Relation of Late Gadolinium Enhancement and Extracellular Volume Fraction to Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HC) represents a major cause of sudden cardiac death in young adults. Late gadolinium enhancement (LGE) and extracellular volume (ECV) by T1 mapping are cardiac magnetic resonance (CMR) techniques to quantify fibrosis in HC. The relationships of LGE and ECV with ventricular arrhythmia, left ventricular (LV) diastolic function, and risk factors for sudden cardiac death (SCD) in HC are unclear. We studied 103 HC patients (mean age 51 ± 14, 42% women) who underwent CMR from 2012 to 2014. Global LGE and mean ECV were evaluated in relation to history of nonsustained ventricular tachycardia (NSVT), diastolic function by echocardiography, and SCD risk factors. LGE was present in 71 (69%) subjects. Wide variation was demonstrated in LGE (0.5% to 45.9%) and mean ECV (17.6% to 47.4%). Prevalence of NSVT increased continuously with LGE and was greater in subjects with ECV above the study population mean (27%). Increased LGE was associated with LV diastolic dysfunction and LV wall thickness. In conclusion, while ECV appears to have a threshold (27%) above which it is associated with NSVT, LGE demonstrates a more robust relationship with NSVT and measures of diastolic dysfunction. **(Am J Cardiol 2020;131:104−108)**

Hypertrophic cardiomyopathy (HC) is characterized by unexplained left ventricular (LV) hypertrophy and variable clinical course.[1] Sudden cardiac death (SCD) is a rare but serious complication of the disease.[2,3] Myocardial fibrosis is a pathologic feature in many patients with HC which can act as a substrate for ventricular tachyarrhythmias.[2] Two contrast enhanced cardiac magnetic resonance (CMR) imaging techniques, late gadolinium enhancement (LGE) and gadolinium extracellular volume (ECV) fraction by T1 mapping, allow for the evaluation of distinct fibrotic patterns.[4−7] LGE preferentially detects replacement fibrosis and the ECV fraction quantifies interstitial fibrosis.[6,8−12] LGE has been shown to correlate with ventricular arrhythmia and SCD in HC,[9,13,14] and ECV has been correlated with diastolic dysfunction.[5] The efficacy of the 2 techniques to identify individuals at risk for ventricular arrhythmia and SCD has been studied,[15] however these relations have not been elucidated. We present an analysis of the relations between LGE, ECV, ventricular arrhythmias, clinical markers of SCD, and impaired diastolic function in patients with HC.

Methods

This study retrospectively analyzed imaging data of 252 patients with a diagnosis of HC who underwent contrast-enhanced CMR at Northwestern Memorial Hospital between January 2012 and December 2014. Inclusion criteria were patients aged 18 through 75 years who had not undergone septal reduction with surgical myectomy or alcohol septal ablation, did not have obstructive coronary disease (defined as previous myocardial infarction, ischemia on stress testing, or cardiac catheterization demonstrating obstructive disease), and who had data available to assess the study's primary parameters. A total of 149 patients were excluded, leaving a final study population of 103 subjects. The mean age at the time of CMR was 51 ± 14 years (18 to 75 years), and 43 (42%) were women. A waiver of consent was approved by the Northwestern University Institutional Review Board.

Clinical parameters were evaluated through retrospective chart review. History of nonsustained ventricular tachycardia (NSVT) was assessed through review of 24 or 48 hour ambulatory Holter monitoring studies. Per inclusion criteria, all subjects had at least 1 documented Holter monitoring study. Other clinical markers of SCD risk included in this study were unexplained syncope, SCD in a first-degree relative, and maximal LV wall thickness. Echocardiographic parameters including the peak resting LV outflow tract gradient, left atrial volume index (LAVI) and ratio of mitral inflow velocity to diastolic lateral mitral annular velocity (E:e' ratio) were included. Echocardiographic measurements were taken from the study date nearest the index CMR study. Subjects without echocardiographic data were nonetheless included in the arrhythmia

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analysis. The maximal LV wall thickness was determined at end diastole at the LV location of maximal thickness in the 3-chamber or short-axis view of the index CMR study.

CMR was performed on a 1.5T or 3T Siemens Avanto/Espree scanner. The CMR protocol consisted of multiplanar cine steady state free precession (SSFP), T1 mapping pre and post-contrast and standard delayed enhanced imaging. Cine SSFP was acquired as a segmented breath held acquisition in 3 chamber, 4 chamber, 2 chamber and stack of short axis orientations. T1 mapping utilized pre- and 12-25 minutes post-contrast balanced SSFP single-shot Modified Look-Locker inversion-recovery with data acquisition over 11 heartbeats (Myomaps, Siemens Medical Systems, Erlangen, Germany).[16] Analysis of native T1 mapping was not performed due to measurement variability of native T1 values between 1.5 and 3 Tesla fields.[17] LGE imaging used conventional segmented, inversion-recovery turboFLASH imaging to generate a stack of short-axis images.

An experienced observer (JC) blinded to clinical findings first evaluated the images for presence or absence of delayed enhancement. Quantification of LGE, defined as percentage of total myocardial mass consisting of scar, was performed in subjects with visually identified scar by a second investigator (JL) using semiautomated software (QMass version 7.6, Medis) applying a 6 standard deviation threshold (Figure 1, left).[18] Patients received 0.1 or 0.2 mmol/kg gadopentetate dimeglumine contrast based on point of care GFR with postcontrast T1 maps acquired between 12 and 25 minutes after contrast. Three short-axis slices (apical, mid-chamber, basal) were used to measure native T1 values with contours inclusive of the entire myocardial wall, with omission of papillary muscles (Figure 1, right). Mean ECV was calculated through measurement of all segments, including those with scar, according to the formula of *Schelbert* et al[19] using hematocrit values. Segmental LGE and ECV values were calculated based on the AHA 16 segment model. In a separate analysis, ECV was averaged over myocardial segments without LGE (LGE (−)) in order to minimize signal from macroscopic scar and assess the extent of true background fibrosis. Variance in measurement between observers and between trials of the primary observer was determined through reassessment of 8 subjects in the cohort.

Analysis comparing the prevalence of NSVT to LGE and ECV used binomial logistical regression. Chi-square tests were used for categorical variables and Wilcoxon rank-sum tests for continuous variables. All p values were 2-tailed. Mean values are reported with ranges in parentheses.

Results

The prevalence of NSVT, syncope, and family history of SCD are reported in Table 1. One aborted SCD event occurred in a patient with a previous history of NSVT.

LGE was present in 71 (69%) of 103 subjects. Mean global LGE in subjects with LGE was 10.2% (0.5% to 45.9%) of LV myocardial mass. Mean ECV in all subjects was 26.6% (17.6% to 47.4%). Subjects without LGE had a mean ECV of 24.9% (20.7% to 32.9%). In subjects with LGE, mean ECV in LGE (−) segments was 25.7% (17.5% to 48.0%). In all subjects, segmental LGE ranged from 0 to 95.5% of segmental mass and segmental ECV ranged from 12.3 to 63.9%.

A significant correlation was present between increasing LGE and prevalence of NSVT ($p < 0.01$). With inclusion of all myocardial segments and the mean ECV of the study population of 27% applied as a threshold, there was a significant increase in NSVT in subjects with ECV ≥27% compared to those with ECV <27% ($p = 0.023$; Figure 2). The difference was not significant when ECV analysis was limited to LGE (−) segments ($p = 0.15$). In subjects with a history of NSVT, mean global LGE was 13.0% (0 to 45.9%) and mean ECV was 28.3% (21.5 to 47.4) compared to LGE of 4.5% (0 to 35.7%, $p < 0.001$) and ECV of 25.9% (17.6% to 34.5%, $p = 0.021$) in subjects without NSVT. In the 2

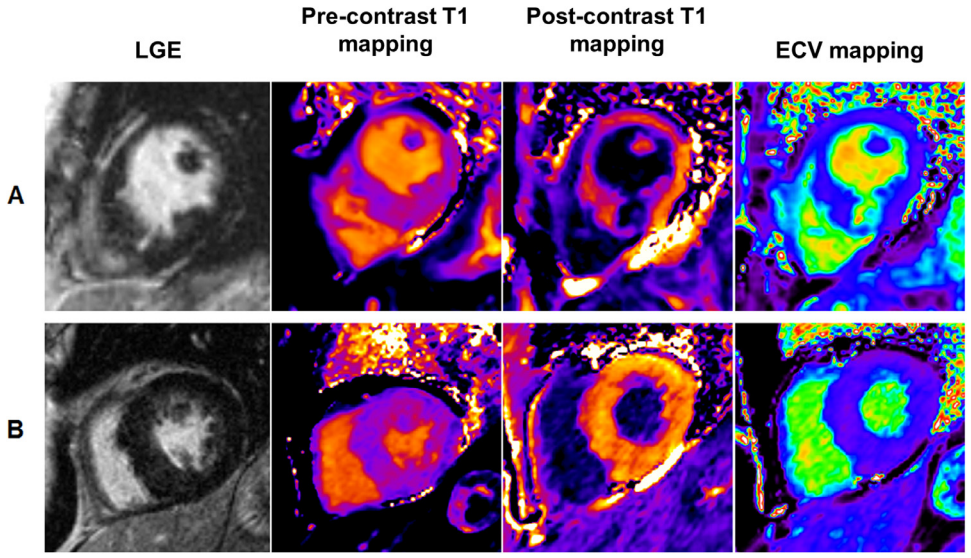

Figure 1. Short axis slices demonstrating methodology for late gadolinium enhancement (LGE), precontrast and postcontrast T1 mapping, and extracellular volume (ECV) mapping. Compared are 2 studies, each without significant LGE, and with abnormal mean ECV (row **A**, ECV = 32.6%) and normal mean ECV (row **B**, ECV = 23.0%) values.

Table 1
Correlates of extracellular volume and late gadolinium enhancement

Variable	Global extracellular volume			Global late gadolinium enhancement			
	<27% (n = 59)	>27% (n = 44)	p value	0% (n = 32)	0-10% (n = 45)	>10% (n = 26)	p Value
Nonsustained ventricular tachycardia	12 (20%)	18 (41%)	<0.05	2 (6%)†,‡	12 (27%)†*	16 (62%)‡*	†<0.05 ‡<0.05 *<0.05
Syncope	9 (15%)	7 (16%)	ns	5 (16%)†,‡	5 (11%)†*	6 (23%)‡*	†ns ‡ns *ns
Family history of sudden cardiac death	2 (3%)	7 (16%)	<0.05	1 (3%)†,‡	2 (4%)†*	6 (23%)‡*	†ns ‡<0.05 *<0.05
Mean maximal wall thickness, mm	19.2	20.4	ns	16.9†,‡	20.3†*	22.3‡*	†<0.05 ‡<0.05 *ns
Left atrial volume index, ml/m^2 (n = 94)	33.6	37.8	ns	30.5†,‡	37.7†*	37.9‡*	†<0.05 ‡<0.05 *ns
E/e' ratio (n = 87)	11	12.5	ns	10.9†,‡	12.4†*	11.5‡*	†ns ‡ns *ns
Peak left ventricular outflow tract gradient, mm Hg (n = 100)	43.3	38.3	ns	37.2†,‡	50.9†*	28.6‡*	†ns ‡ns *ns

* p values for differences between 0% and 0-10% LGE groups.
† p values for differences between 0% and >10% LGE groups.
‡ p values for differences between 0-10% and >10% LGE groups.

subjects with NSVT without LGE, mean ECV values were 21.6% and 22.9%.

The mean maximal wall thickness was 19.7 mm (range 11.2 to 37.7 mm) and 3 (2.9%) subjects had a maximal wall thickness >30 mm. In subjects with available echocardiographic data, the mean E:e' ratio was 11.7 (n = 87, 4.1 to 35.0) and 20 (23%) subjects had E:e' ratio >15, indicating elevated LV filling pressures. Mean LAVI was 35.4 ml/m^2 (n = 94, 11.9 to 79.1 ml/m^2).

Quantification of LGE and ECV was reproducible with no significant bias. For LGE, the intraclass correlation coefficient between observers was 0.848 and between reviews of the same observer was 0.693. For ECV, the intraclass correlation coefficient between observers was 0.970 and between reviews of the same observer was 0.972.

Discussion

Our data indicate a wide range of ECV (17.6% to 47.4%) and LGE (0 to 45.9%) in HC. Segmental analysis reveals further heterogeneity by myocardial region. There is a wide range of ECV (20.7% to 32.9%) in patients without LGE,

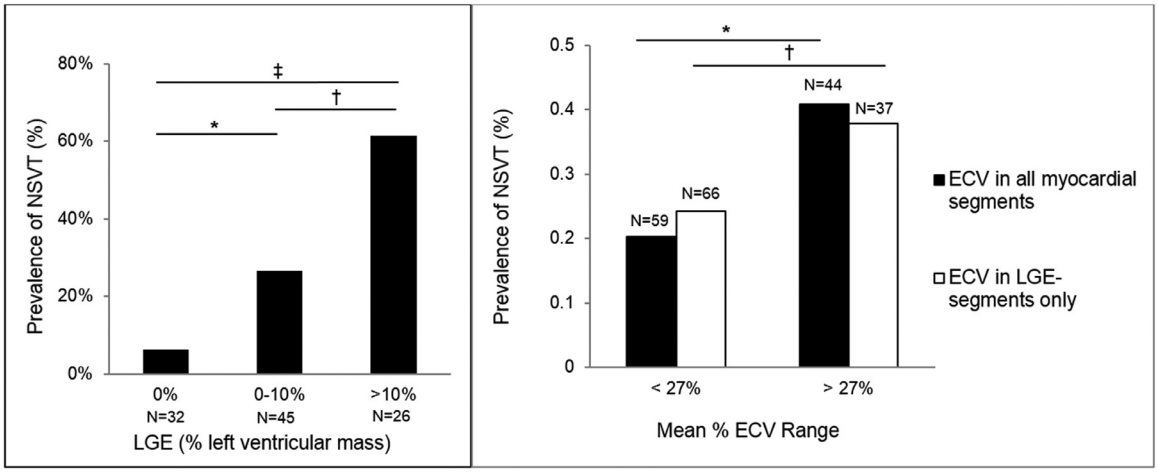

Figure 2. Prevalence of nonsustained ventricular tachycardia (NSVT) as a function of late gadolinium enhancement (LGE) and extracellular volume fraction (ECV). Left: NSVT prevalence increased with the extent of LGE (*p = 0.022, †p = 0.004, ‡p < .0001). Right: %ECV above the study population mean (>27%) was associated with a significant increase in NSVT (*p = 0.02), however the difference was not significant when limited to ECV in LGE (−) segments (†p = .15).

and in all patients, myocardial segments without LGE demonstrate ECV that is variable and frequently elevated.

Both the presence and extent of LGE were significantly correlated with NSVT, with an almost 10-fold increase in NSVT prevalence in subjects with LGE >10% compared with those without LGE. This confirms the previously demonstrated correlation between greater amounts of LGE and a higher prevalence of NSVT.[9,13,14] This study also supports the notion that a mild phenotype of HC with maximal wall thickness <16.0 mm and LGE <10% is unlikely to be associated with NSVT. Importantly, lack of evidence of fibrosis did not preclude the presence of NSVT, as 2 subjects without LGE and 12 subjects with ECV <27% had documented NSVT.

We observed a significant twofold increased prevalence of NSVT in patients with mean ECV above the study population mean of 27% compared with those with mean ECV <27%. This suggests that ECV may be more useful as a threshold value in evaluating arrhythmic risk in comparison with LGE, which remains more robust in its association with NSVT as a continuum. ECV analysis represents a potentially promising modality for risk stratification, especially in patients with low-to-intermediate LGE and patients in whom imaging artifact precludes accurate LGE estimation. Larger studies such as the ongoing Hypertrophic Cardiomyopathy Registry study are expected to further elucidate the relative utility of LGE and ECV in this disease.[20]

In the evaluation of diastolic dysfunction, LGE demonstrated a stronger association with LAVI compared with ECV. The exact mechanism for this finding is unclear, however, the degree of microscopic fibrosis in this population may not have been sufficiently elevated to correlate with LAVI. Neither parameter was associated with E:e′ ratio, a finding which contrasts with a previous study suggesting a link between ECV and diastolic function assessed by e' velocity.[5] The method of ECV quantitation and the difference in patient characteristics may in part account for this difference.

There are several limitations to our analysis. Only 1 aborted SCD event occurred in the population of 103 patients, and therefore, relationships between ECV, LGE, and SCD could not be meaningfully assessed. Although the presence of NSVT on ambulatory Holter monitoring is evidence of arrhythmia with potential for progression to malignant ventricular rhythms, it does not predict the incidence of SCD in all patients.[21] Sampling of 3 short-axis slices for ECV may result in sampling error, with inadvertent omission of scar between slices. Volumetric measurement of ECV threshold mass may provide a more detailed assessment of ECV throughout the myocardium and thus a more thorough comparison with myocardial LGE mass.

In conclusion, this study demonstrates broad heterogeneity in the pattern and extent of LGE mass and ECV. There appears to be a threshold value of ECV (27%) above which it is associated with NSVT, while the relation of LGE with NSVT appears more continuous, corroborating previous CMR studies in HC. This study also demonstrates correlation of LGE but not ECV with LAVI. Future studies are needed to define the potential association of ECV with ventricular arrhythmias and diastolic function in HC.

Compliance With Ethical Standards

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed Consent

A waiver of consent was approved by the Northwestern University Institutional Review Board (IORG #IORG0000247).

Consent to Publish

Consent for publication was obtained for every individual person's data included in the study.

Author Contributions

Jonathan Levine: Conceptualization, Methodology, Investigation, Writing - Original Draft; Jeremy D Collins: Conceptualization, Methodology, Investigation, Writing - Review & Editing; Emmanuel Ogele: Investigation; Gillian Murtagh: Conceptualization, Writing - Review & Editing; James C Carr: Conceptualization, Methodology, Writing - Review & Editing; Robert O Bonow: Writing - Review & Editing; Lubna Choudhury: Conceptualization, Methodology, Writing - Review & Editing, Supervision

Disclosures

Dr. Murtagh is currently an employee of Abbott Diagnostics (since 7/6/15); however, she was employed by Northwestern University at the time of the study. Abbott did not provide any funding and had no role in study design, research, analysis, writing or approval of the publication. The remaining authors have no relationships to disclose relevant to the topic of the manuscript.

1. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. *Cell* 2001;104:557–567.
2. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287:1308–1320.
3. Ho CY. Hypertrophic cardiomyopathy in 2012. *Circulation* 2012;125:1432–1438.
4. Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. *J Am Coll Cardiol* 2000;35:36.
5. Ho CY, Abbasi SA, Neilan TG, Shah RV, Chen Y, Heydari B, Cirino AL, Lakdawala NK, Orav EJ, Gonzalez A, Lopez B, Diez J, Jerosch-Herold M, Kwong RY. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. *Circulation: Cardiovasc Imaging* 2013;6:415–422.
6. Varnava A, Elliott P, Sharma S, McKenna W, Davies M. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* 2000;84:476–482.
7. Maron BJ, Maron MS, Lesser JR, Hauser RG, Haas TS, Harrigan CJ, Appelbaum E, Main ML, Roberts WC. Sudden cardiac arrest in

hypertrophic cardiomyopathy in the absence of conventional criteria for high risk status. *Am J Cardiol* 2008;101:544–547.
8. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, Bonow RO, Judd RM, Kim RJ. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;40:2156–2164.
9. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;130:484–495.
10. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Cardiovasc Magn Res* 2012;14:13.
11. Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM, McGregor C, Moon JC. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation* 2010;122:138–144.
12. Ellims AH, Iles LM, Ling LH, Chong B, Macciocca I, Slavin GS, Hare JL, Kaye DM, Marasco SF, McLean CA, James PA, du Sart D, Taylor AJ. A comprehensive evaluation of myocardial fibrosis in hypertrophic cardiomyopathy with cardiac magnetic resonance imaging: linking genotype with fibrotic phenotype. *Eur Heart J Cardiovasc Imaging* 2014;15:1108–1116.
13. Leonardi S, Raineri C, De Ferrari GM, Ghio S, Scelsi L, Pasotti M, Tagliani M, Valentini A, Dore R, Raisaro A, Arbustini E. Usefulness of cardiac magnetic resonance in assessing the risk of ventricular arrhythmias and sudden death in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2009;30:2003–2010.
14. Kwon DH, Setser RM, Popović ZB, Thamilarasan M, Sola S, Schoenhagen P, Garcia MJ, Flamm SD, Lever HM, Desai MY. Association of myocardial fibrosis, electrocardiography and ventricular tachyarrhythmia in hypertrophic cardiomyopathy: a delayed contrast enhanced MRI study. *Int J Cardiovasc Imaging* 2008;24:617–625.
15. McLellan AJ, Ellims AH, Prabhu S, Voskoboinik A, Iles LM, Hare JL, Kaye DM, Macciocca I, Mariani JA, Kalman JM, Taylor AJ, Kistler PM. Diffuse ventricular fibrosis on cardiac magnetic resonance imaging associates with ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2016;27:571–580.
16. Chow K, Thompson R. Myocardial T1 mapping – comparison of techniques. *MAGNETOM Flash* 2015;49:96.
17. Germain P, El Ghannudi S, Jeung MY, Ohlmann P, Epailly E, Roy C, Gangi A. Native T1 mapping of the heart – a pictorial review. *Clin Med Insights Cardiol* 2014;8(Suppl 4):1–11.
18. Harrigan CJ, Peters DC, Gibson CM, Maron BJ, Manning WJ, Maron MS, Appelbaum E. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. *Radiology* 2011;258:128–133.
19. Schelbert EB, Testa SM, Meier CG, Ceyrolles WJ, Levenson JE, Blair AJ, Kellman P, Jones BL, Ludwig DR, Schwartzman D, Shroff SG, Wong TC. Myocardial extravascular extracellular volume fraction measurement by gadolinium cardiovascular magnetic resonance in humans: slow infusion versus bolus. *J Cardiovasc Magn Res* 2011;13:16.
20. Kramer CM, Appelbaum E, Desai MY, Desvigne-Nickens P, DiMarco JP, Friedrich MG, Geller N, Heckler S, Ho CY, Jerosch-Herold M, Ivey EA, Keleti J, Kim DY, Kolm P, Kwong RY, Maron MS, Schulz-Menger J, Piechnik S, Watkins H, Weintraub WS, P7 Wu, Neubauer S. Hypertrophic cardiomyopathy registry: the rationale and design of an international, observational study of hypertrophic cardiomyopathy. *Am Heart J* 2015;170:223–230.
21. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;42:873–879.