JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 9, 2020

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Ventricular Arrhythmias and Sudden Cardiac Death in Lymphocytic Myocarditis*

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In 2017, the global incidence of myocarditis and cardiomyopathy was 3.1 million or 22 per 100,000 (1). Although cardiomyopathy resulting from acute myocarditis is the best characterized form of the disease, chest pain syndromes and sudden death remain important causes of morbidity and mortality. The proportion of cardiovascular sudden death attributed to myocarditis at autopsy varies by age, causing approximately 2% of infant, 5% of childhood, and ≤10% to 20% of young adult sudden death (2,3). In these case series, sudden death due to myocarditis occurs more commonly in men. The prevalence of ventricular arrhythmias (VAs) also varies by histological type, with sustained and symptomatic VA more frequent in sarcoid, idiopathic giant cell, and hypersensitivity myocarditis than in lymphocytic myocarditis (LM) (4).

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The study by Peretto et al. (5) in this issue of the *Journal* substantially extends our knowledge of VA in endomyocardial biopsy (EMB) (92%) or cardiac magnetic resonance (CMR) (8%)-proven LM (5). They report a prospective case series of 184 patients who presented with VA, defined as ventricular fibrillation, sustained or nonsustained ventricular tachycardia (VT), or Lown grade 2 PVC (>1/min or >30/h). Coronary artery disease was excluded by angiography. LM was defined by immunohistology using European Society of Cardiology (ESC) consensus criteria or histology using Dallas criteria (6). All patients had late gadolinium enhancement (LGE) on CMR at study entry. The overall group was divided into active (AM) and previous myocarditis (PM) based on pre-defined CMR and EMB criteria. Monitoring for VA and clinical events was rigorous with echocardiography and 24-h, 12-lead Holter monitoring performed every 6 months in the previous myocarditis subgroup, and 4 times/year in the active myocarditis subgroup.

Over an average follow-up of 10 months, 30% of the study group (55 of 184) experienced VA and 78 of 184 received an implantable cardioverter-defibrillator (ICD). A total of 66 (36%) required arrhythmia ablation. Polymorphic and irregular VT was more common in AM, and conversely, monomorphic VT was more common in PM or after healing in AM. The 8 ventricular fibrillation events all occurred in subjects with AM. This VA burden occurred in the context of a mildly reduced average left ventricular ejection fraction of 49% (47% AM and 50% PM). Like most lymphocytic myocarditis series, the authors report a male predominance of 69% and a typical age of 44 years. The 20% rate of positive viral genome detection in the myocardium was also similar to other published reports of AM.

The high rate of VA (4% VF, 32% VT, 43% nonsustained VT) in this LM cohort is due to selection of only patients with VA at study entry. The population of biopsy-proven LM with VA is rarely studied, making the present report essentially unique. The rate of subsequent VA in patients with LGE on CMR, a marker for cardiovascular risk (7), and EF >50% was remarkably 10%/year. This may be in part due to high detection rates from unusually frequent 24-h Holter monitoring (average 6.2/patient). As in a previous report where an anteroseptal pattern of LGE was associated with cardiac events (8), the pattern of LGE

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.01.032

in this report was associated with VA (25%/year in anteroseptal vs. 7%/year in inferobasal). The pattern of VA and stage of histological disease may have impacted therapeutic decisions in the study. For example, the use of ICD was lower in the AM (37 of 123) than the PM groups (41 of 62) with VA. Consistent with the author's previous report on the value of serial CMR studies for acute myocarditis (9), AM patients in whom LGE resolved on follow-up CMR had no VA.

The rate of VAs seems high, particularly in the subgroup with inferoseptal LGE and preserved left ventricular ejection fraction (LVEF), raising a possible effect of desmosomal gene mutations. Recurrent myocarditis has been associated with families with gene mutations in desmosomal proteins who are at risk for VA (10). Myocarditis in these patients can overlap with VA. As genetic testing and family history was not included in the present report, it is possible that some of the present cohort had a genetic predisposition to VA and myocarditis. VAs have also been associated with desmosomal protein disruption with VA in GCM and sarcoidosis (11). In cell culture, interleukin-6, tumor necrosis factor-alpha, and interleukin-17 exposure caused translocation of plakoglobin from cell-cell junctions to intracellular sites replicating the in vivo desmosomal protein alterations. These studies support the hypothesis that cytokine-targeted therapies could lower arrhythmia risk through restoration of normal desmosomal architecture in select forms of myocarditis. Collectively, these reports also emphasize that myocarditis is not always a transient condition that either resolves or progresses to cardiomyopathy, but may have a chronic and recurrent course.

Should patients with suspected myocarditis, normal LVEF, and VA have EMB and/or CMR for risk stratification? The 2013 ESC position statement on the management of myocarditis recommends EMB and CMR in this clinical scenario (6). The present study supports the 2013 ESC position statement recommendation. The 2016 American Heart Association scientific statement on the management of cardiomyopathies recommends that EMB should be performed (Class I recommendation) for acute cardiomyopathy complicated by symptomatic or sustained VT (12). CMR is considered a Class IIb/Level of Evidence: C recommendation in cardiomyopathy due to acute myocarditis without symptomatic or sustained VA. Although CMR is often favored to confirm myocarditis in hemodynamically stable patients with suspected myocarditis, in part because of lower risk than EMB, patients with unstable rhythms may not be suitable for imaging. The observed VA rate of >10%/year suggests that EMB and/or CMR for risk stratification in suspected myocarditis with VA may be indicated regardless of LVEF.

Should the present report affect the use of ICD in biopsy-proven LM with VA as defined in this study? The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the management of patients with ventricular arrhythmias recommends ICD be considered (Class IIb recommendation) for patients with giant cell myocarditis who have VF or VT and meaningful survival of at least 1 year (13). Frequent PVCs in the setting of structural heart disease may indicate a greater risk of sudden cardiac death. Because only 21% (38 subjects) of the present cohort had frequent PVC *without* VF/VT/nonsustained VT, it remains unclear whether the conclusions from the overall study findings should be applied to this subgroup or generalized to broader populations. The present single-center study from Northern Italy, although prospective and rigorous, may not be generalizable. Additional studies in diverse cohorts, including more women, are needed to support recommendations regarding ICD use for the primary prevention of sudden death in LM with preserved LVEF.

The present study supports a recommendation that in confirmed myocarditis cases with VA who do not receive an ICD, rhythm monitoring with Holter or another wearable device should be considered regardless of LVEF. Follow-up CMR to detect the minority of AM patients who fully resolve LGE also seems reasonable for risk stratification. However, the utility of CMR to accurately distinguish inflammation from scar in noninflammatory cardiomyopathy after the first weeks of symptoms remains uncertain (14). In the coming years, newer CMR techniques to better identify inflammation and the integration of genomic data with larger clinical and imaging datasets should permit more personalized recommendations for VA management in myocarditis.

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