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ORIGINAL RESEARCH

IMAGING

Association of Epicardial Adipose Tissue and Ventricular Arrhythmias in Patients With Nonischemic Cardiomyopathy

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ABSTRACT

BACKGROUND Risk stratification for sudden cardiac death (SCD) in patients with nonischemic cardiomyopathy (NICM) remains challenging.

OBJECTIVES This study aimed to investigate the impact of epicardial adipose tissue (EAT) on SCD in NICM patients.

METHODS Our study cohort included 173 consecutive patients (age 53 ± 14 years, 73% men) scheduled for primary prevention implantable cardioverter-defibrillators (ICDs) implantation who underwent preimplant cardiovascular magnetic resonance. EAT volume surrounding both ventricles was manually quantified from cine left ventricular short-axis images by summation of the EAT volume of each slice using the modified Simpson rule. The primary endpoint was appropriate ICD therapy.

RESULTS During the mean follow-up of 3.6 years, 24 patients (14%) experienced an endpoint. An inverse and proportional relationship was evident between EAT and subsequent ICD therapies ($P = 0.004$). Even after adjusting for left ventricular mass and ejection fraction, EAT was significantly lower in patients with ICD therapy than those without. Low EAT was independently associated with an increased risk of ICD therapy in NICM patients (HR_{ad} per 10 mL/m^2 decrease, 1.65; 95% CI: 1.17-2.42; $P = 0.007$). EAT ≤50 mL/m^2 demonstrated a 3-fold increase in SCD event risk, with an estimated likelihood of 57% at 5 years. When considered with other potential risk factors, EAT provided incremental prognostic value in predicting ICD therapy.

CONCLUSIONS Low ventricular EAT was associated with increased SCD risk in NICM patients receiving primary prevention ICD implantation, even in the presence of other risk markers. These data suggest a potential clinical role of EAT in selecting NICM patients who would benefit most from ICD implantation. (JACC Adv. 2024;3:101407)

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

CMR = cardiovascular magnetic resonance

EAT = epicardial adipose tissue

EF = ejection fraction

HF = heart failure

ICD = implantable cardioverter-defibrillator

IRB = Institutional Review Board

LGE = late gadolinium enhancement

LV = left ventricular

NICM = nonischemic cardiomyopathy

RV = right ventricular

SCD = sudden cardiac death

VF = ventricular fibrillation

VT = ventricular tachycardia

Implantable cardioverter-defibrillators (ICDs) are an efficacious and established therapy for life-threatening ventricular arrhythmias and sudden cardiac death (SCD).[1,2] However, based on current guidelines, a small minority of ICD recipients receive appropriate ICD therapy, resulting in increased societal costs and potential patient morbidity.[3-6] Furthermore, the benefit of primary prevention ICD in patients with nonischemic cardiomyopathy (NICM) remains controversial, with lower event rates and a more narrow survival advantage than patients with infarct-related cardiomyopathy.[7,8] Therefore, improved risk stratification is needed to identify NICM patients most likely to benefit from ICD implantation.

Epicardial adipose tissue (EAT), which evolves from brown adipose tissue,[9] has anatomical and functional interactions with the heart.[10] Increased peri-coronary and atrial EAT affect the risk of coronary artery diseases and atrial fibrillation, respectively, indicating that EAT's regional distribution is important.[11-13] Also, EAT function and morphology may change under pathological conditions.[14,15] However, the potential role of ventricular EAT for the risk of ventricular tachycardia and/or ventricular fibrillation (VT/VF) in NICM patients is unresolved. Therefore, we sought to assess the relationship between ventricular EAT and SCD in NICM patients receiving ICD.

METHODS

STUDY POPULATION. The study population included consecutive patients who met clinical guidelines to receive a *primary* prevention ICD between 2008 and 2021 at Beth Israel Deaconess Medical Center in Boston, MA, and were referred for a clinical cardiovascular magnetic resonance (CMR) before ICD implantation. Exclusion criteria included infarct-related cardiomyopathy (history of myocardial infarction in the medical record, previous coronary artery bypass surgery, or percutaneous coronary intervention), mixed cardiomyopathy (significant coronary artery disease without a history of myocardial infarction), and any contraindications to CMR. The first evaluation date was the time of the CMR examination. The mean follow-up from study entry to the most recent evaluation (clinic visit or phone interview) or death was 3.6 years. Data on vital, clinical, and survival status were obtained up to December 20, 2022, by hospital visits or telephone contact with patients, family members, and referring physicians as documented in the hospital's electronic medical record. The study was approved by the Medical Center Institutional Review Board (IRB) under 2 separate IRBs. In a subset of patients, we prospectively collected written information before the CMR scan if the patient met our inclusion/exclusion criteria during the screening and staff were available to consent the patient. We also had a second IRB approval, which waived the consent, allowing us to identify patients who received a clinical CMR to allow performing the follow-up. For this cohort, written consent was waived by the IRB.

IMAGE ACQUISITION. All CMR images were acquired with a 1.5-T (Achieva, Philips Healthcare) or 3T CMR (Magnetom Vida, Siemens Healthineers). To assess left/right ventricular (LV/RV) myocardial function, geometry, and mass, 10 to 12 short-axis stack cine images and 4-chamber long-axis image were acquired using a cine balanced steady-state free precession sequence (slice thickness, 8-mm; gap, 2-mm, in-plane spatial resolution 2 × 2 mm, 30 ms temporal resolution). Ten to 20 minutes after injection of 0.1 to 0.2 mmol/kg of Gd-DTPA (Magnevist, Bayer Schering) or Gd-BOPTA (MultiHance, Bracco Imaging SpA), late gadolinium enhancement (LGE) was performed using a 3-dimensional inversion recovery sequence (TR, 5.3 ms; TE, 2.5 ms; FA, 25°; FOV, 320 × 320 × 100-125 mm^3; spatial resolution, 1.5 × 1.5 × 3 mm^3). In 34 patients, short- and long-axis 2-dimensional inversion recovery LGE images were acquired using a breath-hold, segmented inversion-recovery sequence (8-mm slice thickness, 2-mm inter-slice gap, TR, 4.2 ms; TE, 1.8 ms; FA, 20°; FOV, 320 × 320 mm^2; and spatial resolution of 2 mm^2).

IMAGE ANALYSIS. At end-diastole and end-systole, epicardial and endocardial LV borders were manually traced from contiguous short-axis cine images covering the LV apex to mitral valve plane to calculate LV and RV end-diastolic volume and end-systolic volume. From these, stroke volume and ejection fraction (EF) were calculated. LV mass was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/mL) of myocardial tissue (Extend MR WorkSpace, version 2.3.6.3, Philips Healthcare; cvi42, version 5.11.1, Circle Cardiovascular Imaging Inc). Ventricular EAT was manually delineated on the end-diastolic short-axis slices, working from the mitral valve annulus toward the most apical slice around the ventricles, and was defined as the adipose tissue situated between the outer wall of the myocardium and the visceral layer of the pericardium by one observer (F.Y.), which were reviewed by another observer (S.N.). EAT volumes

were calculated by summation of EAT volume of each slice using the modified Simpson rule (QMass MR, version 8.1, Medis Medical Imaging Systems). LGE images were assessed qualitatively and quantitatively. For quantitative assessment, a region of interest was placed in a normal area of the short-axis image to define normal myocardium. An automated computer-aided threshold detection at 5 SDs above the mean signal intensity of normal myocardium was used to identify LGE volume. Endocardial and epicardial borders were manually drawn in the end-diastolic frame and then automatically propagated throughout the cardiac cycle by matching patterns representing anatomical structures. The tracking accuracy was visually assessed and manually adjusted if necessary (cvi42, version 5.11.1, Circle Cardiovascular Imaging Inc).

CLINICAL MANAGEMENT AND FOLLOW-UP. Patients were implanted with a conventional or a biventricular ICD device at the discretion of the implanting physician. All devices were programmed for both anti-tachycardia pacing and shock with 3 zones of therapy, including shock for VF, anti-tachycardia pacing followed by shock for fast VT, and a monitored zone for slower VT (Supplemental Material). This protocol aligns with contemporary standards for therapy-restrictive programming across all major vendors, in which appropriate therapies are applied only to events with relatively high heart rates (or short tachycardia cycle lengths, depending on the vendor) for long durations. Devices were interrogated at 1 and 3 months after implantation and every 6 months thereafter, and adjudication of stored ICD electrograms was performed by an electrophysiologist blinded to CMR findings. Also, when data on vital, clinical, and survival status were obtained for this study, all ICD therapies were independently adjudicated for appropriateness by a board-certificated electrophysiologist (D.B.K.). The primary endpoint for this study was the delivery of appropriate ICD therapy, including anti-tachycardia pacing for fast VT. Hospitalization for acute heart failure (HF) was also assessed irrespective of VT/VF events.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (Q1-Q3) and compared using an unpaired Student's *t*-test or Mann-Whitney nonparametric test if not normally distributed. Categorical variables were reported as counts and percentages and compared using a chi-square test or Fisher exact test, as appropriate. Kaplan-Meier curves were used to estimate the time distribution after the initial CMR evaluation to the first episode of VT/VF. Differences between time-to-event curves were compared with the log-rank test. Skewed distributions were logarithmically transformed before regression analysis, and a regression analysis was performed to investigate possible associations of EAT and LV mass or LVEF. An analysis of covariance was used to test for equality of the regression slopes between patients with and without VT/VF events. Univariable and multivariable Cox proportional hazards models were used to assess the association between each variable and the endpoints. The multivariable model was constructed to adjust for possible confounders using a stepwise selection method with an entrance and stay criteria of $P < 0.10$. All reported associations in this study are HRs and their corresponding 95% CIs. Also, the C-statistic was calculated for all models to predict VT/VF events. The clinical risk score model was also calculated by using demographic, rhythm status, general cardiac status, and laboratory variables as follows: clinical risk score = $-0.2 \times$ age $+ 4 \times$ male $+ 4 \times$ nonsustained VT $+ 5 \times$ atrial fibrillation $- 8 \times$ amiodarone $+ 4 \times$ digoxin $+ 7 \times$ pre-existing pacemaker $- 3 \times$ smoking $- 0.2 \times$ [QRS duration -130] $- 8 \times$ anemia (hemoglobin <12 g/dL) $+ 1.77 \times$ creatinine.[16] Reclassification of patients was determined using net reclassification improvement analysis for VT/VF events and obtained by adding EAT to the clinical risk model. All tests were 2 sided and *P* value <0.05 was considered significant. Statistical analyses were performed using JMP Pro (version 16.2.0, SAS Institute), MedCalc (version 20.211, MedCalc Software Ltd), and R (version 4.2.2, R Project for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Clinical and demographic characteristics of the study group are summarized in Table 1. A total of 173 NICM (mean age; 53 ± 14 years, 73% male) were identified, including 126 (73%) with nonischemic dilated cardiomyopathy, 22 (13%) with hypertrophic cardiomyopathy, and 19 (11%) with cardiac sarcoidosis; 151 (87%) were mildly or moderately symptomatic in NYHA functional class II or III. Over the follow-up period of 3.6 years, 24 (14%) experienced appropriate ICD therapy (10 VF and 14 fast VT events). Patients with VT/VF events had a higher prevalence of cardiac sarcoidosis, lower systolic blood pressure, and lower sodium levels (all $P < 0.05$). The risk of HF admission was higher in the group with VT/VF events (33% vs 11%, $P = 0.008$).

Table 2 summarizes CMR findings between the 2 groups. For the entire group, LVEF was 38%, including 94 (54%) patients with LVEF ≤35%. LGE was present in 102 (59%) patients, occupying 4.2% of

TABLE 1 Clinical and Demographic Characteristics of the NICM Study Group

	All NICM Patients (N = 173)	Patients With VT/VF Events (n = 24)	Patients Without VT/VF Events (n = 149)	*P* Value
Demographics				
Age, y	53 ± 14	51 ± 15	54 ± 14	0.36
Male	126 (73)	18 (75)	108 (72)	0.80
Race				0.60
White	108 (62)	18 (75)	90 (60)	
Black	41 (24)	4 (17)	37 (25)	
Asian	3 (2)	0	3 (2)	
Body surface area, m^2	2.04 ± 0.28	2.02 ± 0.29	2.04 ± 0.28	0.73
Body mass index, kg/m^2	29.0 ± 6.2	28.3 ± 6.7	29.1 ± 6.2	0.60
Obesity (BMI >30 kg/m^2)	40 (23)	5 (21)	35 (23)	0.77
Etiology				0.01
NIDCM	126 (73)	16 (67)	110 (74)	
HCM	22 (13)	0	22 (15)	
Sarcoidosis	19 (11)	6 (25)	13 (9)	
ARVC	5 (3)	1 (4)	4 (3)	
Amyloidosis	1 (0.6)	1 (4)	0	
Hypertension	79 (46)	9 (38)	70 (47)	0.38
Diabetes mellitus	35 (20)	3 (13)	32 (21)	0.42
Dyslipidemia	67 (39)	8 (33)	59 (40)	0.56
Stroke	9 (5)	1 (4)	8 (5)	>0.99
Atrial fibrillation	38 (22)	8 (33)	30 (20)	0.16
Pulmonary disease (COPD/Asthma)	35 (20)	5 (21)	30 (20)	0.94
OSA	30 (17)	2 (8)	28 (19)	0.26
NYHA functional class				0.12
II	123 (71)	18 (75)	105 (70)	
III	28 (16)	2 (8)	26 (17)	
IV	3 (2)	2 (8)	1 (1)	
Time between CMR and implantation, days	62 (14-175)	51 (12-134)	63 (14-184)	0.41
Received biventricular ICD	42 (24)	3 (13)	39 (26)	0.21
VT ablation	6 (5)	2 (10)	4 (4)	0.25
Clinical risk score	5.3 (−1.8-9.3)	7.5 (2.9-10.9)	4.7 (−1.9-9.0)	0.08
Hemodynamics				
Systolic blood pressure, mm Hg	123 ± 23	114 ± 21	124 ± 24	0.04
Diastolic blood pressure, mm Hg	70 ± 13	69 ± 12	71 ± 13	0.51
Heart rate, beats/min	75 ± 16	76 ± 20	75 ± 15	0.80
Blood test				
Sodium, mmol/L	140 ± 3	138 ± 4	140 ± 3	0.02
Blood urea nitrogen, mg/dL	18.5 ± 7.6	20.1 ± 6.1	18.3 ± 7.8	0.21
Serum creatinine, mg/dL	1.02 ± 0.24	1.01 ± 0.19	1.02 ± 0.25	0.92
Hemoglobin, g/dL	13.9 ± 2.4	13.8 ± 1.7	13.9 ± 2.5	0.69
NT-proBNP, pmol/L	769 (305-2,127)	767 (414-2,934)	769 (294-2,051)	0.81
ECG parameter				
QRS duration, ms	118 ± 28	118 ± 24	118 ± 29	0.95
Medication use				
ACEI, ARB	93 (54)	15 (63)	78 (52)	0.35
ARNI	19 (11)	0	19 (13)	0.08
Beta-blocker	137 (79)	17 (71)	120 (81)	0.29
Mineralocorticoid antagonist	61 (35)	8 (33)	53 (36)	0.83
Amiodarone	12 (7)	3 (13)	9 (6)	0.22
Statin	71 (41)	8 (33)	63 (42)	0.40
Digoxin	19 (11)	5 (21)	14 (9)	0.13
Major clinical events				
Length of follow-up, y	3.6 ± 2.5	4.2 ± 2.7	3.5 ± 2.5	0.23
HF admission	24 (14)	8 (33)	16 (11)	0.008
All-cause death	6 (3)	2 (8)	4 (3)	0.20

Values mean ± SD, n (%), median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; ARVC = arrhythmogenic right ventricular cardiomyopathy; BMI = body mass index; CMR = cardiovascular magnetic resonance; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; NIDCM = nonischemic dilated cardiomyopathy; NICM = nonischemic cardiomyopathy; NT-proBNP = N-terminal pro B-type natriuretic peptide; OSA = obstructive sleep apnea; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 2 CMR Findings

	All NICM Patients (N = 173)	Patients With VT/VF Events (n = 24)	Patients Without VT/VF Events (n = 149)	*P* Value
EAT, mL	142 ± 44	122 ± 34	145 ± 45	0.006
BSA-adjusted EAT, mL/m^2	69 ± 18	60 ± 14	71 ± 19	0.002
LV EDV, mL	254 ± 102	273 ± 121	251 ± 99	0.40
LV EDVI, mL/m^2	124 ± 45	135 ± 52	122 ± 43	0.28
LV ESV, mL	171 ± 106	191 ± 127	167 ± 103	0.39
LV EF, %	38 ± 18	36 ± 18	39 ± 18	0.49
LV EF ≤35%	94 (54)	12 (50)	82 (55)	0.60
LV EF ≤30%	73 (42)	11 (46)	62 (42)	0.74
LV mass, g	155 ± 57	152 ± 62	156 ± 56	0.77
LV mass index, g/m^2	76 ± 25	74 ± 26	76 ± 25	0.73
LV mass/LV EDV, g/mL	0.65 ± 0.27	0.58 ± 0.19	0.66 ± 0.29	0.08
LV spherical index	0.61 ± 0.22	0.77 ± 0.40	0.58 ± 0.15	0.045
LV global longitudinal strain, %	8.6 ± 3.8	8.3 ± 4.2	8.6 ± 3.7	0.74
LV LGE presence	102 (59)	20 (83)	82 (55)	0.003
LV LGE/LV mass, %	4.2 (2.8-8.9)	4.0 (2.6-12.8)	4.5 (2.8-8.2)	0.88
RV EDV, mL	178 ± 62	202 ± 78	174 ± 58	0.11
RV EDVI, mL/m^2	87 ± 26	100 ± 34	85 ± 24	0.046
RV ESV, mL	99 ± 59	125 ± 79	95 ± 55	0.09
RV EF, %	47 ± 14	43 ± 16	48 ± 14	0.15

Values are mean ± SD or median (Q1-Q3).

BSA = body surface area; EAT = epicardial adipose tissue; EDV = end-diastolic volume; EDVI = end-diastolic volume index; EF = ejection fraction; ESV = end-systolic volume; LGE = late gadolinium enhancement; LV = left ventricular; RV = right ventricular; other abbreviations as in Table 1.

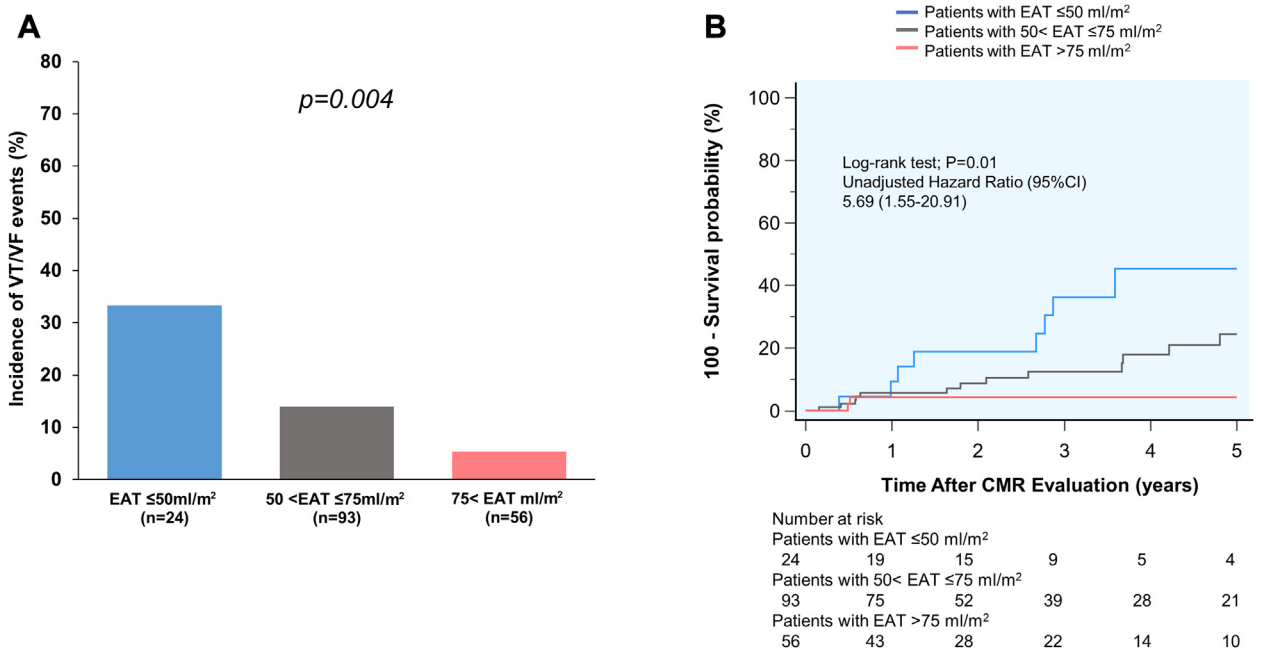
LV mass, and more often seen in patients with VT/VF events ($P = 0.003$). There was a trend toward lower RVEF in patients with VT/VF events ($P = 0.15$), with no differences in LVEF, LV volume, or mass. Absolute EAT was significantly *lower* in patients with VT/VF events ($P = 0.006$), and it remained significant even after adjusting for body surface area (BSA) ($P = 0.002$).

DISTRIBUTION OF EAT AND VT/VF EVENTS. Of the 173 NICM patients, BSA-adjusted EAT was ≤50 mL/m^2 in 24 patients (14%), while >75 mL/m^2 in 56 (32%). An inverse and proportional relationship was evident between EAT and subsequent ICD therapies ($P = 0.004$). Kaplan-Meier curves showed that the estimated likelihood for ICD therapy in patients with EAT ≤50 mL/m^2 was 57% at 5 years, which was different compared to that in patients with EAT >75 mL/m^2 (9% at 5 years) (Figure 1 and Central Illustration).

ASSOCIATION BETWEEN EAT, LV MASS, AND LVEF ACCORDING TO THE VT/VF EVENTS. In the whole population, EAT moderately and positively correlated with LV mass ($r = 0.44$, $P < 0.001$) and mildly and negatively correlated with LVEF ($r = -0.30$, $P < 0.001$). Figure 2 shows the regression analysis of EAT plotted against the LV mass (Figure 2A) and LVEF (Figure 2B) in the NICM cohort with and without VT/VF events. In both groups, the EAT correlates with the LV mass (patients with VT/VF events; $r = 0.43$, $P = 0.04$ and patients without VT/VF events; $r = 0.45$, $P < 0.001$) and the LVEF (patients with VT/VF events; $r = -0.35$, $P = 0.10$ and patients without VT/VF events; $r = -0.31$, $P < 0.001$). However, the lines for the group with VT/VF events lie significantly below those for those without VT/VF events, indicating that patients with appropriate ICD therapy have significantly lower EAT for an equivalent LV mass ($P = 0.01$) and LVEF ($P = 0.009$). Even after adjusting for BSA, the difference in the regression analysis between the line for the patients with VT/VF events and the line for the patients without VT/VF events remained significant ($P = 0.008$ against LV mass, and $P = 0.005$, against LVEF) (Figures 2C and 2D).

PREDICTION OF VT/VF EVENTS BY EAT. Univariate and multivariate Cox proportional hazard analyses for VT/VF events are summarized in Table 3. EAT ≤50 mL/m^2 was associated with a 212% increase in the HR of ICD therapy. Lower EAT was independently associated with an increased risk of ICD therapy in NICM patients (HR_{ad} per 10 mL decrease, 1.65; 95% CI: 1.17-2.42; $P = 0.007$), even after adjustment for other potential risk factors. In addition, when EAT/m^2 is considered together with each risk factor, the incremental prognostic value in predicting ICD therapy is increased significantly (Table 4). The C-statistic of EAT/m^2 for predicting subsequent ICD

FIGURE 1 Relation Between EAT Volume and VT/VF Events



(A) Relationship between EAT volume and incidence of VT/VF events. (B) Hazard plot based on multivariable Cox regression analysis for subsequent VT/VF events. CMR = cardiovascular magnetic resonance; EAT = epicardial adipose tissue; VT/VF = ventricular tachycardia and/or ventricular fibrillation.

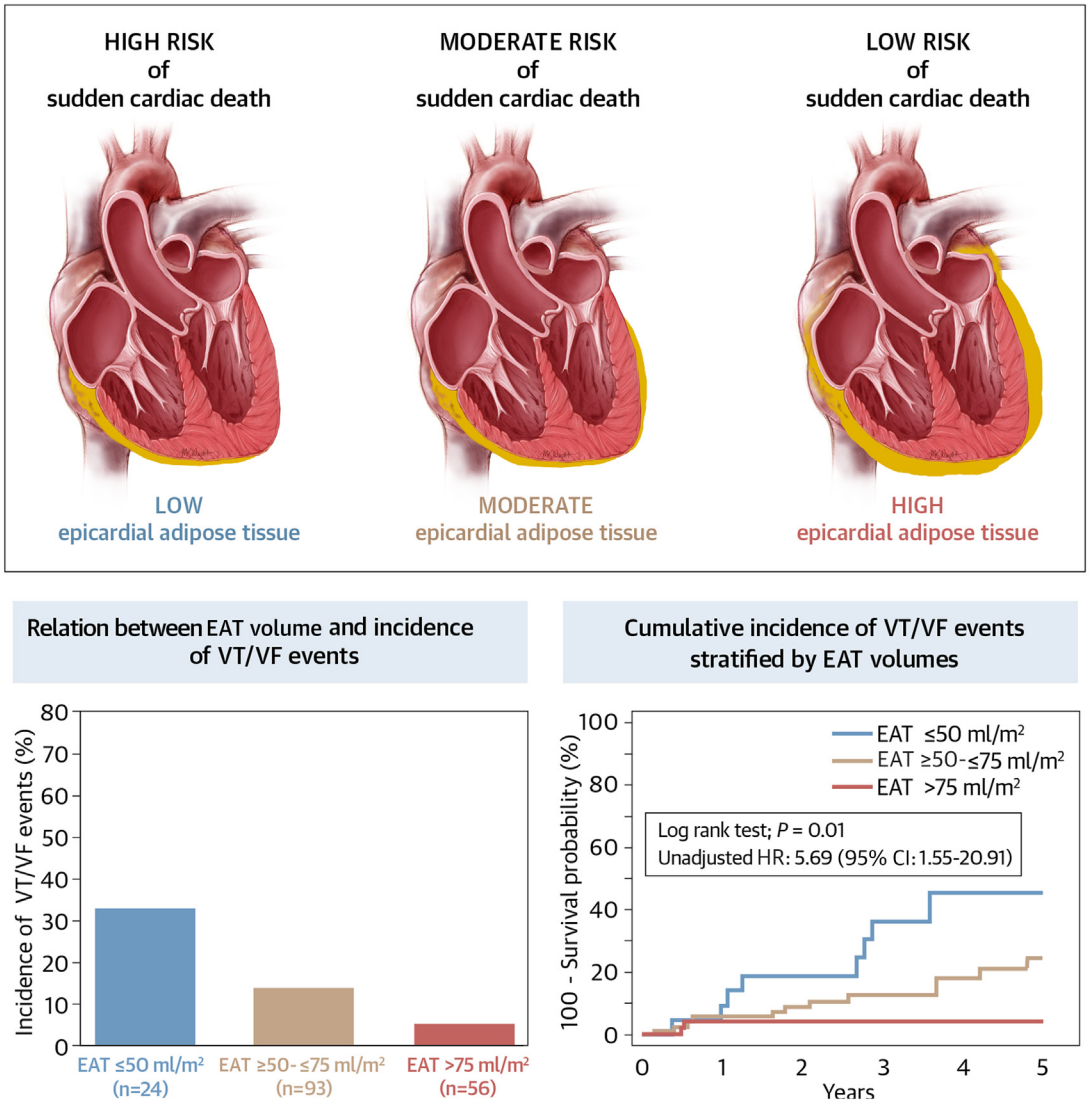
therapy was 0.71 (95% CI: 0.59-0.83). Furthermore, the performance of the clinical risk model was enhanced by EAT measurement in NICM patients with primary prevention ICD (C-statistic; 0.63 [95% CI: 0.51-0.74] vs 0.75 [95% CI: 0.66-0.84], continuous NRI, 0.54; 95% CI: 0.14 to 0.95; $P = 0.009$) (Figure 3).

DISCUSSION

In this study of 173 consecutive NICM patients referred for CMR before primary prevention ICD implantation, low EAT/m^2 was associated with an increased risk of subsequent ICD therapy, even after adjustment for other relevant disease variables. The addition of EAT enhanced the performance of the clinical risk model for predicting SCD.

Despite emerging evidence implicating atrial EAT with atrial fibrillation risk,[10,12,13] it is unclear whether similar effects are conferred for ventricular arrhythmias. Studies reported that increased EAT was associated with the presence of fragmented QRS in healthy populations[17] and the frequency of premature ventricular beats in the patients without LV dysfunction.[18] In a study by Wu et al of 50 patients with HF, increased pericardial fat volume was associated with VT/VF.[19] In another retrospective study of 61 patients, EAT thickness predicted VT recurrence after ablation.[20] However, those studies retrospectively evaluated a healthy or heterogeneous population with a small sample size and did not address the SCD risk stratification of NICM. In this large cohort of NICM patients receiving ICD, low EAT/m^2 was associated with an increased risk of ICD therapy in NICM patients, even after adjustment for other relevant disease variables. Also, an inverse and proportional relationship was evident between EAT/m^2 and subsequent ICD therapies. The C-statistic of EAT/m^2 for predicting ICD therapy is comparable to those of LGE presence and extent. Furthermore, the performance of the clinical risk model was enhanced by the addition of EAT/m^2 for ICD shock in NICM patients receiving primary prevention ICD. EAT has a promising potential to

CENTRAL ILLUSTRATION Association Between EAT and Ventricular Arrhythmia



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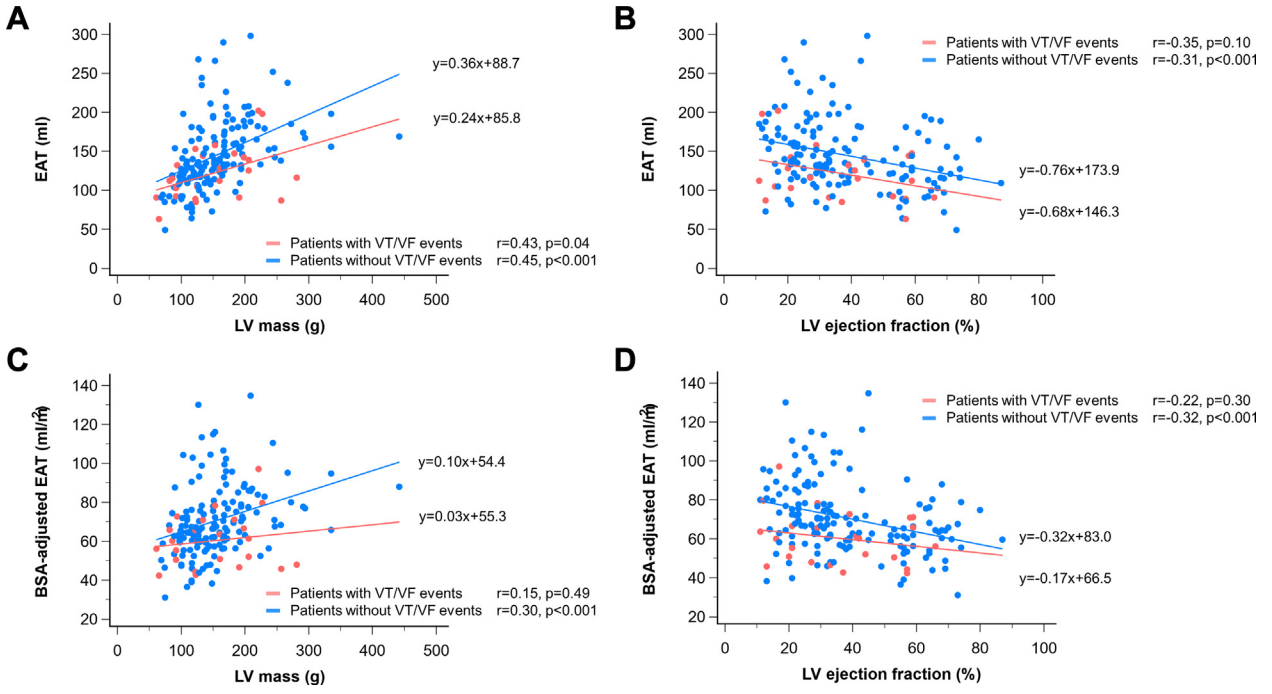
Abbreviations as in Figure 1.

clarify the recommendation of current guidelines and risk stratification of NICM patients at risk of SCD.

We found that EAT moderately and positively correlated with LV mass, which aligns with a previous autopsy study reporting a parallel increase in EAT and cardiac mass.[21] Also, these findings may be proposed by previous hypotheses of a role for EAT as local energy.[9] In fact, our study allowed us to estimate that the average amount of ventricular EAT for each gram of myocardial tissue was 0.24 g in the group with VT/VF events and 0.34 g in the group without VT/VF events, albeit in patients without LV systolic dysfunction this value was 0.53 g.[22] Thus, patients with subsequent VT/VF events showed a 70% reduction in EAT/LV mass ratio compared with those without VT/VF events, indicating that it cannot meet the metabolic requests of a compensatory increased

FIGURE 2 Correlations Between (With and Without BSA Adjustment) EAT and LV Mass and Ejection Fraction Stratified by VT/VF Events



(A) The regression line for the patients with VT/VF events lies significantly below the line for the patients without VT/VF events ($P = 0.01$), although the EAT correlates with the LV mass in both groups (patients with VT/VF events [pink plots]; $r = 0.43$, $P = 0.04$ and patients without VT/VF events [blue plots]; $r = 0.45$, $P < 0.001$). (B) Similarly, patients with VT/VF events have significantly lower EAT for an equivalent LV ejection fraction ($P = 0.009$). (C, D) These trends are observed in BSA-adjusted EAT ($P = 0.008$ and 0.005, respectively). LV = left ventricular; other abbreviations as in Figure 1.

LV mass.[23] This observation that EAT as a nutritive role is reduced in NICM patients with subsequent ICD therapy may correspond to the expression of a catabolic and adverse phenotype and highlight the importance of the association between cardiac metabolism and VT/VF. Also, cardiac energy demand increases as the myocardium becomes progressively dysfunctional, leading to the consumption of

TABLE 3 Univariate and Multivariate Cox Proportional Hazards Regression Analyses of the Relationship Between Baseline CMR Parameters and Outcome in the NICM Cohort

	Univariate HR (95% CI)	*P* Value	Model 1 Multivariate HR (95% CI)		Model 2 Multivariate HR (95% CI)	*P* Value
EAT ≤50 mL/m^2	3.12 (1.26-7.12)	0.009			2.62 (1.10-6.24)	0.03
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	0.03	1.65 (1.17-2.42)	0.007		
LVEF (per 10% decrease)	1.10 (0.88-1.39)	0.42				
LV mass index (per 10 g/m^2 increase)	0.99 (0.91-1.07)	0.84				
LV mass/LV EDV (per 0.1 g/mL increase)	0.86 (0.67-1.05)	0.14				
LV spherical index (per 0.1 increase)	1.30 (1.05-1.57)	0.02				
RVEF (per 10% decrease)	1.21 (0.94-1.57)	0.14				
LGE presence	4.83 (1.43-16.34)	0.01			4.28 (1.26-14.58)	0.02
%LGE (per 1% increase)	1.06 (1.01-1.11)	0.004	1.08 (1.03-1.13)	0.001		

Abbreviations as in Tables 1 and 2.

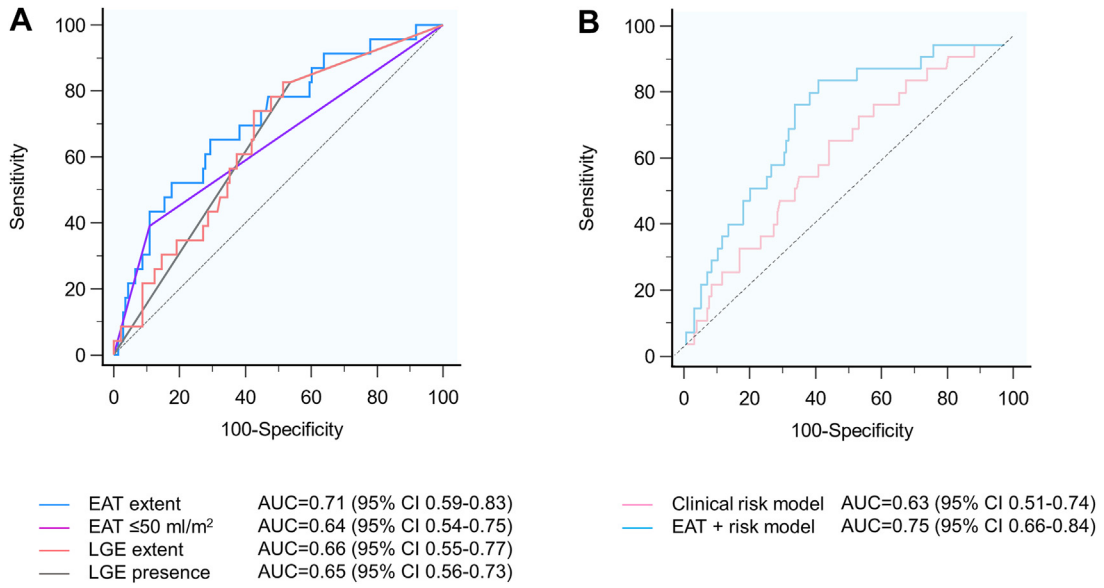
TABLE 4 Univariate and Bivariate Analyses of the EAT and Potential Risk Factors Among NICM With Primary Prevention ICD

	Univariate HR (95% CI)	Model Global Wald Chi-Square	*P* Value	Bivariate HR (95% CI)	*P* Value	Model Global Wald Chi-Square	*P* Value
LVEF ≤35%	0.87 (0.39-1.92)	0.122	0.73	1.18 (0.51-2.72)	0.70	4.880	0.09
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	4.447	0.03	1.37 (1.03-1.85)	0.04		
NYHA II or III	1.21 (0.28-5.13)	0.065	0.8	0.96 (0.23-4.11)	0.96	4.989	0.08
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	4.447	0.03	1.35 (1.03-1.82)	0.03		
Clinical risk score	1.03 (0.98-1.09)	1.470	0.23	1.06 (1.00-1.12)	0.04	9.286	0.01
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	4.447	0.03	1.49 (1.11-2.04)	0.01		
LGE presence	4.83 (1.43-16.34)	6.430	0.01	4.58 (1.35-15.52)	0.01	13.078	0.001
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	4.447	0.03	1.30 (1.00-1.72)	0.06		
LGE extent	1.06 (1.01-1.11)	8.242	0.004	1.08 (1.03-1.13)	0.001	14.701	0.0006
EAT (per 10 mL/m^2 decrease)	1.36 (1.04-1.83)	4.447	0.03	1.65 (1.17-2.42)	0.007		

Abbreviations as in Tables 1 to 3.

surrounding EAT as a local energy supplier, releasing free fatty acids into the heart, and increased VT/VF risk.[24] Furthermore, in patients with unhealthy hearts, the expression of genes encoding proteins related to adipocyte browning and thermogenic activation is found to be downregulated in EAT.[25] Therefore, in addition to a lower EAT volume, downregulation of EAT transcriptome may contribute to the high risk of lethal ventricular arrhythmias in NICM patients receiving ICD implantation. Under pathological conditions such as NICM requiring primary prevention ICD implantation, EAT could play a cardioprotective role through the secretion of protective adipokines like adiponectin, adrenomedullin, and omentin in

FIGURE 3 ROC Curves for Appropriate ICD Therapy in NICM Patients With Primary Prevention ICD



(A) ROC curve and corresponding area under the curve describing the comparison of EAT and LGE to predict future ICD therapy and (B) the incremental prognostic performance of EAT for ICD therapy beyond the clinical risk score model. ICD = implantable cardioverter-defibrillators; LGE = late gadolinium enhancement; ROC = receiver-operating characteristic; NICM = nonischemic cardiomyopathy; other abbreviation as in Figure 1.

response to myocardial damage and EAT-secreted adiponectin could attenuate cardiac remodeling and increased VT/VF risk.[26] Further studies are needed to assess whether EAT can adapt to various metabolic conditions and function like brown fat.

STUDY LIMITATIONS. Our study has several limitations. This study is one of the CMR studies with the highest number of NICM patients evaluated for primary prevention ICD implantation, but it is a single-center study with a relatively small sample size and short follow-up period, and the result should only be considered as hypothesis-generating. It is observational; thus, association cannot be assumed as causality. Clinical management might have changed over the course of this follow-up period. We assessed ventricular EAT at a single time. Changes in EAT volume may be more predictive of future VT/VF than a single baseline measurement. Although we rigorously exclude pericardial effusion using phase-sensitive inversion recovery images, EAT may be overestimated. We have not evaluated the EAT separately for the RV and LV. We were also unable to assess the relationship between peri-atrial EAT and lethal ventricular arrhythmias because we did not have enough short-axis stack images of both atriums to assess peri-atrial EAT volume.

CONCLUSIONS

Low EAT/m^2 is associated with increased VT/VF risk in NICM patients receiving primary prevention ICD implantation, even in the presence of other clinical risk markers. These data suggest a potential role of EAT/m^2 in identifying NICM patients at increased risk of SCD, and as a guide for implantation therapy. Further multicenter studies are warranted to confirm the potential use of EAT as a clinical tool to reduce unnecessary ICD implantation in NICM patients and to further explore the biological underpinnings of the relationship identified in this study.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this study of NICM patients referred for CMR before primary prevention ICD implantation, low EAT/m^2 was associated with an increased risk of subsequent ICD therapy, even after adjustment for other relevant disease variables. The addition of EAT enhanced the performance of the clinical risk model for predicting SCD.

TRANSLATIONAL OUTLOOK: Further studies are necessary to confirm whether EAT can be used as a clinical tool to reduce unnecessary ICD implantation in NICM patients and explore the underlying biological mechanisms of the relationship identified in this study.

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KEY WORDS **cardiovascular magnetic resonance, epicardial adipose tissue, implantable cardioverter-defibrillator, nonischemic cardiomyopathy, primary prevention, ventricular fibrillation, ventricular tachycardia**

APPENDIX **For supplemental material, methods, and results as well as supplemental tables, please see the online version of this paper.**