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Ventricular Arrhythmias in Myocarditis

Characterization and Relationships With Myocardial Inflammation

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ABSTRACT

BACKGROUND Ventricular arrhythmias (VAs) have never been systematically investigated in patients with myocarditis at different stages.

OBJECTIVES The purpose of this study was to compare baseline and follow-up characteristics of VAs in patients with active myocarditis (AM) versus previous myocarditis (PM).

METHODS A total of 185 consecutive patients (69% males, age 44 ± 15 years, left ventricular ejection fraction 49 ± 14%) with myocarditis and VA at index hospitalization, including ventricular fibrillation, ventricular tachycardia (VT), nonsustained ventricular tachycardia (NSVT), and Lown's grade ≥2 premature ventricular complexes, were enrolled. AM and PM groups were defined based on endomyocardial biopsy and cardiac magnetic resonance findings. A subset of patients (n = 46, 25%) also underwent electroanatomic mapping and VA transcatheter ablation.

RESULTS At presentation, AM patients (n = 123, 66%) more commonly had ventricular fibrillation (8 cases vs. 0 cases; $p = 0.053$), and both irregular (61% vs. 11%; $p < 0.001$) and polymorphic VA (NSVT and VT: 19% vs. 2%; $p = 0.002$; premature ventricular complexes: 63% vs. 16%; $p < 0.001$). Only in PM patients with NSVT or VT, the dominant morphology (right-bundle branch block with superior axis) was 100% predictive of abnormal LV inferoposterior substrate at both cardiac magnetic resonance and electroanatomic mapping. At 27 ± 7 months prospective follow-up, 55 patients (30%) experienced malignant VA (AM vs. PM, $p = 0.385$). Although a prevalence of polymorphic and irregular VA was confirmed in AM patients with persistent inflammation in follow-up (58%), a predominance of monomorphic and regular VA was found in AM patients after myocarditis healing (42%), as well as in PM patients (all $p < 0.001$).

CONCLUSIONS In myocarditis patients, polymorphic and irregular VA are more common during the active inflammatory phase, whereas monomorphic and regular VA are associated with healed myocarditis.

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A wide spectrum of ventricular arrhythmias (VAs) has been described in patients with myocarditis at different inflammatory stages (1). However, compared with the other clinical presentations of myocarditis (2), VA have been poorly characterized so far.

The issue is particularly relevant because ventricular tachycardia (VT) and fibrillation (VF) represent a significant cause of sudden cardiac death and mortality in the general population as well as in myocarditis patients (3). Also, nonsustained ventricular tachycardia (NSVT) and frequent premature

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ventricular complexes (PVCs), in turn associated with an increased cardiovascular mortality (4), have never been systematically evaluated in inflammatory heart disease.

To the best of our knowledge, pathophysiological mechanisms leading to VA may significantly differ during the "hot" and "cold" phases of inflammatory heart disease (1). However, in the absence of large comparative studies, little is known about VA characteristics at different myocarditis stages.

Our scientific hypothesis was that VA features may differ in patients with active versus previous myocarditis, ultimately playing as a new potential marker of disease activity. Thus, we aimed at characterizing VA in a wide population of myocarditis patients, to evaluate: 1) their baseline characteristics; 2) their relationships with underlying substrate; and 3) their follow-up changes according to different inflammatory stages.

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METHODS

STUDY DESIGN. This is a single-center prospective study. We screened, from January 2013 to September 2017, 256 consecutive adult patients admitted to the hospital for new-onset symptoms and clinically suspected myocarditis, with any clinical presentation (2). The study design is summarized in **Figure 1**. After excluding significant coronary artery disease by either coronary angiography or computed tomography scan, all of the patients underwent both cardiac magnetic resonance (CMR) and endomyocardial biopsy (EMB). Furthermore, complete baseline blood examinations with cardiac biomarkers (T-troponin, N-terminal pro-B-type natriuretic peptide) and inflammatory indexes, continuous 12-lead electrocardiography (ECG) telemonitoring, and transthoracic color Doppler echocardiogram were collected in all of the cases. Patients with recurrent episodes of symptomatic VT (n = 46), refractory to at least 2 different antiarrhythmic drugs either alone or in association, also underwent electroanatomic mapping (EAM) and transcatheter ablation.

We finally enrolled patients (n = 185) with a confirmed diagnosis of myocarditis and evidence of VA at index hospitalization, including: VF, VT, NSVT, and grade ≥2 PVC according to the Lown's classification (i.e., >1 PVC/min or >30 PVCs/h) (5). At enrollment, patients were divided into active myocarditis (AM) and previous myocarditis (PM) groups, as shown in **Figure 1**. Complete definitions about myocarditis stages, VA subtypes, and specific diagnostic techniques are reported in the Online Methods. Therapeutic choices, including cardiological medical treatment, immunosuppressive therapy, implantable cardioverter-defibrillator (ICD), and VA transcatheter ablation, were upon clinical indication, integrating international guideline recommendations (2–4) and the experience of a tertiary level center for VA management.

FOLLOW-UP. Following discharge, all of the patients underwent twice-yearly prospective reassessment through 12-lead 24-h Holter ECG monitoring and device interrogation when appropriate. Furthermore, echocardiographic and laboratory data were collected at each time point. As for AM patients, follow-up was stricter (4 times/year) in the first year, and standard (2 times/year) later. All of the AM patients underwent at least 1 follow-up CMR by 1-year follow-up until myocarditis healing (Online Methods).

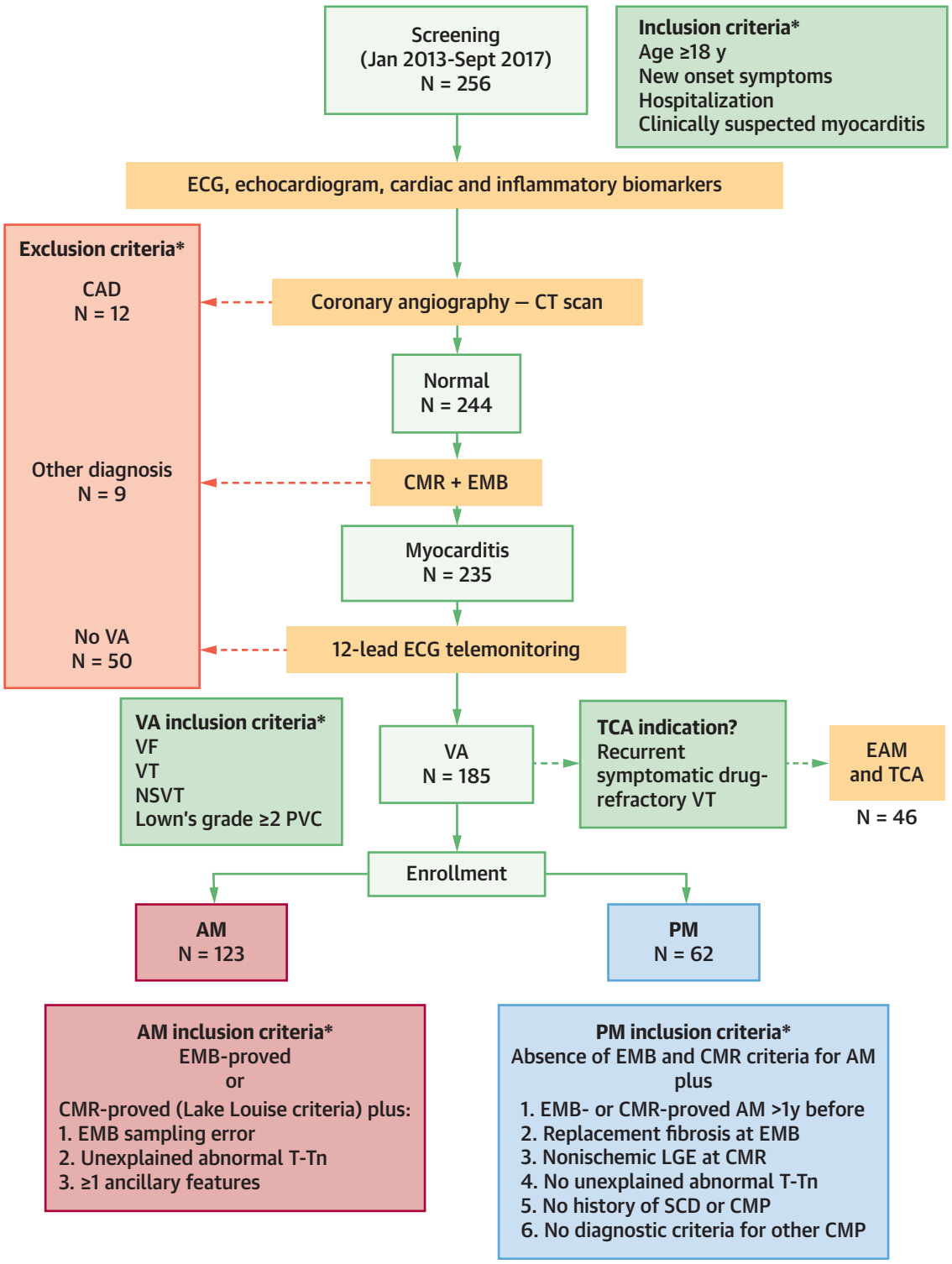
ENDPOINTS. VA occurrence, subtypes, and characteristics, including morphology and regularity (Online Methods), were analyzed in the AM and PM groups, both at baseline and during follow-up. In each group, relationships between baseline VA features and abnormal substrate localization and extension were analyzed at both CMR and—when performed—EAM. During follow-up, occurrence of malignant VA (including VT, VF, or appropriate ICD therapy) were assessed in AM versus PM groups, together with changes in VA characteristics according to myocarditis stage. When transcatheter ablation was performed, clinical VT recurrences were also reported.

STATISTICAL ANALYSIS. SPSS version 20 (IBM Corp., Armonk, New York) was used for analysis and graphic presentations. Continuous variables were expressed as mean ± SD, or as median and interquartile range of 25th to 75th percentiles, depending on the distribution of data. Accordingly, they were compared by parametric (Student's *t*-test) or nonparametric (Mann-Whitney *U*) tests, respectively. Categorical variables were reported as counts and percentages, and were compared by using the Fisher exact test. Mixed models were built to compare groups while accounting for the longitudinal nature of data. Where relevant, 2-sided p values <0.05 were considered statistically significant. Confidence intervals were set at 95%. Classification tree method was used to summarize study findings (Online Methods).

ABBREVIATIONS AND ACRONYMS

AM = active myocarditis
CMR = cardiac magnetic resonance
EAM = electroanatomic mapping
EMB = endomyocardial biopsy
ICD = implantable cardioverter-defibrillator
LV = left ventricle
LVA = low-voltage area
NSVT = nonsustained ventricular tachycardia
PM = previous myocarditis
PVC = premature ventricular complex
RS = right superior (right bundle branch block with superior axis)
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

FIGURE 1 Study Flowchart



Overview of the study design is shown in a flowchart, presenting inclusion and exclusion criteria, diagnostic tools, and active versus previous myocarditis definitions (further detail in Online Methods). *Complete definitions and supporting refrences are reported in the Online Methods. AM = active myocarditis; CAD = coronary artery disease; CMP = cardiomyopathy; CMR = cardiac magnetic resonance; EAM = electroanatomic mapping; EMB = endomyocardial biopsy; LGE = late gadolinium enhancement; NSVT = nonsustained ventricular tachycardia; PM = previous myocarditis; PVC = premature ventricular complexes; SCD = sudden cardiac death; T-Tn = T troponin; TCA = transcatheter ablation; VA = ventricular arrhythmias; VT = ventricular tachycardia.

RESULTS

GENERAL CHARACTERISTICS OF THE POPULATION. Overall, 185 patients (69% men, mean age 44 ± 15 years) were enrolled. At baseline, 123 (66%) subjects were diagnosed with AM, and 62 (34%) PM. In the AM group, myocarditis was EMB-proven in 113 patients (92%) and CMR-proven in 10 (8%). Myocarditis histotype was lymphocytic in all of the cases. Compared with the PM group, AM patients were younger (mean age 42 years vs. 49 years) and more commonly had acute coronary syndrome-like presentation (33% vs. 11%), viral etiology (20% vs. 5%), and signs of associated pericarditis (28% vs. 3%), all $p < 0.05$. Consistently, ST-segment abnormalities at ECG, as well as alterations in T-troponin and inflammatory biomarkers, were more common in the AM group (**Table 1**). Conversely, PM patients had a greater prevalence of left ventricular (LV) dilation (47% vs. 31%; $p = 0.037$), but no significant differences in LV ejection fraction (47 ± 14% vs. 50 ± 14%; $p = 0.156$). Within the AM group, EMB-proven replacement fibrosis and cardiac myocytes hypertrophy were found only in patients with chronic myocarditis. Complete baseline characteristics of AM versus PM patients are shown in **Table 1** and Online Table 1.

BASELINE CHARACTERIZATION OF VA. At presentation, 8 patients (4%) had VF, 59 (32%) VT, 79 (43%) NSVT, and 185 (100%) grade ≥2 PVC. All of the patients with VF had AM ($p = 0.053$). No significant differences between AM and PM groups were found in distribution of other VA subtypes (**Table 1**), including PVC burden (median 651/patient daily). Compared with the PM group, in AM patients both NSVT and VT were more commonly irregular (61% vs. 11%; $p < 0.001$) and polymorphic (19% vs. 2%; $p = 0.002$). Also, PVC were more commonly polymorphic in the AM group (63% vs. 16%; $p < 0.001$). Complete data about VA in AM versus PM patients are reported in **Table 2**, with representative examples in **Figure 2**.

For each VA subtype, right bundle branch block with superior axis (RS) was the dominant 12-lead ECG morphology, occurring in >50% of the population (Online Table 2). Consistently, both late gadolinium enhancement (LGE) at CMR and low-voltage areas (LVA) at EAM showed a nonischemic pattern with a predominant involvement of the LV inferoposterior wall in the whole population. However, only in PM patients presenting with NSVT or VT, RS morphology was 100% predictive of abnormal inferoposterior substrate at both diagnostic techniques (**Figure 3**). Of note, as shown in **Table 3**, patients with polymorphic PVC had a greater basoapical extension of both LGE and LVA (both $p < 0.001$), whereas those with irregular VA had greater substrate transmurality ($p \leq 0.020$). Overall, CMR and EAM findings were concordant for both extension and localization of abnormal substrate (Online Figure 1).

Baseline laboratory and echocardiographic findings in patients with different VA subtypes are shown in Online Table 3.

TREATMENT AND FOLLOW-UP. Before discharge, ICDs were implanted more frequently in the PM group (41 of 62 vs. 37 of 123; $p = 0.001$), with a secondary prevention indication in 67% of cases (AM vs. PM, $p = 0.235$). Indications for early ICD implant in AM patients are reported in Online Table 4. Also, VA transcatheter ablation was more commonly performed in PM patients (23 of 62 vs. 23 of 123; $p = 0.011$), including epicardial approach in 63% of cases. Overall, 97% of patients were discharged on medical treatment (Online Table 4).

Follow-up duration was 27 ± 7 months. Overall, a reduction in PVC burden was observed in the whole population, with 138 patients presenting PVC at last follow-up (median 166/patient daily; AM vs. PM, $p = 0.216$). However, by 10 ± 9 months follow-up, 55 cases (30%) experienced malignant VA, with no remarkable differences between groups (Online Figure 2). Malignant arrhythmic episodes showed no association with viral genome at EMB (5 of 28 virus-positive vs. 50 of 157 virus-negative; $p = 0.179$), or with QRS duration >120 ms at baseline ECG (12 of 34 broad QRS vs. 43 of 151 narrow QRS; $p = 0.534$); however, they occurred in 2 of 11 patients (18%) with borderline myocarditis (2) and LV ejection fraction >50%. Among patients with baseline LGE and LV ejection fraction >50% ($n = 103$), malignant VA rate was 10%/year, with significant differences in anteroseptal ($n = 20$) versus inferoposterior ($n = 83$) LGE patterns (25% vs. 7%/year, respectively). Significantly, no arrhythmic events occurred in AM patients ($n = 22$ of 123) in the absence of LGE at follow-up CMR. Furthermore, malignant VAs were documented in 7 of 23 AM versus 0 of 23 PM patients who underwent successful (Class A) transcatheter ablation ($p = 0.009$). Following malignant VA episodes, 5 new patients (4 AM vs. 1 PM; $p = 0.665$) underwent ICD implant. Myocarditis healing was documented in 71 AM patients (58%) by 10 ± 5 months. No myocarditis recurrences were observed in follow-up. Four AM cases underwent successful redo transcatheter ablation after myocardial healing, with no further malignant VA recurrences.

FOLLOW-UP CHARACTERIZATION OF VA. Overall, compared with cases with healed myocarditis, AM

TABLE 1 Baseline Characteristics of the Population

	Total (N = 185)	Active Myocarditis (n = 123)	Previous Myocarditis (n = 62)	p Value
Clinical features				
Caucasian	169 (91)	111 (90)	58 (94)	0.584
Male	127 (69)	83 (68)	44 (71)	0.737
Age, yrs	44 ± 15	42 ± 14	49 ± 16	0.001
ACS-like	48 (26)	41 (33)	7 (11)	0.001
HF	46 (25)	32 (26)	14 (23)	0.719
VA	91 (49)	50 (41)	41 (66)	0.002
Pericarditis	36 (20)	34 (28)	2 (3)	<0.001
Fam SCD	5 (3)	5 (4)	0 (0)	0.170
Fam CMP	7 (4)	7 (6)	0 (0)	0.097
Symptoms				
Fever last 30 days	72 (39)	57 (46)	15 (24)	0.004
Syncope	43 (23)	32 (26)	11 (18)	0.269
Palpitation	97 (52)	60 (49)	37 (60)	0.212
Chest pain	81 (44)	63 (51)	18 (29)	0.005
Dyspnea	88 (48)	55 (48)	33 (53)	0.280
NYHA functional class	1 (1–2)	1 (1–2)	2 (1–2)	0.328
Blood examinations				
CB abnormalities	103 (56)	79 (64)	24 (39)	0.002
T-Tn, ng/l	40.2 (12.8–403.6)	52.6 (17.7–600.0)	23.4 (8.4–114.0)	0.012
NT-proBNP, pg/ml	257 (103–1,094)	225 (81–859)	308 (124–1,559)	0.206
IB abnormalities	61 (33)	50 (41)	11 (18)	0.002
CRP, mg/l	6.4 (1.7–50.4)	10.0 (1.8–61.9)	4.2 (1.3–15.5)	0.004
ESR, mm/h	9 (4–27)	11 (5–32)	7 (3–18)	0.012
ECG				
HR, min^{-1}	75 ± 20	77 ± 21	71 ± 17	0.031
PQ, ms	168 ± 27	166 ± 28	171 ± 26	0.250
QRS, ms	103 ± 22	101 ± 23	106 ± 19	0.115
QTc, ms	427 ± 41	427 ± 43	427 ± 35	0.952
Abnormal T waves	94 (51)	60 (49)	34 (55)	0.533
Abnormal ST	32 (17)	28 (23)	4 (7)	0.007
Arrhythmia monitoring				
In-hospital	185 (100)	123 (100)	62 (100)	1.000
Holter ECG	185 (100)	123 (100)	62 (100)	1.000
ICD	78 (42)	41 (33)	37 (60)	0.001
Pauses >2 s	28 (15)	18 (15)	10 (16)	0.829
1st degree AVB	20 (11)	11 (9)	9 (15)	0.316
2nd degree AVB	11 (6)	10 (8)	1 (2)	0.103
3rd degree AVB	6 (3)	6 (5)	0 (0)	0.181
Any SVT	78 (42)	42 (34)	36 (58)	0.003
AF	42 (23)	21 (17)	21 (34)	0.015
PVC	185 (100)	123 (100)	62 (100)	1.000
NSVT	79 (43)	45 (37)	34 (55)	0.353
VT	59 (32)	30 (24)	29 (47)	0.082
VF	8 (4)	8 (7)	0 (0)	0.053
Transthoracic Doppler echocardiogram				
LV dilatation*	67 (36)	38 (31)	29 (47)	0.037
LV EDVi, ml/m^2	68.9 ± 26.8	64.5 ± 22.8	77.8 ± 31.7	0.001
LV EF, %	49 ± 14	50 ± 14	47 ± 14	0.155
Regional WMA	106 (57)	65 (53)	41 (66)	0.115
E/E′	8.5 ± 3.6	8.3 ± 3.5	8.9 ± 3.8	0.265
RV EDD, mm	32 ± 5	31 ± 5	33 ± 6	0.015
TAPSE, mm	22 ± 4	22 ± 4	21 ± 4	0.198
S′-TDI, cm/s	13 ± 3	13 ± 3	12 ± 3	0.128

Continued on the next page

TABLE 1 Continued

	Total (N = 185)	Active Myocarditis (n = 123)	Previous Myocarditis (n = 62)	p Value
CMR				
Lake Louise criteria	103 (56)	103 (84)	0 (0)	<0.001
STIR	101 (55)	101 (82)	0 (0)	<0.001
EGE	22 (12)	22 (18)	0 (0)	<0.001
LGE	185 (100)	123 (100)	62 (100)	1.000
Ventricular EAM				
EAM	46 (25)	23 (19)	23 (37)	0.011
LVA	46 (25)	23 (19)	23 (37)	0.011
EMB				
Myocarditis†	113 (61)	113 (92)	0 (0)	<0.001
Nonlymphocytic	0 (0)	0 (0)	0 (0)	1.000
Virus+	28 (15)	25 (20)	3 (5)	0.005
Necrosis	102 (55)	102 (83)	0 (0)	<0.001
Fibrosis	144 (78)	82 (67)	62 (100)	<0.001

Values are n (%), mean ± SD, or median (interquartile range). Baseline characteristics in patients with active versus previous myocarditis are shown. *Cutoffs for dilatation were referred to updated international standards (Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-270). †Myocarditis diagnosis was biopsy-proved according to updated criteria (Caforio et al. [2]).

ACS = acute coronary syndrome; AF = atrial fibrillation; AVB = atrioventricular block; CB = cardiac biomarkers; CMP = cardiomyopathy; CRP = C-reactive protein; EAM = electroanatomic mapping; EDD = end-diastolic diameter; EDVi = end-diastolic volume (indexed); EF = ejection fraction; EGE = early gadolinium enhancement; ES = electrical storm; ESR = erythrocyte sedimentation rate; Fam = family history; HF = heart failure; HR = heart rate; IB = inflammatory biomarkers; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LV = left ventricle; LVA = low-voltage areas; NSVT = nonsustained ventricular tachycardia; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PVC = premature ventricular complexes; RV = right ventricle; SCD = sudden cardiac death; SVT = supraventricular tachycardia; T-Tn = T troponin; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia; WMA = wall motion abnormality.

patients with persistent inflammation had a significantly higher occurrence of polymorphic PVC (36 of 52 vs. 11 of 71; $p < 0.001$) and irregular NSVT or VT (16 of 22 vs. 3 of 17; $p = 0.001$; polymorphic 7 of 22 vs. 1 of 17; $p = 0.106$) in follow-up. Conversely, no significant VA changes were found in PM patients (Online Table 5).

By the end of follow-up, 1,038 24-Holter ECGs were analyzed, combined with ICD interrogations when applicable. Of them, 471 and 525 examinations were recorded, respectively, during the active and post-inflammatory phases of myocarditis. As shown in **Table 4**, during the active phase, both NSVT and VT were more commonly irregular (with 76 ± 16 ms cycle length variability), and PVC were polymorphic (all $p \leq 0.001$). Of note, as reported in Online Table 6, both baseline and follow-up findings did not change, after excluding AM patients diagnosed by CMR only (n = 10).

SUMMARY MODEL. Overall, baseline polymorphic PVC, as well as irregular NSVT or VT, had high specificity in identifying AM (specificity = 84%, 91%, and 86%, respectively); the capability of ruling out PM was even higher in the presence of polymorphic NSVT or VT (specificity = 100% and 97%, respectively). Taken alone, however, VA features had low sensitivity in detecting AM (sensitivity = 63%, 62%, and 60%, for polymorphic PVC and irregular NSVT or VT, respectively). Thus, referring to histology as the gold standard, and based on our results, an integrated model was generated to predict myocarditis stage in our population, and improve sensitivity in identifying AM (Online Methods). The results are summarized in **Figure 4**. In particular, following CMR, PVC morphology was the only significant predictor of

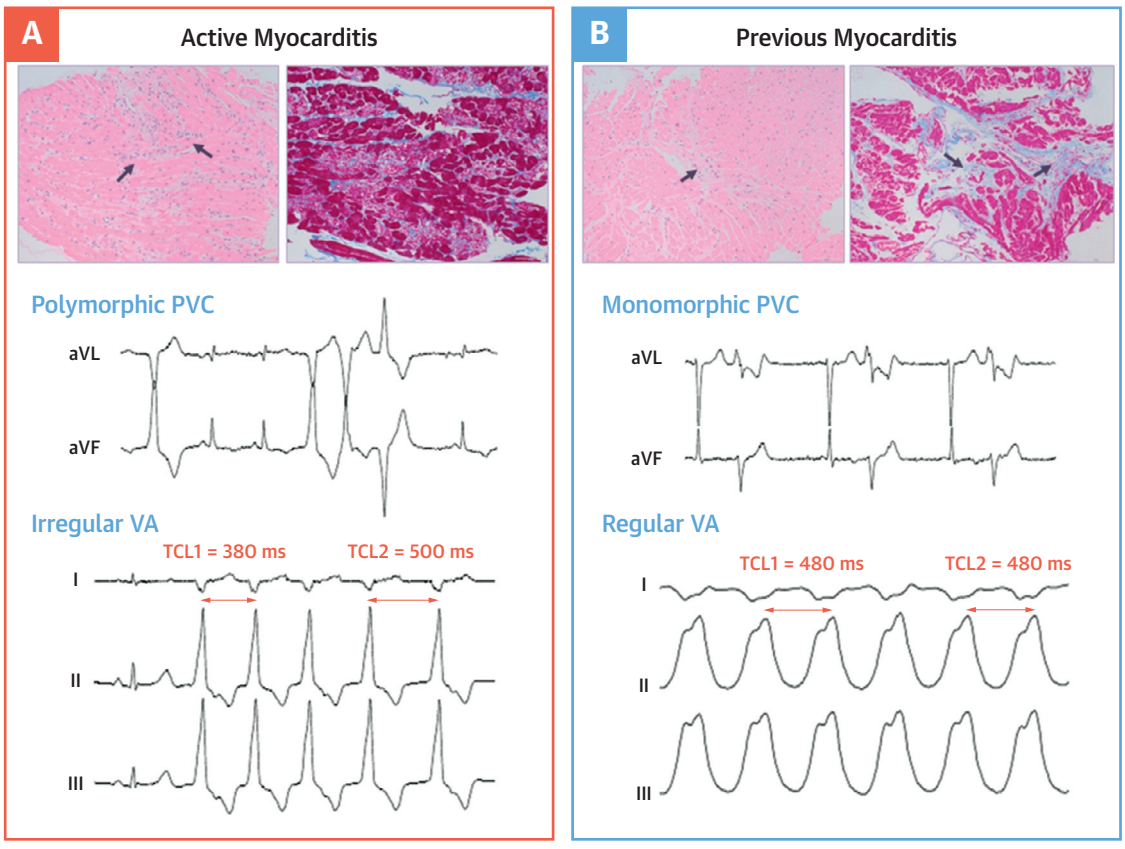
TABLE 2 Characterization of Baseline Ventricular Arrhythmias

	Total	Active Myocarditis	Previous Myocarditis	p Value
PVC	185	123	62	
N PVC	651 (106–2,925)	510 (65–2,752)	1,105 (272–3,829)	0.146
Polymorphic	88 (48)	78 (63)	10 (16)	<0.001
NSVT	79	45	34	
HR	129 ± 27	132 ± 31	123 ± 18	0.135
Beats	13 ± 9	17 ± 12	8 ± 5	<0.001
Irregular	31 (39)	28 (62)	3 (9)	<0.001
Polymorphic	7 (9)	7 (16)	0 (0)	0.018
Interdifferent	12 (15)	9 (20)	3 (9)	0.216
VT	59	30	29	
HR	166 ± 33	174 ± 35	156 ± 28	0.034
Unstable	12 (20)	9 (30)	3 (10)	0.104
Irregular	22 (37)	18 (60)	4 (14)	<0.001
Polymorphic	8 (14)	7 (23)	1 (3)	0.052
Interdifferent	11 (19)	7 (23)	4 (14)	0.506

Values are n, median (interquartile range), n (%), or mean ± SD. Baseline features of ventricular arrhythmias in patients with active versus previous myocarditis are shown. As for cycle length regularity, the number of discordant judgements requiring a third observer were <1%.

N PVC = daily premature ventricular complexes number; other abbreviations as in **Table 1**.

FIGURE 2 Histology Findings and Ventricular Arrhythmias in Patients With Active Versus Previous Myocarditis



Representative examples of histology and VA in AM **(A)** versus PM patients **(B)** are shown. Both hematoxylin-eosin **(left)** and Azan-Mallory stains **(right)** are shown (bar scale = 100 micron). Myocardial necrosis with massive inflammatory infiltrates are common in AM **(A, arrows)**, whereas replacement fibrosis, still accompanied by leukocyte infiltration with no myocyte necrosis, is typical in PM **(B, arrows).** Furthermore, polymorphic and irregular VAs are dominant among AM patients, whereas monomorphic and regular VAs are found in PM cases. TCL = tachycardia cycle length; other abbreviations as in **Figure 1**.

myocarditis stage in the whole population. In detail, polymorphic PVC led to reclassification of 24 patients (13%) with negative Lake Louise criteria from the PM to AM group. Furthermore, excluding CMR, irregular VA alone correctly identified 79% of true AM patients. An additional quote of AM cases were identified by regular VA associated with T-troponin values ≥72 ng/ml. Inflammatory indexes, LV dilation, and N-terminal pro-B-type natriuretic peptide had no role in stage prediction.

DISCUSSION

We presented detailed characterization of VA in patients with myocarditis at different inflammatory stages. Overall, we found that arrhythmic burden was not significantly different in AM versus PM patients (**Central Illustration**). Furthermore, previously defined negative prognostic factors, like viral genome at EMB (6) or QRS duration >120 ms (7), showed no significant associations with major arrhythmic events. Of note, malignant VA also occurred in patients with borderline myocarditis, despite a documented preserved LV ejection fraction and a previously reported excellent prognosis (8). Also, in contrast to previous studies about myocarditis patients of any clinical presentation and evidence of LGE at CMR (9,10), we documented a significantly higher annual event rate in our series of cases with arrhythmic onset, even with baseline LV ejection fraction >50%. Of note, we reported a worse outcome in patients with anteroseptal LGE localization, consistent with the results of previous studies focusing on either CMR (11) or EAM abnormalities (12).

FIGURE 3 Ventricular Arrhythmias Morphology and Localization of Abnormal Substrate

A

PVC	RS+	RS-	Tot
LGE IP+	87	40	127
LGE IP-	10	48	58
Tot	97	88	185

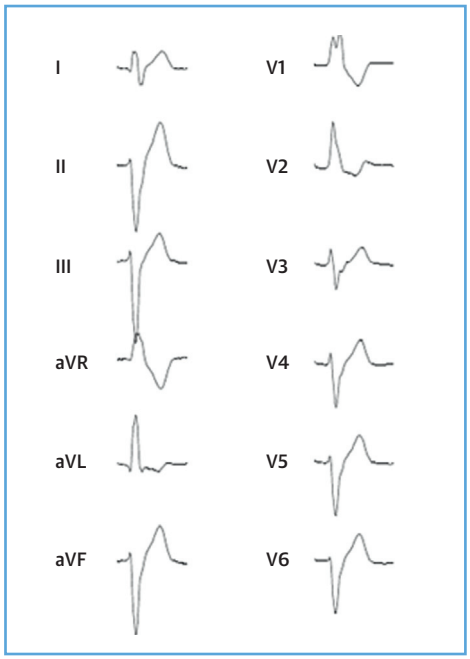
PPV = 90 (83-94) %
AM: 57/65 = 88 (79-93) %
PM: 30/32 = 94 (80-98) %

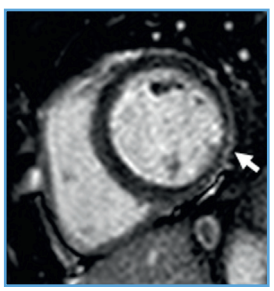
NSVT	RS+	RS-	Tot
LGE IP+	44	15	59
LGE IP-	4	16	20
Tot	48	31	79

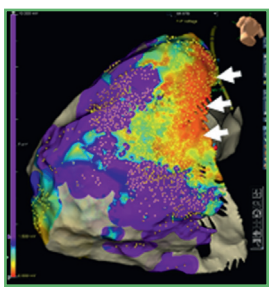
PPV = 92 (82-96) %
AM: 14/18 = 78 (59-89) %
PM: 30/30 = 100%

VT	RS+	RS-	Tot
LGE IP+	29	13	42
LGE IP-	3	14	17
Tot	32	27	59

PPV = 91 (77-97) %
AM: 11/14 = 79 (58-91) %
PM: 18/18 = 100%







B

PVC	RS+	RS-	Tot
LVA IP+	21	7	28
LVA IP-	8	10	18
Tot	29	17	46

PPV = 72 (60-82) %
AM: 6/10 = 60 (36-80) %
PM: 15/19 = 79 (67-87) %

NSVT	RS+	RS-	Tot
LVA IP+	17	8	25
LVA IP-	4	11	15
Tot	21	19	40

PPV = 81 (64-91) %
AM: 4/8 = 50 (25-75) %
PM: 13/13 = 100%

VT	RS+	RS-	Tot
LVA IP+	21	6	27
LVA IP-	3	13	16
Tot	24	19	43

PPV = 88 (71-95) %
AM: 6/9 = 67 (41-85) %
PM: 15/15 = 100%

Relationship between dominant VA morphology (RS) and localization of abnormal substrate (IP left ventricular wall) at both CMR and EAM is shown for each VA subtype (PVC, NSVT, and VT). Abnormal substrate was defined as the presence of LGE at CMR **(A)**, or as the presence of LVA at EAM **(B)**. PPV and relative 95% confidence intervals are reported below each table. IP = inferoposterior; LVA = low-voltage areas; PPV = positive predictive value; RS = right superior; other abbreviations as in Figure 1.

As a major study finding, we documented for the first time that AM patients more commonly had irregular and polymorphic VA, compared with PM patients. This is consistent with the dynamic nature of arrhythmogenic substrate described in AM (1). In fact, polymorphic PVCs suggest a multifocal origin, as demonstrated by greater basoapical extension of both the LGE and LVA in AM cases. Similarly, even when monomorphic, NSVT and VT showed an irregular cycle length, consistent with deeper substrate and focally transmural VA re-entry circuits, with dynamic endocardial or epicardial exit sites (13). Of note, because known factors associated with irregular VA, such as myocardial ischemia, have all been ruled out (14,15), these findings are likely to directly depend on myocardial inflammation. Conversely, regular and monomorphic VA were more common among PM patients, consistent with stable scar-related re-entry circuits, as described in VA occurring late after myocarditis (1,16,17).

Notably, our hypothesis was confirmed by follow-up findings. In fact, differently from patients with persistent inflammation, healed AM cases showed prevalence of monomorphic regular VA and bigeminal/trigeminal PVC, both suggesting static or "cold" substrate (Figure 2).

TABLE 3 Abnormal Substrate Extension in Different Ventricular Arrhythmias Subtypes

Cardiac magnetic resonance			
PVC (n = 185)	Polymorphic (n = 88)	Monomorphic (n = 97)	p Value
LGE segments (N/17)	5.8 ± 3.2	5.1 ± 3.1	0.133
LGE base-apex (N/3)	2.2 ± 0.7	1.3 ± 0.8	<0.001
LGE layers (N/3)	1.5 ± 0.6	1.5 ± 0.5	1.000
NSVT (n = 79)	Irregular (n = 31)	Regular (n = 48)	
LGE segments (N/17)	7.2 ± 5.0	6.2 ± 5.4	0.411
LGE base-apex (N/3)	1.3 ± 0.6	1.1 ± 0.5	0.152
LGE layers (N/3)	1.7 ± 0.6	1.3 ± 0.7	0.011
VT (n = 59)	Irregular (n = 22)	Regular (n = 37)	
LGE segments (N/17)	9.0 ± 6.2	8.6 ± 5.8	0.804
LGE base-apex (N/3)	1.1 ± 0.3	1.1 ± 0.4	1.000
LGE layers (N/3)	1.7 ± 0.7	1.3 ± 0.5	0.013
Electroanatomic mapping			
PVC (n = 46)	Polymorphic (n = 15)	Monomorphic (n = 31)	p Value
LVA segments (N/17)	6.9 ± 3.4	5.3 ± 3.2	0.126
LVA base-apex (N/3)	2.3 ± 0.8	1.3 ± 0.9	<0.001
LVA layers (N/3)	1.5 ± 0.6	1.4 ± 0.6	0.599
NSVT (n = 40)	Irregular (n = 16)	Regular (n = 24)	
LVA segments (N/17)	7.4 ± 4.7	6.3 ± 5.1	0.495
LVA base-apex (N/3)	1.5 ± 0.7	1.3 ± 0.7	0.382
LVA layers (N/3)	1.8 ± 0.7	1.2 ± 0.8	0.020
VT (n = 43)	Irregular (n = 17)	Regular (n = 26)	
LVA segments (N/17)	9.5 ± 6.8	8.8 ± 6.3	0.732
LVA base-apex (N/3)	1.5 ± 0.7	1.3 ± 0.6	0.323
LVA layers (N/3)	1.9 ± 0.8	1.3 ± 0.6	0.008

Values are mean ± SD unless otherwise indicated. Extension of abnormal substrate at baseline cardiac magnetic resonance (CMR) and electroanatomic mapping (EAM) are shown in patients with different ventricular arrhythmias subtypes. Abnormal substrate was evaluated in terms of surface extension (number of left ventricular segments involved, range 1 to 17); basoapical extension (number of wall segments from base to apex, range 1 to 3); transmural extension (number of wall layers from subepicardium to subendocardium, range 1 to 3).

Abbreviations as in Table 1.

TABLE 4 Characterization of Ventricular Arrhythmias During Follow-Up

	Total Examinations (N = 1,038)	Active Phase Records (n = 471)	Post-Inflammatory Phase Records (n = 567)	p Value
PVC				
Cases	981	456	525	
12 leads	981 (100)	456 (100)	525 (100)	1.000
Max N PVC/pt	582 (74–3,116)	402 (66–3,028)	698 (87–3,232)	0.499
Polymorphic	399 (48)	337 (74)	62 (12)	<0.001
Complex	694 (71)	318 (70)	376 (72)	0.003
Couples	511 (52)	277 (61)	234 (45)	0.083
Triplets	349 (36)	194 (43)	155 (30)	0.283
Bigeminism	440 (45)	168 (37)	272 (52)	<0.001
Trigeminism	506 (52)	191 (42)	315 (60)	<0.001
Early	67 (7)	43 (9)	24 (5)	0.746
NSVT				
Cases	146	59	87	
Irregular	47 (32)	40 (68)	7 (8)	<0.001
12 leads	90	39	51	
Polymorphic	9 (10)	9 (23)	0 (0)	<0.001
Interdifferent	20 (22)	9 (23)	11 (22)	0.897
VT				
Cases	94	40	54	
Unstable	19 (20)	12 (30)	7 (13)	0.262
Irregular	32 (34)	27 (68)	5 (9)	<0.001
12 leads	60	29	31	
Polymorphic	17 (28)	14 (48)	3 (10)	0.070
Interdifferent	18 (30)	9 (31)	9 (29)	0.597

Values are n, n (%), or median (interquartile range). Follow-up features of ventricular arrhythmias in patients during myocarditis active versus post-inflammatory phases, as recorded by 24-h Holter ECG integrated by ICD telemetric interrogations (when applicable). Of 1,038 recordings, 471 were performed during active phase of myocarditis (including AM patients before myocarditis healing and those with chronic active myocarditis) and 567 during post-inflammatory phase (including PM cases and AM patients after myocarditis healing). The mean number of Holter ECG recordings per patient was 6 ± 2, with < 1% missing data. Multiple (>1) NSVT and VT episodes were documented in 109 and 39 patients, respectively (AM vs. PM, p > 0.05 for both). Morphology was evaluated only in ventricular arrhythmias recorded by 12-lead ECG. As for tachycardia cycle length regularity, the number of discordant judgments requiring a third observer were <1%.

AM = active myocarditis; PM = previous myocarditis; Pt = patient; other abbreviations as in Table 1.

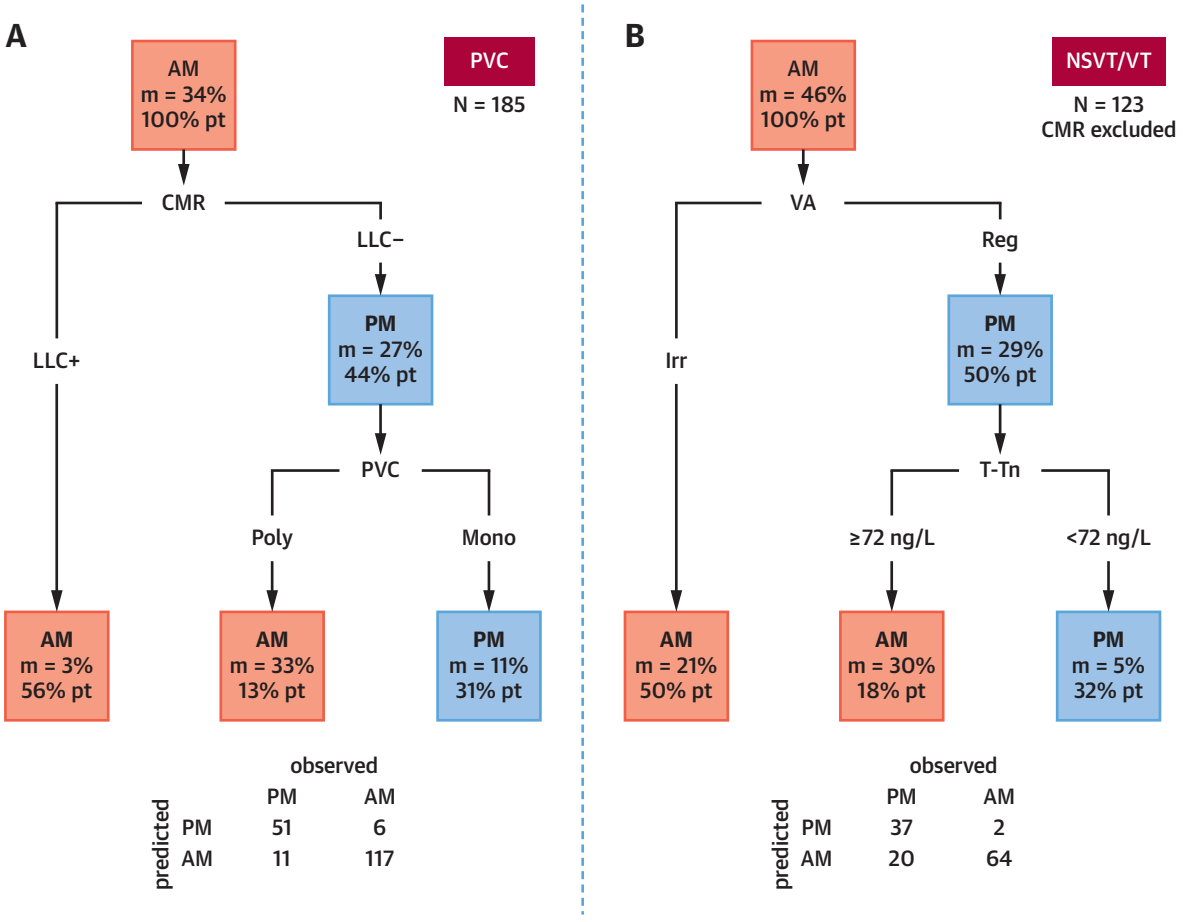
Certainly, it should be mentioned that genetic factors, such as altered desmosomal protein expression (18,19), may play an additional role in determining both VA occurrence and morphology changes during the hot phases of an underlying disease: new studies are called for in the next future to investigate the role of genetics in modulating myocardial inflammation and arrhythmogenesis.

As summarized in **Figure 4**, we finally presented a new model to help clinicians in identifying myocarditis stage in patients presenting with VA. Applications may be promising at both diagnostic and therapeutic levels. For instance, in cases with unexplained VA and contraindications to CMR, polymorphic or irregular VA would support a hypothesis of active myocarditis and indicate EMB as a confirmatory test. Similarly, if active myocarditis is diagnosed following VA analysis, the indication to ICD might be withdrawn, as currently recommended by guidelines (2–4).

Furthermore, our data confirmed a nonischemic substrate pattern, as previously described in myocarditis patients at both CMR and EAM (20,21). However, we showed that, in each VA subtype, RS morphology correlated with inferoposterior LGE and LVA: although consistent with previous reports on nonischemic cardiomyopathies (12,22), this was never described before in myocarditis patients specifically. Of note, RS morphology predictivity was maximal in PM patients with NSVT or VT.

Because of the documented prevalence of focal monomorphic VA in PM patients, our findings also explain the excellent results of VA transcatheter ablation in this group (21). Conversely, a high proportion of polymorphic and irregular VA, together with greater extension of abnormal substrate, are probably responsible for VA recurrences in AM patients, even following a successful ablation.

FIGURE 4 **Integrated Model for Myocarditis Staging**



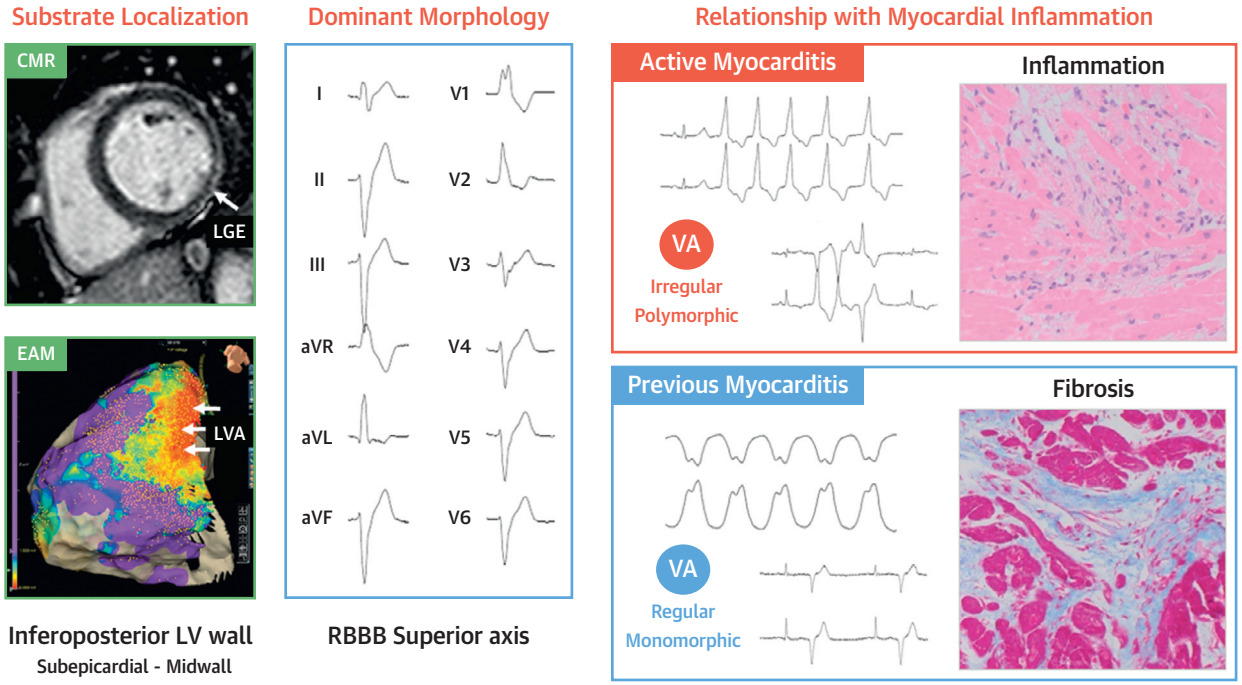
To summarize the main study findings, the new role of VA in classifying active versus previous myocarditis is shown. The classification tree method was used (detail in Online Methods). Referring to histology as the diagnostic gold standard (2), the following variables were tested as candidate predictors of myocarditis stage: CMR Lake Louise criteria, cardiac and inflammatory biomarkers, left ventricular dilation, and VA characteristics. Following automated discard of irrelevant variables, hierarchy of predictors is shown in both panels **([A]** for PVC patients, n = 185; and **[B]** for NSVT or VT patients, n = 123). In each leaf, both proportion of misclassified cases (m) and total percentage of patients (pt) are shown. Accuracy of the model is summarized in a **table at the bottom of each panel**. **(A)** The model suggests that, following CMR, PVC morphology is the second most important variable in defining myocarditis stage (overall model sensitivity = 95%, specificity = 82%). **(B)** In VA patients, excluding CMR, NSVT/VT regularity is the most important predictor of myocarditis stage, followed by T-Tn (with an estimated cutoff of 72 ng/l) in PM group (overall model sensitivity = 97%, specificity = 61%). Irr = irregular; LLC = Lake Louise criteria; Mono = monomorphic; Poly = polymorphic; Reg = regular; T-Tn = T troponin; other abbreviations as in Figure 1.

STUDY LIMITATIONS. We presented results from a single-center study performed at a referral center for VA management. Thus, both the prevalence and burden of arrhythmias might have been overestimated. Furthermore, study power and predictivity were limited by relatively small sample size and unknown disease prevalence. Modern T mapping sequences were missing at CMR. As compared with 12-lead Holter ECG recordings, lack of morphological data, as well as NSVT and VT overdetection, should be considered in ICD carriers. Finally, incidence and features of follow-up malignant VA may have been modified in patients who underwent transcatheter ablation.

CONCLUSIONS

We found no significant differences in both baseline and follow-up occurrence of VA in patients with myocarditis at different inflammatory stages. However, a greater proportion of polymorphic and irregular VA has been documented in patients with active myocardial inflammation, as opposed to those with

CENTRAL ILLUSTRATION **Ventricular Arrhythmias in Myocarditis**



Peretto, G. et al. J Am Coll Cardiol. 2020;75(9):1046–57.

Characteristics of ventricular arrhythmias (VAs) in patients with myocarditis. **(Left)** Localization of abnormal substrate at subepicardial-midwall IP left ventricular (LV) wall, as assessed by both cardiac magnetic resonance (CMR) (late gadolinium enhancement [LGE], **arrows**) and electroanatomic mapping (EAM) (low-voltage areas [LVA], **arrows**). **(Middle)** Dominant VA morphology, showing right bundle branch block (RBBB) superior axis, consistent with LV inferoposterior localization of abnormal substrate. **(Right)** Relationship between VA characteristics and myocarditis stage at histology: polymorphic and irregular VA are typical in active myocarditis **(top)**, while monomorphic and regular VA are common in previous myocarditis **(bottom).**

previous or healed myocarditis. Although RS morphology was the most common finding for any VA subtype, its predictivity of abnormal inferoposterior substrate at both CMR and EAM was maximal in PM patients with NSVT or VT. Our findings may help in identifying myocarditis stage in patients with VA, with promising future applications in diagnostic and therapeutic choices.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Polymorphic and irregular VAs are more common during AM, whereas monomorphic and regular VAs are associated with previous myocarditis.

TRANSLATIONAL OUTLOOK: VA features may be considered as markers of inflammatory activity in myocarditis patients, allowing for tailored diagnostic and therapeutic decisions.

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KEY WORDS cardiac magnetic resonance, electroanatomic mapping, endomyocardial biopsy, myocarditis, ventricular arrhythmias

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.