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ORIGINAL RESEARCH

ARRHYTHMIAS - PATHOPHYSIOLOGY

Clinical Characterization of Arrhythmia-Induced Cardiomyopathy in Patients With Tachyarrhythmia and Idiopathic Heart Failure

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ABSTRACT

BACKGROUND Arrhythmia-induced cardiomyopathy (AIC) is a known entity, but prospective evidence for its characterization is limited.

OBJECTIVES This study aimed to: 1) determine the relative frequency of the pure form of AIC in the clinically relevant cohort of patients with newly diagnosed, otherwise unexplained left ventricular systolic dysfunction (LVSD) and tachyarrhythmia; 2) assess the time to recovery from LVSD; and 3) identify parameters for an early diagnosis of AIC.

METHODS Patients were prospectively included, underwent effective rhythm restoration, and were followed-up at 2, 4, and 6 months to evaluate clinical characteristics, biomarkers, and cardiac imaging including cardiac magnetic resonance imaging. Patients with recurred arrhythmia were excluded from analysis.

RESULTS 41 of 50 patients were diagnosed with AIC 6 months after rhythm restoration. Left ventricular (LV) ejection fraction increased 2 months after rhythm restoration from 35.4% ± 8.2% to 52.7% ± 8.0% in AIC patients vs 37.0% ± 9.5% to 43.3% ± 7.0% in non-AIC patients. From month 2 to 6, LV ejection fraction continued to increase in AIC patients (57.2% ± 6.1%; $P < 0.001$) but remained stable in non-AIC patients (44.0% ± 7.8%; $P = 0.628$). Multivariable logistic regression analysis revealed that lower LV end-diastolic diameter at baseline could be used for early diagnosis of AIC, whereas biomarkers and other morphological or functional parameters, including late LV gadolinium enhancement, did not show suitability for early diagnosis.

CONCLUSIONS We observed a high prevalence of AIC in patients with otherwise unexplained LVSD and concomitant tachyarrhythmia, suggesting that this condition may be underdiagnosed in clinical practice. Most patients recovered fast, within months, from LVSD. A low initial LV end-diastolic diameter may constitute an early marker for diagnosis of AIC.

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Persistent supraventricular tachyarrhythmia can worsen left ventricular (LV) function, with or without pre-existing heart disease. More than one-third of patients with newly diagnosed atrial fibrillation (AF) have heart failure (HF), and more than one-half of patients with newly diagnosed HF have concomitant AF.[1] AF and atrial flutter (AFL) can cause LV systolic dysfunction (LVSD) and thus arrhythmia-induced cardiomyopathy (AIC), which is classified as a subset of dilated cardiomyopathy.[2] However, the causal relationship between tachyarrhythmia and LVSD is often difficult to assess because essentially any form of LVSD can also, conversely, lead to arrhythmia—a classic "chicken-and-egg" situation.[3]

The typical AIC phenotype can be curatively treated with rhythm restoration.[4-6] Although AIC is commonly encountered during routine clinical practice, both its incidence and prevalence remain unclear.[7-10] The classic feature of AIC—but also its diagnostic dilemma—is that a correct diagnosis can be made only retrospectively, when LV function has recovered after rhythm restoration, making a precise early diagnosis impossible. It has been reported that the time to full recovery can range from a few weeks to several months, but detailed and prospective studies in this area are lacking, most importantly in comparison to nonresponders of rhythm restoration.[4,5,8,11] Therefore, the first aim of this study was to assess the frequency of AIC in this specific and clinically relevant cohort of patients with newly diagnosed and otherwise unexplained LVSD.

An appropriate diagnosis of AIC requires accurate information on the time required for recovery from LVSD. Therefore, the second aim of this study was to investigate the time required for recovery from LVSD after rhythm restoration. In addition, as AIC can be diagnosed only retrospectively, we also aimed to identify potential predictors of AIC that may help to predict and eventually diagnose AIC at the time of first presentation. Accordingly, distinguishing patients with AIC from patients without AIC (ie, idiopathic LVSD) should provide a more nuanced understanding of this disease and potentially facilitate earlier and more effective treatment.

METHODS

STUDY DESIGN AND PATIENT SELECTION. This prospective, multicenter, observational study aimed to investigate the AIC frequency, the time to recovery, and potential factors for early diagnosis of AIC in patients with tachycardic AF or AFL (heart rate >100 beats/min) and newly diagnosed LVSD (LV ejection fraction [LVEF] <50%) (**Figure 1A**). The inclusion and exclusion criteria are listed in the Supplemental Appendix. Alternative diagnoses (eg, valvular heart disease, myocarditis, relevant coronary artery disease) were excluded by a variety of diagnostic procedures that included echocardiography, coronary angiography, and cardiac magnetic resonance imaging (CMR).

All patients underwent a rhythm control strategy according to current guidelines and following local clinical procedures.[12,13] Follow-up visits were scheduled to occur at 2, 4, and 6 months after rhythm therapy and involved a clinical evaluation, electrocardiogram (ECG), echocardiography (geometric and functional parameters), and laboratory testing of serum samples for N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT). To make the main conclusion of the paper as valid as possible, we excluded patients from analysis who showed recurrent arrhythmia until the end of the observation period. AIC was only diagnosed after the last follow-up visit when the effect of the therapy is assessed (*diagnoses ex juvantibus*), if other reasons for the LVSD except the arrhythmia itself could be excluded by applying a panel of diagnostic criteria used in previous AIC trials.[7,14-16]

Patients with either an absolute increase in LVEF of ≥15% or by ≥10% with an absolute LVEF ≥50% were categorized as AIC; all others were classified as non-AIC (**Figure 1B**). Patients were recruited at 3 trial sites in Germany (University Hospital Regensburg, Caritas Hospital St. Josef, and University Hospital Leipzig). The study complies with the Declaration of Helsinki, and local ethics committees at the University of Regensburg (18-1072-101) and University of Leipzig (467/19-lk) issued favorable ethical opinions

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

AIC = arrhythmia-induced cardiomyopathy

CMR = cardiac magnetic resonance imaging

ECG = electrocardiogram

HF = heart failure

hs-cTnT = high-sensitivity cardiac troponin

LA = left atrial

LGE = late gadolinium enhancement

LV = left ventricular

LVEDD = left ventricular end-diastolic diameter

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

LVSD = left ventricular systolic dysfunction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SR = sinus rhythm

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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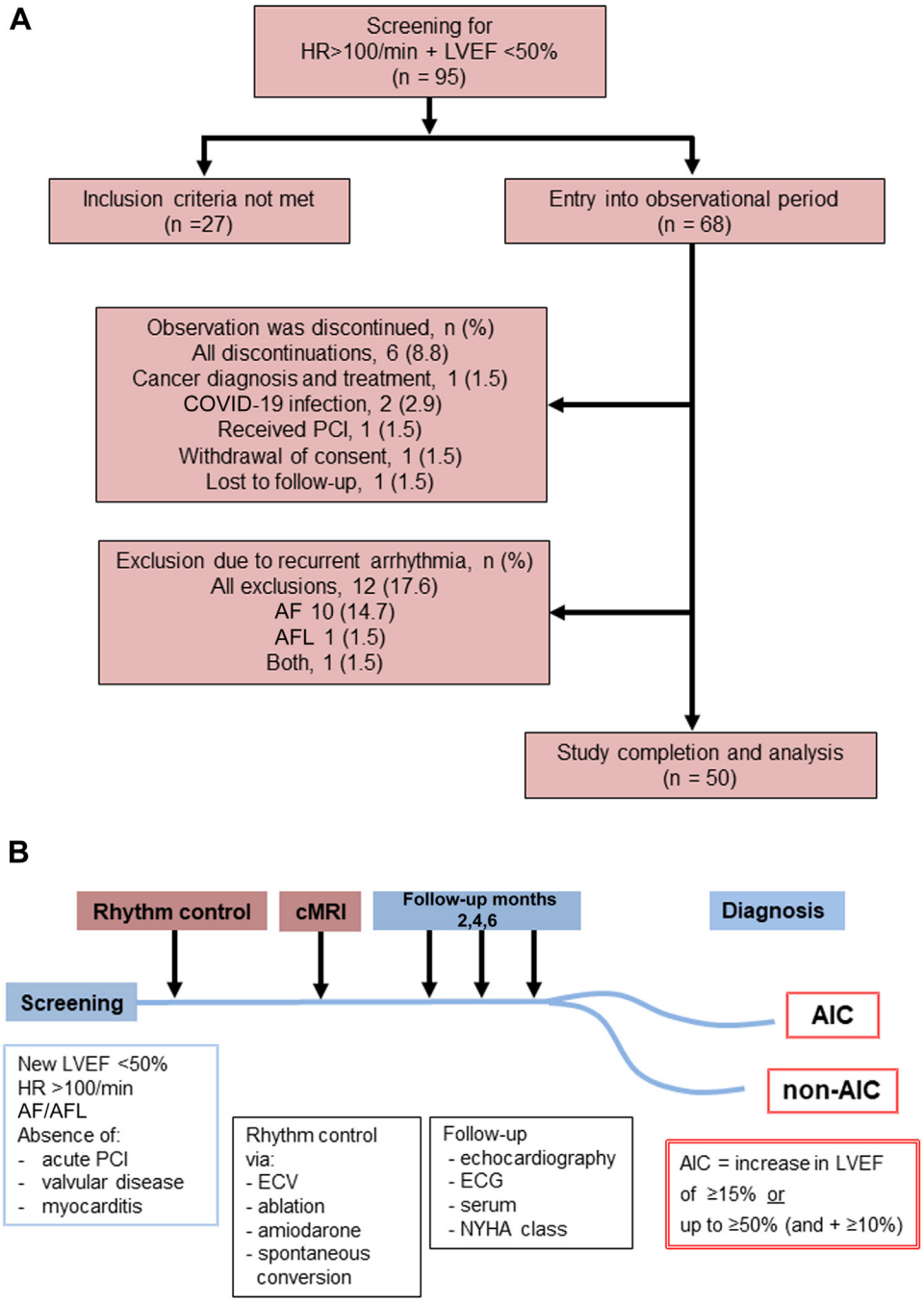
FIGURE 1 Participant Disposition Chart and Diagnosis of AIC



(A) Flow chart illustrating subject disposition. (B) Enrolled patients received rhythm control, underwent cardiac magnetic resonance imaging (cMRI), and were then followed-up at 2, 4, and 6 months. Diagnosis was made when the effect of the therapy has been assessed (*diagnoses ex juvantibus)* after the last study visit: if left ventricular ejection fraction (LVEF) increased ≥15% absolute or ≥50% with an increase of ≥10% absolute compared with the initial LVEF, patients were considered as arrhythmia-induced cardiomyopathy (AIC); all others were considered to be non-AIC. AF = atrial fibrillation; AFL = atrial flutter, ECG = electrocardiography; ECV = electrical cardioversion; HR = heart rate; PCI = percutaneous coronary intervention.

on the research before commencement of the study. The trial protocol is available online on the DRKS (German Clinical Trial Register) website under the reference number DRKS00017515.

ECHOCARDIOGRAPHIC AND MAGNETIC RESONANCE IMAGE ANALYSIS. Acquisition and analysis of echocardiographic images was performed at the local study centers by an experienced cardiologist. All images obtained by CMR were analyzed at a core facility (University Hospital Leipzig) by 2 experienced radiologists. A detailed description can be found in the Supplemental Appendix.

RHYTHM CONTROL STRATEGY. The type of rhythm control strategy used was at the discretion of the local clinical team. The interventions are described in detail in the Supplemental Methods. In brief, electrical or pharmacological cardioversion, pulmonary vein isolation, ablation of the cavotricuspid isthmus, and long-term pharmacological antiarrhythmic therapy were options for rhythm control. Rhythm control had to be effective, and combinations of different strategies were permitted, if clinically required.

PRIMARY AND SECONDARY ENDPOINTS. The primary endpoints were the AIC frequency and the time to recovery from LVSD in this specific collective. AIC frequency was calculated by dividing the number of patients diagnosed with AIC by the total number of patients analyzed. Recovery meant restoration of systolic LV function above the prespecified LVEF thresholds defined for AIC. The time to recovery is presented as the proportion of recovered patients at each time point of the follow-up schedule. Prespecified secondary endpoints to identify potential early markers for AIC were geometric parameters (LV end-diastolic diameter [LVEDD], LV end-systolic diameter [LVESD], left atrial [LA] area), functional parameters (degree of mitral regurgitation), biomarkers (NT-proBNP and hs-cTnT), LV late gadolinium enhancement (LGE), and NYHA functional class. Medication use was assessed at inclusion and at the end of follow-up.

STATISTICAL ANALYSIS. Data were examined for normal distribution using the Shapiro-Wilk test. Continuous variables are expressed as mean ± SD or as median (Q1-Q3), categorical variables as absolute numbers and percentages. Changes in echocardiographic parameters, biomarkers, and NYHA functional class over time within both groups (AIC and non-AIC) and comparisons between both groups were analyzed by 2-way analysis of variance (or mixed model) with Tukey's (to analyze the influence of time course) and Šídák's (influence of group) multiple comparison tests. A paired *t*-test was used to compare only 2 time points within the same group, as indicated in the text where appropriate. Logistic regression analysis was performed to identify

TABLE 1 Baseline Characteristics (N = 50)

Clinical characteristics	
Age, y	68.1 ± 11.1
Male	33 (66)
Weight, kg	89.0 ± 23.8
Height, cm	172.6 ± 10.8
BMI, kg/m^2	29.4 ± 5.9
BSA, m^2	2.1 ± 0.3
Diabetes	10 (20)
Arterial hypertension	38 (76)
Renal insufficiency	15 (30)
CHA_2DS_2-VASc score	3.2 ± 1.8
Smoker status	7 (14)
Previous PCI/CABG	6 (12)
NYHA functional class	2.9 ± 0.7
Biomarkers	
hs-cTnT, ng/L	26.1 ± 20.7
NT-proBNP, pg/mL	2,577 (1,091-6,122)
ECG and echocardiography	
Heart rate, beats/min	125.9 ± 15.7
Atrial fibrillation	36 (72)
Atrial flutter	12 (24)
Atrial fibrillation and flutter	2 (4)
LVEF, %	35.7 ± 8.5
LVEDD, mm	54.5 ± 6.8
LVESD, mm	44.5 ± 7.2
Mitral regurgitation grade	1.6 ± 0.8
LA area, cm^2	27.2 ± 5.7
LAVI, mL/m^2	50.3 ± 19.0
RVEDD, mm	36.3 ± 5.8
TAPSE, mm	15.8 ± 4.5
Medication	
Beta-blocker	41 (82)
ACEI	35 (70)
ARNI	7 (14)
Mineralocorticoid antagonist	8 (16)
Calcium antagonist	11 (22)
Diuretics	30 (60)
Digoxin	3 (6)
Amiodarone	2 (4)
Statin	14 (28)
ASA	3 (6)
$P2Y_{12}$ inhibitor	2 (4)
NOAC	32 (64)
VKA	3 (6)

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

ACEI = angiotensin converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; ASA = acetylsalicylic acid; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; ECG = electrocardiography; hs-cTnT = high-sensitivity cardiac troponin T; LA = left atrial; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; NOAC = novel oral anticoagulant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; RVEDD = right ventricular end-diastolic diameter; TAPSE = tricuspid annular plane systolic excursion; VKA = vitamin K antagonist.

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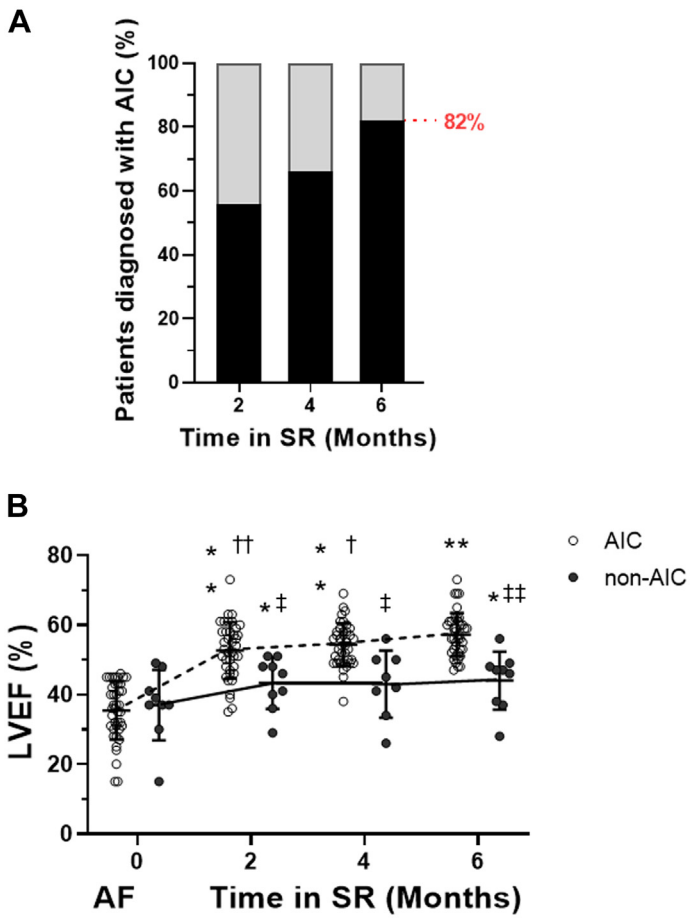
FIGURE 2 Primary Endpoints: AIC Frequency and Time to Recovery From AIC



(A) Bar graphs representing the frequency of patients diagnosed AIC (black) or non-AIC (grey). (B) Scatter plots (central bars represent mean, error bars SD) showing the time course of LVEF for patients with AIC compared with patients without AIC at admission and during follow-up. Dotted (solid) lines connect the mean values for the AIC (non-AIC) group. *$P < 0.05$ vs 0 months, **$P < 0.0001$ vs 0 months, †$P < 0.05$ vs 6 months, ††$P < 0.001$ vs 6 months, ‡$P < 0.05$ vs the respective AIC group, ‡‡$P < 0.01$ vs the respective AIC group. AF = atrial fibrillation or atrial flutter; SR = sinus rhythm; other abbreviations as in Figure 1.

parameters for early diagnosis of AIC, using simple and multivariable models of echocardiographic parameters, biomarkers, LGE, and NYHA functional class. To determine the optimal cutoff value for receiver-operating characteristic analysis, the Youden index was calculated.[17] Data were analyzed using standard statistical software (SPSS, version 26, IBM and GraphPad Prism, version 9).

RESULTS

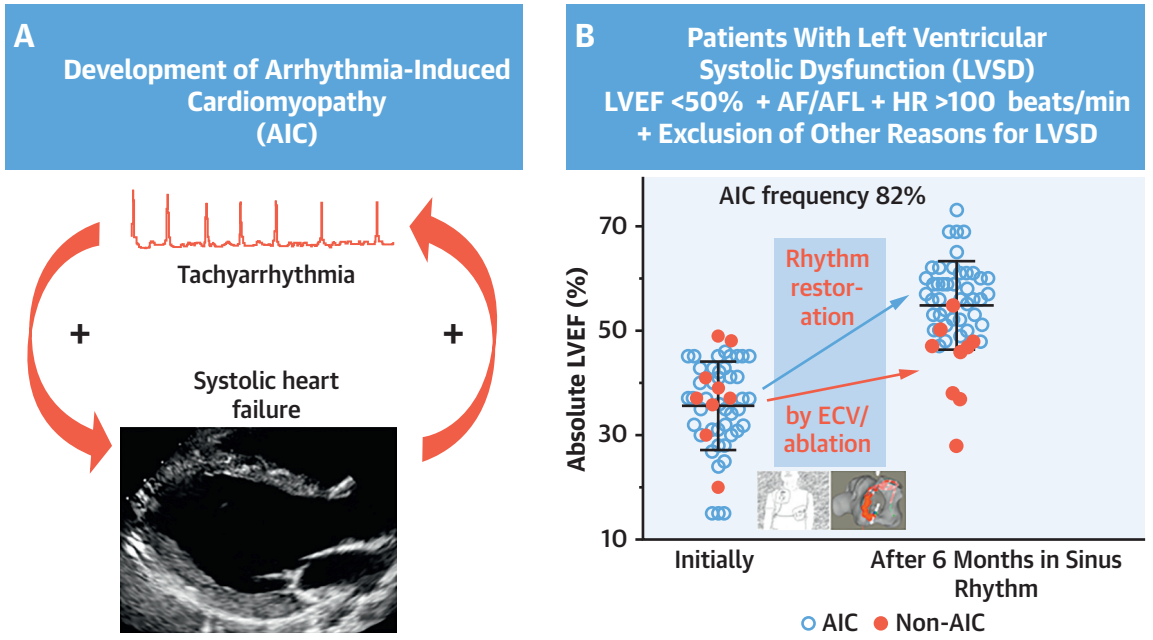
STUDY POPULATION. Between August 2018 and October 2020 a total of 95 patients were screened for AFib/AFlut with a heart rate >100 beats/min and new onset LVSD (EF <50%) at 3 sites in Germany. Sixty-eight patients fulfilled the inclusion criteria, 18 of whom had to be excluded per protocol for the statistical analysis. The majority of exclusions (n = 12) were due to recurrent arrhythmia (exclusion per protocol); all other reasons for exclusion are presented in Figure 1A.

BASELINE CHARACTERISTICS. Fifty patients (age 68 ± 11 years, 66% male) had sinus rhythm during the follow-up period. Heart rate and LVEF were 126 ± 16 beats/min and 35.7% ± 8.5%, respectively (frequency distributions are shown in Supplemental Figure 1), LA was moderately enlarged (LA area 27.5 ± 4.9 cm^2), and the risk for stroke was increased (CHA_2DS_2-VASc score 3.2 ± 1.8); 70% of the patients took oral anticoagulation, 4% were on antiarrhythmic medication (further details in Table 1; for differences in medication between the groups, see Supplemental Table 1). Six patients had prior coronary revascularization; coronary angiography ruled out significant stenosis (results are shown in Supplemental Table 2).

THERAPEUTIC APPROACH FOR RHYTHM CONTROL. Thirty-six patients presented with AF, 12 with AFL, 2 had both arrhythmias. Sinus rhythm (SR) was achieved using electrical cardioversion in 32 patients and ablation in 15 patients (5 pulmonary vein isolations, 8 cavotricuspid ablations, 2 patients received both procedures). Two patients converted to SR spontaneously, and 1 converted after amiodarone infusion. Of 4 patients in whom electrical cardioversion was initially unsuccessful, 3 underwent ablation (2 for AFL, 1 for AF), and 1 spontaneously converted to SR (Supplemental Figure 2). Four patients received additional antiarrhythmic medication, and 5 patients with AFL were ablated during the course after primary rhythm control to prevent recurrent arrhythmia.

PRIMARY ENDPOINTS. Already 29 patients (58%) fulfilled AIC criteria after 2 months, 34 (68%) after 4 months, and finally after 6 months, a total of 41 patients were diagnosed with AIC, resulting in a disease frequency of 82% in this specific cohort of patients presenting with newly diagnosed, otherwise unexplainable LVSD and tachyarrhythmia (Figure 2A). LVEF increased in AIC patients from 35.4% ± 8.2% to 57.2% ± 6.1% ($P < 0.0001$) and in non-AIC patients from 37.0% ± 9.5% to 44.0% ± 7.8% ($P = 0.003$) (Central Illustration) 6 months after rhythm restoration. Analysis of the time to recovery revealed that the change in LVEF (ΔEF) primarily occurred within the first 2 months of follow-up: +17.4% ± 8.1% vs +6.3% ± 4.6% ($P < 0.001$) in the AIC vs non-AIC

CENTRAL ILLUSTRATION **Rhythm Control Leads to Recovery of LVEF in Patients With AIC**



Schach C, et al. J Am Coll Cardiol EP. 2024;10(5):870–881.

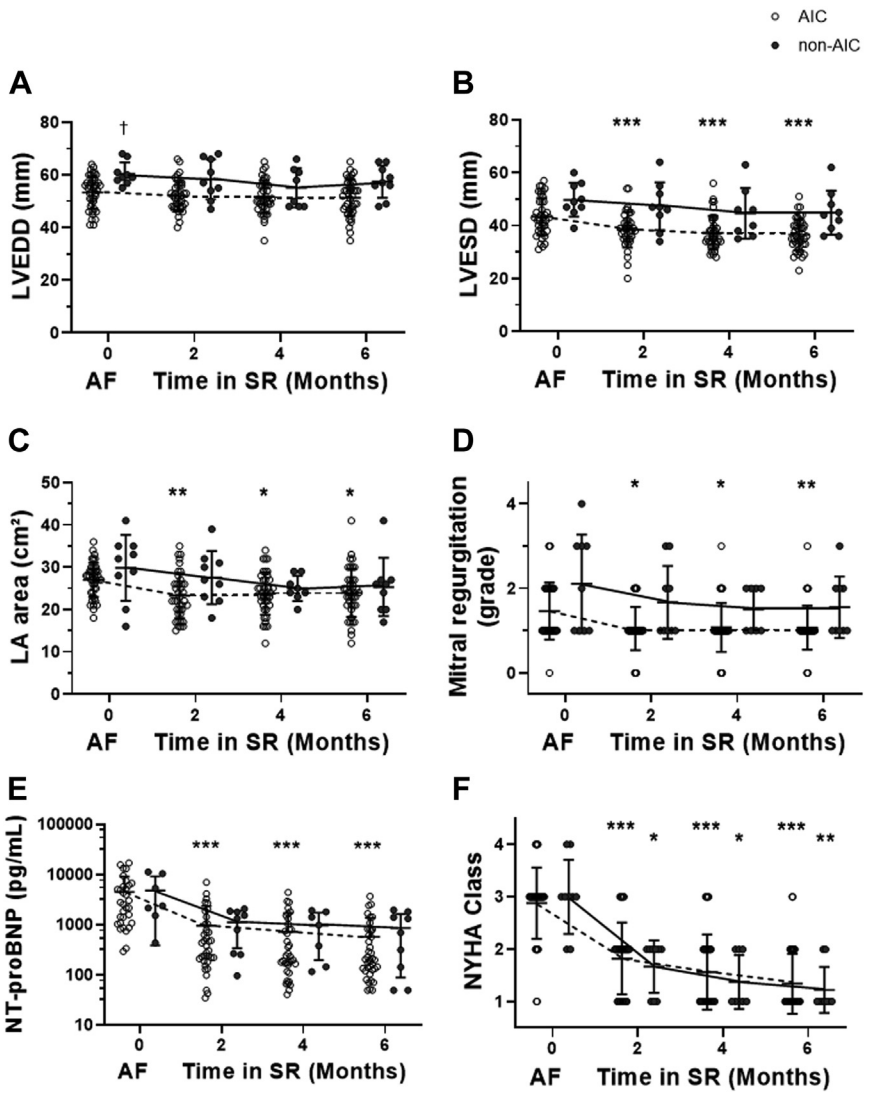
(A) Tachycardic arrhythmias can trigger systolic heart failure, and vice versa, atrial fibrillation/atrial flutter (AF/AFL) can lead to arrhythmia-induced cardiomyopathy (AIC). (B) Illustration of the 2 primary endpoints: frequency of AIC and time to left ventricular ejection fraction (LVEF) recovery following rhythm restoration in patients with tachycardic AF/AFL concomitant left ventricular dysfunction (LVEF <50%). Other causes of left ventricular dysfunction (eg, valvular disease, ischemic heart disease, myocarditis, cumulative disease) were excluded. ECV = electrical cardioversion; HR = heart rate; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction.

group, representing 79% of the overall magnitude of LVEF recovery in AIC patients (compare Figure 2B). During the second 2-month period (until month 4), the change in EF was 1.7% ± 3.2% for AIC compared with 0.9% ± 3.2% for non-AIC ($P = 0.208$). In the third 2-month period (until the end of follow-up), the change in EF was 2.9% ± 2.8% for AIC compared with −0.1% ± 2.7% for non-AIC ($P = 0.037$). Therefore, the AIC group showed a slight recovery in LVEF between months 2 and 6 (from 52.7% ± 8.0% to 57.2% ± 6.1%; $P < 0.0001$), whereas the non-AIC group did not (from 43.3% ± 7.0% to 44.0% ± 7.8%; $P = 0.628$, paired *t*-test in both comparisons).

As the exact definition of AIC diagnosis remains a matter of debate, we also calculated complete recovery (LVEF >50%), which was reached in 69%, 74%, and 90% of AIC patients after 2, 4, and 6 months, respectively (Supplemental Figure 3A). Furthermore, the proportion of patients with LVEF <35% is of high therapeutic interest, as this threshold represents 1 criterion for prophylactic implantable cardioverter-defibrillator implantation. None of the AIC patients remained in this category 4 months after rhythm restoration, whereas 2 patients (22%) in the non-AIC group did (Supplemental Figure 3B).

SECONDARY ENDPOINTS. Time course of clinical parameters in AIC and non-AIC patients. LV and left atrial geometry of AIC patients changed during follow-up. Although no significant change in LVEDD was detectable over time with analysis of variance (or mixed model) (Figure 3), a statistically significant decrease in LVEDD 6 months after rhythm control (51.3 ± 6.8 mm) vs baseline (53.4 ± 6.1 mm) was detected in AIC by a paired Student's *t*-test ($P = 0.043$). The change in LVEDD was not significantly different between the AIC and non-AIC groups. In the first 2 months, the change was 1.5 ± 4.7 mm in the AIC group and 2.1 ± 4.8 mm in the non-AIC group ($P = 0.750$), in the second 2-month period 0.4 ± 3.9 mm vs 2.5 ± 26 mm ($P = 0.158$), and in the last 2-month period until the end of follow-up, the change

FIGURE 3 Secondary Endpoints: Time Course of Echocardiographic Parameters, Biomarkers and NYHA Functional Class



Scatter plots (central bars represent mean, errors bars SD) of left ventricular end-diastolic diameter (LVEDD) (A), left ventricular end-systolic diameter (LVESD) (B), left atrial (LA) area (C), mitral regurgitation (D), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (E) and NYHA functional class (F) over time. Dotted (solid) lines connect the mean values for the AIC (non-AIC) group. *$P < 0.01$ vs 0 months, **$P < 0.001$ vs 0 months, ***$P < 0.0001$ vs 0 months, †$P < 0.001$ vs AIC. Abbreviations as in Figures 1 and 2.

in LVEDD was 0.2 ± 5.2 mm (AIC) and −1.8 ± 3.1 mm (increase, non-AIC; $P = 0.355$). LVESD decreased over time, but the change was not statistically significant (compare Figure 3B). The change until month 2 was 5.0 ± 5.9 mm in AIC compared with 2.4 ± 5.1 mm in non-AIC ($P = 0.547$); until month 4, it was 1.4 ± 5.6 mm vs 2.9 ± 2.6 mm ($P = 0.585$); and until the end of follow-up, it was 0.4 ± 6.1 mm vs −0.4 ± 2.0 mm (increase, $P = 0.856$). Furthermore, during the follow-up period in the AIC group, the LA area, grade of mitral regurgitation, NT-proBNP level, and NYHA functional class decreased (Figures 3C to 3F), whereas hs-cTnT remained unchanged (not shown).

Potential markers for early diagnosis of AIC according to clinical parameters. Simple logistic regression analysis revealed a significant relationship between LVEDD, LVESD, and mitral regurgitation measured at baseline and subsequent AIC diagnosis (Table 2). Receiver-operating characteristic analysis showed the highest area under the curve score for

LVEDD (0.82), followed by LVESD (0.76) and mitral regurgitation (0.65) (Figure 4). In a multivariable logistic regression model that included baseline LVEDD, LVESD, and degree of mitral regurgitation, only LVEDD proved to be an early marker for AIC (Table 3). Logistic regression analysis showed that LVEDD had an OR of 0.76 (95% CI: 0.59-0.91) for predicting AIC/non-AIC outcome, with an area under the curve of 0.82 and a *P* value of 0.002.

The optimal cutoff value was an LVEDD of 56.5 mm, with values below this being indicative of AIC (Figure 4).

Late gadolinium enhancement in AIC and non-AIC patients. CMR was performed in 78% of the patients and showed no inter-group difference in LV LGE (Figure 5A). There was no difference in the distribution of LGE-positive and -negative patients between the groups ($P = 0.682$) (Figure 5B) or in absolute LV LGE levels between the groups (Figure 5C). Furthermore, the increase in LVEF measured from baseline until the end of follow-up (ΔLVEF) in the AIC group was virtually identical between LGE-positive and LGE-negative patients (Figure 5D).

TABLE 2 Simple Logistic Regression Models on Outcome AIC

	AIC	Non-AIC	OR (95% CI)	*P* Value
LVEF, %	35.4 ± 8.2	37.0 ± 9.5	0.98 (0.88-1.06)	0.612
LVEDD, mm	53.4 ± 6.1	60.4 ± 4.1	0.76 (0.59-0.91)	0.010
LVESD, mm	43.4 ± 6.9	49.8 ± 6.0	0.87 (0.76-0.97)	0.025
LA area, (cm^2)	27.0 ± 4.0	29.9 ± 7.3	0.88 (0.74-1.02)	0.116
Mitral regurgitation grade	1.5 ± 0.7	2.1 ± 1.0	0.40 (0.15-0.94)	0.041
NT-proBNP,[a] pg/mL	4,525 ± 4,536	4,794 ± 4,077		0.886
Log NT-proBNP	3.4 ± 0.5	3.5 ± 0.5	0.81 (0.13-4.82)	0.820
hs-cTnT, ng/L	27.0 ± 21.8	22.9 ± 15.7	1.01 (1.00-1.07)	0.606
LV LGE, %	5.8 ± 6.3	5.1 ± 5.6	1.02 (0.89-1.18)	0.769
NYHA functional class, (grade)	2.9 ± 0.7	3.0 ± 0.7	0.75 (0.22-2.20)	0.622

Values are mean ± SD unless otherwise indicated. [a]Non-normally distributed, CIs are omitted.
AIC = arrhythmia-induced cardiomyopathy; LV LGE = left ventricular late gadolinium enhancement; other abbreviations as in Table 1.

DISCUSSION

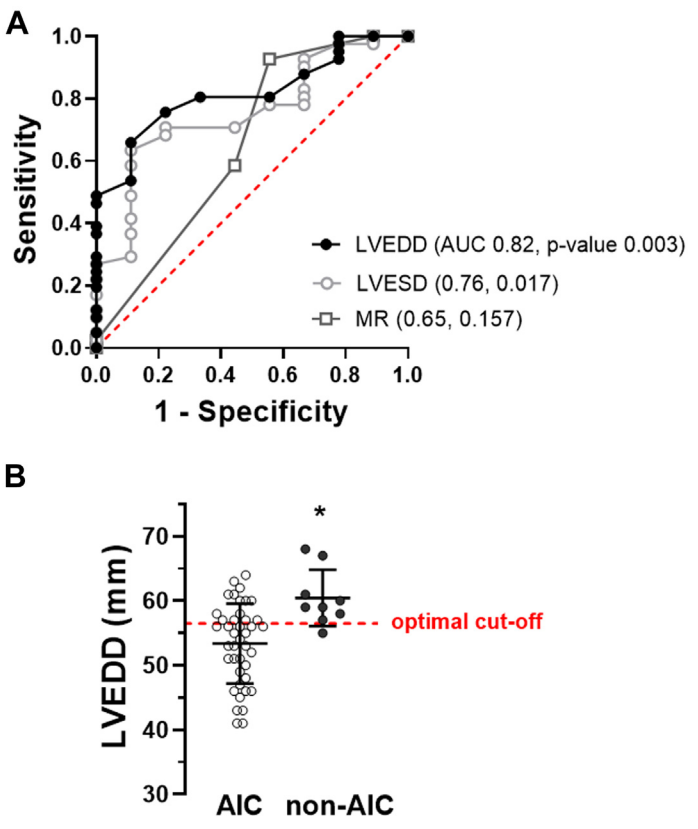
In this prospective, multicenter study we assessed the frequency of AIC and the time to recovery from LVSD and for the first time identified a marker for early diagnosis of AIC in patients with newly diagnosed, otherwise unexplained LVSD and persistent tachyarrhythmia. The magnitude of recovery from LVSD was greatest within 2 months following rhythm restoration. However, recovery also continued in the AIC group for up to 6 months, whereas LVEF in the non-AIC group did not change significantly after the 2-month follow-up. Multivariable logistic regression analysis revealed that low LVEDD at baseline could detect AIC, whereas biomarkers and other morphological or functional parameters did not.

DEFINITION AND FREQUENCY OF AIC. In previous AIC studies, the upper limit of LVEF for patient inclusion has ranged from 40% to 50%, corresponding to the thresholds for HF with reduced and preserved LVEF.[13,18] Several studies in this field have used these limits as thresholds for patient eligibility without adopting uniform criteria for LVEF recovery.[7,14,16,19] Our study set an LVEF of <50% for inclusion and defined recovery either as a ≥15% absolute increase or an increase of ≥10% with an absolute LVEF of ≥50% within 6 months, to act as a composite of the criteria employed in the studies cited above. The proportion of patients diagnosed with AIC—82%—was very high, clearly higher than in patients with "idiopathic" cardiomyopathy referred for ablation of AFib.[19,20] Earlier studies of patients undergoing atrioventricular node ablation have suggested that AIC is present in up to 50% of cases[21,22] and may even be underestimated.[23]

In the light of this, there is a great confusion regarding the characteristics and also frequency of a pure form of AIC in different clinical trials. Thus, large studies such as CASTLE-AF (Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF) and EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) cannot be used for this purpose or compared with our study because of the heterogeneous collectives in these trials with, for example, pre-existing and sometimes significant HF and for example, coronary artery or valvular disease.[6,24] These trials were not designed to precisely investigate AIC but rather to determine the effects of rhythm restoration on clinical outcomes independent of the cause for potential underlying LVSD. In our study, every patient underwent coronary angiography and subsequent echocardiography, and 78% of participants were also examined by CMR. Therefore, our trial provides unique and novel insights in specific patients with suspected AIC.

TIME TO LVSD AND TIME TO RECOVERY. The exact time for LVSD to develop as a result of AIC is widely unknown, but typically varies from a few days to several months after the onset of tachycardia.[4,5,10,23,25] When testing animal models

FIGURE 4 Early Markers for AIC According to Secondary Endpoints



Receiver operating characteristic curves of LVEDD, LVESD, and mitral regurgitation (MR) (A), scatter plot of LVEDD (B, central bars represent mean, error bars SD). The dotted red line represents the optimal cutoff estimated by the Youden index. AUC = area under the curve; other abbreviations as in Figures 1 and 3.

under controlled conditions, LVSD can be observed days after tachypacing, finally leading to end-stage HF after 3 to 4 weeks.[26,27] Atrial remodeling associated with AF has been shown to consist of 2 potential components, one due the rapid irregular atrial rate and the other related to rapid ventricular response.[28] In addition, AF is known to cause a rapid electrical and structural remodeling of human left ventricular cardiomyocytes.[29,30] Conversely, termination of pacing leads to an improvement in systolic LV function and cardiac output after only 48 hours and to full normalization after 2 weeks in animals.[26] In a previous clinical trial, catheter ablation of AF in patients with LVSD resulted in an LVEF recovery period up to 6 months after intervention[4]; approximately 55% of patients had no concomitant heart disease in this study, and the greatest improvement in LVEF was observed in patients in whom the LVSD could be attributed solely to arrhythmia. As the coexistence of other heart diseases may add to the arrhythmic effect and intensify LVSD, the contribution of AIC in such a mixed model is hard to evaluate. A recent study in such patients with end-stage HF showed that the combination of rhythm control and optimal medical therapy was superior in terms of mortality, implantation of LV assist device, or urgent heart transplantation vs medical therapy alone.[31]

In another study focusing on the early recovery phase, a rapid increase in LVEF was observed in patients with persistent or long-standing AF as early as 3 days after rhythm control.[5] Continued recovery was noted after 40 days, which was particularly pronounced in patients who maintained sinus rhythm. The initial rapid increase in LVEF after rhythm restoration may arise in part from the rhythm therapy itself and could be attributed to acute adaptive, rather than contractile, myocardial changes.[32,33] This effect may partially explain the minor increase in LVEF demonstrated by non-AIC patients at 2 months of follow-up in our study. Progressive LVEF recovery after weeks and months following rhythm restoration most likely depends on LV remodeling. These trials, however, analyzed all patients together without comparing responders (AIC) and nonresponders to rhythm restoration.

Although we observed only a slight decrease in LVEDD, there was a marked decrease in LVESD during follow-up. This is consistent with findings from ablation studies, which also uncovered a pronounced decrease in LVESD (compared with LVEDD) after rhythm restoration.[4,7] Hsu et al[4] showed the greatest improvement in patients without concurrent structural heart disease, and inadequate rate control before ablation and recovery from LVSD predominantly occurred during the first few months after rhythm control, lasting until the sixth month¯similar to the dynamics of LVEF recovery observed in our study. The time course of recovery must be distinguished from patients without AIC, that is, idiopathic cardiomyopathy or non-AIC, as it is denoted here. In the CHAMP-HF (Change the Management of Patients with Heart Failure) cohort, patients with chronic HF

TABLE 3 Multivariable Logistic Regression Model on Outcome AIC

	OR (95% CI)	*P* Value	C Index
LVEDD	0.71 (0.48-0.95)	0.042	0.82
LVESD	1.09 (0.89-1.34)	0.397	
Mitral regurgitation	0.39 (0.10-1.23)	0.131	

The model includes all variables with $P < 0.10$ in the simple regression analysis in Table 2.
Abbreviations as in Tables 1 and 2.

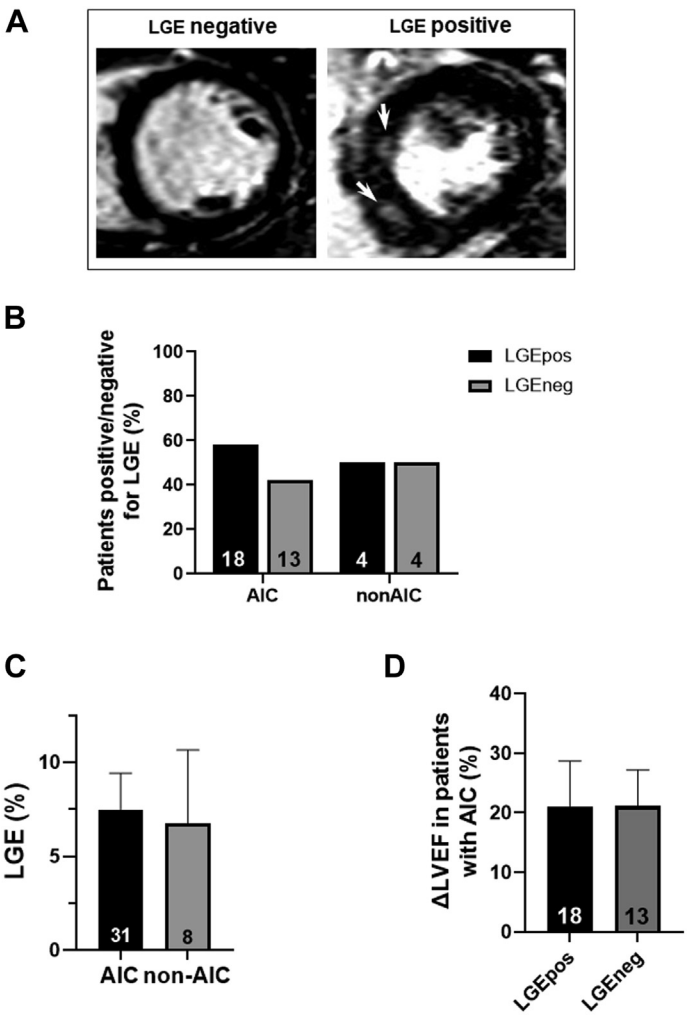
showed a 4% change in mean LVEF after a median follow-up period of 16 months.[34] In the PROVE-HF (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes) cohort of patients with new-onset HF (or without angiotensin converting enzyme inhibitors or angiotensin receptor blockers at baseline), LVEF improved by 7% within 6 months of starting treatment with sacubitril/valsartan.[35] By contrast, AIC patients in our study exhibited an improvement in LVEF of 22% ± 7% 6 months after rhythm restoration, indicating that our composite criteria for diagnosing AIC were not overly stringent. Of course, responsiveness to heart failure medication could also have influenced improvements in LVEF in our study. However, there was no nominal difference between the groups (Supplemental Table 1).

LVEDD HAS PROGNOSTIC VALUE IN EARLY DETECTION OF AIC. Follow-up assessments in AF ablation trials revealed decreasing LV geometric measures over time, as mentioned in the preceding.[4,7,20] In our study, a low LVEDD at baseline had a high probability for detection of an AIC (**Tables 2 and 3**), with larger ventricles acting as indicators of non-AIC. Accordingly, smaller left ventricles have been shown to be predictive of favorable outcomes in various clinical manifestations of HF.[36-38] We calculated an optimal cutoff value of 56.5 mm for LVEDD to identify patients with a strong probability of having AIC at presentation. Other morphological and functional parameters, including biomarkers, did not correlate with AIC.

In contrast to previous studies,[7,39] the percentage of LV LGE as an indicator of myocardial scar did not differ between groups and may support a model of subtle cardiomyopathy that is exacerbated by tachyarrhythmia: Prabhu et al[40] demonstrated that LV fibrosis decreased 6 months after rhythm control but was still higher than in healthy controls. In addition, Wijesurendra et al[41] showed that myocardial energetics are impaired in patients with lone AF, which may be a sign of occult cardiomyopathy, independent of arrhythmia. This type of model is consistent with our observation of LGE in AIC and non-AIC patients in the current study and aligned with the dynamics of recovery from LVSD over several months observed in this and previous studies. However, this field is still poorly understood, and very likely results are not conflicting as there are a large number of very heterogeneous and differently defined patient groups with various comorbidities.

STUDY LIMITATIONS. Our study cannot exclude whether occult cardiomyopathy or other predispositions (eg, genetic) were previously present in some cases. In addition, recurrent arrhythmias may have introduced selection bias, because it is unclear to which group the excluded patients would have been assigned. However, without exclusion of these patients, the trigger to cause LVSD would persist and a valid assessment of the AIC frequency and the time to recovery of arrhythmia-induced LVSD would not have been possible. In this case, we would have underestimated the frequency and time course of AIC because there would be no sufficient improvement of

FIGURE 5 LV LGE Cannot Be Used to Distinguish AIC Patients From Non-AIC Patients



(A) Original cardiac magnetic resonance imaging short-axis view. White arrows indicate regions with late gadolinium enhancement (LGE). (B) Contingency analysis of patients with (LGEpos) or without (LGEneg) LGE. N is given at the bottom of each bar. (C) Bar chart showing the mean (error bars 95% CI, numbers = n) proportion of left ventricular LGE in each group. (D) Bar chart showing the ΔLVEF (value at 6 months minus baseline value) observed in AIC patients. Abbreviations as in **Figure 1**.

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LV function with persistent arrhythmias. Thus, the quite-selected cohort is required, although it does not constitute the AIC prevalence for the general population. Although an ECG was obtained at each follow-up visit, and 65% of the patients were further monitored by Holter ECG or a wearable/implanted device, we cannot exclude the final possibility of a detection bias of subclinical paroxysmal arrhythmic episodes. Not every patient underwent CMR, owing to claustrophobia or renal insufficiency. Therefore, bias in detection of myocardial scar tissue cannot be excluded.

CONCLUSIONS

Our results demonstrate that in patients with newly diagnosed, unexplained LVSD and concomitant tachyarrhythmia, the frequency of AIC is unexpectedly high. Most of the recovery occurred within 2 months following rhythm control and continued until the end of follow-up after 6 months. Patients with relatively lower initial LVEDD are more likely to recover from LVSD. We therefore advocate routine determination of LV function and geometry at admission and within 2 months after rhythm restoration to enable early AIC diagnosis. Final diagnosis should not be made before 6 months after rhythm restoration. This is especially important, as AIC showed a high frequency in this clinically relevant population, suggesting that AIC is normally underestimated in daily clinical practice and supporting the argument that this condition justifies increased attention. Further studies aimed at developing diagnostic scores to differentiate between patients with and without AIC are now warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The occurrence of AIC was unexpectedly high in patients with newly diagnosed and unexplained left ventricular systolic dysfunction, suggesting a potential underestimation in present clinical practice. Patients with AIC recovered from LVSD within a few months of rhythm control, which differentiates them from those with chronic heart failure. Patients with lower initial LVEDD are more likely to recover from LVSD, thus identifying them as group amenable to earlier, definitive rhythm control.

TRANSLATIONAL OUTLOOK: Measuring LVEF and LVEDD at presentation and LVEF at timely follow-up visits (eg, 2 months) after rhythm control enhances the accuracy of AIC diagnosis, leading to more effective therapy adjustment. Patients with newly diagnosed LVSD and arrhythmia have a high probability of recovering from LVSD after rhythm control, given that other causes are excluded. Therefore, these patients should receive long-term rhythm control, regular monitoring, and conservative device therapies.

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KEY WORDS arrhythmia-induced cardiomyopathy, atrial fibrillation, left ventricular dysfunction, heart failure, tachycardiomyopathy, tachymyopathy

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.