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Ventricular arrhythmias and myocardial inflammation: Long-term follow-up of patients with suspected myocarditis

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ABSTRACT

Background: Inflammatory heart disease is known to be associated with ventricular arrhythmias (VA) and impaired ventricular function at presentation or during follow-up. We aimed to investigate the need for implanted cardioverter defibrillator (ICD) due to ventricular dysfunction and occurrence of VA during long-term follow-up in patients admitted with suspected myocarditis.
Methods: Between 2000 and 2016, 191 patients (age 43 ± 13 years, 71% male, mean left ventricular ejection fraction (LVEF) 33 ± 15%) with clinically suspected myocarditis, who underwent endomyocardial biopsies (EMB), were prospectively enrolled and followed up in 6-months-intervals (median follow-up was 83 (49–156) months). The primary endpoint was deterioration of cardiac function (LVEF ≤ 35%) or occurrence of VA leading to ICD implantation.
Results: According to EMB results, patients were stratified in three diagnostic groups: acute myocarditis (5%), chronic myocarditis (50%) and dilated cardiomyopathy (DCM) (45%). An ICD implantation was performed in 58 patients (30%, n = 38 for primary prevention). Besides LVEF at baseline, chronic myocardial inflammation was the only independent predictor of ICD implantation for primary prevention (hazard ratio 2.48 (95% confidence interval 1.02–5.5); p = 0.045). VA requiring ICD therapy occurred in 29 of 58 patients (50%) after a median of 14 (2–37) months without a significant difference between presence and absence of myocardial inflammation.
Conclusions: Nearly one third of patients with suspected myocarditis require an ICD due to impaired LVEF or occurrence of VA. Half of these patients experienced VA with adequate ICD therapy.

1. Introduction

The clinical presentation of myocarditis is complex with a high variability of symptoms [1,2]. In young people dying from sudden cardiac death (SCD), a highly variable autopsy prevalence of myocarditis, ranging from 2 to 44% of cases, has been reported [2–4]. Myocardial inflammation may lead to ventricular impairment and progressive heart failure (HF) as well as ventricular arrhythmias (VA). ICD implantation is indicated for primary prevention of SCD in patients with symptomatic heart failure and left ventricular ejection fraction (LVEF) ≤ 35% after >3 months of optimal medical heart failure therapy [5]. ICDs are mandated after documented ventricular fibrillation (VF) or hemodynamically not tolerated ventricular tachycardia (VT) in the absence of reversible causes [2]. As myocarditis has the potential to recover, indication for permanent ICD implantation and its timing remain controversial [6]. Therefore, we studied the rate of ICD implantations according to cardiac function and the occurrence of VA in patients with suspected myocarditis.

2. Methods

2.1. Study subjects and design

This explorative analysis enrolled 191 patients with clinically suspected myocarditis who underwent EMB at our institution between April 2000 and January 2015. Patients were included if they were at least 16 years of age and experienced an episode of infections of the bronchial tree, the gut, or the urinary tract within the last 6 months before admission. Further inclusion criteria were at least one of the following features not related to myocardial ischemia: a) impaired global or regional left ventricular systolic function, b) increase in serum concentrations of myocardial necrosis markers (creatine kinase, creatine kinase MB, troponin T), c) pericardial effusion, d) sustained or non-sustained ventricular tachycardia or ventricular fibrillation of unknown cause [7,8]. They were followed up until February 2016. All patients gave written informed consent to

Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsies; HF, heart failure; HTx, heart transplantation; HR, hazard ratio; ICD, implanted cardioverter defibrillator; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death; VA, ventricular arrhythmia; VT, ventricular tachycardia; VF, ventricular fibrillation.

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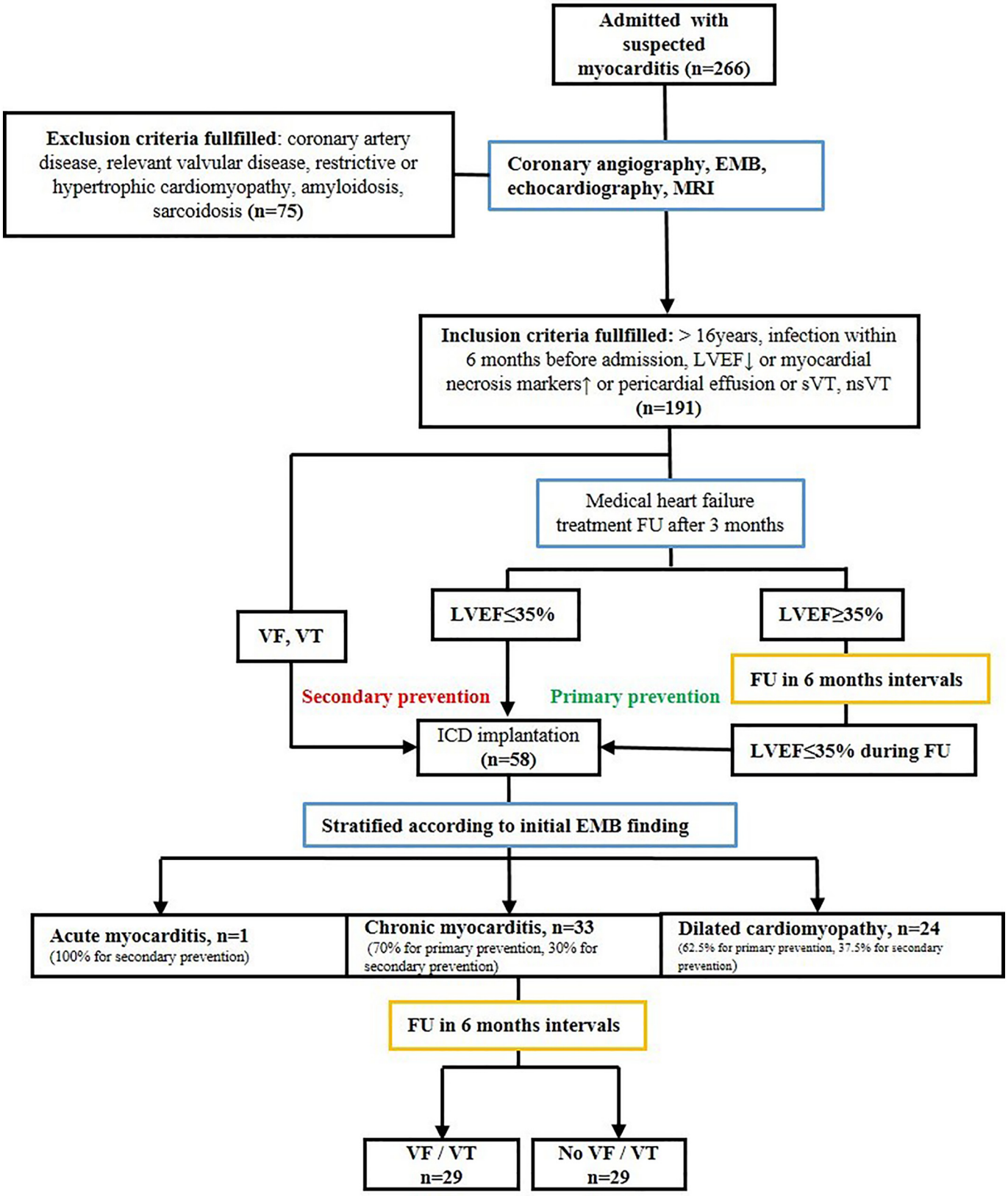

Fig. 1. Algorithm of initial evaluation and follow-up of patients with suspected myocarditis (CONSORT flow diagram). EMB: endomyocardial biopsy, MRI: magnetic resonance imaging, FU: follow-up.

be enrolled in the registry (Homburg Myocarditis Registry), to EMB, and further for analyses of their data for scientific reasons. The study was approved by the local ethics committee (Ethik-Kommission des Saarlandes Nr. 180/11). The analysis was designed as a prospective longitudinal evaluation with patient follow-up scheduled at 6 months intervals in our outpatient clinic. The median follow-up time was 83 (49–156) months. All patients with signs or symptoms of heart failure received evidence-based medical treatment. The primary endpoint of the study was persistence or deterioration of heart failure (LVEF ≤ 35%) or occurrence of symptomatic ventricular arrhythmias (VA) leading

to ICD implantation. Further analyses included the occurrence of VA requiring therapy after ICD implantation (Fig. 1).

2.2. Cardiac catheterization and endomyocardial biopsy

Coronary angiography was performed before EMB to exclude significant coronary artery disease as cause of heart failure in each patient. Relevant valvular disease, restrictive or hypertrophic cardiomyopathy, and congenital heart diseases were excluded by echocardiography or cardiac magnetic resonance imaging. LVEF was measured by contrast ventriculography, by echocardiography, or by cardiac magnetic resonance imaging. The biopsy sites were chosen according to pathological findings of echocardiography or cardiac magnetic resonance imaging. EMB were investigated by histopathology immunochemistry, and by molecular biological detection of viral genomes as previously described [1,2,7]. EMB was considered to be inflamed by positive immunohistochemical detection of focal or diffuse infiltrates (CD3+ T lymphocytes and/or CD68+ macrophages) with >14 cells/mm^2, in addition to enhanced expression of HLA-class II molecules according to the World Health Organization/International Society and Federation for Cardiology Task Force on the Definition and Classification on Cardiomyopathies [1,9] with or without myocyte degeneration and necrosis of non-ischemic cause. Acute myocarditis was defined by lymphocytic infiltrates and signs of acute myocardial injury (myocyte necrosis). Chronic myocarditis was characterized by lymphocytic infiltrates and fibrosis without acute myocyte necrosis. EMB which were classified as dilated cardiomyopathy (DCM) revealed no immune cell infiltrates. Viral genomes investigated by nested (RT-) PCR/real time (RT-) PCR were enteroviruses, parvovirus B19 (PVB19), adenoviruses, Epstein-Barr-virus (EBV), human cytomegalovirus, human herpesvirus 6 (HHV6), human herpesvirus 7 and hepatitis C virus.

2.3. ICD implantation

An ICD implantation was performed for primary or secondary prevention according to current guidelines [6]. After 3 months on intensified heart failure therapy and thereafter in 6-month-intervals left ventricular size and function was assessed by echocardiography. An ICD was implanted for primary prevention in patients in whom LVEF remained ≤35% after 3 months of optimal medical heart failure therapy after EMB or due to a deterioration of left ventricular function (LVEF ≤ 35%) during follow-up (FU). An ICD with cardiac resynchronization therapy (CRT) was implanted in case of symptomatic heart failure (NYHA class ≥ II) and left bundle branch block (QRS duration ≥ 120 ms). ICD implantation for secondary prevention of SCD was performed in case of occurrence of symptomatic VA (sustained VT or VF) according to current guidelines [6].

2.4. Data analysis

Comparisons between groups were performed using the Wilcoxon rank sum test for continuous variables and the Pearson Chi Square Test for categorical variables. Survival curves of the patients grouped by pre-specified variables were calculated by the Kaplan-Meier method and compared with the log rank test. Comparison between groups of time after EMB to an event was analyzed with the Wilcoxon rank sum test. Continuous variables were redefined as categorical and dichotomized to allow presentation in a Kaplan-Meier plot. Cox regression analysis using forward selection was performed to identify univariable and multivariable predictors of outcome. Particularly, the aim was to investigate the association between the probability of an ICD implantation for primary prevention and results of EMB as well as clinical parameters. All analyses were performed with SPSS statistical software (version 23.0, SPSS, Inc., Chicago, IL, USA). All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

3. Results

3.1. Patient population at time of EMB (baseline characteristics)

The baseline characteristics of the 191 enrolled patients are depicted in Table 1. Patients were relatively young (mean age 43.4 years) and 71% were male. Mean LVEF was 32.9 ± 14.8% and more than half of all patients (62%) were in NYHA functional class III (45%) or IV (17%). According to EMB (for more details see Online Table 1) a chronic myocarditis was diagnosed in 96 patients (50.3%), acute myocarditis in 10 patients (5.2%), while dilated cardiomyopathy (DCM) was diagnosed in 85 cases (44.5%). Based on the clinical findings and medical history of the latter patient group (previous infection, longer duration of symptoms), the etiology of cardiomyopathy has to be discussed as post-inflammatory DCM. In 67 patients (35%) viral genomes were detected in the myocardium by nested (RT-) PCR/real time (RT-) PCR, in 41 patients (39%) with biopsy proven myocarditis and in 26 patients (31%) with DCM. Most frequently detected viruses were PVB19 in 41 cases (61.2%) followed by human herpesvirus 6 in 15 cases (22.4%). In 9 patients (13.4%) there was evidence for a double virus infection. For more details, see Online Table 2. The role of immunosuppression was negligible in the present registry as only three patients received immunosuppressive therapy. Further studies are warranted to investigate this treatment modality in myocarditis.

3.2. Characteristics of ICD devices for primary and secondary prevention

Implantations and types of devices are summarized in Online Table 3. In total, 58 patients (30.4%) underwent an ICD implantation. 23 patients with chronic myocarditis as well as 15 patients with DCM who showed persistence (chronic myocarditis n = 15, DCM n = 3) or worsening of cardiac function (chronic myocarditis n = 8, DCM n = 12) despite medical HF therapy, received an ICD for primary prevention. For secondary prevention, 10 patients with chronic myocarditis (5 patients with VF, 5 patients with sustained VT), 9 patients with DCM (6 patients with VF, 3 patients with sustained VT) and 1 patient with acute myocarditis (sustained VT) underwent an ICD implantation. A cardiac resynchronization therapy defibrillator (CRT-D) system was implanted in 14 patients with chronic myocarditis and in 9 patients with DCM. An upgrade to a CRT-D system was required in three patients during follow-up due to medical therapy refractory HF and development of left bundle branch block (in 2 patients with chronic myocarditis 7.5 and 81 months after EMB and in 1 patient with DCM 57.2 months after EMB).

3.3. Follow-up

Referring to the time from EMB to ICD implantation for primary and secondary prevention the three EMB diagnosis groups (acute myocarditis, chronic myocarditis and DCM) did not vary significantly (log rank p = 0.135, Fig. 2B). Interestingly, a significantly higher number of patients with chronic myocardial inflammation had persistent or worsening cardiac function (LVEF ≤ 35%) and received an ICD for primary prevention compared with patients without inflammation (log rank p = 0.042, Fig. 2C). In patients with chronic myocarditis the median time after EMB to ICD implantation was 3.8 (1.6–35) months compared to 27 (2–50.4) months in patients with DCM (p = 0.045). There was no association between detection of viral genomes and the need of ICD implantation (log rank p = 0.56; Online Fig. 1). Only EF at baseline, NYHA class and chronic myocardial inflammation were univariable predictors of ICD implantation for primary prevention. In multivariable analysis including age and gender only EF at baseline (HR 0.94 (CI 0.9–0.98); p = 0.002) and chronic myocardial inflammation (HR 2.48 (CI 1.02–5.5); p = 0.045) proved to be independent predictors.

During median follow-up of 83 months, 29 patients (15.2%) died from cardiac causes (12 patients with chronic myocarditis, 8 patients with DCM) or underwent heart transplantation (HTx; 5 patients with chronic myocarditis, 4 patients with DCM). Patients with chronic myocarditis were at higher risk for cardiac death or HTx compared to DCM (p = 0.04; Online Fig. 2). During index hospital stay, no patient died; within the first 6 months (180 days) after discharge 1 patient with chronic myocarditis underwent HTx (LVEF 12%); between 6 and 12 months after EMB one patient with chronic myocarditis suffered cardiac death (baseline LVEF 12%) and one more patient with DCM underwent a HTx (LVEF at baseline 39%, no ICD). In the group of patients who did not receive an ICD (n = 133), 10 patients suffered from cardiac death and 4 underwent heart transplantation after a median of 16 (13–34) months.

3.4. Occurrence of ventricular arrhythmias in patients with ICD

In total, 29 (50%) patients experienced VA which were detected and treated by the ICD. Median time to first ICD therapy was 13.7 (2.3–37)

Table 1
Patient characteristics according to endomyocardial biopsy (EMB) results.

Characteristic	All (n = 191)	Acute myocarditis (n = 10)	Chronic myocarditis (n = 96)	DCM (n = 85)	p
Age (years)	43.4 ± 12.6	34.9 ± 14.8	43.1 ± 12.8	44.7 ± 12.6	0.062
Male sex	136 (71%)	8 (80%)	67 (70%)	61 (72%)	0.785
BMI (kg/m^2)	27.3 ± 5.1	25.8 ± 5.5	27.2 ± 4.8	27.6 ± 5.4	0.552
Hypertension	82 (43%)	1 (10%)	41 (43%)	40 (47%)	0.081
Diabetes	15 (8%)	0 (0%)	11 (11%)	4 (5%)	0.154
Duration of symptoms (days)	30 (14–90)	9 (6–44)	30 (14–60)	60 (21–150)	0.03
Elevated troponin/CK-MB at admission	42 (22%)	5 (50%)	24 (25%)	13 (15%)	0.003
Arrhythmias during hospital stay					
Non-sustained VT	37 (19%)	0 (0%)	19 (20%)	18 (21%)	0.274
VT/VF	17 (9%)	1 (10%)	8 (8%)	8 (9%)	0.961
AVB II/III	2 (1%)	0 (0%)	2 (2%)	0 (0%)	0.372
Cardiac arrest	8 (4%)	0 (0%)	4 (4%)	4 (5%)	0.778
Haemodynamic support during acute phase	24 (13%)	3(30%)	11 (11%)	7 (8%)	0.112
NYHA class at presentation					0.197
I	25 (13%)	3 (30%)	12 (12%)	10 (12%)	
II	47 (25%)	1 (10%)	20 (21%)	26 (31%)	
III	87 (45%)	4 (40%)	43 (45%)	40 (47%)	
IV	32 (17%)	2 (20%)	21 (22%)	9 (10%)	
LVEF at admission (%)	32.9 ± 14.8	36.7 ± 18.2	33.9 ± 15.2	31.3 ± 13.8	0.357
LVEF ≤ 35%	123 (64%)	6 (60%)	57 (59%)	60 (71%)	0.278
LVEDD at admission (mm)	63.4 ± 10.1	62.2 ± 19.1	62.6 ± 10.4	64.4 ± 8.1	0.461
SBP at EMB (mm Hg)	125.4 ± 26.3	119 ± 11.2	126.3 ± 27.1	125.1 ± 26.9	0.704
DBP at EMB (mm Hg)	77.3 ± 16.1	76.7 ± 11.7	75.9 ± 15.2	78.9 ± 17.6	0.468
Heart rate at EMB (bpm)	82.7 ± 21.8	83.8 ± 27	81.6 ± 20.2	83.9 ± 23	0.781
Viral genome in EMB	67 (35%)	4 (40%)	37 (39%)	26 (31%)	0.505
Medication at hospital discharge					
Beta blocker	148 (77%)	6 (60%)	77 (80%)	65 (76%)	0.331
ACEI or ARB	176 (92%)	8 (80%)	90 (94%)	78 (92%)	0.302
MRA	108 (57%)	5 (50%)	60 (63%)	43 (51%)	0.248
Diuretics	144 (75%)	6 (60%)	71 (74%)	67 (79%)	0.382
Digoxin/digitoxin	46 (24%)	1 (10%)	22 (23%)	23 (27%)	0.457
Amiodarone	22 (12%)	1 (10%)	7 (7%)	14 (16%)	0.153

Values are n (%) or mean ± standard deviation or median (interquartile range) when appropriate. DCM, dilated cardiomyopathy; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; bpm, beats per minute; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker, MRA, mineralocorticoid receptor antagonist.

months. There were no significant differences between the presence and absence of myocardial inflammation concerning the occurrence of the first ICD therapy (Fig. 3). Seven (20.5%) patients with myocarditis and none in the DCM group experienced an ICD therapy within the first year after EMB. The median time to first ICD therapy was 36.6 (2.9–54.8) months in the myocarditis group and 31.1 (63.5–158.6) months in the DCM group (p = 0.024). The patient characteristics according to the occurrence of VA are depicted in Online Table 4. No significant differences existed in terms of age, gender, NYHA class, LVEF at the time of ICD implantation, detection of virus genome and indication of ICD implantation. There were no significant predictors for later arrhythmic events. The total number of VA requiring ICD intervention is shown in Online Fig. 3. During FU, 32% of ICD patients experienced more than three episodes of VA requiring ICD intervention.

4. Discussion

The present study showed that according to guidelines, 30% of patients with suspected myocarditis required an ICD or CRT-D device and half of these experienced at least one episode of ventricular arrhythmias with appropriate ICD therapy. Compared to DCM, patients with chronic myocardial inflammation were at higher risk for implantation of an ICD for primary prevention earlier after EMB.

Patients with inflammatory or post-inflammatory cardiomyopathy may exhibit important differences in the clinical course compared to patients with other etiologies of chronic HF as ischemic cardiomyopathy. These patients are rather young (herein mean age 43 years), have less cardiovascular comorbidities and have a shorter onset of symptoms [2]. However, severe HF was present as 62% of our patients were in NYHA class III or IV and mean LVEF was 33 ± 15% at admission. Furthermore, the course of myocarditis is highly variable ranging from complete recovery to severe persistent HF and death [1]. Predictors of outcome include clinical presentation and parameters as NYHA class and myocardial inflammation in EMB [7]. In the present study, myocardial inflammation was associated with higher rates of cardiac death and heart transplantation (HTx). In a recent study by Ammirati et al. in patients with myocarditis, a fulminant course, defined as need of inotropes or mechanical circulatory support, was associated with a higher risk for in-hospital death or HTx, but had a similar long-term survival after discharge compared to a non-fulminant course [10]. The study by Ammirati et al. focused more on patients in a clinically unstable situation with a recent onset of symptoms (duration of symptoms in all patients < 1 month) whereas the present study enrolled more patients in a non-acute setting with longer duration of symptoms and advanced HF illustrating the different patient populations.

Although there may be differences in patients with a cardiomyopathy due to an inflammatory cause, medical treatment is performed according to current recommendations for patients with HF [11]. Implantation of an ICD is recommended if patients experienced hemodynamic relevant VA (secondary prevention) or if LVEF remains ≤35% despite of ≥3 months of optimal medical therapy (primary prevention). In our study, 30% of all enrolled patients fulfilled these criteria and required an ICD or CRT-D during follow up (primary prevention in 64%). There were important differences concerning timing of ICD implantation between the main groups of patients with chronic myocarditis and DCM. Although baseline characteristics including LVEF and medical treatment were similar, patients with chronic myocardial inflammation in EMB had higher rates of an ICD implantation for primary prevention after a shorter follow-up time compared to patients with DCM. These findings suggest that myocardial inflammation is associated with less improvement of myocardial function.

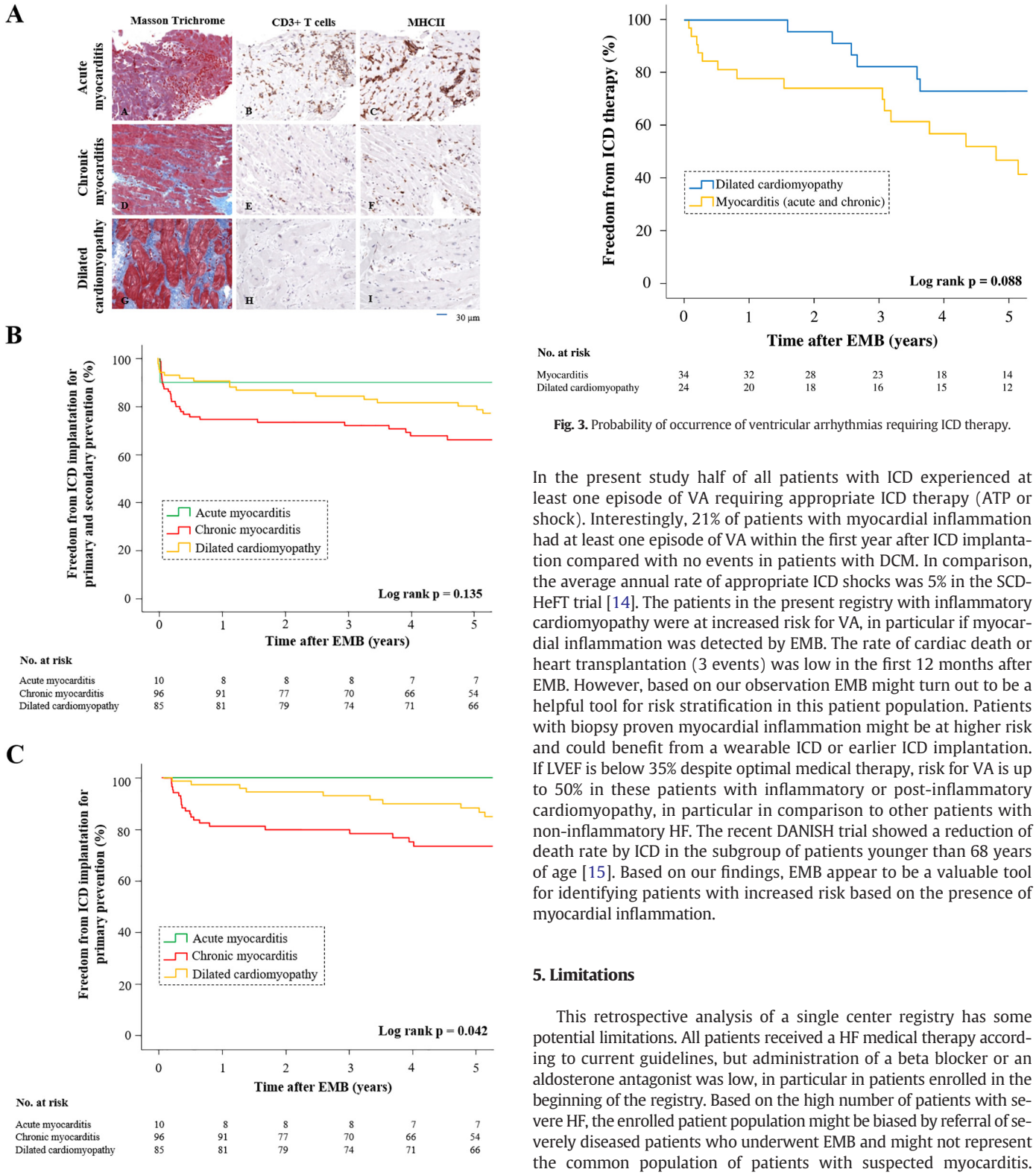

Fig. 2. Histological and immunohistological patterns of EMB (A), probability of ICD implantation due to primary and secondary prevention (B), and probability of ICD implantation due to primary prevention (C) according to EMB results. Histological and immunohistological patterns of acute lymphocytic myocarditis (A–C), chronic lymphocytic myocarditis (D–F), dilated cardiomyopathy without inflammation (G–I). Bar = 30µm. From left to right column: Masson Trichrom stain, immunohistochemical stain for CD3 and MHCII+ (mainly macrophages).

Myocardial inflammation is often associated with ventricular arrhythmias [12]. The mechanisms underlying the arrhythmogenesis in myocardial inflammation are currently not fully understood [13].

Fig. 3. Probability of occurrence of ventricular arrhythmias requiring ICD therapy.

In the present study half of all patients with ICD experienced at least one episode of VA requiring appropriate ICD therapy (ATP or shock). Interestingly, 21% of patients with myocardial inflammation had at least one episode of VA within the first year after ICD implantation compared with no events in patients with DCM. In comparison, the average annual rate of appropriate ICD shocks was 5% in the SCD-HeFT trial [14]. The patients in the present registry with inflammatory cardiomyopathy were at increased risk for VA, in particular if myocardial inflammation was detected by EMB. The rate of cardiac death or heart transplantation (3 events) was low in the first 12 months after EMB. However, based on our observation EMB might turn out to be a helpful tool for risk stratification in this patient population. Patients with biopsy proven myocardial inflammation might be at higher risk and could benefit from a wearable ICD or earlier ICD implantation. If LVEF is below 35% despite optimal medical therapy, risk for VA is up to 50% in these patients with inflammatory or post-inflammatory cardiomyopathy, in particular in comparison to other patients with non-inflammatory HF. The recent DANISH trial showed a reduction of death rate by ICD in the subgroup of patients younger than 68 years of age [15]. Based on our findings, EMB appear to be a valuable tool for identifying patients with increased risk based on the presence of myocardial inflammation.

5. Limitations

This retrospective analysis of a single center registry has some potential limitations. All patients received a HF medical therapy according to current guidelines, but administration of a beta blocker or an aldosterone antagonist was low, in particular in patients enrolled in the beginning of the registry. Based on the high number of patients with severe HF, the enrolled patient population might be biased by referral of severely diseased patients who underwent EMB and might not represent the common population of patients with suspected myocarditis. Furthermore, the need of ICD or CRT-D implantation was decided by the treating physician according to current guidelines. LVEF during follow-up was mainly assessed by echocardiography, which underlies the issue of interobserver variability. Additionally, no further EMB during follow-up were performed. The power to clearly evidence the association of arrhythmias, LVEF and inflammation to ICD implantation is numerically too low to achieve a substantially powered difference.

Furthermore, presence of viral genomes in the myocardium alone was associated neither with ICD implantation nor with occurrence of VA. 19% of patients had myocarditis with detection of viral genome, whereas 14%

had a DCM with viral persistence. The most common virus detected was PVB19 in 61%, which targets myocardial endothelial cells and has been associated with myocyte ischemia as well as the development of chronic dilated cardiomyopathy [16]. While acute viral myocarditis has a good prognosis, the course of a virus-associated chronic myocarditis is controversially discussed. Case series describe an association between viral infection and VA, however, no prospective studies are available [17]. The most prevalent virus in our study was PVB19, therefore our findings cannot be generalized to other virus species, which may be associated with a higher risk for VA, such as enterovirus infections [18,19]. The number of patients with other viral infections as HHV6 or EBV was low in the present registry. Based on our finding, no sufficient conclusion can be drawn on the role of the detected viruses in the myocardium on cardiac function and arrhythmic potential.

6. Conclusions

Myocardial inflammation is associated with an increased risk for cardiac death or HTx, and VA. Based on these findings, endomyocardial biopsies are recognized as valuable tools for risk stratification in patients with suspected myocarditis. Further studies and registries investigating the relevance of myocardial inflammation on progressive heart failure and arrhythmogenesis are ongoing (Euro Observational Registry Programme (EORP) "Cardiomyopathy and Myocarditis Registry" of the European Society of Cardiology).

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.07.142.

References

[1] I. Kindermann, C. Barth, F. Mahfoud, et al., Update on myocarditis, J. Am. Coll. Cardiol. 59 (9) (2012) 779–792.
[2] A. Caforio, A. Pankuweit, E. Arbustini, et al., Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 34 (2013) 2636–2648.
[3] C. Basso, F. Calabrese, D. Corrado, G. Thiene, Postmortem diagnosis in sudden cardiac death victims: macroscopic, microscopic and molecular findings, Cardiovasc. Res. 50 (2) (2001) 290–300.
[4] C. De la Chapelle, C. Kossmann, Myocarditis, Circulation 10 (1954) 747–765.
[5] P. Ponikowski, A.A. Voors, S.D. Anker, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 37 (27) (2016) 2129–2200m.
[6] D. Zipes, J. Camm, M. Borggrefe, et al., ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, Eur. Heart J. 8 (9) (2015) 746–837.
[7] I. Kindermann, M. Kindermann, R. Kandolf, et al., Predictors of outcome in patients with suspected myocarditis, Circulation 118 (6) (2008) 639–648.
[8] C. Ukena, F. Mahfoud, I. Kindermann, R. Kandolf, M. Kindermann, M. Böhm, Prognostic electrocardiographic parameters in patients with suspected myocarditis, Eur. J. Heart Fail. 13 (4) (2011) 398–405.
[9] P. Richardson, W. Mckenna, M. Bristow, et al., Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies, Circulation 93 (5) (1996) 841–842.
[10] Ammirati, et al., Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis, Circulation 136 (2017) 529–545.
[11] W. Wijns, P. Kolh, N. Danchin, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart, Eur. Heart J. 31 (14) (2010) 2369–2429.
[12] A.J. Baksi, G.S. Kanaganayagam, S.K. Prasad, Arrhythmias in viral myocarditis and pericarditis, Card. Electrophysiol. Clin. 7 (2) (2015) 269–281.
[13] H. Park, H. Park, D. Lee, et al., Increased phosphorylation of Ca^{2+} handling proteins as a proarrhythmic mechanism in myocarditis, Circ. J. 78 (2014) 2292–2301.
[14] H. Bardy, K. Lee, D. Mark, et al., Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure, N. Engl. J. Med. 352 (3) (2005) 225–237.
[15] G. Wolff, Y. Lin, A. Karathanos, M. Brockmeyer, et al., Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials, Clin. Res. Cardiol. 106 (7) (2017) 501–513.
[16] C.T. Bock, K. Klingel, R. Kandolf, Human parvovirus B19 – associated myocarditis, N. Engl. J. Med. 362 (13) (2010) 1248–1249.
[17] S. Mavrogeni, K. Spargias, C. Bratis, G. Kolovou, E. Papadopoulou, G. Pavlides, EBV infection as a cause of VT: evaluation by CMR, J. Am. Coll. Cardiol. Img. 4 (5) (2011) 561–562.
[18] G. Tse, J.M. Yeo, Y.W. Chan, E.T.H. Lai, B.P. Yan, What is the arrhythmic substrate in viral myocarditis? Insights from clinical and animal studies, Front. Physiol. 7 (2016), 308.
[19] S. Steinke, F. Sachse, N. Ettischer, et al., Coxsackievirus B3 modulates cardiac ion channels, FASEB J. 27 (10) (2013) 4108–4121.