DO APICAL ANEURYSMS PREDICT SUDDEN CARDIAC DEATH IN HYPERTROPHIC CARDIOMYOPATHY?

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Background

Hypertrophic cardiomyopathy (HCM) is a common heart muscle disorder which causes premature death from ventricular arrhythmia, heart failure and stroke. Extensive research over many decades has identified a number of disease features associated with an increased risk of sudden cardiac death (SCD), and current ESC and AHA clinical practice guidelines recommend their incorporation into systematic risk algorithms designed to assist targeted primary prevention with ICDs.

Although annualised SCD rates in contemporary HCM registries are less than 1%, ongoing concern about residual risk propels the search for new risk markers. Left ventricular (LV) apical aneurysms, defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the ventricle, were first reported in patients with HCM more than 30 years ago. Their cause is unknown, but they are often associated with mid-cavity obstruction [1] and it has been hypothesized that they are the result of myocardial ischaemia caused by high intracavity systolic pressures. Very limited data is available regarding aneurysm progression in relation the severity of mid-cavity gradients, with no data on the long-term impact of gradient reduction.

The first descriptions of LV apical aneurysms in HCM suggested an association with sustained monomorphic ventricular tachycardia (VT) [2] – an otherwise extremely rare occurrence in HCM – but the notion that they are a predictor of SCD only emerged in 2008 following the publication of small series of patients (n=28) from two centres [3]. The same group published an expanded series in 2017 (n=93) and reaffirmed their conclusion that apical aneurysms are a novel SCD risk factor in HCM [4].

A recent systematic review and meta-analysis identified a total of four studies that reported SCD equivalent events in patients with HCM and apical aneurysm [5]. Along with the

aforementioned papers [4], the meta-analysis included two small series that described a selected subgroup of patients with HCM and midventricular obstruction. Neither of these reports recorded a higher incidence of SCD events in those with apical aneurysm [6,7]. The fourth study included in the meta-analysis was larger (apical aneurysm n=24) and described patients with apical HCM and/or midventricular obstruction and/or apical aneurysm [8]. It reported a high rate of SCD or equivalent events, that occurred in 8/24 (33%) patients with apical aneurysm, however these patients had a higher risk profile (family history of SCD, non-sustained VT and syncope were all more frequent). More recently, the largest series to date reported 160 Canadian patients with apical aneurysm identified over a 24-year period and similarly concluded that apical aneurysms are associated with an increased risk of ventricular arrhythmias [9].

Based on the increased SCD event rate reported in these studies (1.8-4.7% / year [4,9] vs ~1% / year in HCM overall [4] – including both primary and secondary prevention ICDs). LV aneurysms were included in the 2011 AHA/ACC HCM guidelines as a "*risk modifier*" that should prompt consideration of an ICD in the presence of another established risk factor [10]. In the more recent 2020 AHA/ACC HCM guidelines, apical aneurysms are considered a major independent SCD risk factor and a reasonable indication for an ICD based solely on this finding [11]. This recommendation has important clinical implications and the data supporting it require careful scrutiny.

How frequent are LV aneurysms in HCM?

The prevalence of LV aneurysms in patients with HCM is uncertain as their location at the LV apex means that they are often overlooked on routine (non-contrast enhanced) echocardiography. This is not the case with cardiac magnetic resonance imaging (CMR), and in the largest prospective study to date (n=2755) the prevalence of LV aneurysms was 3% [12].

This is broadly in line with the published retrospective series (prevalence 3-5%), [4,9] but the predominant use of echocardiography in most other studies almost certainly led to a selection bias since it is very likely that some smaller aneurysms were not detected. On the other hand, it should also be noted that the prospective CMR registry selected a lower risk population by excluding patients with an ICD in place [13].

Sudden death or non-fatal ventricular arrhythmia?

A frequently encountered challenge for prognostic studies in cardiomyopathies is the interpretation of tolerated episodes of sustained VT which may trigger therapy from an ICD but may not necessarily equate to SCD. In HCM, the relatively low frequency of sustained VT compared to ventricular fibrillation (VF) has meant that appropriate shocks are generally accepted as a SCD equivalent, but analysis of the published data suggest that this cannot be assumed in the subset of patients with LV apical aneurysm.

In the only series [4] that provides a detailed analysis of SCD events, the vast majority were appropriate ICD interventions for monomorphic VT. In detail, the 21 SCD events reported included a single actual SCD, 2 resuscitated cardiac arrests, and 18 appropriate ICD interventions. It is not stated if these were all appropriate shocks or also included anti-tachycardia pacing therapies, but 89% (16/18) of ICD interventions were for monomorphic VT, and only 11% (2 patients) for ventricular fibrillation (VF). In the latest Canadian series, half of the events (7/14) were resuscitated cardiac arrest and half appropriate ICD interventions but details of the underlying rhythm were not reported [9].

Confounding effect of other risk factors

The small absolute number of events in the published series precludes analysis of the independent predictive value of apical aneurysms. This is important since a significant

proportion of those who experienced SCD events had confounding, well-established risk factors for SCD. Around 1/3 of patients with SCD events [4,9] had survived a sustained VT/VF event at or prior to the baseline evaluation (i.e. recognition of the apical aneurysm). This is crucial given that a prior episode of VF or sustained VT is a strong predictor of subsequent SCD events [14] and is the only class I recommendation for an ICD in HCM in both the AHA/ACC and ESC guidelines [11,15]. The high proportion of patients with prior VT/VF is another indication of bias toward the inclusion of more severely affected patients in these series.

The second important confounder is the presence of a reduced LV ejection fraction (≤50%) (prevalence 24-36% [4,9]). A small number of mostly retrospective studies have examined the relation between prognosis in patients with HCM and LV systolic dysfunction. All consistently report an increased rate of SCD events. As with LV aneurysms, the independent value of LV systolic dysfunction compared to other validated risk markers in unknown, but the association between the two parameters again highlights the complex nature of the relation between aneurysm formation and subsequent SCD events.

Finally, no aneurysm features have been shown to be clearly associated with an increased SCD risk. Aneurysm size has been inconsistently associated with increased SCD risk [4,9] and when it has been, this has been with a very high degree of uncertainty due to the particularly low number of events supporting the subgroup analysis [9].

Conclusions

While LV apical aneurysms are probably associated with monomorphic VT, significant selection bias and the presence of important confounders such as previous VT/VF or reduced LV ejection fraction lead us to suggest that the available data do not support their use as an independent predictor of SCD in HCM. Prospective studies of large cohorts that represent the

full spectrum of disease may help resolve the debate. Until then, clinicians should continue to make individualised decisions based on well-established risk factors, an ICD should be considered for secondary prevention and in those with an aneurysm large enough to cause a reduced LV ejection fraction, but ICD decisions should not be based solely on the presence or absence of an LV apical aneurysm.

Data availability

There are no new data associated with this article.

Disclosure

ML has received consultancy fees from Pfizer. PME has received an unrestricted educational grant from Sarepta; consulting fees from Pfizer, Biomarin, Bristol Myers Squibb, Cytokinetics, Novo Nordisk, and Freeline; speaker fees from Pfizer and Sanofi; he is a board member of the European Society of Cardiology, the president of Cardiomyopathy UK, and is the chairman of the International Cardiomyopathy Network.

References

1. Minami Y, Kajimoto K, Terajima Y, Yashiro B, Okayama D, Haruki S, et al. Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2011;**57**:2346–2355.

2. Alfonso F, Frenneaux MP, McKenna WJ. Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm. *Br Heart J* 1989;**61**:178–181.

3. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation* 2008;**118**:1541–1549.

4. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, et al. Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm: Implications for Risk Stratification and Management. *J Am Coll Cardiol* 2017;**69**:761–773.

5. Papanastasiou CA, Zegkos T, Karamitsos TD, Rowin EJ, Maron MS, Parcharidou D, et al. Prognostic role of left ventricular apical aneurysm in hypertrophic cardiomyopathy: A systematic review and meta-analysis. *Int J Cardiol* 2021;**332**:127–132.

6. Efthimiadis GK, Pagourelias ED, Parcharidou D, Gossios T, Kamperidis V, Theofilogiannakos EK, et al. Clinical characteristics and natural history of hypertrophic cardiomyopathy with midventricular obstruction. *Circ J* 2013;**77**:2366–2374.

7. Yan L-R, Zhao S-H, Wang H-Y, Duan F-J, Wang Z-M, Yang Y-J, et al. Clinical characteristics and prognosis of 60 patients with midventricular obstructive hypertrophic cardiomyopathy. *J Cardiovasc Med (Hagerstown)* 2015;**16**:751–760.

8. Minami Y, Haruki S, Hagiwara N. Phenotypic overlap in hypertrophic cardiomyopathy: Apical hypertrophy, midventricular obstruction, and apical aneurysm. *J Cardiol* 2014;**64**:463–469.

9. Lee DZJ, Montazeri M, Bataiosu R, Hoss S, Adler A, Nguyen ET, et al. Clinical Characteristics and Prognostic Importance of Left Ventricular Apical Aneurysms in Hypertrophic Cardiomyopathy. *JACC Cardiovasc Imaging* 2022;**15**:1696–1711.

10. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American As. *J Am Coll Cardiol* 2011;**58**:e212-60.

11. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2020;**76**:e159–e240.

12. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, et al. Distinct Subgroups in Hypertrophic Cardiomyopathy in the NHLBI HCM Registry. *J Am Coll Cardiol* 2019;**74**:2333–2345.

13. Kramer CM, Appelbaum E, Desai MY, Desvigne-Nickens P, DiMarco JP, Friedrich MG, et al. Hypertrophic Cardiomyopathy Registry: The rationale and design of an international, observational study of hypertrophic cardiomyopathy. *Am Heart J* 2015;**170**:223–230.

14. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;**33**:1596–1601.

15. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J* 2014;**35**:2733–2779.

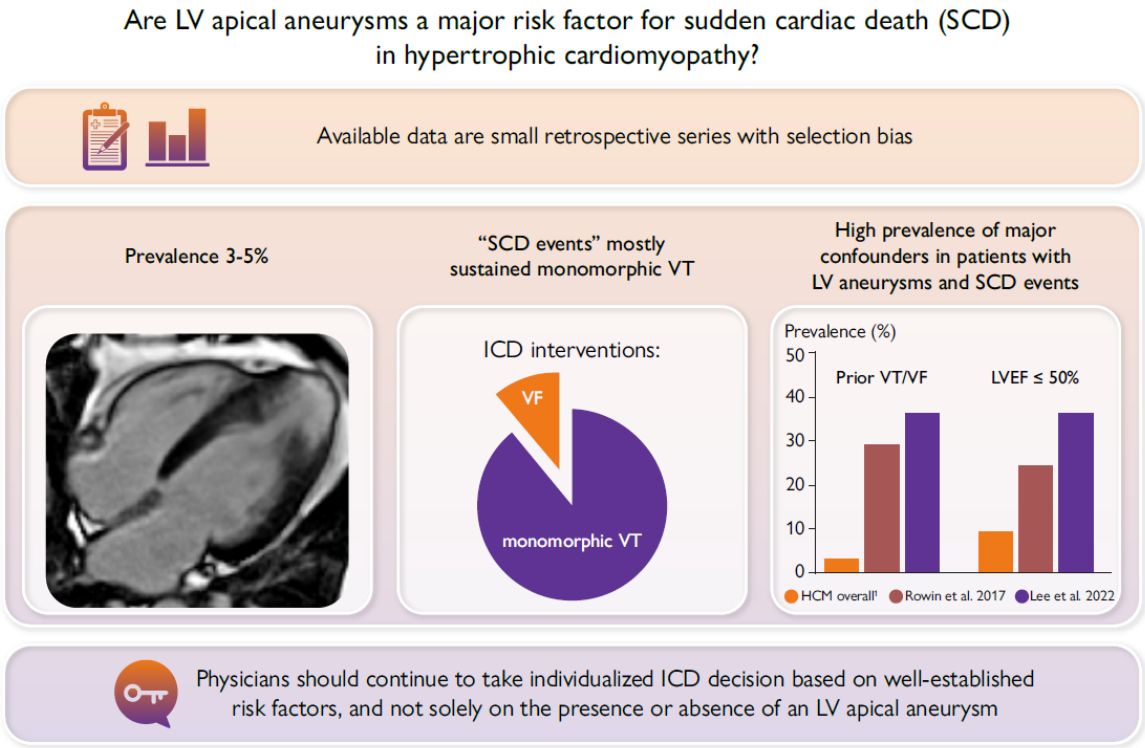

Figure Legend

The current AHA/ACC HCM guideline recommendation for a primary prevention ICD is based on restrospective series that have important limitations. These include selection bias, the fact that "SCD events" are appropriate ICD interventions for monomorphic VT in the vast majority of cases, and a high prevalence of major confounders in patients with apical aneurysm and SCD events. HCM: hypertrophic cardiomyopathy; SCD: sudden cardiac death; LV: left ventricular; LVEF: left ventricular ejection fraction; VF: ventricular fibrillation; VT: ventricular tachycardia.

[1] Lorenzini M et al. Mortality Among Referral Patients With Hypertrophic Cardiomyopathy vs the General European Population. *JAMA Cardiology* 2020;5:73-80.