systolic excursion (TAPSE) < 16 mm were independently associated with outcome (HR 3.98; 95% CI 1.2 to 13.0, p = 0.02; and HR 3.66; 95% CI 1.38 to 9.69, p = 0.009, respectively). LV dysfunction and higher pulmonary pressures were independent correlates of RV dysfunction. RV systolic pressure was available in a subgroup of patients (n = 201). In this subgroup, TAPSE < 16 mm and RV systolic pressure >35 mm Hg were reported as independent correlates of outcome (HR 5.6; 95% CI 2.0 to 15.6, p = 0.001 and HR 3.6; 95% CI 1.3 to 9.9, p = 0.016, respectively).

**Right Atrium**

Limongelli, et al. [40] studied 160 HCM patients of which 22 patients (14%) showed a right-atrial enlargement. The right-atrial enlargement was associated with systolic and diastolic LV dysfunction and increased pulmonary pressure. Multivariate analysis identified right-atrial enlargement as an independent predictor of the combined end-point of cardiac death, cardiac transplant, resuscitated cardiac arrest, or appropriate ICD discharge (HR = 2.6; 95% CI 1.5 to 4.6; p = 0.001).

**Summary**

Three studies were found in this review that focused on the right ventricle. One study found that increased RV E/e’ ratio was correlated with heart failure mortality and shortened tricuspid E wave deceleration time was associated with SCD. One study found that extreme

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RV hypertrophy was an independent predictor of cardiovascular mortality. RV dysfunction was an independent predictor of death or heart transplantation in one study. In another study right-atrial enlargement was an independent predictor of poor outcome. Thus, these studies underline the importance of evaluating the right-sided chambers of the heart rather than focusing only on the LV and left atrium.

Impaired Coronary Artery flow

Ferreiro, et al. [41] reported impaired coronary flow in the left anterior descending artery, right coronary artery and circumflex coronary artery in 25 HCM patients compared to 10 healthy age- and gender-matched controls. The coronary flow was assessed with transthoracic color Doppler echocardiography. The echocardiographic findings indicating impaired coronary flow were: increased peak diastolic coronary flow velocity, steeper coronary flow diastolic deceleration slope, and reverse coronary systolic flow. (All arteries in the control group presented a positive systolic spectral signal. In the HCM-group 28.8% [n = 19] presented a positive flow [p = 0.0001], 15.1% [n = 10] had no systolic flow [p < 0.05], and 56.1% [n = 37] had reverse flow [p < 0.0001]). When analyzing all three coronary arteries together, the HCM patients showed impaired coronary flow compared to controls (peak diastolic flow velocity = 30 cm/s [25 to 41] vs. 25.5 cm/s [21 to 33]; p < 0.02, and diastolic deceleration slope = 0.3 m/s² [0.2 to 0.5] vs. 0.2 m/s² [0.15 to 0.25]; p < 0.0005). The findings were independent of the type of hypertrophy and magnitude of the intraventricular pressure gradient in patients with obstructive HCM.

Kim, et al. [42] did a case-control study on 48 HCM patients with normal coronary arteries on angiography and divided them into two groups depending on the flow patterns in the intra-myo-cardial coronary artery derived from the left anterior descending artery. The group with a steep deceleration slope with diastolic deceleration time <300 ms (average diastolic deceleration time 166 ± 67 ms resulting in a no-reflow like pattern, n = 21) had a higher incidence of cardiovascular symptoms (chest pain or syncope, 67% vs. 26%, p < 0.01) and more frequent exercise-induced ischemia detected on thallium-201 scintigraphy (67% vs. 0%, p < 0.01), compared to the group with a slow deceleration slope (average diastolic deceleration time 989 ± 338 ms). There were no significant differences in the clinical characteristics and flow velocity profiles in the left anterior descending artery between the two groups.

Cortigiani, et al. [43] studied 68 HCM patients and 74 age- and sex-matched controls and found that coronary flow reserve in the left anterior descending artery (assessed by Doppler on echocardiography) was significantly decreased in the HCM-group compared to the controls (2.12 ± 0.39 vs. 2.78 ± 0.58, p < 0.0001). CFR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A coronary flow reserve value ≤ 2 was considered abnormal. During a mean follow-up of 22 ± 13 months, there were 22 events (death, nonfatal myocardial infarction, unstable angina, progression of heart failure, syncope, atrial fibrillation, and intracardiac defibrillation) out of 31 patients with abnormal coronary flow reserve and 7 events out of 37 patients with normal coronary flow reserve (71% vs. 19%, p = 0.0001). Multivariate analysis revealed abnormal coronary flow reserve to be an independent predictor of outcome (HR 3.85; 95% CI 1.22 to 12.18; p = 0.02).

Summary

Impaired coronary flow seems to be a promising novel marker for detecting microvascular dysfunction and ischemia according to the three case-control studies found in this review. Impaired coronary flow was more common in HCM patients compared to controls. Two of the three studies also focused on the relation between impaired coronary flow and outcome. Both found a correlation. Abnormal coronary flow reserve in the left anterior descending artery was revealed to be an independent predictor of poor outcome in multivariate analysis.

In the second study a no-reflow-like pattern in the intramyocardial coronary artery was related to myocardial ischemia detected on myocardial scintigraphy in HCM patients. Interestingly, all patients had normal coronary arteries verified by angiography. This suggests that microvascular dysfunction is the main cause of ischemia in these patients and could be a novel risk marker for predicting SCD. One might argue that microvascular ischemia not only explains deteriorating heart failure in HCM patients, but could also be the cause of myocardial scarring as well as fibrosis leading to ventricular arrhythmias.

Limitations

HCM is characterized by its heterogeneity and includes diverse phenotypic expressions. Typically, studies only account for predictors at baseline and the longitudinal modifiers are unknown.

Several of the studies are subject to statistical error due to small sample sizes. Furthermore, follow-up durations varied widely among the studies and most HCM patients have an extended life-expectancy.

The end-points differ among studies and often include composite end-points. Thus, the associations with SCD are suggested and not necessarily proven. Often appropriate ICD therapy is used as a surrogate for SCD, however not all aborted arrhythmias would have led to SCD, as many ventricular arrhythmias self-terminate.

Because of the lack of uniform predictors and outcome measurements, a systematic meta-analysis seems impossible. Future large studies with prospective outcome measurements are warranted.

Conclusion

According to recent studies, myocardial dysfunction assessed with echocardiographic speckle tracking strain analysis or with TDI is correlated with fibrosis and LGE on CMR. Impaired LS and longer mechanical dispersion, as well as increased E'/e'-ratio measured with TDI is associated with poor outcome and these could be promising new risk markers for predicting SCD. Furthermore, HCM patients seem

Citation: Peter Magnusson., et al. "Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review". EC Cardiology 5.10 (2018): 675-697.
to have impaired coronary flow assessed with transthoracic color Doppler echocardiography, compared to controls. Impaired coronary flow was associated with poor prognosis and ischemia, even when the coronary arteries proved to be normal on angiography. This indicates some degree of microvascular dysfunction in HCM patients and could be a useful novel echocardiographic predictor of outcome. However, stronger evidence from large studies and new reference values need to be established.

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Declaration of Conflicting Interests
Peter Magnusson has received lecture fees from Abbott, Boehringer Ingelheim, Novo Nordisk, and Pfizer.

<table>
<thead>
<tr>
<th>First author</th>
<th>Publ Year</th>
<th>Title</th>
<th>Setting</th>
<th>Study type</th>
<th>Study population</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almaas [16]</td>
<td>2014</td>
<td>Noninvasive assessment of myocardial fibrosis in patients with obstructive hypertrophic cardiomyopathy</td>
<td>Norway</td>
<td>Prospective</td>
<td>32 HCM (21 MR)</td>
<td>Preoperative LS correlated with NSVT on Holter monitoring, and with total (r = 0.50; p = 0.01) and interstitial fibrosis (r = 0.40; p = 0.03) in myectomy specimens, but not with replacement fibrosis or LGE on CMR. Percentage LGE did not correlate with fibrosis in myectomy specimens.</td>
</tr>
<tr>
<td>Biagini [32]</td>
<td>2009</td>
<td>Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy</td>
<td>Italy</td>
<td>Case control</td>
<td>239 HCM</td>
<td>Restrictive filling pattern was a strong and independent marker of increased risk for SCD and cardiovascular mortality. Median follow-up 9.7 years. (HR for SCD 3.51; 95% CI 1.37 to 8.95; p = 0.009)</td>
</tr>
<tr>
<td>Candan [20]</td>
<td>2017</td>
<td>Mechanical dispersion and global longitudinal strain by speckle tracking echocardiography: Predictors of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy</td>
<td>Turkey</td>
<td>Case control</td>
<td>63 HCM (17 with ICD therapy)</td>
<td>Median follow-up 3 years. Mechanical dispersion (77.1 ± 21.8 ms vs. 62.4 ± 17.1 ms; p = 0.007) and lower global peak LS (10.6 ± 2.8 %vs. -12.7 ± 3.5%; p = 0.03) were independent predictors of appropriate ICD therapy.</td>
</tr>
<tr>
<td>Correia [21]</td>
<td>2011</td>
<td>Longitudinal left ventricular strain in HCM: correlation with nonsustained ventricular tachycardia</td>
<td>Portugal</td>
<td>Case control</td>
<td>32 HCM: with NSVT n = 9, without NSVT n = 23</td>
<td>There were no differences in gender, age, heart failure symptoms, and number of SCD risk factors, beta blockade, or BNP between patients with or without NSVT. Lower end-systolic peak LS obtained by 2D speckle tracking was a predictor of NSVT in HCM patients.</td>
</tr>
</tbody>
</table>
### Table of Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Description</th>
<th>Country</th>
<th>Study Design</th>
<th>Patients</th>
<th>Methods</th>
</tr>
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<tr>
<td>Cortigiani</td>
<td>2008</td>
<td>Prognostic implications of coronary flow reserve on left anterior descending coronary artery in hypertrophic cardiomyopathy</td>
<td>Italy</td>
<td>Case control</td>
<td>68 HCM, 74 controls</td>
<td>Multivariate analysis revealed abnormal CFR in the left anterior descending artery to be an independent predictor of outcome in patients with HCM (HR 3.85; 95% CI 1.22 to 12.18; ( p = 0.02 )).</td>
</tr>
<tr>
<td>Di Salvo</td>
<td>2010</td>
<td>Non sustained ventricular tachycardia in hypertrophic cardiomyopathy and new ultrasonic derived parameters</td>
<td>Italy</td>
<td>Case control</td>
<td>93 HCM, 30 controls (with hypertension)</td>
<td>No significant associations between NSVT on Holter monitoring and LVOT-gradient, NYHA class, syncpe, tissue synchronization imaging values, average LS, and medical therapy. In multivariate analysis, the presence of &gt;3 LV segments with LS &gt;-10 ( (p &lt; 0.0001) ) was an independent predictor of NSVT.</td>
</tr>
<tr>
<td>Ferreiro</td>
<td>2013</td>
<td>Assessment of coronary flow with transthoracic color Doppler echocardiography in patients with hypertrophic cardiomyopathy</td>
<td>Argentina</td>
<td>Case control</td>
<td>25 HCM, 10 controls</td>
<td>Impaired coronary flow in HCM patients compared to healthy controls. (Increased peak diastolic coronary flow velocity [30 cm/s (25-41)] vs. 25.5 cm/s [21-33], ( p &lt; 0.02 )), steeper coronary flow diastolic deceleration slope (0.3 m/s² [0.2-0.5] vs. 0.2 m/s² [0.15-0.25], ( p &lt; 0.0005 )) and reverse coronary systolic flow (all arteries in the control group presented a positive systolic spectral signal. In the HCM-group 28.8% (( n = 19 )) presented a positive flow (( p &lt; 0.0001 )), 15.1% (( n = 10 )) had no systolic flow (( p &lt; 0.05 )), and 56.1% (( n = 37 )) had reverse flow (( p &lt; 0.0001 )).</td>
</tr>
</tbody>
</table>

**Citation:** Peter Magnusson, *et al.* "Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review*. *EC Cardiology* 5.10 (2018): 675-697.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Year</th>
<th>Study Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Number of Subjects</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Finocchiaro [39]</td>
<td>2014</td>
<td>Prevalence and clinical correlates of right ventricular dysfunction in patients with hypertrophic cardiomyopathy</td>
<td>Italy</td>
<td>Case control</td>
<td>324 HCM, 99 controls</td>
<td>LV ejection fraction &lt;50% (HR 3.98; 95% CI 1.2 to 13.0, ( p = 0.02 )) and TAPSE &lt;16 mm (HR 3.66; 95% CI 1.38 to 9.69, ( p = 0.009 )) were independent correlates of death or heart transplantation.</td>
</tr>
<tr>
<td>Funabashi [17]</td>
<td>2013</td>
<td>Regional Peak Longitudinal-Strain by 2D Speckle-Tracking TTE Provides Useful Information to Distinguish Fibrotic from Non-Fibrotic Lesions in LV Myocardium on Cardiac MR in Hypertrophic Cardiomyopathy</td>
<td>Japan</td>
<td>Prospective</td>
<td>29 HCM</td>
<td>Decreased peak LS was significantly lower in fibrotic lesions compared to non-fibrotic lesions detected with LGE on CMR (-8.9 ± 5.6% vs. -11.3 ± 5.9%, respectively, ( p = 0.001 )).</td>
</tr>
<tr>
<td>Funabashi [22]</td>
<td>2013</td>
<td>Risk stratification using myocardial peak longitudinal-strain on speckle-tracking transthoracic-echocardiogram to predict major adverse cardiac events in non-ischemic hypertrophic cardiomyopathy subjects confirmed by MDCT</td>
<td>Japan</td>
<td>Retrospective</td>
<td>44 HCM</td>
<td>Composite outcome consisted of cardiac death, heart failure, syncope, sustained VT, VF, and appropriate ICD therapy. Median follow-up period was 18 months. Global peak LS was significantly lower in HCM patients that reached the end-point, than in those that did not (-8.2 ± 2.0% vs. -10.6 ± 2.5%; ( p &lt; 0.001 )).</td>
</tr>
<tr>
<td>Ghio [31]</td>
<td>2009</td>
<td>Regional abnormalities of myocardial deformation in patients with hypertrophic cardiomyopathy: correlations with delayed enhancement in cardiac magnetic resonance</td>
<td>Italy</td>
<td>Case control</td>
<td>58 HCM, 15 controls</td>
<td>Delayed CMR enhancement (LGE) was associated with lower peak systolic strain (( p = 0.007 )).</td>
</tr>
</tbody>
</table>

Guo [38] 2016 The Prevalence and Long-Term Outcomes of Extreme Right versus Extreme Left Ventricular Hypertrophic Cardiomyopathy China Retrospective 31 RV 194 LV The prevalence of extreme RV hypertrophy and extreme LV hypertrophy was 1.3% and 8.0%, respectively. 10-year cardiovascular-related mortality and morbidity were significantly greater in the extreme RVH group (p < 0.05). Multivariate analysis demonstrated 3 independent predictors for cardiovascular mortality: extreme RVH, left ventricular end-diastolic dimension ≥ 50 mm, and age ≤ 18 years at baseline.

Haland [15] 2016 Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. Norway Case control 150 HCM 50 controls Patients with ventricular arrhythmias had lower global LS (-16.3 ± 3.4% vs. -14.1 ± 3.6%; p < 0.01), greater mechanical dispersion (59 ± 16 ms vs. 79 ± 27 ms; p < 0.001) and higher percentage of LGE on CMR (0% [0 – 8%, n = 66] vs. 2% [0 – 23%, n = 19]; p < 0.001) compared to patients without ventricular arrhythmias.

Hiemstra [27] 2017 Global Longitudinal Strain and Left Atrial Volume Index Provide Incremental Prognostic Value in Patients With Hypertrophic Cardiomyopathy The Netherlands Prospective 427 HCM Follow-up period of 6.7 years. Global LS was independently associated with the end point of all-cause mortality and appropriate ICD therapy on multivariable Cox regression analysis (HR 1.10; 95% CI 1.03-1.19; p = 0.007).

<table>
<thead>
<tr>
<th>Citation</th>
<th>Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Cohort Details</th>
<th>Findings</th>
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<tr>
<td>Jalanko [19]</td>
<td>2016</td>
<td>Case control</td>
<td>Finland</td>
<td>31 HCM, 20 controls</td>
<td>Increased mechanical dispersion was associated with NSVT in HCM patients on 24-h Holter monitoring (HR: 1.60; 95% CI 1.05 to 2.45; p = 0.030)</td>
</tr>
<tr>
<td>Kalra [37]</td>
<td>2016</td>
<td>Prospective</td>
<td>USA</td>
<td>274 HCM, 27 controls</td>
<td>In HCM patients without LVOT obstruction at rest, diastolic dysfunction evidenced by DTI-reduced lateral e', was associated with adverse long-term HF outcome (HR 0.77; 95% CI 0.65 to 0.91; p = 0.003) but was unrelated to SCD.</td>
</tr>
<tr>
<td>Kim [42]</td>
<td>2008</td>
<td>Case control</td>
<td>Japan</td>
<td>27 HCM vs. 21 HCM with no reflow</td>
<td>Group B (with no reflow-like pattern) had a higher incidence of cardiovascular symptoms (chest pain or syncope) 67% vs. 26%, p &lt; 0.01). Exercise-induced ischemia detected by thallium-201 scintigraphy was significantly more frequent in group B than in group A (67% vs. 0%, p &lt; 0.01).</td>
</tr>
<tr>
<td>Kitaoka [34]</td>
<td>2013</td>
<td>Prospective</td>
<td>Japan</td>
<td>85 HCM</td>
<td>Follow-up period of 4.5 ± 1.7 years. Multivariate analysis revealed the deceleration time of E (OR 0.97; 95% CI 0.009 to 0.053; p = 0.008) and the septal E/e' ratio (OR 1.43; 95% CI -0.67 to -0.12; p = 0.008) were independent predictors of cardiovascular events.</td>
</tr>
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</table>
**Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Method</th>
<th>Country</th>
<th>Design</th>
<th>Number of Patients</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Kitaoka [33]</td>
<td>2011</td>
<td>Tissue doppler imaging and plasma BNP levels to assess the prognosis in patients with hypertrophic cardiomyopathy</td>
<td>Japan</td>
<td>Retrospective</td>
<td>130 HCM</td>
<td>Follow-up period of 3.7 ± 1.7 years. A high septal E/e’ ratio, in addition to a history of syncope and documentation of atrial fibrillation, were a significant predictor of the combined endpoints consisting of SCD, appropriate ICD therapy, heart failure, stroke or progression to NYHA class III (HR 6.2, p = 0.03).</td>
</tr>
<tr>
<td>Limongelli [40]</td>
<td>2017</td>
<td>Clinical and genetic characterization of patients with hypertrophic cardiomyopathy and right atrial enlargement</td>
<td>Italy</td>
<td>Case control</td>
<td>160 HCM (22 RAE)</td>
<td>Multivariable analysis identified RA enlargement as an independent predictor of the combined end-point of cardiac death, cardiac transplant, resuscitated cardiac arrest, or appropriate ICD discharge (HR = 2.6; 95% CI 1.5 to 4.6, p = 0.001).</td>
</tr>
<tr>
<td>Liu [24]</td>
<td>2017</td>
<td>Role of Global Longitudinal Strain in Predicting Outcomes in Hypertrophic Cardiomyopathy</td>
<td>USA</td>
<td>Prospective</td>
<td>400 HCM</td>
<td>Patients with global LS &gt; -10% had significantly higher event rates (new onset sustained VT/VF, heart failure, cardiac transplantation, and all-cause death) and four times the risk of events compared with global LS ≤ -16% (p = 0.006).</td>
</tr>
<tr>
<td>Moon [35]</td>
<td>2011</td>
<td>Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy</td>
<td>Republic of Korea</td>
<td>Prospective</td>
<td>454 ApHCM</td>
<td>S’(HR 0.83; 95% CI 0.72 to 0.96; p = 0.014) and E/e’ ratio (HR 1.04; 95% CI 1.00 to 1.09; p = 0.030) on multivariate analysis were independent predictors of the cumulative end-point consisting of unplanned heart failure hospitalization, stroke, or cardiovascular mortality.</td>
</tr>
</tbody>
</table>
### Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Study Design</th>
<th>Country</th>
<th>Cases</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Moon [30]</td>
<td>2013</td>
<td>Prospective</td>
<td>Republic of Korea</td>
<td>46 HCM</td>
<td>Changes in $e'$ and $s'$ during exercise were significantly lower in the group with LGE ≥ 6% (n = 23) compared to the group with LGE &lt; 6% (n = 23). ($\Delta e'$: 2.8 ± 1.8 cm/s vs. 1.5 ± 1.0 cm/s, $p = 0.007$; $\Delta s'$: 2.2 ± 1.2 cm/s vs. 0.9 ± 0.8 cm/s, $p &lt; 0.0001$).</td>
</tr>
<tr>
<td>Ozawa [23]</td>
<td>2017</td>
<td>Retrospective</td>
<td>Japan</td>
<td>41 HCM</td>
<td>Mean follow-up period was 32.1 ± 23.2 months. Global LS was a significant predictor of the composite end-point of all-cause death, hospitalization due to heart failure, sustained VT, VF, and appropriate ICD therapy (HR 2.14; 95% CI 1.2 to 3.9; $p = 0.013$) by multivariable analysis.</td>
</tr>
<tr>
<td>Pagourelis [36]</td>
<td>2011</td>
<td>Prospective</td>
<td>Greece</td>
<td>386 HCM</td>
<td>Patients presenting with an increased RV E/E(r) ratio had a 1.6 times greater risk for HF mortality (HR 1.6; 95% CI 1.1 to 2.4; $p = 0.03$) while patients with shortened tricuspid E wave deceleration time had a 1.1 greater risk for SCD (HR 1.1; 95% CI 1.01 to 1.2; $p = 0.03$).</td>
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Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study Year</th>
<th>Study Details</th>
<th>Country</th>
<th>Study Type</th>
<th>Study Population</th>
<th>Follow-up Period</th>
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<tr>
<td>Reant [25]</td>
<td>2015</td>
<td>Comparison of resting and exercise echocardiographic parameters as indicators of outcomes in hypertrophic cardiomyopathy</td>
<td>France</td>
<td>Prospective</td>
<td>115 HCM</td>
<td>Mean follow-up period was 19 ± 11 months. The composite outcome consisted of HCM-related death, sustained VT, appropriate ICD therapy or aborted SCD, and progression of symptoms to NYHA functional class III or IV. A Cox backward-entry selection model reported that global LS ≥-15% at rest and LVOT gradient ≥ 50 mmHg at peak exercise, were independently associated with an increased risk for the composite end-point in patients with HCM (HR, 3.84; 95% CI 1.27 to 11.62; (p = 0.017) and HR 3.29; 95% CI 1.14 to 9.50; (p = 0.028), respectively).</td>
</tr>
<tr>
<td>Reant [26]</td>
<td>2016</td>
<td>Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy</td>
<td>France</td>
<td>Retrospective</td>
<td>472 HCM</td>
<td>Median follow-up period was 4.3 years. Reduced global LS was an independent risk factor for the combined end point of all-cause mortality, heart transplantation, aborted SCD, and appropriate ICD therapy, after multivariate Fine-Gray proportional hazard analyses (HR 0.90; 95% CI 0.83-0.98; (p = 0.018)) independently of age, LV end-systolic volume, and maximal provoked LVOT gradient.</td>
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Table 1: Articles included in the review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Study Group</th>
<th>Median follow-up period</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vergé [29]</td>
<td>2018</td>
<td>Prospective</td>
<td>France</td>
<td>179 HCM</td>
<td>2.8 ± 1.5 years</td>
<td>Characterization of hypertrophic cardiomyopathy according to global, regional, and multi-layer longitudinal strain analysis, and prediction of sudden cardiac death. Transmural global LS correlated with the percentage of LGE on CMR ($r = -0.32$), and mean LS in the LV hypertrophic area correlated with maximal LVWT ($r = -0.47$). Univariate analysis revealed that mean transmural LS in the hypertrophic area was significantly predictive of SCD and appropriate ICD therapy (10 events, HR = 0.83; 95% CI 0.72 to 0.95; $p = 0.01$).</td>
</tr>
<tr>
<td>Yajima [18]</td>
<td>2012</td>
<td>Case control</td>
<td>Japan</td>
<td>10 HCM</td>
<td>10 controls</td>
<td>In patients with HCM, the regional peak LS was significantly impaired in fibrotic versus non-fibrotic lesions detected on CT ($p &lt; 0.05$). Absolute values of regional peak LS were significantly lower in both fibrotic and non-fibrotic lesions in HCM subjects compared to healthy controls ($p &lt; 0.01$).</td>
</tr>
</tbody>
</table>

CI: Confidence Interval; CMR: Cardiac Magnetic Resonance; CT: Computed Tomography; HCM: Hypertrophic Cardiomyopathy; HR: Hazard Ratio; ICD: Implantable Cardioverter Defibrillator; LAVi: Left Atrium Volume Index; LGE: Late Gadolinium Enhancement; LS: Longitudinal Strain; LV: Left Ventricular; LVOT: Left Ventricular Outflow Tract; LVWT: Left Ventricular Wall Thickness; NSVT: Non Sustained Ventricular Tachycardia; NYHA: New York Heart Association; OR: Odds Ratio; RA: Right Atrium; RS: Radial Strain; RV: Right Ventricular; SCD: Sudden Cardiac Death; TAPSE: Tricuspid Annular Plane Systolic Excursion; TDI: Tissue Doppler Imaging; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia.
Bibliography


Novel Echocardiographic Risk Factors for Unfavorable Outcomes in Patients with Hypertrophic Cardiomyopathy- A Systematic Review


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