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Article

Exercise Stress Test Late after Arrhythmic versus Nonarrhythmic Presentation of Myocarditis

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Abstract: ***Background***. Exercise stress test (EST) has been scarcely investigated in patients with arrhythmic myocarditis. ***Objectives***. To report the results of EST late after myocarditis with arrhythmic vs. nonarrhythmic presentation. ***Methods***. We enrolled consecutive adult patients with EST performed at least six months after acute myocarditis was diagnosed using gold-standard techniques. Patients with ventricular arrhythmia (VA) at presentation were compared with the nonarrhythmic group. Adverse events occurring during follow-up after EST included cardiac death, disease-related rehospitalization, malignant VA, and proven active myocarditis. ***Results***. The study cohort was composed of 128 patients (age 41 ± 9 y, 70% males) undergoing EST after myocarditis. Of them, 64 (50%) had arrhythmic presentation. EST was performed after 15 ± 4 months from initial diagnosis, and was conducted on betablockers in 75 cases (59%). During EST, VA were more common in the arrhythmic group (43 vs. 4, $p < 0.001$), whereas signs and symptoms of ischemia were more prevalent in the nonarrhythmic one (6 vs. 1, $p = 0.115$). By 58-month mean follow-up, 52 patients (41%) experienced adverse events, with a greater prevalence among arrhythmic patients (39 vs. 13, $p < 0.001$). As documented both in the arrhythmic and nonarrhythmic subgroups, patients had greater prevalence of adverse events following a positive EST (40/54 vs. 12/74 with negative EST, $p < 0.001$). Electrocardiographic features of VA during EST correlated with the subsequent inflammatory restaging of myocarditis. Nonarrhythmic patients with uneventful EST both on- and off-treatment were free from subsequent adverse events. ***Conclusions***. Late after the arrhythmic presentation of myocarditis, EST was frequently associated with recurrent VA. In both arrhythmic and nonarrhythmic myocarditis, EST abnormalities correlated with subsequent adverse outcomes.

Keywords: exercise stress test; physical activity; myocarditis; ventricular arrhythmia; cardiac magnetic resonance; endomyocardial biopsy

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1. Introduction

Exercise stress test (EST) is an informative diagnostic tool allowing assessment of both inducible myocardial ischemia and arrhythmia [1]. To date, however, EST is underinvestigated in myocarditis, an inflammatory disease of the myocardium initiated by viral

infections, toxic agents, or dysimmune processes and frequently affecting young and otherwise healthy subjects [2]. In fact, due to the potentially harmful effects of strenuous physical activity during the active inflammatory stage of the disease [3], EST is currently contraindicated in patients diagnosed with acute myocarditis [2,4]. On the other hand, EST is considered a safe and informative technique after myocarditis healing [2,4]. Consistently, international guideline documents agree in recommending the use of EST after six months from acute myocarditis before resuming competitive sport participation [4,5]. In this setting, the absence of arrhythmia and ischemia signs is needed to demonstrate safety during incremental physical activity [6]. Remarkably, the evidence currently supporting the role of EST in myocarditis focuses on the classic acute coronary syndrome (ACS)-like presentation of myocarditis, which is the most common and benign scenario [7–9]. Currently, there is a lack of consistent data about EST in the remaining clinical presentations, in particular in patients with ventricular arrhythmia (VA) at the time of diagnosis. The issue is demanding since VA associated with myocarditis may be life-threatening and have been described both during the acute and chronic phases of the disease [10].

The aim of our study is to compare the results of EST at late stage of arrhythmic vs. nonarrhythmic presentation of myocarditis.

2. Materials and Methods

2.1. Study Design

This study, observational and prospective, was performed at a referral center for the management of arrhythmic myocarditis. Following the local institutional review board approval, written informed consent was obtained from all participants (MYOCAR, 24/01/2018). From January 2013 to January 2021, we enrolled consecutive inhospital patients with myocarditis, undergoing EST late after clinical presentation. In detail, inclusion criteria were: (1) age $\geq$ 18 years; (2) acute clinical presentation with myocarditis diagnosed by gold standard techniques, namely cardiac magnetic resonance (CMR) and/or endomyocardial biopsy (EMB); (3) EST performed at least six months after myocarditis diagnosis.

Patients presenting with VA constituted the study group and were compared with controls without VA. For the purposes of the study, VA included ventricular fibrillation (VF), either sustained or nonsustained ventricular tachycardia (VT; NSVT), or ventricular ectopies (VE) of Lown's grade $\geq$2 [11].

Exclusion criteria were: catheter ablation of VT performed before EST; EST not performed or contraindicated due to clinical instability; and loss to follow-up.

2.2. Myocarditis Diagnosis

EMB-proven active myocarditis was defined, as recommended [2], based on histological (inflammatory infiltrates and myocyte degeneration fulfilling the Dallas criteria), immunohistochemical ($\geq$14 leucocytes/mm^2 and CD3+ T-lymphocytes $\geq$7 cells/mm^2), and molecular criteria (polymerase chain reaction, to identify or exclude viral etiology). EMB was performed by percutaneous right ventricular sampling under fluoroscopic and echocardiographic guidance [12]. CMR-proven myocarditis was defined by the standard and updated Lake Louise criteria (LLC) [13,14] in patients enrolled before and after 2016, respectively. In detail, CMR was performed on a 1.5 T scanner (Achieva dStream; Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 32-channel phased-array coil. Myocardial edema was evaluated using black blood T2 short-tau inversion recovery (STIR) images. Modified Look-Locker inversion recovery sequences and gradient-(echo planar imaging) and spin-echo multi-echo sequences were used for T1 mapping and T2 mapping, respectively. Late gadolinium enhancement (LGE) images were acquired 10 min after gadolinium injection using 2D T1 weighted segmented inversion-recovery gradient-echo sequences, and analyzed on two orthogonal planes. The correct inversion time was determined using the Look-Locker technique. Extracellular volume (ECV) was obtained according to recommended standards [15].

2.3. Treatment and Follow-Up

Treatment for myocarditis was patient-tailored, including optimal medical treatment and cardiac device implant, based on international guideline recommendations [16,17] and the experience of the center [18]. Upon clinical indication, immunosuppressive therapy (IST) was applied to patients with virus-negative myocarditis [19]. In particular, IST use was driven by persistent symptomatic troponin release, left ventricular systolic dysfunction, and sustained or recurrent VA. For all patients, regular follow-up at a dedicated outpatient multidisciplinary facility [20] was obtained every three months by multimodal reassessment (blood exams including cardiac biomarkers, transthoracic echocardiogram, and 12-lead 24-h Holter ECG). To allow myocarditis restaging, either CMR or EMB was repeated during follow-up based on patient symptoms and clinical reassessment. In patients with implanted cardiac devices or contraindications to CMR, 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) scan was obtained instead [21].

2.4. EST

As per protocol and routine clinical practice, EST was performed at least six months after diagnosis of acute myocarditis. Judgement of clinical stability, including normalization of T-troponin, absence of episodes of sustained VT or VF over the last six months, and no worsening in left ventricular ejection fraction (LVEF), as compared to baseline assessment, was obtained before indicating EST. For patients receiving IST, treatment termination was an additional required condition.

EST was conducted in designed labs by personnel blinded to the study purposes, in compliance with the American College of Cardiology/American Heart Association guidelines [1]. The modified Bruce protocol [22] was applied. 12-lead ECG, heart rate, and blood pressure were closely monitored, symptoms constantly evaluated, and parameters such as maximal rate pressure product and metabolic equivalents (METs) of estimated exercise capacity systematically reported [22,23].

EST was terminated by the physician in patients with: (a) maximal test, defined as an increase in heart rate either to $\geq$85% of the maximum predicted value off betablockers, or to $\geq$75% of the threshold on betablockers; EST was otherwise defined as submaximal; (b) sustained VT/VF, symptomatic NSVT, or significant increase in VE burden on effort, including polymorphic or bi/trigeminal beats; (c) angina and/or ST-T changes, including ST depression of $\geq$2 mm read at 60 to 80 ms from the J point, or new-onset negative T waves in at least two consecutive leads. EST was deemed uninterpretable for ischemia in the presence of baseline left bundle branch block.

For all VA documented on EST, 12-lead morphology and cycle length regularity were assessed as previously described [24].

2.5. Endpoints

The study endpoints, evaluated for both the study and control groups, included: (1) occurrence of VA during EST; (2) documentation of signs and/or symptoms of ischemia (diagnostic ST-T changes; angina-like chest pain with subsequent documentation of T-troponin raise) during EST; (3) occurrence of adverse events, namely cardiac death, disease-related hospital readmissions, malignant VA (sustained VT, VF, appropriate ICD treatment), and active myocarditis proven either by EMB, CMR, or FDG-PET after EST until the end of study (1 June 2022).

2.6. Statistical Analysis

SPSS Version 20 (IBM Corp., Armonk, NY, USA) was used for analysis and graphic presentations. Continuous variables were expressed as mean and standard deviation, or as median and interquartile range (IQR), depending on the distribution of data. Accordingly, they were compared by parametric (unpaired Student T) or non-parametric (Mann-Whitney U) tests, respectively. Survival curves were generated by the Kaplan-Meier method and

compared by the log-rank test. Confidence intervals (CI) were set at 95%. Where relevant, 2-sided p-values < 0.05 were considered as statistically significant.

3. Results

3.1. Study Population

The study population is composed of 128 consecutive patients (mean age 41 ± 9 years, males 70%) undergoing EST at least six months after myocarditis. Patient selection process and excluded cases are shown in Figure 1.

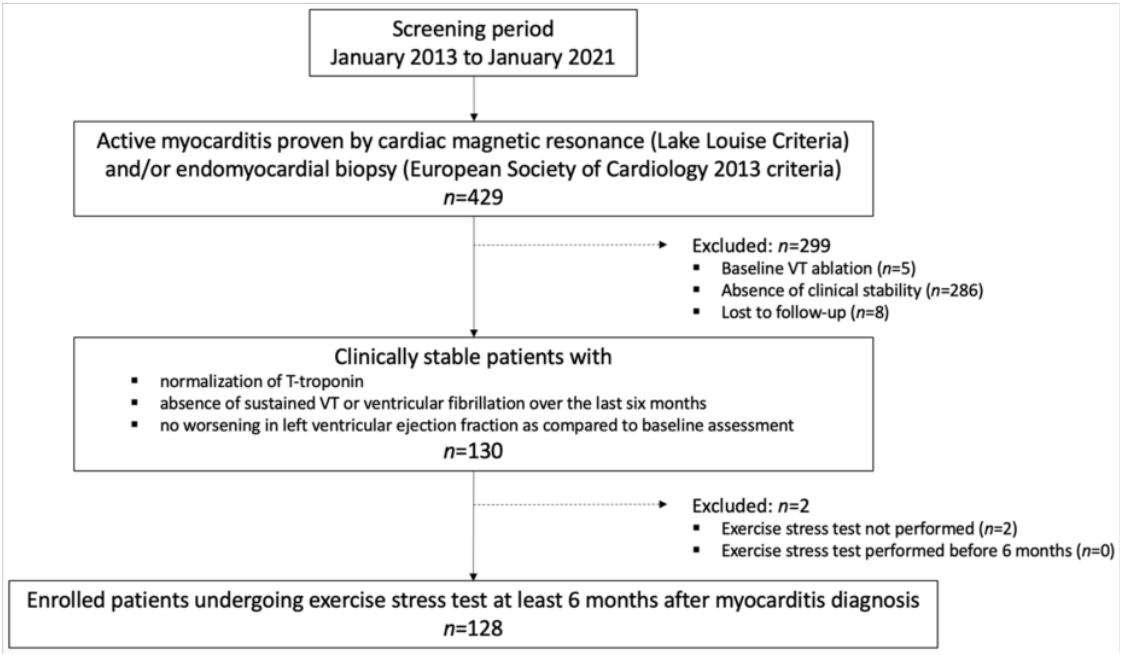

Figure 1. Patient selection. The study flowchart is shown to highlight the selection of the 128 patients undergoing an exercise stress test. VT = ventricular tachycardia.

Of the 128 included patients, 64 (50%) presented with VA, namely VF/sustained VT in n = 32, NSVT in n = 18, and Lown's grade ≥ 2 VE in n = 14 cases. Within the control group (n = 64), 34 (53%) had ACS-like clinical onset, while the remaining 30 (47%) presented with heart failure (HF). The cohort included up to 37 athletes (29%) who were previously eligible for agonistic sports practice. Overall, myocarditis was proven by CMR in 97 cases (76%, mainly nonarrhythmic), and by EMB in 116 (91%, mainly arrhythmic). Eighty-five patients (66%) had a diagnosis confirmed by both techniques. There were no cases of COVID-19-associated myocarditis. Patients were discharged from the hospital after 11 ± 4 days. Complete baseline characterization of the population and treatment strategies is shown in Table 1. Beta-blockers, antiarrhythmics, implantable cardioverter defibrillators, and immunosuppressants were all more commonly used in the arrhythmic group.

Table 1. Baseline characteristics of population (n = 128).

		Arrhythmic n = 64	Nonarrhythmic n = 64	p
Clinical features				
Age (y)	Mean ± SD	42 ± 10	40 ± 9	0.237
Male gender	n (%)	45 (70)	44 (68)	1.000
History of myocarditis	n (%)	3 (5)	4 (6)	1.000
History of SCD or CMP	n (%)	5 (8)	4 (6)	1.000
Agonism	n (%)	17 (27)	20 (31)	0.697
Anemia	n (%)	7 (11)	6 (9)	1.000
Thyroid dysfunction	n (%)	9 (14)	7 (11)	0.790
SIDs	n (%)	6 (9)	4 (6)	0.744
Presentation				
ACS-like	n (%)	0 (0)	34 (53)	<0.001
HF	n (%)	0 (0)	30 (47)	<0.001
Sustained VT/VF	n (%)	32 (50)	0 (0)	<0.001
NSVT	n (%)	18 (28)	0 (0)	<0.001
VE Lown's grade $\geq$ 2 *	n (%)	14 (22)	0 (0)	<0.001
Blood exams				
T-Troponin (ng/L)	Median ± IQR	46 (19–312)	78 (22–517)	0.326
NTproBNP (pg/mL)	Median ± IQR	507 (118–1965)	396 (89–2170)	0.512
C-reactive protein (mg/L)	Median ± IQR	5 (3–14)	6 (3–25)	0.618
ECG				
PQ (ms)	Mean ± SD	174 ± 39	168 ± 42	0.404
QRS (ms)	Mean ± SD	103 ± 24	99 ± 26	0.368
QTc (ms)	Mean ± SD	416 ± 31	409 ± 33	0.218
LBBB	n (%)	3 (5)	5 (8)	0.718
Echocardiogram				
LVEDVi (mL/m^2)	Mean ± SD	72 ± 20	68 ± 28	0.404
LVEF (%)	Mean ± SD	50 ± 10	52 ± 16	0.398
E/E'	Mean ± SD	7 ± 2	7 ± 3	1.000
RVEDD (mm)	Mean ± SD	29 ± 3	29 ± 4	1.000
TAPSE (mm)	Mean ± SD	21 ± 3	22 ± 4	0.312
Pericardial effusion	n (%)	2 (3)	6 (9)	0.273
Myocarditis diagnosis				
CMR-proven (LLC)	n (%)	39 (61)	58 (91)	<0.001
STIR, T2	n (%)	39 (61)	58 (91)	<0.001
LGE, T1, ECV	n (%)	60 (94)	60 (94)	1.000
EMB-proven (ESC criteria)	n (%)	62 (97)	54 (84)	0.030
CD3+ TCL > 7/mm^2	n (%)	62 (97)	54 (84)	0.030
Viral PCR	n (%)	7 (11)	13 (20)	0.223
Treatment at discharge				
ACE-inhibitors	n (%)	56 (88)	50 (78)	0.241
Betablockers	n (%)	61 (95)	47 (73)	0.001
Diuretics	n (%)	7 (11)	14 (22)	0.151
Antiarrhythmics	n (%)	50 (78)	3 (5)	<0.001
IST	n (%)	49 (77)	37 (58)	0.038
ICD	n (%)	30 (47)	9 (14)	<0.001

Baseline clinical features of the population (n = 128) and comparison between arrhythmic and nonarrhythmic groups are shown. * Lown's grade $\geq$ 2 indicates > 1 VE per min, or > 30 VE per h. ACE = angiotensin converting enzyme; ACS = acute coronary syndrome; CD = cluster of differentiation; CMP = cardiomyopathy; CMR = cardiac magnetic resonance; ECV = extracellular volume; EMB = endomyocardial biopsy; ESC = European Society of Cardiology; HF = heart failure; ICD = implantable cardioverter defibrillator; IST = immunosuppressive therapy;