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ORIGINAL ARTICLE
Vascular and cardiac imaging

Speckle tracking echocardiography-derived parameters as new prognostic markers in hypertrophic cardiomyopathies

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Aims Hypertrophic cardiomyopathies (HCM) are caused in 30–60% of cases by mutations in cardiac sarcomere genes but can also be an expression of cardiac involvement in multi-systemic metabolic diseases, such as Anderson–Fabry disease (AFD). HCM entails a risk of sudden cardiac death (SCD) of 0.9%/year and is the most common cause of SCD in young adults. Recent studies suggested mechanical dispersion (MD) by speckle tracking echocardiography (STE) as an additional arrhythmic risk marker. The aim of the study was to evaluate left ventricle global longitudinal strain (LV-GLS) and MD, in patients with HCM or AFD cardiomyopathy, and the association with ventricular arrhythmias (V-AR).

Methods and results We evaluated 40 patients with HCM, 57 with AFD (12 with LV hypertrophy and 45 without), and 40 healthy subjects, between January 2014 and June 2022. We performed a comprehensive echocardiographic study and analysed systolic and diastolic functions, LV-GLS, and MD. We also analysed V-AR, including ventricular fibrillation and sustained/non-sustained ventricular tachycardia, by Holter electrocardiogram (Holter-EKG), in a subset of hypertrophic patients. Data were analysed by unpaired Student *t*-test or chi-square/Fisher's exact test as appropriate and binary logistic regression (SPSS Statistics ver.26). LV-GLS was significantly lower in the V-AR group compared with patients without V-AR (median −10.2% vs. −14%, $P = 0.038$); MD was significantly higher in the V-AR group (85.5 ms vs. 61.1 ms, $P = 0.004$). V-AR were found significantly associated with MD (OR, 1.030; 95% CI, 1.003–1.058; $P = 0.03$).

Conclusions MD is a useful additional index in the evaluation of patients with HCM and may be a promising prognostic predictor of increased arrhythmic risk.

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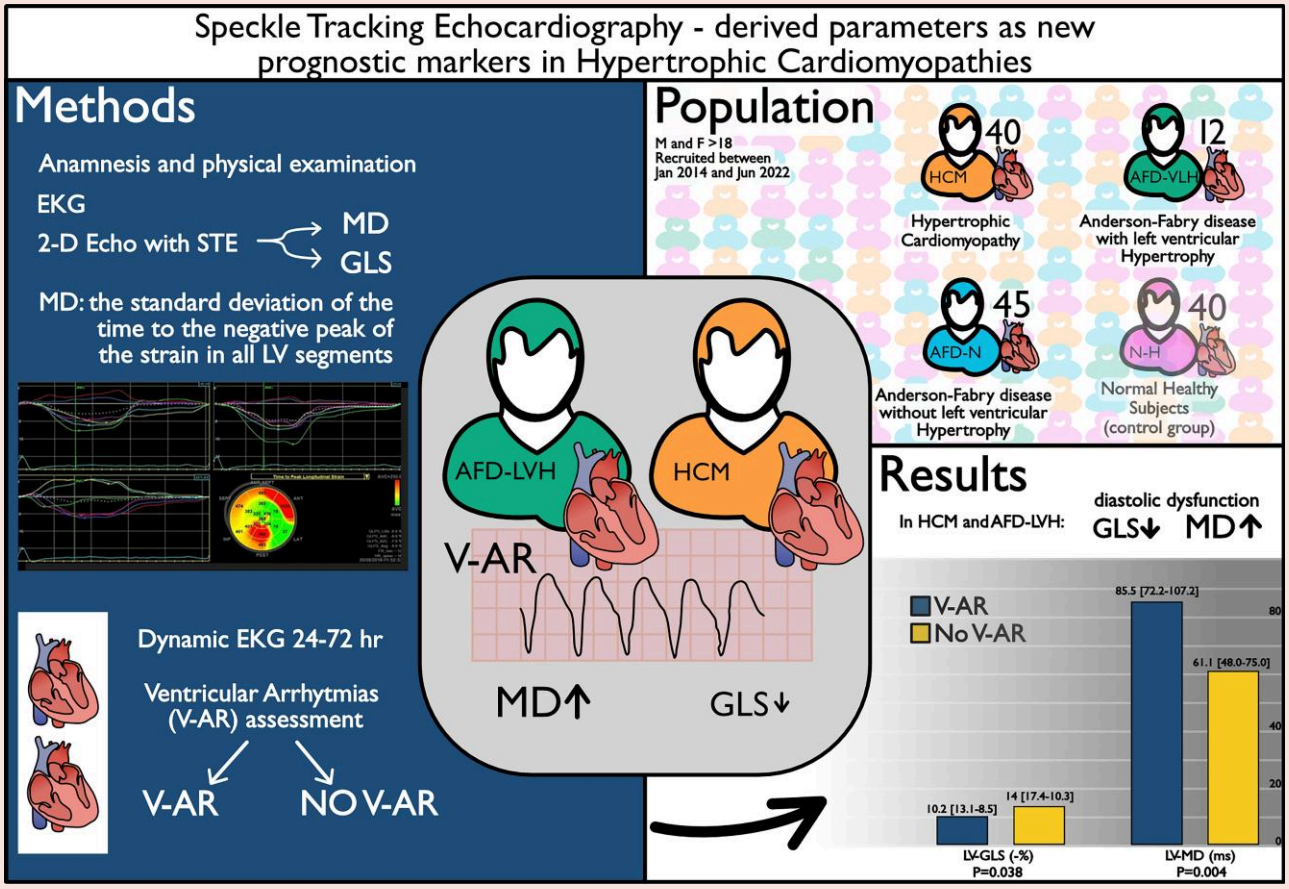
Graphical Abstract



EKG, electrocardiogram; STE, speckle tracking echocardiography; GLS, global longitudinal strain; MD, mechanical dispersion.

Keywords Hypertrophic cardiomyopathy • Anderson–Fabry disease • Cardiac arrhythmias • Speckle tracking echocardiography • Mechanical dispersion

Introduction

ESC 2014 Guidelines define hypertrophic cardiomyopathy (HCM) as the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions.[1] It entails a risk of sudden cardiac death (SCD) of 0.9%/year[2] and is the most common cause of SCD in adolescents and young adults, mainly due to ventricular fibrillation (VF). HCMs are caused in 30–60% of cases by mutations in cardiac sarcomere protein genes but also include metabolic diseases, such as Anderson–Fabry disease (AFD) with a prevalence of ~0.5–1% in patients aged 35–40 years. A meta-analysis about AFD[3] reported a 5.9% cardiovascular mortality rate, ventricular tachycardia (VT) prevalence of 15.3%, and SCD incidence of 0.34–1.4% per year. Over several decades, studies focused on risk stratification and the penetration of implantable cardioverter defibrillators (ICDs) into clinical practice have reduced significantly HCM-related mortality.[4]

HCM Risk-SCD, a predictive model for 5-year SCD, includes age, left atrium size, SCD family history, maximum wall thickness > 30 mm, unexplained syncope, left ventricle outflow tract (LVOT) gradient, and VT episodes. Patients are classified into three risk categories: high (>6%), intermediate (4–6%), and low (<4%); ICD implantation is recommended in high- and intermediate-risk patients.[1,5] Such mathematical risk score has shown to be associated with low sensitivity and would exclude some high-risk patients from ICD implantation;[2] moreover, it doesn't apply to metabolic and infiltrative diseases. Therefore, the most updated guidelines[4,6] recommend to consider several clinical risk markers in risk assessment especially in patients with intermediate or low calculated score: family SCD history from HCM, massive hypertrophy (wall thickness ≥ 30 mm), unexplained syncope, LV systolic dysfunction (EF ≤ 50%), apical aneurisms, non-sustained VT (NSVT) on ambulatory EKG monitoring, the presence of sarcomeric mutation, and extensive late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), which has been shown to be a strong predictor of ventricular arrhythmias (V-AR) and adverse events.[6–10]

Regarding AFD, to date, ICD is recommended in patients who survived a cardiac arrest due to VT or VF, or with sustained VT (SVT) causing syncope or hemodynamic compromise.[11]

Recent studies demonstrate that LV mechanical dispersion (LV-MD), obtained by speckle tracking echocardiography (STE), can be a novel adjunctive marker of arrhythmic risk, even in patients with preserved EF, related to the prevalence of myocardial fibrosis on CMR.[12,13] MD combined with LV global longitudinal strain (LV-GLS) has been considered an independent variable associated with the presence of VT in patients with HCM.[14,15] In AFD, a possible association of MD, fibrosis at CMR with VT, and SCD has been hypothesized.[8,11,16]

The aim of our study was to assess systolic and diastolic functions, LV-GLS, and LV-MD in patients with HCM or AFD and their association with V-AR, to clarify if they could be useful as prognostic markers for arrhythmic risk stratification.

Methods

Study design and population

In this retrospective, observational, single center study we included patients > 18 years old followed in our Clinical EchoLab of Rare Cardiomyopathies, between January 2014 and June 2022. Patients were selected according to the following inclusion criteria and divided into three groups:

(1) HCM: patients selected according to ESC 2014 Guidelines[1] transthoracic echocardiography (TTE) criteria: max wall thickness ≥ 15 mm or ≥13 mm for family members, with or without identification of the genetic mutation
(2) AFD–left ventricular hypertrophy (LVH): patients with AFD with a hypertrophic phenotype
(3) AFD-normal (N): patients with AFD but without hypertrophic phenotype.

A group of normal healthy (NH) subjects was added as a control group.

The patients underwent check-up annually with the following exams: anamnesis (with a family tree chart), general physical, cardiac examination and blood pressure measurement, routine laboratory tests, electrocardiogram (EKG), 2D-color Doppler TTE, a 12-lead 24–72 h Holter-EKG, or ICD interrogation. In HCM and AFD–LVH patients, we recommended to continue the diagnostic assessment with CMR imaging with and without contrast (in the absence of contraindication and according to patients' consent and compliance). All patients with LV hypertrophy, whether they had given informed consent, underwent a complete genetic counselling and assessment of a panel of genetic tests for mutations associated with HCM, and patients with a strong suspicion of AFD were tested for alpha galactosidase A activity (DBST method) and plasmatic globotriaosylsphingosine

Table 1 General characteristics of the patients

	HCM (*N* = 40)	AFD–LVH (*N* = 12)	AFD-N (*N* = 45)
Age	60.0 (48.7–65.0)	61.5 (54.7–63.0)	39.0 (28.0–48.5)
M	33 (82)	3 (25)	11 (25)
F	7 (18)	9 (75)	34 (75)
Hypertension	19 (47)	8 (66)	12 (27)
Diabetes	4 (10)	3 (25)	7 (15)
Smoke	6 (15)	2 (17)	11 (24)
Dyslipidaemia	15 (37)	1 (8)	6 (13)
Chronic kidney failure	3 (7)	5 (42)	2 (4)
Stroke/TIA	2 (5)	1 (8)	2 (4)
Syncope	6 (15)	1 (8)	4 (9)
Family history SCD	8 (20)	1 (8)	0
Family history HCM/AFD	13 (32)	9 (75)	18 (40)
Myectomy	6 (15)	0	0
Kidney transplantation	0	4 (33)	1 (2)
NYHA 1	9 (22)	4 (33)	35 (78)
NYHA 2	23 (57)	7 (58)	10 (22)
NYHA 3	8 (20)	1 (8)	0
NYHA 4	0	0	0
BP-sys (mmHg)	130 (120–140)	140 (126.2–143.7)	120 (110–130)
BP-dia (mmHg)	80 (70–80)	80 (71.2–83.7)	70 (70–80)
HR (bpm)	62 (55.2–75.5)	65.5 (52.5–75.2)	72 (66–75)
ERT-AFD		6 (50)	9 (20)
Migalastat-AFD		1 (8)	4 (9)
ICD	4 (10)	1 (8)	0
PM	0	1 (8)	0
CRT-D	1 (2)	0	0
Genetics positive	9 (22)	12 (100)	45 (100)
AFD mutation: classic		5 (42)	8 (18)
Late onset		4 (33)	18 (40)
VUS		1 (8)	16 (35)
Polymorphism		2 (17)	3 (7)

Where not specified, data are expressed as number and percentage.
TIA, transitory ischemic attack; NYHA, New York Heart Association; BP, blood pressure; sys, systolic; dia, diastolic; HR, heart rate; ERT, enzyme replacement therapy; ICD, implantable cardioverter defibrillator; PM, pacemaker; CRT-D, cardiac resynchronization therapy defibrillator; VUS, variant of uncertain significance.

(Lyso-Gb3) levels, and for mutations in the GLA gene. Next, we carried out a retrospective data analysis with the aim of studying the association between V-AR on Holter-EKG and echocardiographic parameters.

Echocardiography

A complete TEE was performed by Vivid7 or Vivid-E95 ultrasound machine (GE Horten, Norway) equipped with a 2.5 MHz phased array transducer and a software-based beamforming algorithm, in which we evaluated all the parameters, according to our laboratory standards and the EACVI/ASE recommendations.[17,18] In this study, we reported the following parameters: diastolic interventricular septum (IVSd) and posterior wall (PWd) thickness, LV mass index (LVMi), LV EF with the Simpson biplane method, left atrial volume index (LAVi), E wave mitral doppler velocity, tissue doppler imaging (TDI) at the septal and lateral mitral annulus (e') and the E/e' ratio, LVOT gradient (LVOT), and tricuspid regurgitation velocity (TR-V). STE analysis was performed offline using a dedicated software (EchoPAC ver.2.02, GE). LV-GLS was analysed from the apical views (3-4-2 chambers), at 60–70 fpm, from the average of three consecutive cardiac cycles, and MD was automatically obtained (as the standard deviation (SD) of the time to the negative peak of the strain in all LV segments). TTEs were performed by two operators (D.C.F. and V.L.) and validated by a single supervisor (I.P.M.). The imaging data reported refer to the first evaluation at our centre. From the initial database, we included in our study all patients with optimal image quality (due to good acoustic window and/or patient's cooperation), suitable for the speckle tracking analysis.

Arrhythmias

The arrhythmic episodes were detected in a subsequent follow-up, after the first clinical and imaging assessment with Holter-EKG monitoring or device interrogation in patients with ICD or implantable loop recorder (ILR). We included episodes of SVT (>30 s) and NSVT (≥3 beats, but <30 s, and HR > 120 bpm). Premature ventricular complexes (PVC) were not included in the analysis. To estimate the SCD risk, we used the ESC HCM Risk-SCD Score,[1] and in the analysis of all the hypertrophic patients (HCM and AFD) together, we applied it also to AFD–LVH patients, with the awareness that in clinical practice it is not validated for these patients.

In the arrhythmias (outcome) analysis, we included only patients who presented at regular follow-up visits and have undergone Holter-EKG or device interrogations.

Statistical analysis

Data are expressed as mean ± SD for continuous variables with normal distribution, as median and interquartile range (IQR) for data with no normal distribution (after the Kolmogorov–Smirnov test was performed), and as number and percentage for categorical ones. Data were compared with unpaired Student's *t*-test or Mann–Whitney *U* test for continuous variables as appropriate based on the distribution and chi-square test and Fisher's exact test for non-continuous ones: statistical significance was defined for $P < 0.05$, two-tailed test. We applied Pearson correlation and subsequently binary logistic regression to study the association of the echocardiographic and non-echocardiographic parameters with the clinical outcome of V-AR. The software was IBM SPSS Statistics ver.26.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained at the time that the tests were performed.

Results

Study population

We included 97 patients, divided into three groups: 40 HCM, 12 AFD–LVH, 45 AFD-N, and a control group of 40 NH. The median age of all patients was 51.0 years (IQR 36.5–62.0), and 48% were males. Complete data are shown in *Table 1*.

Among HCM patients, 15% (vs. 8% of AFD–LVH and 9% of AFD-N) reported at least one syncopal episode; 20% had a family history of SCD. The median follow-up was 32 months (IQR 16–46). Most patients with hypertrophy were in the New York Heart Association

Table 2 EKG data

	HCM (*N* = 40)	AFD–LVH (*N* = 12)	AFD-N (*N* = 45)	*P*
RBBB	1 (2)	1 (8)	3 (7)	0.53
LBBB	4 (10)	0	0	0.06
AVB-III	0	1 (8)	0	0.12
Short PR	2 (5)	3 (25)	0	0003
Arrhythmic death	1 (2)	1 (8)	0	0.11
Holter EKG	33 (82)	8 (66)	3 (7)	<0.001
VT/NSVT	13 (32)	5 (42)	0	<0.001
Recurring PVCs	12 (30)	1 (8)	0	<0.001
AF	7 (17)	7 (58)	0	<0.001
PSVT	8 (20)	6 (50)	1 (2)	<0.001
HCM Risk-SCD (%)	2.4 (1.4–3.7)	1.4 (0.8–1.7)		0.12
Low (<4%)	32 (80)	9 (75)		0.71
Intermediate (4–6%)	5 (13)	2 (17)		0,71
High (>6%)	3 (7)	1 (8)		0.92

Where not specified, data are expressed as number and percentage.
RBBB/LBBB, right/left bundle branch block; AVB, atrioventricular block; SVT/NSVT, sustained/non-sustained ventricular tachycardia; PVC, premature ventricular complex.

(NYHA) 2 class, while AFD-N were mostly in NYHA 1. Only in 22% we identified the genetic mutation, while among AFD patients, 42% were carriers of a classic mutation and 33% of a late-onset mutation. One patient was identified as carrier of both HCM (MYH7) and GLA mutation (D313Y), with a phenotypic expression of non-obstructive hypertrophy and V-AR at Holter-EKG; indeed, another patient was a carrier of a multigenic genotype (mutations of uncertain significance in MYOM1, LDBE, and SGCD genes), with a phenotype of biventricular severe hypertrophy, heart failure, and NSVT runs on Holter-EKG. In AFD patients, a unique mutation was not found in the subgroup with hypertrophy, but five of them were carriers of classic mutations and four of late-onset ones; 50% of AFD–LVH and 20% of AFD-N patients were under enzyme replacement therapy (ERT).

Table 2 shows data of EKG, Holter-EKG, and SCD score. In the HCM group, 32% (13/32 patients) reported VT/NSVT episodes, and the percentage was even higher in the AFD–LVH group (5/12 patients, 42%). The median HCM-SCD score was 2.4% (IQR 1.4–3.7), with 80% of patients in the low-risk, 13% in the intermediate-risk, and 7% in the high-risk range. In the AFD–LVH group, three patients showed short PR interval and delta wave at baseline EKG; in the same group, one patient underwent pacemaker implantation after a syncopal episode due to complete atrioventricular block, and another patient, with pre-excitation at baseline EKG (and no identifiable accessory pathways at electrophysiological study), underwent ICD implantation after V-AR were found on ILR. AFD–LVH patients who developed arrhythmias were mostly carriers of classic mutations.

A subset of patients underwent CMR (38/97 in the overall population). Among HCM patients who underwent CMR (28/40, 70%), three out of four tested positive for LGE. The distribution of LGE coincided mainly with the areas of more pronounced hypertrophy (IVS and anterior wall); in few patients, it involved the areas of septal-LV free wall junction and the papillary muscles. In the AFD–LVH group, 58% (5/12) of patients underwent CMR: of these, 71% showed LGE, with constant involvement of the infero-lateral medio-basal wall. Two AFD-N patients, who are currently on ERT, underwent CMR due to evidence of cardiac involvement (reduced LV-GLS with a typical infero-lateral medio-basal distribution, papillary muscle hypertrophy, and exertional dyspnoea): one of them showed a limited area of LGE in a typical location for AFD (medio-basal segment of the infero-lateral wall) and the other one will undergo follow-up CMR again shortly.

Two patients (one AFD–LVH and one HCM) died during follow-up. The AFD 64-year-old patient, who was a carrier of a classic mutation (E341X) and showed a short PR at baseline EKG, severe concentric hypertrophy with diastolic dysfunction, markedly reduced LV-GLS (−4%), and increased MD (231 ms), had VF and cardiac arrest in the last hospitalization for acute heart failure. The HCM 60-year-old patient was in NYHA 2 class and showed a severe asymmetric hypertrophy pattern with severe mitral regurgitation and died suddenly during the night. Both patients tested positive for LGE: the AFD patient showed a complex LGE pattern, with enhancement of infero-lateral-basal segments typical of AFD and transmural LGE of distal antero-lateral segments and the apex, consistent with ischemic outcomes.

Echocardiographic analysis: diastolic function, GLS, and MD compared between the groups (*Table 3*).

All patients displayed normal LV volumes and EF. More than 75% HCM patients had asymmetric hypertrophy, 13% apical hypertrophy, 45% LVOT obstruction, and 22% systolic anterior motion (SAM) of the mitral valve, while 66% of AFD–LVH had concentric hypertrophy, without a significant LVOT gradient or SAM.

Table 3 Comparison of echocardiographic parameters

	HCM (*N* = 40)	AFD–LVH (*N* = 12)	AFD-N (*N* = 45)	NH (*N* = 40)	*P*	*P*-value				
						HCM vs. NH	HCM vs. AFD-N	HCM vs. AFD–LVH	AFD–LVH vs. AFD-N	AFD–LVH vs. NH	AFD-N vs. NH
IVS (mm)	15.5 (14–18)	13 (11.3–17.3)	8 (6.4–9)	8.7 (7.1–9.4)	**<0.001**	**<0.001**	**<0.001**	0.11	**<0.001**	**<0.001**	0.14
PW (mm)	11.5 (10–13)	11.8 (10.2–14)	8 (7–9)	8.9 (7–10)	**<0.001**	**<0.001**	**<0.001**	0.45	**<0.001**	**<0.001**	0.14
LVMi(g/mq)	132 (113–166.2)	116 (104.7–180.7)	68 (54.5–79.5)	76.8 (60.2–89.7)	**<0.001**	**<0.001**	**<0.001**	0.42	**<0.001**	**<0.001**	**0.02**
EF%	64 (60–70)	65.0 (61.2–69.2)	66 (62.5–70)	64.5 (62–66.7)	0.61	0.92	0.36	0.64	0.83	0.58	0.18
LAVi(mL/mq)	38.5 (31.2–51)	42.5 (33.2–54)	22 (17–27)	19 (14.7–27)	**<0.001**	**<0.001**	**<0.001**	0.57	**<0.001**	**<0.001**	0.35
E/e'	12.6 (8.9–15)	11.5 (8.5–17)	7 (6–9)	7 (6–8)	**<0.001**	**<0.001**	**<0.001**	0.85	**0.001**	**<0.001**	0.56
TR-Vmax(m/s)	2.2 (1.8–2.5)	2.3 (2.0–2.4)	2.3 (2–2.4)	2.1 (1.9–2.3)	0.67	0.80	0.69	0.57	0.70	0.27	0.22
LV-GLS (−%)	13.4 (10.1–15.5)	11.8 (9.2–17.5)	18 (16.5–20)	20 (18–21)	**<0.001**	**<0.001**	**<0.001**	0.71	**0.001**	**<0.001**	**0.01**
LV-MD (ms)	72.5 (55.7–87.5)	74.0 (59.2–90)	36 (29–47)	31 (27–41)	**<0.001**	**<0.001**	**<0.001**	0.80	**<0.001**	**<0.001**	0.12

Data are expressed as median interquartile range and *n*°(%) as appropriate. Bold values specify statistically significant *P* values.
IVS, interventricular septum; PW, posterior wall; LVMi, LV mass index; EF, ejection fraction; LAVi, left atrial volume index; E/e', ratio between E wave of mitral flow and e' at tissue Doppler; TRV, tricuspid regurgitation velocity; GLS, global longitudinal strain; MD, mechanical dispersion.

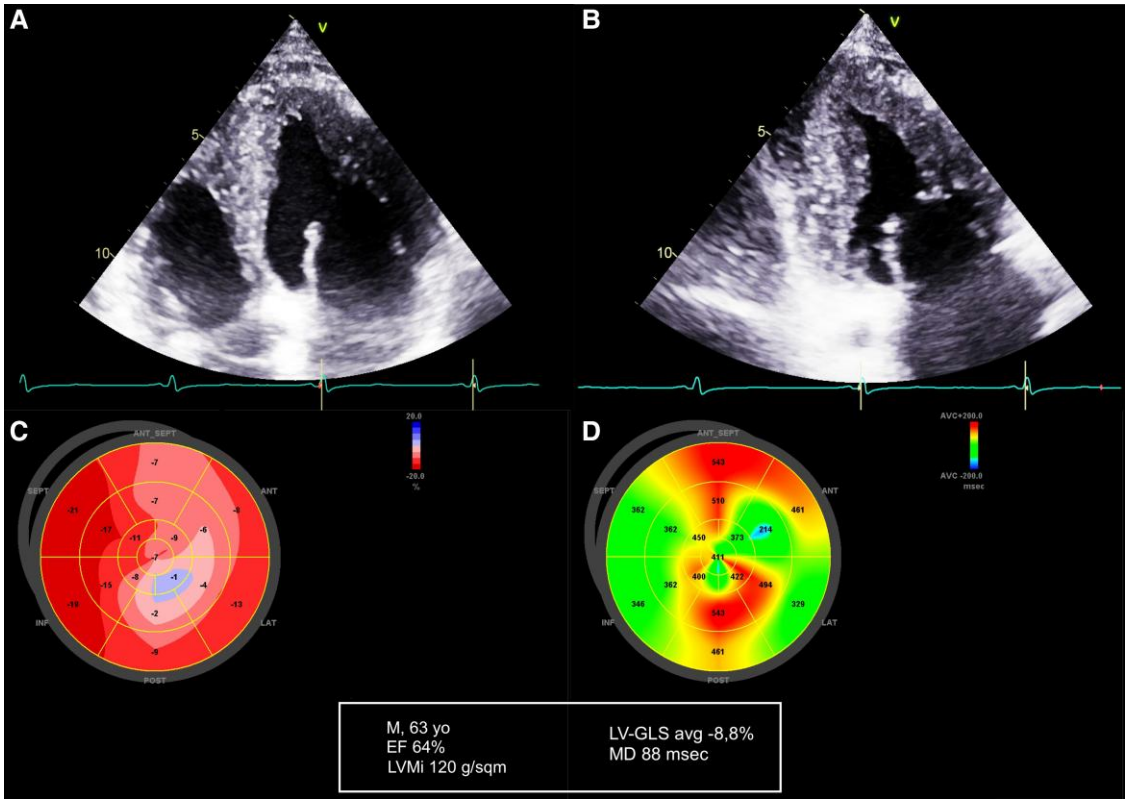


Figure 1 Patient with hypertrophic cardiomyopathy. (*A*) Apical four-chamber view; (*B*) apical two-chamber view; (*C*) global longitudinal strain; (*D*) mechanical dispersion.

In both HCM and AFD–LVH, we found different patterns of diastolic function compared with AFD-N and NH: a significantly higher E/e' and LAVi and higher TR-Vmax, although not significantly. Respectively, in HCM and AFD–LVH groups, median E/e' were 12.6 and 11.5 and median LAVi 38.5 and 42.5 mL/mq.

LV-GLS was significantly reduced in HCM and AFD–LVH (median −13.4% and −11.8%, respectively), compared with the other groups, and also in AFD-N compared with NH ($P = 0.01$). MD was increased in HCM (72.5 ms, IQR 55.75–87.5), with a significant difference compared with AFD-N and NH (both $P < 0.001$); in AFD–LVH, it was also slightly even greater (74 ms, IQR 59.2–90), with a significant difference compared with AFD-N ($P = 0.02$) and NH ($P = 0.008$) (*Figures 1–3*). Pearson correlation showed a strong correlation (>0.5) of MD with LVMi, LAVi, E/e', and LV-GLS.

Outcome analysis: V-AR and MD in LVH patients

To investigate the prognostic role of LV-GLS and MD in V-AR, we selected from the general group a subset of all hypertrophic patients (both HCM and AFD–LVH) who underwent at least one Holter-EKG (or ICD interrogation) and gathered them together in one comprehensive group of 'hypertrophic patients' (41 patients: 33 HCM and eight AFD–LVH). These patients were divided into two groups based on the presence (V-AR) or absence (NO V-AR) of major VA, and the differential characteristics were analysed (*Table 4*). V-AR patients had a median SCD score of 3.6% vs. 2.3% in the NO V-AR group ($P = 0.05$).

Comparing the two groups with *t*-test, in the V-AR group, LV-GLS was significantly lower (median −10.2% vs. −14%, $P = 0.038$) and MD was significantly higher (median 85.5 ms, IQR 72.2–107.2 vs. 61.1 ms, IQR 48.0–75.0, $P = 0.004$) (*Figure 4*). At binary logistic regression, there was a significant association of V-AR with MD ($P = 0.03$, OR 1.030, 95% CI 1.003–1.058).

Discussion

LV-GLS and MD in the hypertrophic phenotype: physio-pathological considerations and result analysis

In our work, we compared clinical and echocardiographic data of a group of HCM patients, a group with LVH secondary to AFD, a group of AFD without LVH, and a control normal group. Data analysis showed that HCM and AFD–LVH, compared with normal and AFD-N, exhibit impaired diastolic function (significantly higher LAVi and E/e' and higher TR-V max, even if not significantly), a significantly reduced longitudinal function (LV-GLS) despite preserved EF, and markedly increased dyssynchrony (MD).

In the outcome analysis, we found a great percentage of HCM patients showing V-AR (32%); V-AR incidence was even higher in AFD–LVH patients (42%, although with the limitation of the small sample size).

Our results show that an increased MD, and together with it the risk of V-AR, is closely correlated with the development of the hypertrophic phenotype, and this applies to both groups of patients with LVH, regardless of the aetiology (sarcomeric or accumulation).

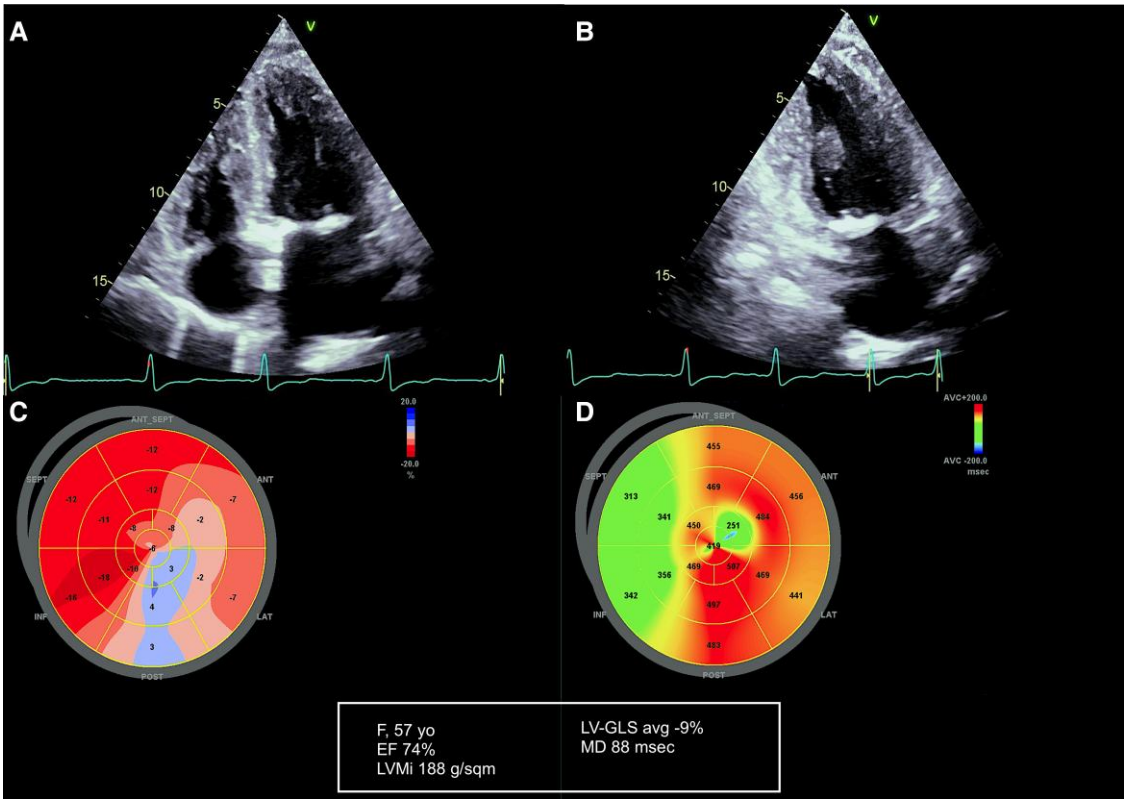


Figure 2 Patient with AFD–LVH. (*A*) Apical four-chamber view; (*B*) apical two-chamber view; (*C*) global longitudinal strain; (*D*) mechanical dispersion.

In HCM ventricular hypertrophy, fibre disarray, changes in myocyte diameter, and microvascular dysfunction can lead to myocardial ischaemia and fibrosis, causing unidirectional blockage, conduction delay, and heterogeneity, thus creating an anatomical substrate for the formation of re-entry circuits. Hypertrophic patients who develop arrhythmias show increased electrical dispersion of the impulse and inhomogeneity of intraventricular conduction.[12,19] In AFD, lyso-Gb3 accumulation in myocytes, together with the activation of a complex chronic inflammatory pathway, leads to progressive LVH and heart failure with preserved ejection fraction (HFpEF), while fibrosis and involvement of conduction tissue, together with the alteration of the electrical properties of cardiomyocytes (ion channel expression and/or cell membrane trafficking), entail the development of V-AR and conduction disturbances.[20]

LV systolic function, as traditionally measured by EF, is generally preserved in patients with HCM or AFD until advanced stages of the disease, concealing several critical issues, as the presence of symptoms of heart failure, and placing such cardiomyopathies among the causes of HFpEF.

Diastolic dysfunction in the hypertrophic phenotype has a complex multi-factorial pathogenesis, linked to mutations in myocardial contractile proteins that code for abnormal sarcomere proteins with impaired contraction and relaxation, changes in the reciprocal affinity, calcium sensitivity, and energetic efficiency, influenced by morphological factors such as the degree of hypertrophy, fibre disarray and interstitial fibrosis, reduced LV systolic volume, obliteration of the cavity, and LVOT obstruction, which lead to LV reduced distensibility.[21] AFD–LVH patients showed even lower LV-GLS and increased MD than HCM patients, even if not statistically significant.

Furthermore, going beyond the macroscopic assessment of EF and wall motion impairment, the added value of STE, through the assessment of GLS and MD, allows us to unveil early sub-clinical longitudinal systolic dysfunction, which is the first to appear even at the very early stages of cardiac involvement, and the related progressive contractile dyssynchrony.

To our knowledge, this is the first work that compares HCM with AFD patients for MD, as the works published so far have studied MD in HCM patients, comparing them with healthy controls and analysing the association with V-AR.[15,19] The results regarding HCM patients are consistent with the literature. In our patients, we found LV-GLS values of −13.4% and MD 72.5 ms. A correlation emerged between MD and LV-GLS, LVMi, LAVi, and E/e', as they are all linked to the mechanism of diastolic dysfunction and ventricular dyssynchrony, related to arrhythmic risk. Indeed, an intraventricular delay calculated between six baseline segments > 45 ms has been associated with an increased risk of V-AR and SCD.[22] The values in our population are similar to the ones reported in Haland *et al.*[15] (LV-GLS −15.7 ± 3.6%; MD 64 ± 22 ms) and in Ternacle *et al.*'s work, which compared HCM patients with moderate LVH to professional athletes and controls (LV-GLS −15 ± 3%, MD 66 ± 20 ms).

Association between echocardiographic parameters and ventricular arrhythmias

Since the patients with AFD–LVH were only 12 and the echocardiographic data were substantially comparable with the HCM group, we created one comprehensive group of 'hypertrophic' patients (HCM + AFD) to carry out a subsequent analysis of arrhythmias, including the patients who underwent arrhythmic assessment with Holter-EKG or device interrogation (41 patients). Of these patients, 18 (44%) had V-AR, and 23 did not.

Data analysis showed MD 85.5 ms in V-AR patients vs. 61.1 ms in NO V-AR (24.4 ms difference between the median values) and median

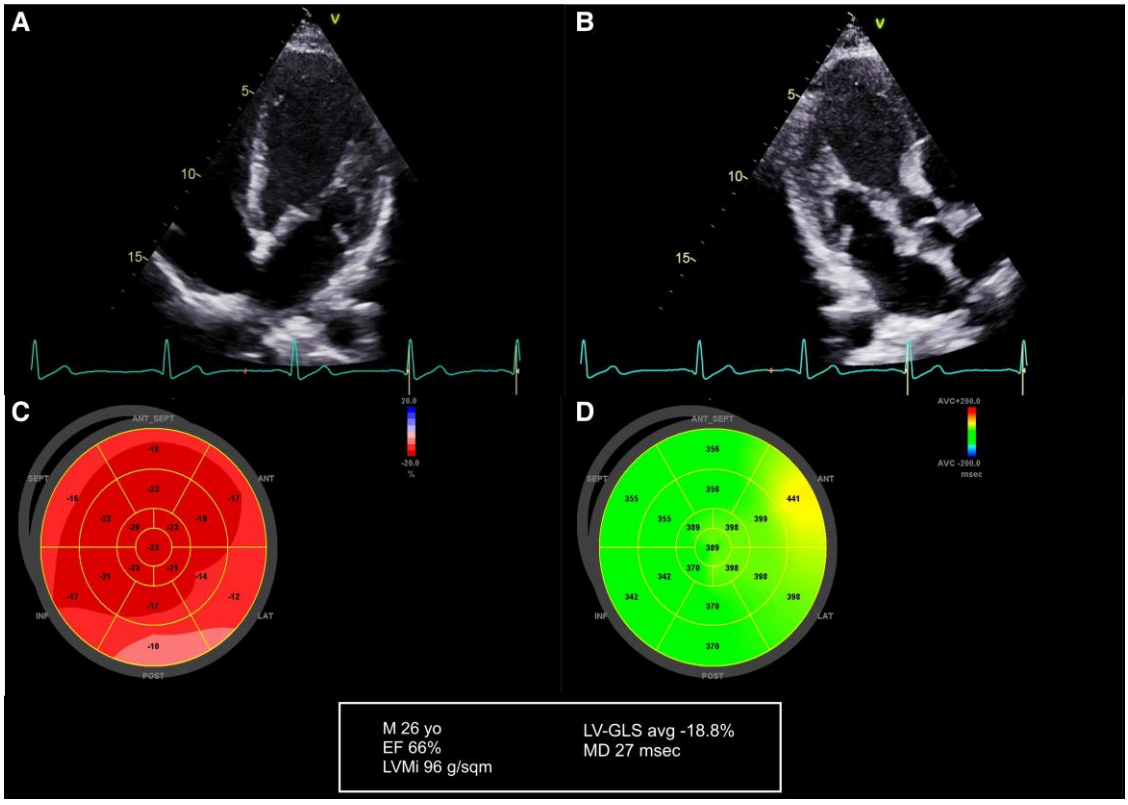


Figure 3 Patient with Anderson–Fabry disease without left ventricular hypertrophy. (*A*) Apical four-chamber view; (*B*) apical three-chamber view; (*C*) global longitudinal strain; (*D*) mechanical dispersion.

Table 4 Comparison between hypertrophic patients with ventricular arrhythmias (LVH V-AR) and without (LVH NO V-AR). This analysis included all patients who underwent Holter-EKG

	LVH V-AR (*N* = 18)	LVH NO V-AR (*N* = 23)	*P*-value	Binary log. regression (V-AR)—*P*
IVS (mm)	16.5 (14–18)	15.5 (13–18)	0.85	0.94
PW (mm)	12 (9.7–14)	12.0 (10.0–14.0)	0.87	0.52
LVMi (g/mq)	129.5 (117.5–1897)	132 (112–188)	0.62	0.65
EF%	62.5 (57.7–67.7)	65 (60–70)	0.29	0.29
LAVi (mL/mq)	41.5 (33–64.7)	38 (30–52)	0.21	0.09
E/e'	13.2 (10–17)	12.6 (8–14.2)	0.33	0.54
TR-Vmax (m/s)	2.35 (1.8–2.6)	2.1 (1.7–2.4)	0.41	0.45
LV-GLS (−%)	10.2 (8.5–13.1)	14 (10.3–17.4)	**0.038**	0.059
LV-MD (ms)	85.5 (72.2–107.2)	61.1 (48–75)	**0.004**	**0.03, OR 1.030 (95% CI 1.003–1.058)**
HCM risk-SCD (%)	3.6 (2.3–4.2)	2.3 (1.2–3.4)	**0.02**	0.05

Bold values specify statistically significant *P* values.

LV-GLS −10.2% (vs. −14% in NO V-AR patients), with a significant relationship between V-AR and MD (as expression of LV dyssynchrony). Our results are consistent with those that emerged in a recent metanalysis that confirmed that MD has a superior predictive value over EF and LV-GLS for risk stratification, as each 10 ms increment of MD was significantly and independently associated with V-AR.[13] Our data also confirm Haland *et al.*'s results[15], in which 25% of HCM patients had V-AR, with a significant difference between patients with and without V-AR for MD and LV-GLS, and are also broadly in line with the cut-offs found in the work on ROC analysis (greater V-AR risk for MD > 67 ms and LV-GLS > −15%); indeed, they are more pronounced.

Jalanko *et al.*'s study[14] showed higher MD in patients with NSVT at Holter-EKG (93 ± 41 vs. 50 ± 18 ms), concluding that MD was the only variable independently associated with the presence of NSVT

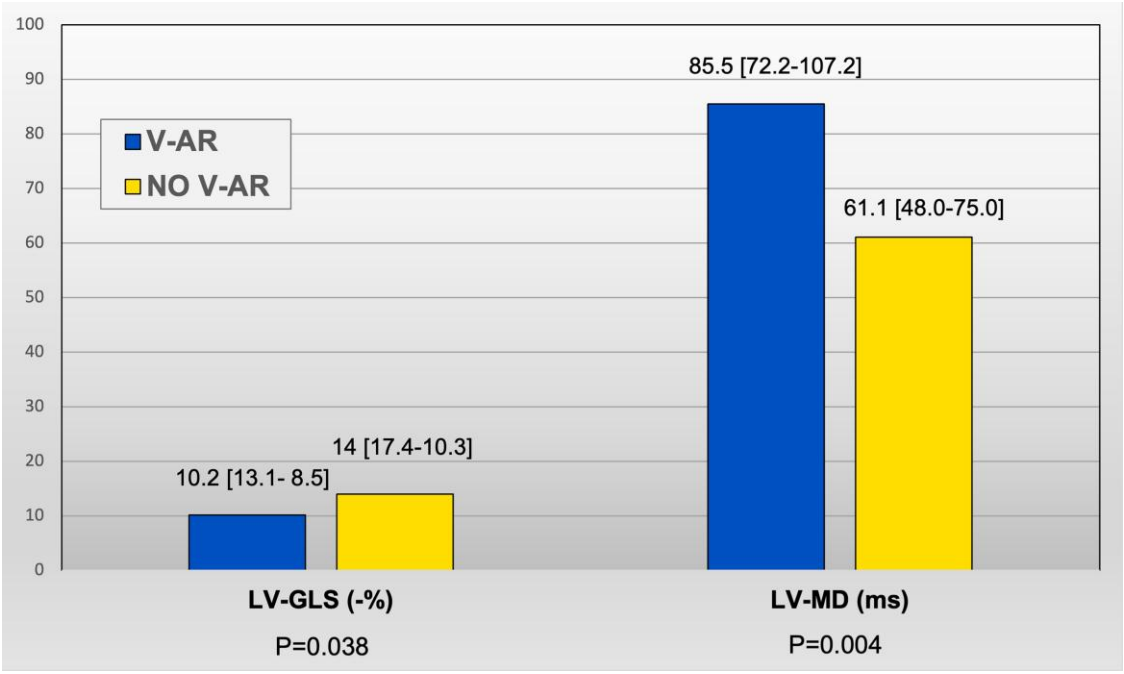


Figure 4 Comparison of LV-GLS and LV-MD in hypertrophic patients with ventricular arrhythmias (V-AR) and without (NO V-AR).

and the only discriminant between HCM patients with or without NSVT. Candan *et al.*[12] compared 63 HCM patients with ICD implantation, divided in two subgroups based on the presence of ICD appropriate interventions for sustained V-AR. Patients with appropriate ICD interventions showed significantly higher MD and LAVi and reduced LV-GLS, with conclusions consistent with ours.

Arrhythmic risk and mechanical dispersion in Anderson-Fabry disease

In AFD, the indications for ICD implantation are still unclear and variable, since HCM risk calculators specifically exclude patients with AFD, and to date, equivalent scores are not available.

According to the current literature, in AFD, the incidence of SCD is 0.34–1.4% per year, like that of HCM. The frequency of malignant VA varies widely from 5% to 30%: risk factors identified for SCD and VA include the male gender, older age (>40 years in males, as phenotype development in FD is more age dependent than in HCM), LVH (moderate association), and LGE on CMR.[3]

A recent retrospective study comparing AFD patients with HCM patients matched by sex and age showed that V-AR requiring antitachycardia pacing and/or defibrillation, SVT shocks, and atrial fibrillation burden are greater in the AFD group; moreover, they found more ICD implantations for secondary prevention, based on arrhythmic burden, in AFD patients than in HCM, demonstrating that AFD is more arrhythmogenic than previously thought.[23] Our results confirm and reinforce this trend, although considering the limited sample size, with a striking incidence of NSVT/VT detected at Holter-EKG monitoring and device interrogation (42%, higher than HCM), one ICD implantation, three patients with pre-excitation, and one case of SCD out of 12 AFD–LVH patients.

An apparently confounding variable is the difference in median age between hypertrophic patients (both HCM and AFD) and non-hypertrophic ones (AFD-N), with the latter being less symptomatic for heart failure and conduction disturbances: we tried to find an explanation in the fact that AFD-N patients were intercepted at an earlier stage of the disease, in which they are asymptomatic and in the absence of organ damage (many of them are family members of a proband and have only genetic positivity in the absence of clinical manifestations). This also is consistent with the current concept of FD-related cardiomyopathy as a progression with age that found support in the work of Nordin *et al.*,[24] which identifies, in the natural history of AFD, a progressive cardiac involvement in three stages, moving from an initial asymptomatic phase with lysoGB3 accumulation, without signs of inflammation, LVH, and fibrosis. The next phase is characterized by inflammation, with progressive myocardial dysfunction, initially sub-clinical: this phase is the most important for early diagnosis and changes at STE and CMR may sometimes precede the LVH development. The third phase is characterized by severe LVH and fibrosis, high biomarker levels, and advanced symptoms (heart failure, arrhythmias, and angina), with irreversible organ damage and poor response to therapy.

Cianciulli *et al.*[16] showed MD prevalence in hypertrophic and non-hypertrophic AFD patients compared with a healthy group: MD was significantly higher in hypertrophic AFD than the other groups, without difference between the non-hypertrophic and healthy groups. In our work, we found the same trend, with higher MD values in AFD hypertrophic patients and slightly higher in AFD non-hypertrophic ones. This, together with reduced LV-GLS (and impaired regional strain) underlines the importance of detecting cardiac involvement in AFD at a subclinical stage and pre-empting the development of fibrosis that means an irreversible damage.

Our study in addition analysed clinical outcomes (V-AR) and established a relationship between MD and arrhythmic risk: a hope for the future is to collect a greater number of AFD–LVH cases to analyse them independently, draw more solid conclusions for risk stratification

in AFD, and identify early prognostic markers to establish the right timing to start an effective disease-modifying therapy (ERT or chaperone therapy).

Study limitations

Our work's limitations are related to the limited sample size (as it is a single-centre study, involving patients affected by rare diseases) and its design (observational/retrospective). Another issue is that not all patients have undergone Holter-EKG, so the subset of patients for arrhythmia analysis is for now numerically limited.

Conclusions

STE-derived parameters are useful indices in the evaluation of patients with LV hypertrophy (sarcomeric or storage diseases), despite apparently that preserved EF occurs in the early stages of disease. MD is associated with a higher risk of V-AR, so it could be considered an additional reliable prognostic predictor in risk stratification.

Lead author biography

Short biography for EHJ open, Dr Denise Cristiana Faro. Dr Denise Cristiana Faro is a graduate of Medicine and Surgery in July 2013 and got the Postgraduate Diploma in Cardiology in December 2019, both at the University of Catania. She is currently a holder of a research grant in cardiology at the Department of General Surgery and Medical-Surgical Specialties, University of Catania. During the residency program and afterwards, she has deepened her training and clinical research activity in the field of heart failure, cardiovascular imaging, and cardiomyopathies, with particular interest in the field of rare cardiomyopathies with hypertrophic phenotype (HCM, Anderson–Fabry disease, and amyloidosis).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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