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The Potential of Late Gadolinium Enhancement to Serve as a Predictor of Ventricular Arrhythmias in Hypertrophic Cardiomyopathy Patients

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Abstract: Hypertrophic cardiomyopathy, the most common inherited cardiomyopathy is well known to be the leading cause of sudden cardiac death in young people. However, amongst the population of patients, a small subset bears increased risk of sudden cardiac death and would benefit from implantation of a defibrillator, currently recognized utilizing a series of established risk factors. This risk stratification model is hampered by low positive predictive value. Therefore, novel predictors of sudden death are sought. The advent of cardiac magnetic resonance and late gadolinium enhancement has allowed accurate quantification of regional fibrosis, a key element of hypertrophic cardiomyopathy, pathophysiologically linked to increased arrhythmogenicity. We sought to review currently available data on the utility of late gadolinium enhancement to serve as a novel predictor of arrhythmias and sudden death. In conclusion, significantly diverse methodological approaches and subsequent findings between available studies on the topic have hampered such use, highlighting the need for uniformly designed large scale, prospective studies in order to clarify which aspects of myocardial fibrosis could serve as predictors of arrhythmic events.

Keywords: Cardiac magnetic resonance, Hypertrophic cardiomyopathy, Late gadolinium enhancement, Myocardial fibrosis, Sudden cardiac death.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic familial disease inherited as an autosomal dominant trait. Its key characteristic is unexplained left ventricular hypertrophy (LVH) associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that could explain LVH [1].

In general population, HCM presents in about 1/500 adults and generally leads a benign course, with the majority of patients having a normal life span and minimal symptoms. However, a small subset of clinically recognized patients with HCM is at increased risk for sudden cardiac death (SCD), with an event rate of about 1% per year [1]. Therefore, early stratification for the recognition of HCM patients at risk for SCD is imperative. Currently established risk factors for sudden death are maximal wall thickness >30mm, family history of SCD, an abnormal blood pressure response in cardiopulmonary exercise testing, history of syncope and non-sustained ventricular tachycardia (NSVT) on Holter monitoring [1].

The utility of these factors yields a high negative (87 to 98%) but low positive predictive value (<10 to 28%), allowing for the exclusion of low risk patients rather than identifying those at high risk [2]. Additionally, although risk of SCD would be expected to increase incrementally in patients with multiple risk factors, simply summing up risk

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factors appears to have low sensitivity in identifying patients at risk for SCD. Even in patients deemed as high risk based on established risk factors who received an implantable cardioverter defibrillator (ICD) for primary prevention, discharge rates did not exceed 4%/year, subjecting the remainder of patients to the potentially unnecessary and even detrimental burden of an ICD [3]. Moreover, decision making for ICD implantation for primary SCD prevention in patients with none or even one of the aforementioned risk factors, also appears to be a field of continuous debate [4]. Interest has shifted in an effort to develop more accurate predictive models, based on existing risk stratification factors [5], or to investigate the potential of novel factors in order to determine increased risk in HCM patients, with myocardial fibrosis appearing as a highly promising marker on this regard.

In HCM, mutations result in disoriented or dysfunctional myocytes, which at a histopathological level lead to myocardial disarray intertwined with areas of interstitial fibrosis [6]. These findings, along with small intramural coronary arteriole disease, especially in areas of hypertrophy, provide an ideal arrhythmogenic substrate [7]. The magnitude of these histopathological findings has been associated with an unfavorable outcome in HCM patients due to SCD [8, 9]. Attempts to quantify myocardial fibrosis *in vivo*, utilizing circulating serum biomarkers of collagen turnover, have provided evidence of a relationship between myocardial fibrosis and SCD [10]. However, the utility of such markers is hampered by low specificity and most importantly, inability to localize myocardial scar.

Over the past decade, the advent of cardiac magnetic resonance (CMR) has provided the most accurate modality for the assessment of cardiac morphology and hypertrophy distribution [11, 12]. Moreover, the ability of gadolinium-based contrast agents to identify areas of focal fibrosis, has allowed the *in vivo* study of myocardial fibrosis in terms of localization, distribution and quantification using the late gadolinium enhancement (LGE) technique [13, 14]. Recently, the presence of LGE has been shown to be associated with adverse outcomes in HCM.

The aim of this review is to present available data on the prognostic value of LGE in HCM with a particular focus on the prediction of arrhythmic events.

Search Strategy and Study Selection Criteria

A PubMed/Medline search was performed using the following terms "Cardiomyopathy, Hypertrophic"[Mesh] AND "Tachycardia, Ventricular"[Mesh] OR "Ventricular Fibrillation"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] AND "Late Gadolinium enhancement" OR "Myocardial Scar" OR "Myocardial Fibrosis". Additionally, a search with the same terminology was performed in the Scopus database. The bibliography of the retrieved articles was manually searched for relevant references. Overall, the search yielded 8 observational studies in which the relationship between LGE and detected arrhythmias was investigated and an additional 7 studies and 2 meta-analyses providing information on SCD and related events as endpoints. Study characteristics and key points are presented in Tables 1 and 2.

Table 1. Characteristics of studies investigating the relationship between LGE detected fibrosis and ventricular arrhythmias.

| # | Author | Total, n | Age, yrs | LGE Quantification | LGE+ | Mean LVEF, % | Wall thickness | NYHA Class I/II/≥III | Key Outcomes |
|---|---------------------------|----------|----------|---|-------|--|---|-------------------------------|--|
| 1 | Dumont <i>et al.</i> [16] | 104 | 51 | Visual assessment, presence of LGE per segments | 48% | Per LGE+ LV segments <ul style="list-style-type: none"> ▪ 1 Segment 76 (7) ▪ 2 Segments 74 (8) ▪ 3 Segments 70 (9) ▪ 4 segments 69 (10) <p>$p=0.001$</p> | Per LGE+ segments <ul style="list-style-type: none"> ▪ 1 Segment 171 (67) ▪ 2 Segments 200 (75) ▪ 3 Segments 237 (74) ▪ 4 Segments 252 (91) <p>$(p<0.001)$</p> | I: 50% II: 48% ≥III: 2% | LGE+/NSVT+ <ul style="list-style-type: none"> ▪ 1 Segment (14%) ▪ 2 Segments (17%) ▪ 3 Segments (20%) ▪ 4 Segments (37%) <p>$(p=0.04)$</p> |
| 2 | Paya <i>et al.</i> [18] | 120 | 47±16 | Semi-automatic quantification | 69.2% | LGE+ 68±12 LGE- 64±9 $(p=0.021)$ | MWT, mm LGE+ 22±5 LGE- 17±3 $(p<0.001)$ | I: 41% ≥II: 59% | NSVT+/LGE+ 38% vs NSVT+/LGE- 8% $(p=0.001)$. LGE+ yielded an OR 8.19 (95%CI 1.38-48.53; $p=0.020$) for NSVT. |

(Table 1) cont....

| # | Author | Total, n | Age, yrs | LGE Quantification | LGE+ | Mean LVEF, % | Wall thickness | NYHA Class I/II/≥III | Key Outcomes |
|---|------------------------------|----------|------------|---|------------------------------|--|--|-----------------------------------|---|
| 3 | Dimitrow <i>et al.</i> [20] | 47 | 42 ± 12 | Visual quantification | N/A | NSVT+ 68±9 NSVT- 70±5 <i>p</i> >0.05 | LV Mass, g NSVT+ 233 ± 80 NSVT-215 ± 64 <i>p</i> >0.05 | N/A | NSVT+/LGE+ 97% NSVT-/LGE+ 60% (<i>p</i> <0.05) |
| 4 | Leonardi <i>et al.</i> [21] | 108 | 42±15 | Visual assessment (segmental LGE presence) | 85% | VT/VF- 62.1+8.8 VT/VF+ 60.2+12.3 (<i>p</i> =0.34) | LV Mass index, g/m ² VT/VF - 79 (67-100) VT/VF+ 85 (76-115) (<i>p</i> =0.016) | I: 78% II: 18.5% ≥III: 3.5% | Total LGE score was the sole predictor for VT/VF on multivariate analysis (<i>p</i> =0.004) |
| 5 | Kwon <i>et al.</i> [7] | 60 | 51±14 | >2SD, semi automatic quantification | 63% | LGE+ 64±3 LGE- 65±4 (<i>p</i> =0.2) | MWT, cm LGE+ 2.3±0.7 LGE- 1.8±0.2 (<i>p</i> =0.008) | ≥III: 100% | VT+/LGE+ 27% vs VT+/LGE- 5% (<i>p</i> =0.03) |
| 6 | Adabag <i>et al.</i> [22] | 177 | 41±16 | ≥6SD, semi-automatic quantification | 41% | N/A | MWT, mm LGE+ 23.5±5 LGE- 19.5±4 (<i>p</i> =0.0001) | I: 77% II: 18% ≥III: 5% | LGE+/NSVT+ vs LGE-/NSVT+ 28% vs 4% (<i>p</i> <0.0001). In LGE+ patients RR for NSVT 7.3, (95% CI 2.6-20.4; <i>p</i> <0.0001). |
| 7 | Kwon <i>et al.</i> [23] | 68 | 44 (34-56) | >2SD, semi automatic quantification | 57% | N/A | AUC 0.80 (<i>p</i> <0.001) for septal thickness to predict LGE | N/A | NSVT+/LGE>18% 50% NSVT+/LGE<18% 11% (<i>p</i> <0.002) |
| 8 | Appelbaum <i>et al.</i> [24] | 145 | 43±15 | High intensity LGE ≥6SD Intermediate intensity LGE 6-4SD | 50% of initial cohort of 288 | No statistically significant difference between groups | No statistically significant difference between groups | I: 64% ≥II: 36% | Mean LGE (≥6SD) % in NSVT+ 15.1±5.5% Mean LGE (≥6SD) % in NSVT- 9.1±6.3% (<i>p</i> <0.005) |

LGE indicates late gadolinium enhancement; LGE+, LGE present, LGE- LGE absent; SD, standard deviation above greyscale threshold; LV, left ventricular; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; VF, ventricular fibrillation; NSVT, non-sustained ventricular tachycardia; LVMI, left ventricular mass index; MWT, maximal wall thickness; AUC, area under the curve; NYHA, New York Heart Association; N/A, data not available; RR relative risk.

Table 2. Characteristics and key outcomes of studies investigating the relationship between LGE detected fibrosis and sudden cardiac death.

| Study No | Author | Total, n | Age, yrs | Follow up | Mean LVEF total, % | Mean LVMI total, g/m2 | LGE Quantification | LGE+, % | Mean LVEF, % | | Mean LVMI, g/m2 | | Primary Endpoint | Outcomes |
|----------|--------------------------|----------|------------|---------------|--------------------|-----------------------------------|-----------------------|---------|--------------|-------|-----------------|-------|-------------------------------|---|
| | | | | | | | | | LGE + | LGE - | LGE + | LGE - | | |
| 1 | Prinz <i>et al.</i> [25] | 87 | 49.9± 13.6 | 3.5±2.6 years | 61.8± 7.5 | Maximal IVS thickness 22.0±8.0 mm | Visual quantification | 90% | N/A | | N/A | | Appropriate ICD interventions | LGE extent correlated with VT (<i>p</i> <0.01) in multilinear regression |

(Table 2) *contd....*

| Study No | Author | Total, n | Age, yrs | Follow up | Mean LVEF total, % | Mean LVMI total, g/m ² | LGE Quantification | LGE+, % | Mean LVEF, % | Mean LVMI, g/m ² | Primary Endpoint | Outcomes |
|----------|--------------------------------|----------|-------------|---------------|--------------------|-----------------------------------|-----------------------|---------|--|---|---|--|
| 2 | Bruder <i>et al.</i> [26] | 220 | 58 (47-68) | 1090 days | 71 (65-77) | 84 (68-97) | >2SD | 67.2 | 71.0 vs 70.5 (p=0.95) | 85.0 vs 76.0 (p=0.001) | <ul style="list-style-type: none"> ▪ SCD | LGE presence yielded an OR 5.14 for SCD, (p=0.057) |
| 3 | O'Hanlon <i>et al.</i> [27] | 217 | 53.2±15.1 | 3.1±1.7 years | 73.9 (10.6) | 108.9 (37.4) | FWHM | 63 | 72.7 (11.6) vs 75.9 (8.4) (p=0.03) | 118.2 (41.3) vs 93.2 (22.3) (p<0.001) | <ul style="list-style-type: none"> ▪ Composite arrhythmic endpoint ▪ Sustained VT or VF ▪ Appropriate ICD discharge ▪ SCD | LGE presence yielded a HR 3.15 for the arrhythmic endpoint, (p=0.138). |
| 4 | Rubinshtein <i>et al.</i> [28] | 424 | 55±16 | 43±14 months | 67±9 (30 - 88) | Maximal IVS thickness 20.5±5 mm | Visual quantification | 57 | 66±10 vs 69±8 (p=0.001) | N/A | <ul style="list-style-type: none"> ▪ SCD ▪ Appropriate ICD discharge ▪ SCD | 4 SCD + 4 appropriate ICD discharge all LGE+. |
| 5 | Klopotoski <i>et al.</i> [29] | 328 | 45 (29-58) | 37 (24-48) | 69 (63-75) | 87 (67-114) | >6SD | 68.9 | 70 (64-75) vs 68 (63-75) vs 69 (63-73) (p=0.384) | 93 (71-128) vs 90 (71-114) vs 77 (61-105) (p=0.003) | <ul style="list-style-type: none"> ▪ SCD ▪ Appropriate ICD discharge ▪ SCD | LGE presence outside interventricular insertion points yielded an OR 10.01 for the endpoint, (p=0.033) |
| 6 | Ishmail <i>et al.</i> [30] | 711 | 56.3 | 3.5 years | 74.6±9 | 101.9±37.0 | FWHM | 66.2 | 73.3±9.5 vs 77.1±7.1 (p<0.001) | 108.4±40.1 vs 88.7±25.1 (p<0.001) | <ul style="list-style-type: none"> ▪ SCD ▪ Aborted SCD | LGE presence yielded a HR: 2.69, p=0.073) LGE extent yielded a HR 1.24/5% increase in LGE (p=0.007) LGE not predictive of SCD in multivariate analysis |
| 7 | Chan <i>et al.</i> [31] | 1293 | 46±17 years | 3.3 | 67±9 | 83.0±34.0 | Visual quantification | 42 | N/A | N/A | <ul style="list-style-type: none"> ▪ SCD ▪ Appropriate ICD discharge | LGE extent yielded an adjusted HR, 1.46/10% increase in LGE (p=0.002) |

Relationship of Fibrosis to Ventricular Arrhythmias

Evidence of an association between risk factors and LGE was provided by Moon *et al.* in a study of 53 patients that showed a significant association between simultaneous presence of LGE and ≥ 2 risk factors for SCD, a finding even more pronounced in younger patients [15]. Focusing on the correlation of ventricular arrhythmias and LGE, Dumont *et al.* enrolled 104 HCM patients who underwent CMR, as per protocol. Ninety six of these patients also underwent a 24 hour Holter recording [16]. The investigators quantified LGE depending on affected segments, utilizing a standardized 17-segment model [17]. Non-sustained VT appeared to correlate in a positive manner with increasing number of segments presenting with LGE (p<0.04). In general, patients with larger degrees of LGE, tended to be diagnosed at an earlier age, presented with increased left ventricular (LV) mass and decreased LV ejection fraction (LVEF), overall exhibiting a worse clinical profile.

In another study of 120 HCM patients, increased prevalence of NSVT was found in patients with fibrosis (38% vs 8%, $p<0.001$) [18]. On multivariate analysis, a significant, linear correlation between NSVT and presence of LGE was shown ($p=0.011$). Notably, LGE was associated with more significant LVH and worse systolic function. Additionally, patients with LGE exhibited increased levels of NT pro-BNP which has been strongly associated with worse heart failure status and outcome in HCM patients [19].

From an inverse perspective, *i.e.* whether patients with NSVT presented with a greater extent of fibrosis on LGE, 47 HCM patients underwent 48 hour Holter monitoring and CMR [20]. Although some degree of LGE (1 g to 76 g) was found in the vast majority (97%) of patients with NSVT, compared to 60% of patients without NSVT ($p<0.05$), there was no difference regarding its extent between the two groups.

In contrary, a significant association between the extent of fibrosis and the occurrence of VT/VF was shown by Leonardi *et al.* [21]. Fibrosis was visually assessed in 108 patients, utilizing a semi-quantitative method and scoring its extent in each of 17 myocardial segments, [17] with 0, 1, 2 and 3 points if 0%, >0-25%, 25-50% and >50% of the segment area presented with LGE respectively. On bivariate analysis LV mass index and total LGE score were significant predictors of arrhythmias, with the latter remaining as the sole predictor on multivariate analysis.

Focusing mainly on the histopathological association between small vessel disease and LGE, 60 patients planned to undergo septal myectomy for symptomatic LVOT obstruction were investigated [7]. NSVT runs were significantly more frequent on 48 hour Holter recordings in patients with LGE compared to those without. It should be noted that in this study, small vessel disease was also significantly associated with myocardial fibrosis and indirectly linked with NSVT, providing useful insight in arrhythmogenicity in HCM.

In the largest observational study so far, the prevalence and frequency of ventricular arrhythmias, including premature ventricular contractions, couplets and NSVT runs in relation to LGE was studied in 177 patients [22]. All arrhythmic events, but most importantly NSVT presence and frequency of runs, were significantly more pronounced in patients with LGE compared to patients without fibrosis. The presence of LGE yielded a 7-fold increased probability of NSVT, and remained the only predictor of NSVT on multivariate analysis. It should be noted that the latter correlation occurred after adjustment for age and wall thickness as patients with LGE were older and had more pronounced LVH. Notably, there was no significant correlation between the extent of LGE and arrhythmias.

A retrospective observational study in 68 patients showed similar sensitivity and specificity characteristics regarding the ability of LGE to predict ventricular tachyarrhythmias in 48 hour Holter monitoring [23]. A cut-off point of 18% was found to be predictive of NSVT episodes with AUC in ROC analysis being 0.71 (95% CI not reported, $p<0.01$). The presence of LGE yielded a 14-fold probability of ventricular arrhythmias being recorded ($p<0.001$). In this case, the extent of LGE was significantly associated with the detection of ventricular arrhythmias, either demonstrated as a percentage of myocardial mass 13% (6-19) vs. 6% (0-10), $p=0.01$ or affected myocardial segments 10 (8-12) vs. 6 (0-12), $p<0.05$.

Finally, the ability of intermediate-signal intensity LGE 4-6 standard deviations (SD) to predict ventricular arrhythmias (PVCs, ventricular couplets and NSVT on 24h Holter recordings) in comparison to high intensity LGE (>6SD) was investigated in a cohort of 145 patients [24]. Patients presenting with arrhythmic events were found to exhibit significantly increased amounts of LGE, regardless of the quantification method used.

Relationship of Fibrosis to Sudden Cardiac Death

At present, few studies have explored the relationship between fibrosis on LGE-CMR and variable aspects of HCM-related morbidity and mortality, providing data on several distinct arrhythmic endpoints.

A surrogate, although of debatable validity, marker of aborted SCD in HCM patients is appropriate ICD interventions. A study included 87 high risk patients (mean risk factors 1.9 ± 0.8) with an indication for ICD implantation mainly for primary prevention (98%) [25]. Prior to implantation, a CMR study was undertaken and patients were subsequently followed up for a mean of 3.5 years. Fibrosis quantification was based on affected segments and categorized as absent, point-shaped, single segment and multiple segments. During follow-up, patients with severe fibrosis (30% of the cohort) received appropriate ICD interventions, contrary to patients with lesser degrees of LGE who remained free of events. In multivariate analysis, the presence of extensive fibrosis remained the sole predictor of sustained arrhythmic events in this high risk cohort.

A study by Bruder *et al.* in 220 patients, followed up for a period of 1090 days after undergoing a CMR study, implied that LGE could serve as a better predictor of SCD than the established risk factor model [26]. LGE presence was associated with a higher LV mass. Systolic function was similar between patients with and without fibrosis. None of the patients without LGE had a history of spontaneous VT versus 8.1% in the LGE group ($p=0.05$). Patients with 2 risk factors for SCD, deemed as high risk using the current clinical risk stratification model, presented with a mean fibrotic burden of 3.8%. This represented significantly less fibrosis in comparison to 11 patients who died suddenly, with a mean scar burden of 11.8%. Additionally, only 3 of the latter patients had any of the established risk factors for SCD. Although LGE quantity was found to be increased in patients with increasing number of risk factors, this finding was not associated with SCD events. On the other hand, the presence of fibrosis yielded an odds ratio (OR) of 5.14 for SCD, which marginally did not reach statistical significance ($p=0.057$).

Another study enrolled 217 patients, prospectively followed up for 3.1 ± 1.7 years [27]. Patients with fibrosis exhibited significantly increased LV mass and reduced LVEF and overall presented with a worse functional status compared to patients without fibrosis. Despite the fact that significantly more patients with LGE received b-blockers and antiarrhythmics, they presented more frequently with a history of documented NSVT 11.8% vs. 3.7% ($p=0.04$), but not with a history of sustained VT or VF. Additionally, 7.3% of the patients in the LGE group reached the composite arrhythmic end point (sustained VT or VF, appropriate ICD discharge, SCD) versus 2.5% of patients without detected fibrosis, a difference that did not reach statistical significance [hazard ratio (HR): 3.15, 95% CI 0.69 - 14.4; $p=0.138$]. In this study, both the presence and the amount of LGE served as predictors of arrhythmic events in the univariate analysis, with the latter yielding an HR of 1.30 (95% CI: 1.05 - 1.61; $p=0.014$).

In a series of 424 patients data available over a period of 43 ± 14 months (range 16 to 94) was retrospectively analyzed [28]. In this cohort, significantly increased LV mass and reduced LVEF in the patients with fibrosis was not reflected in differences in NYHA classification. This study provided further evidence on the association between LGE and the detection of self-terminating arrhythmias (PVCs, ventricular couplets, NSVT). The presence of LGE was associated with increased prevalence of NSVT (27% vs. 8.5%, $p<0.001$), with more frequent runs per patient 4.5 ± 12 (range 1 to 66) vs. 1.1 ± 0.3 (range 1 to 2); $p=0.04$. Similarly, patients with LGE exhibited significantly more PVCs and episodes of couplets or bigeminy. In terms of sustained arrhythmic events, 4 patients suffered SCD and 4 patients had appropriate ICD discharges over the follow up period. Six out of these patients presented with some degree of fibrosis, while 4 of them showed large degree of LGE, deemed by the investigators as $>5\%$ of LV mass. In multivariate analysis, the presence of LGE was considered as a significant predictor of adverse arrhythmic events, together with presence of NSVT. Estimated 6 year event free survival was statistically significantly lower in patients with fibrosis compared to patients without (96% vs. 100%, $p=0.01$).

In a series of 328 patients, a study sought to investigate whether, apart from the presence of LGE per se and its extent, distribution of fibrosis would be associated with increased risk of SCD or appropriate ICD therapy [29]. Patients with fibrosis in this cohort expressed a worse clinical profile, with increased wall thickness and LV mass, more frequent NSVT episodes and abnormal hemodynamic responses to exercise, as well as increased NT-proBNP levels. Therefore they were more actively treated, both medically, in particular with b-blockers, amiodarone and spironolactone, and with more ICD implantations. The study endpoint was reached by 14 patients, all of which exhibited some degree of LGE. Importantly, in all but one of these patients, fibrosis was located away from the interventricular insertion points, where it is most commonly described. This particular distribution of LGE was associated with significantly increased risk of fulfilling the study endpoint on multivariate analysis including the established risk factors for SCD (HR 10.01, 95% CI 1.21-83.86, $p=0.033$).

Finally, data from two of the largest prospective HCM cohorts yet was recently published, and results appear to be equivocal. Ismail *et al* recruited 711 patients, who were followed up for a median of 3.5 years after undergoing a CMR scan [30]. The presence of late enhancement was associated with significantly increased LVH as well as decreased LV systolic function, although this did not correspond to differences in functional status. Patients in this cohort were enrolled as minimally or mildly symptomatic, with 93% of them being classified as NYHA class I/II. In terms of risk stratification, since fibrosis was associated with LVH >30 mm and NSVT, significantly more patients with LGE were deemed as "high risk" for SCD. In line with the higher risk profile, the presence of LGE was associated with increased but not statistically significant SCD rates, aborted or not (HR: 2.69, 95% CI: 0.91-7.97; $p=0.073$). On the other hand, the amount of detected fibrosis was significantly associated with increased risk of SCD, (HR per 5% increase in LGE 1.24, 95% CI 1.06-1.45; $p=0.007$). It should be noted that more patients presenting with fibrosis were also on b-blockers. However, on multivariate analysis fibrosis did not maintain its prognostic value and only decreased LVEF

was found to be a reliable predictor of SCD events.

Contrary to the results of the aforementioned study, myocardial fibrosis was found to be an independent predictor of SCD in a multicenter cohort of 1293 patients followed up for a median of 3.3 years [31]. The combined endpoint of SCD, aborted cardiac arrest, appropriate ICD discharge occurred in 37 patients, 70% of which exhibited some degree of LGE. Interestingly, 21 of these patients were considered as low risk based on clinical risk stratification. While the absence or even the presence of minimal LGE was associated with minimal estimated risk for SCD (3.4 and 3.5-4.1%/5 years respectively), the amount of detected fibrosis significantly increased risk (up to 15%/5 years in patients with LGE \geq 20% of LV mass). In particular, a linear association between LGE extent with risk for SCD was found, with every 10% increase in the former leading to a 40% increase in the latter (adjusted HR 1.46/10% increase in LGE; 95% CI, 1.12–1.92; $p=0.002$), regardless of confounding factors such as age, systolic function, medication regime and presence of other risk factors. In fact, LGE remained a strong predictor of SCD even in patients who, according to current clinical risk stratification, were deemed as low risk. Additionally, the extent of LGE also served as a predictor of end stage HCM development (adjusted HR, 1.80/10% increase in LGE; 95% CI, 1.40–2.40; $p=0.03$), without however also predicting heart failure related mortality. Finally, inclusion of LGE% in the currently utilized risk prediction model, greatly increased performance for the prediction of SCD related events AUC increased from 0.71 (95% CI, 0.632–0.788) to 0.741 (95% CI, 0.664–0.818).

Two meta-analyses on the prognostic value of LGE have been published, with contradictory results, leading to further debate on the issue. In order to delineate the effect of LGE on clinical outcomes in HCM, a meta-analysis utilized data from 3 studies, published until 2010, [26 - 28] and additionally a study by Maron *et al.* [32] that did not explicitly provide data on arrhythmic events and SCD. Pooled data from these 4 studies showed a significant association of the presence of fibrosis with cardiac mortality (pooled OR 2.92, 95% CI: 1.01-8.42; $p=0.047$), heart failure mortality (pooled OR: 5.68, 95% CI: 1.04-31.07; $p=0.045$) but only a trend towards SCD related events (pooled OR: 2.39, 95% CI: 0.87-6.58; $p=0.091$) [33].

Contrary to that, a meta-analysis of 3067 patients [34], additionally including the large cohorts by Chan [31] and Ismail *et al.* [30], found the presence of myocardial fibrosis to be associated with increased rates of SCD (OR 2.52, 95% CI 1.44 - 4.4; $p=0.001$), cardiac death, all-cause mortality (OR 1.80, 95% CI 1.21 - 2.67; $p=0.003$) but only a trend towards HF related death (OR 2.47, 95% CI 0.98 - 6.24; $p=0.06$). Notably, no significant association between the extent of LGE and endpoints was found on meta-regression analysis, probably attributed to the small number of patients with significant amounts of LGE throughout the study population.

DISCUSSION

Over the past decade, research on the utilization of CMR and its role in the assessment of HCM has provided significant insights with regards to cardiac structure and function and subsequently in HCM patient management. Currently, CMR represents the modality of choice in patients with suboptimal or inconclusive echocardiographic studies [35], yielding high sensitivity in detecting LVH [12], especially in patients with focal [36], apical [37], or right ventricular hypertrophy [38]. It has also provided valuable information on the structural characteristics of the mitral valve leaflets [39] and subvalvular apparatus [40], contributing to the mechanism of LVOT obstruction in HCM.

On the other hand, although the identification of myocardial fibrosis with LGE-CMR has provided important insights in terms of tissue characterization and diagnosis in borderline cases, the available data on its utility as a predictor of SCD remains ambiguous. To date, in available guidelines on HCM, LGE-CMR is not a part of the proposed predictive model for SCD (HCM Risk-SCD) and no recommendation on its use as a risk factor is provided [1, 5, 41]. Although the vast majority of published studies so far utilized uniform standardized measures in terms of population enrollment, patient characteristics and CMR image acquisition, a number of study aspects such as endpoint definitions or LGE quantification method are largely diverse. Regarding the variability in endpoint selection amongst available studies, the small frequency of SCD events in HCM populations subsequently leads to an inherent inability of studies to provide robust data on hard endpoints; therefore in most cases composite endpoints were utilized. In order to achieve this goal, larger cohorts with more prolonged follow up periods are required. Additionally, although the majority of studies implemented a signal intensity >2 SD above the average of normal myocardium in order to determine the extent of LGE [42], some data derived from different thresholds such as 4-6 SD, >6 SD [24], or the “full width half maximum” (FWHM) technique [27]. It has been established that different quantification thresholds, yield different results with regards to LGE extent [43, 44].

Apart from the aforesaid variability in study methodology, deriving results regarding numerous issues have been equivocal. Although LGE is detected along the full spectrum of LV function, almost all available data suggests a strong association between increased LV mass, decreasing LVEF and presence of fibrosis; however, an analogous association with decreasing functional capacity has not been clearly established. Similarly, the degree to which myocardial fibrosis serves as a predisposing factor for the development of end-stage HCM is unknown; although an association has been suggested this has not been uniform across available studies [15]. Whether arrhythmogenicity is a synchronous process with more severe or progressive disease, linearly associated with the development and increment of fibrosis is a hypothesis remaining unanswered. In an akin fashion, no consistent association has been found in available data linking characteristics of fibrosis with different risk factor profiles [15, 16, 18, 21, 26]. Notably, LGE has also been found in patients with none of the established risk factors for SCD [45].

Whether the presence of fibrosis per se, the topographic distribution of LGE, or the extent of fibrosis is associated with arrhythmogenicity is an issue yet unresolved. Although the extent and not just the presence of LGE has been demonstrated to be the sole predictor of inducibility of VT during electrophysiological testing [46], evidence regarding spontaneous arrhythmic events is conflicting.

Finally, currently available data on fibrosis and its relation to arrhythmogenicity and risk of SCD are based solely on the quantification of focal fibrosis by LGE. The advent of novel techniques such as T1 mapping which are able to identify and quantify diffuse myocardial fibrosis appears as a promising tool that has the potential to further advance our knowledge on the relationship between fibrosis and risk for SCD in HCM [47 - 50]. Such novel techniques for the detection and quantification of myocardial fibrosis, together with large scale registry based analysis with substantially prolonged follow up periods, such as the HCM registry (NCT01915615) [51], are expected to shed more light onto the crucial matter of precise risk stratification in HCM patients in the future.

CONCLUSION

The value of LGE in the prediction of arrhythmic events has been investigated in a significant number of studies, however with largely inconclusive or even conflicting results. Therefore, this concept still remains under debate, mainly due to methodological discrepancies and inherent low power of available data to provide sound associations with sudden death, deriving from the small number of events. Further large scale, prospective studies, with uniform design in terms of fibrosis definition and adjudication of endpoints are required in order to clarify if LGE could indeed be used as a risk index for sudden cardiac death.

ABBREVIATIONS

| | | |
|--------------|---|--|
| AUC | = | area-under-the-curve |
| CI | = | confidence intervals |
| CMR | = | cardiac magnetic resonance |
| FWHM | = | full width – half maximum |
| HCM | = | hypertrophic cardiomyopathy |
| HR | = | hazard ratio |
| ICD | = | implantable cardioverter defibrillator |
| LGE | = | late gadolinium enhancement |
| LV | = | left ventricular |
| LVEF | = | left ventricular ejection fraction |
| LVH | = | left ventricular hypertrophy |
| LVOT | = | left ventricular outflow tract |
| NSVT | = | non-sustained ventricular tachycardia |
| NYHA | = | New York Heart Association |
| OR | = | odds ratio |
| PVC's | = | premature ventricular contractions |
| RR | = | relative risk |
| SCD | = | sudden cardiac death |
| SD | = | standard deviation |

| | | |
|----|---|--------------------------|
| VF | = | ventricular fibrillation |
| VT | = | ventricular tachycardia |

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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