4. Discussion

4.1. Main Study Findings

We reported the results of EST late after myocarditis in a sizable cohort of patients with a balanced distribution between arrhythmic and nonarrhythmic presentations. We showed that: (1) the occurrence of VA during EST was more common in the arrhythmic presentation, whereas ischemic manifestations were more prevalent in the nonarrhythmic one; (2) in both arrhythmic and nonarrhythmic groups, adverse events occurred more frequently among patients with abnormal EST; (3) EST was an informative technique for the subsequent clinical management of patients with myocarditis.

4.2. EST after Myocarditis: Role of the Clinical Presentation

To the best of our knowledge, we provided the first report comparing the results of EST in patients with arrhythmic and nonarrhythmic myocarditis. Myocarditis was diagnosed by gold standard techniques [2,13,14] and followed at a dedicated outpatient clinic with multidisciplinary facilities [20]. Furthermore, in compliance with the current recommendations [4,5], EST was performed at least six months after acute myocarditis and provided a clinical judgment of stability for at least six months. In keeping with the current knowledge, EST was safe in the nonarrhythmic cohort, where malignant VA was never documented. As opposed, we documented a high prevalence of VA, including five cases of malignant ones, among patients with an arrhythmic presentation. Results are not unexpected, since VA may complicate both the active and the post-inflammatory stages of myocarditis [10,24]. Furthermore, evidence suggests that presentation with malignant VA predicts the subsequent occurrence of arrhythmic events in patients with myocarditis [25]. Our findings suggest that in patients with an arrhythmic presentation of myocarditis, EST should be requested with caution. Regarding inducible ischemia, we identified no patients with detectable abnormalities in epicardial coronary arteries (Table 3). Due to the subsequent diagnosis of chronically active myocarditis in most cases, the observed ST-T changes likely occurred secondary to structural heart disease-associated coronary microvascular dysfunction [26], as already demonstrated in patients with myocarditis secondary to viruses with endothelial tropism like parvovirus B19 [27].

4.3. Significance of EST

Figure 3 shows that the vast majority of adverse events during follow-up occurred in patients with abnormal findings at EST. To be noted, a number of known prognostic factors in patients with myocarditis, including male gender [28], LVEF [9], LGE [25], viral genomes [29], and wide QRS complex from left bundle branch block [30] displayed a balanced distribution between groups (Table 1). Also, relevant comorbidities [31–33] showed no major differences in arrhythmic vs. nonarrhythmic cases. However, a major difference between groups was found in medical treatment. In particular, beta-blockers and antiarrhythmic agents were largely more prevalent among the arrhythmic patients, who nevertheless experienced a greater rate of adverse events (Table 4).

Table 4 shows that the majority of adverse events occurred in patients with abnormal EST. However, multiple factors might have contributed to our findings. First, the majority of adverse events occurred in the arrhythmic group, which is already known for being associated with worse outcomes [6,7,25]. Second, a non-trivial subset of patients with abnormal EST (7 of 35, 20%) received a diagnosis of active myocarditis following the subsequent disease restaging: this observation suggests that adverse prognostic significance may be carried out by active myocardial inflammation, as previously reported [34]. Beyond any prognostic significance, EST remains an informative technique in daily clinical practice since the new documentation of VA may help identify high-risk patients who warrant treatment upgrade and close follow-up.

4.4. Additional Clinical Implications of EST

Our study was notable for a number of additional findings that may guide the clinical decision-making in patients undergoing EST late after myocarditis. First, the features of VA at 12-lead ECG may be a useful tool to identify the inflammatory stage of myocarditis. Previously, polymorphic and irregular VA was shown to be associated with active-phase myocarditis, whereas monomorphic and regular ones suggested post-inflammatory scar-related VA [24]. This distinction has been proven to turn into relevant differences in treatment strategies, ranging from immunosuppression for the former condition [35] and catheter ablation for the latter one [34]. Overall, the results of the current study are in keeping with this observation (Figure 4) and suggest that persistently active myocarditis could be suspected even in clinically-stable patients who show polymorphic and irregular VA on EST performed late after the acute presentation.

A second relevant point is that a normal EST may guide the withdrawal of medical treatment. In our experience, all nonischemic patients had uneventful EST even later, under off-treatment conditions. Most importantly, all of them had no adverse events during follow-up. These data suggest that, at least in patients with nonarrhythmic presentation and no alternative indications (i.e., heart failure), beta-blockers may be safely interrupted after uneventful EST. These findings are relevant, in particular for young patients requesting readmission to competitive sports participation [4,5], who constituted a non-neglectable subset of our cohort (29%). As opposed, an arrhythmic presentation may constitute a limitation for the subsequent readmission to sports practice. Our data are meant to be preliminary and deserve confirmation by larger, multicenter studies.

4.5. Study Limitations

Our study was single-center and took place at a referral center for arrhythmic myocarditis [18]. This may have led to an overestimation of the prevalence of VA as compared to the classic ACS-like and HF presentations of myocarditis [3]. Considerable overlap between acute and chronically active myocarditis, as well as improved diagnostic yield of modern CMR following the introduction of parametric mapping, constitute additional biases. Continuous electrical monitoring by cardiac devices in many patients allowed greater sensitivity for arrhythmia detection as compared with the classic approach based on repeated Holter ECG [36,37]. Due to the limited sample size, the statistical model allowing assessment of the independent prognostic value for EST was prevented.

5. Conclusions

In this study, we showed that EST, performed late after the clinical onset of myocarditis, is more commonly associated with VA in patients with arrhythmic presentation compared to nonarrhythmic ones. Furthermore, we showed that EST abnormalities are associated with adverse outcomes during subsequent follow-ups in both arrhythmic and nonarrhythmic groups. These preliminary findings suggest that EST should be requested and performed with caution in patients with myocarditis, in particular following the arrhythmic presentation. Confirmatory evidence by larger studies is needed.

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Abbreviations

ACS = acute coronary syndrome; CMR = cardiac magnetic resonance; ECG = electrocardiogram; EMB = endomyocardial biopsy; EST = exercise stress test; FDG-PET = 18F-Fluorodeoxyglucose positron emission tomography; HF = heart failure; ICD = implantable cardioverter defibrillator; IST = immunosuppressive therapy; LGE = late gadolinium enhancement; LLC = Lake Louise criteria; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VA = ventricular arrhythmia; VE = ventricular ectopies; VF = ventricular fibrillation; VT = ventricular tachycardia.

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