Incidence, Risk Factors, and Outcome of Life-Threatening Ventricular Arrhythmias in Giant Cell Myocarditis

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Background—Ventricular tachyarrhythmias are characteristic of giant cell myocarditis, but their true incidence, predictors, and outcome are unknown.

Methods and Results—Our work involved 51 patients with giant cell myocarditis (35 women) aged 52±12 years. Their medical records were reviewed for history, results of laboratory and imaging studies, and occurrence of serious cardiac events, including life-threatening ventricular tachyarrhythmias. Sudden cardiac death (fetal or aborted) was the primary end point of our analyses, whereas the composite of sudden cardiac death and ventricular tachycardia requiring treatment constituted the secondary end point. Giant cell myocarditis presented as nonfatal ventricular tachyarrhythmia in 10 patients and as a fatal cardiac arrest in 1 patient. Overall, 14 of 50 patients suffered a sudden cardiac death during follow-up, with a cumulative incidence of 22% at 1 year and 26% at 5 years from presentation. The composite incidence of sudden cardiac death or ventricular tachycardia was 41% at 1 year and 55% at 5 years. The incidence of arrhythmias was associated with high plasma concentrations of troponin-T and N-terminal brain natriuretic propeptide, as well as with moderate-to-severe fibrosis on myocardial biopsy and history of ventricular tachyarrhythmias at presentation (P<0.05 for all). An intracardiac cardioverter defibrillator was implanted in 31 patients, of whom 17 had altogether 114 appropriate antiarrhythmic therapies by the device and none suffered an arrhythmic death.

Conclusions—In giant cell myocarditis, the risk of life-threatening ventricular arrhythmias exceeds 50% at 5 years from admission, being related to the presenting clinical manifestation and markers of myocardial injury and scarring.

(Circ Arrhythm Electrophysiol. 2016;9:e004559. DOI: 10.1161/CIRCEP.116.004559.)

Key Words: cardiac arrhythmia ▪ biopsy ▪ implantable cardioverter-defibrillator ▪ myocarditis ▪ sudden cardiac death
WHAT IS KNOWN

- Almost half of giant cell myocarditis patients experience life-threatening ventricular arrhythmias.

WHAT THE STUDY ADDS

- In giant cell myocarditis, sudden ventricular arrhythmias are a more common cause of death than heart failure.
- Biomarkers at presentation (cardiac troponin T and NT-proBNP) and the extent of myocardial fibrosis on diagnostic biopsy are related to the occurrence of ventricular arrhythmias.
- Implantable cardioverter defibrillator effectively terminates sustained ventricular arrhythmias (in majority of cases with antitachycardia pacing alone) in giant cell myocarditis patients.

the patients (n=46) described in our latest report on transplant-free survival and its predictors16 and 5 new patients diagnosed between May 2014 and January 2016. Of the 51 cases, 43 cases were diagnosed from endomyocardial (n=39) or surgical myocardial biopsies (n=4), the remaining 8 cases being detected at autopsy (n=5) or after transplantation (n=3). As reported earlier,10 the diagnosis of GCM required myocardial histology showing myocyte injury with or without necrosis associated with multinucleated giant cells and an inflammatory infiltrate variably composed of lymphocytes, histiocytes, and eosinophils. To avoid mistaking sarcoidosis for GCM, any unequivocal granuloma formation excluded the diagnosis of GCM.

Data Collection

The procedures of data collection have been specified in our preceding reports.10 In short, medical records were reviewed for patient demographics, comorbidities, main clinical manifestations, results of laboratory tests and imaging studies, as well as for the details of treatment with drugs and devices. The methods to measure plasma concentrations of N-terminal brain natriuretic propeptide (NT-proBNP) and cardiac troponin T (cTnT) have also been described earlier10 as have been the methods to assess cardiac studies with contrast-enhanced magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (PET). For the present work, MRI studies were reviewed for the presence of pathological myocardial late gadolinium enhancement (LGE) (yes/no) and the PET studies for the presence of abnormal focal myocardial 18F-fluorodeoxyglucose accumulation, suggestive of active inflammation (yes/no). All available materials from diagnostic myocardial biopsies were reevaluated by 2 experienced cardiac pathologists. The extent of cardiomycocyte necrosis and the number of eosinophils were graded visually from hematoxylin–eosin–stained samples using a semiquantitative 4-point scale (0, 1, 2, and 3 for none, mild, moderate, and severe, respectively) as detailed earlier with supporting illustrations.10 The presence and extent of myocardial fibrosis was scored in similar manner from slices stained with Masson’s trichrome. All scores were based on the pathologists’ consensus.

Serious cardiac events, that included death, cardiac transplantation and life-threatening ventricular tachyarrhythmias, were recorded till the end of April 2016. Life-threatening tachyarrhythmias were defined as (1) sudden cardiac death (SCD); (2) aborted SCD, which was defined as the date of first medical contact because of symptoms that led to the diagnosis of GCM. The time point of diagnosis was defined as the date of myocardial biopsy confirming the diagnosis of GCM. The primary end point of the study was SCD, fatal or aborted. As a secondary end point, we analyzed the composite of SCD and any VT requiring treatment (see above). Life-threatening arrhythmias as the presenting manifestation were not taken as end point events. Cardiac transplantation or death caused by terminal heart failure were considered competing events.12 Cause-specific cumulative incidence analysis was used to plot the incidence–time curves,12 and the Gray test was used to analyze group differences in the occurrence of end point events. To analyze the association of end point arrhythmias with characteristics of patients and their disease, the Fine and Gray model was used to calculate subdistribution hazard ratios and their 95% confidence intervals (CI).12 The validity of proportional hazards assumption was tested by calculating Schoenfeld (partial) residuals and plotting them against follow-up time. The assumption was considered valid if no statistically significant time-dependent correlation was observed. In all analyses, P values <0.05 were considered statistically significant. The statistics was calculated using the Xlstat Biomed (Addinsoft, Paris, France) and R software (R Development Core Team) in cumulative incidence analyses and SPSS–21 for Macintosh (SPSS Inc, IL) in all other tests.

Results

Patient Characteristics

The study population consisted of 35 women (69%) and 16 men aged 52±12 years at symptom onset. Their key characteristics at presentation are summarized in Table 1. Because of the long recruitment period, data on some important variables (NT-proBNP, cTnT, MRI, and PET) were not available for all patients (see Table 1 for details). The form of GCM presentation was sustained VT in 7 patients (14%) and out-of-hospital cardiac arrest because of VF in 4 patients (8%). One of the arrested patients died at the scene of the event and could not be included in further analyses. Half of the patients (52%) had severe left ventricular dysfunction (ejection fraction <35%) at the time of presentation, and nearly all who were studied by modern cardiac imaging had abnormal myocardial LGE on MRI (24 of 25 patients) and focal 18F-fluorodeoxyglucose uptake on PET, suggestive of myocardial inflammation (14 of 15 patients).

Myocardial samples from lifetime diagnostic biopsies were available in 42 patients. Grade 2 to 3 (moderate-to-severe) myocyte necrosis was found in 12 patients (29%) and grade 2 to 3 myocardial fibrosis in 7 patients (17%). The number of eosinophilic cells was graded 2 to 3 in 14 (33%) individuals. Of the 7 patients with myocardial material available only from autopsy or transplantation, grade 2 to 3 necrosis was found in 2 patients and grade 2 to 3 fibrosis in 4 patients.

Treatment

Table 2 summarizes the treatments given to the 50 patients alive at presentation. Forty-two of the 43 patients who...
were diagnosed prior to transplantation or autopsy received GCM-targeted immunosuppressive drugs; 1 patient could not be treated because of an early death. All 50 patients were given β-adrenergic blockers, and 29 of them (57%) received amiodarone for the control of ventricular arrhythmias. A permanent ICD was implanted in 31 patients, of whom 23 and 8 individuals received the device for primary and secondary prevention, respectively. Altogether, 11 of the 50 patients (22%) were considered poor candidates for a permanent ICD because of rapidly progressive heart failure and poor survival probability without early transplantation. Thus, among patients eligible for permanent ICD, 31 of 39 (80%) received the device.

**Total Mortality and Transplantations**

The follow-up time from symptom onset to death, transplantation, or end of study ranged from 0.1 to 161 months (median, 19 months). Over the course of the follow-up, 7 patients died (all of cardiac cause) and 19 patients underwent cardiac transplantation. Five of the 7 cardiac deaths were caused by a fatal arrhythmia and 2 by terminal heart failure and cardiogenic shock. Of the 19 transplantations, 16 were made because of intractable heart failure and 3 mainly because of ventricular tachyarrhythmias defying all therapies.

**Occurrence and Correlates of End Point Arrhythmias**

Figure 1 illustrates the cumulative incidence of the primary and secondary end point arrhythmias.

Altogether, 14 of 50 patients suffered a fatal (n=4) or aborted (n=10) SCD with a 1-year and 5-year cumulative incidences of 22% (95% CI 13%–38%) and 26% (95% CI 16%–42%), respectively. Secondary end point arrhythmias were recorded in 27 patients with a cumulative incidence of 41% (95% CI 29%–57%) in 1 year and 55% (95% CI 41%–72%) in 5 years from symptom onset.

These 27 events broke down into 4 fatal SCDs, 8 aborted SCDs, and 15 VTs requiring intervention (antitachycardia pacing by ICD, n=7; defibrillation by ICD, n=3; and external cardioversion or defibrillation, n=5).

Table 3 shows the association of the end point arrhythmias with the clinical, laboratory, and histological characteristics of patients at presentation of their GCM. The data show that the occurrence of SCD was associated with high circulating concentrations of NT-proBNP and cTnT, whereas the composite of SCD and VT was related to moderate-to-severe myocardial fibrosis and to VT or VF as the presenting manifestation. By contrast, arrhythmic events were not statistically significantly associated with age, sex, New York Heart Association class,
left ventricular ejection fraction, grades of myocardial necrosis or eosinophils on diagnostic biopsy, or use of triple drug immunosuppression. Because of the small number of cardiac MRI and PET studies, the association of end point events with these studies could not be assessed. Figure 2 demonstrates the association of SCD with plasma cTnT at presentation, and Figure 3 shows the composite incidence of SCD and VT in relation to the extent of myocardial fibrosis (Figure 3A) and to the presenting GCM manifestation (Figure 3B). The analysis shown in Figure 3B was repeated in the subgroup of 39 patients considered eligible for a permanent ICD (see above). Among them, 31 individuals were free of VT or VF at presentation and, thus, did not have an indication for an ICD as secondary prevention. Their cumulative incidence of SCD or VT was 23% (95% CI 12%–45%) in 1 year and 42% (95% CI 26%–67%) in 5 years of follow-up.

**Observations on Outcome With Antiarrhythmic Therapy**

Amiodarone was given to 29 patients to prevent recurrent symptomatic episodes of VT. It had no clinical effect in 6 patients, reduced the frequency of VT episodes in 14 patients, and produced a complete symptomatic remission in 9 patients. Catheter or surgical ablation for medically uncontrollable VT was attempted in 4 patients. The result was partial in every case: the procedure reduced the recurrences but did not abolish VTs completely. Of the 31 patients who received an ICD, in all, 17 patients had 1 or more appropriate ICD therapies during follow-up (Figure 4). Detailed ICD reports were available on altogether 114 such therapies; they are summarized in Table 4. Four patients (13%) received inappropriate ICD shocks because of supraventricular tachyarrhythmia (3 cases) or sinus tachycardia (1 case). No device infections were observed, despite the strong concomitant immunosuppressive therapy.

**Discussion**

Our present work provides the first systematic analysis of the incidence and risk factors of life-threatening ventricular tachyarrhythmias in GCM. The following observations deserve to be raised in particular. First, as many as 22% of patients presented with either sustained VT or with VF causing cardiac arrest, and these individuals bore a particularly high risk of ventricular arrhythmias also during follow-up. Second,
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the risk of SCD and VT requiring therapy was at its highest during the first weeks from presentation but persisted throughout the disease course and resulted in an incidence as high as 55% at 5 years from symptom onset. Third, fatal SCD was much more common as a cause of death in nontransplanted GCM than terminal heart failure. Fourth, ventricular arrhythmias were associated with plasma cTnT and NT-proBNP at presentation and the extent of myocardial fibrosis on diagnostic biopsy, together with the form of disease presentation. Finally, medical and invasive therapies against VTs appeared variably and at most partially effective. ICDs, instead, reliably terminated life-threatening ventricular tachyarrhythmias, and no patient having the device suffered a fatal SCD.

The association of ventricular tachyarrhythmias with GCM was recognized soon after the first lifetime diagnoses had been made in the 1980s. Davidoff et al\textsuperscript{13} and Cooper et al\textsuperscript{14} each reported 5 patients with idiopathic GCM who all had ventricular tachyarrhythmias either at presentation or during follow-up. These 2 patient series were included also in the 1997 multicenter GCM registry of 63 patients, among whom VT was the second most common presenting manifestation after heart failure and almost half developed sustained VT during the disease course.\textsuperscript{2} In 2003, Okura et al\textsuperscript{3} reported from the same registry, which by then had grown to 73 patients worldwide, that 32% had VT (29%) or VF (3%) at hospital presentation. These reports\textsuperscript{2,3} did not, however, afford detailed data on the incidence, risk factors, or outcome of ventricular tachyarrhythmias, including their contribution to mortality. A more recent multicenter study of 1-year GCM survivors found that 6 of 26 patients experienced recurrent VTs during a mean follow-up of 5.5 years, but no new VTs were observed in patients free of arrhythmic tachyarrhythmias at presentation.\textsuperscript{8} Although the above studies and several case reports\textsuperscript{15–20} have suggested that ventricular tachyarrhythmias are both common and important in GCM, no in-depth research focusing on this subject has been published from outside our institution.

As reported earlier by Granér et al,\textsuperscript{9} multiple forms of relatively slow monomorphic VTs are common in individual patients with GCM. VTs are usually inducible at the electrophysiological study, and delayed atrioventricular conduction is also a common concomitant.\textsuperscript{9} These observations from our center suggest that monomorphic VTs are related to areas of injury, replacement fibrosis, and strands of viable myocardium, providing the substrate for reentry tachyarrhythmias. Recently, the expression of myocardial plakoglobin, a desmosomal protein of the intercalated discs, was found to be reduced in GCM similarly to the findings in arrhythmogenic right ventricular dysplasia and cardiac

Figure 2. Cumulative incidence of fatal or aborted sudden cardiac death (SCD) in relation to the median plasma cardiac troponin-T (cTnT) at presentation. In all, 10 events in 49 patients were analyzed.

Figure 3. Cumulative incidence of sudden cardiac death (SCD) or ventricular tachycardia (VT) requiring therapy (secondary end point) in giant cell myocarditis (GCM) patients with none-to-mild (grade 0–1) vs moderate-to-severe (grade 2–3) fibrosis on diagnostic myocardial biopsy (A) and in patients with vs without life-threatening ventricular tachyarrhythmia at presentation (B). The former analysis (A) was made on 22 arrhythmic events in 42 patients and the latter (B) on 27 events in 50 patients. VF indicates ventricular fibrillation.
sarcoidosis.21 A role for disrupted myocyte-to-myocyte connections in the high arrhythmogenicity of GCM is, thus, possible but unproven today.

Our analyses showed that SCD during follow-up was associated with markedly elevated circulating cTnT (>130 ng/L) at presentation of GCM, while the composite risk of SCD and VT requiring therapy was linked more to the extent of myocardial fibrosis. These associations, mere statistical as they are, suggest that active myocyte injury may trigger VF, in particular, while myocardial fibrosis of old injury promotes sustained VT. Myocardial injury and scarring eventuate in cardiac dysfunction, which explains the correlation of plasma NT-proBNP with study end points, although the association of left ventricular ejection fraction did not reach statistical significance. As expected, VT or VF as the presenting manifestation correlated with a particularly high risk of life-threatening arrhythmia during follow-up. Although the respective risk in patients free of presenting arrhythmias was less, the incidence of SCD and VT requiring therapy was considerable in these individuals, too. Here our findings seem to contrast sharply with the report by Maleszewski et al8 of no ventricular arrhythmias during long-term follow-up in patients without arrhythmias at presentation. The contrast is lessened, however, recognizing that Maleszewski et al8 only included patients who had survived the first year of GCM, that is, the period when the risk of fatal arrhythmias is highest in this disease (see our Figure 1). Still, some discrepancy remains because there were patients in our series first experiencing VT or VF after an uneventful year of the disease (see Figure 3B).

There exist no previous observational let-alone prospective data regarding the treatment of ventricular arrhythmias in GCM. Some case reports have suggested that immunosuppression may suppress arrhythmias, too,17,19 but other reports show failures.15,20 In our study, the response of VTs to standard amiodarone therapy was inconsistent, although the frequency of recurrences was reduced in most patients. Catheter or surgical ablation was attempted in only a few cases unresponsive to medical management. The procedure diminished the number of VT episodes but did not produce complete long-term remission in any patient. This result may be because of the common existence of multiple reentrant pathways in GCM and also to ongoing inflammation, leading to further fibrosis and new reentrant circuits during the disease course. Our most important observation regarding the treatment of arrhythmias in GCM was the frequency and success of ICD therapies. Altogether, 55% of patients with an ICD experienced appropriate treatments, and of the VT episodes recognized by the device, 80% responded to antitachycardia pacing, minimizing the need of shocks. Even more importantly, in patients with an ICD, the device successfully prevented SCD in all 9 VF episodes encountered. The American College of Cardiology/American Heart Association/Heart Rhythm Society 2012 update on guidelines for device-based therapy gives a Class Ia indication (should be considered) for a permanent ICD in GCM, without specifying other criteria than the diagnosis.22 The 2015 European Society of Cardiology guidelines on ventricular arrhythmias state that a permanent ICD is not recommended in myocarditis until the resolution of the acute phase, and that a wearable cardioverter defibrillator (life vest) should be considered during recovery.23 However, they also state that because of the known high arrhythmic risk, ICD implantation might be considered earlier in GCM.23 Our observations indicate that the absence of VT or VF at presentation does not save the GCM patients from later SCD or VT and that their arrhythmia risk is highest during the early weeks after symptom onset and presentation. The risk is also poorly appreciable from left ventricular ejection fraction, the traditional predictive factor in dilated and ischemic cardiomyopathy.22,23 Although markers of myocardial injury and fibrosis can point toward patients with the highest risk, we subscribe to the American College of Cardiology/American Heart Association/Heart Rhythm Society consensus23 and think that, in GCM, a permanent ICD should be considered and implanted soon after presentation in each patient free of a fulminant course and an early need of transplantation. Selected patients with fulminant GCM considered unsuitable for permanent ICD could be safeguarded with a life vest during the transplant waiting period.
The size of our study is both a strength and a limitation of our work. By 2012, <300 cases of GCM had been reported in the literature, and our 51 consecutive patients constitute by far the largest and less selected single-center population of this rare disease. On the other hand, for statistical analyses of incidence and associated factors, the number of patients and end point events remained small, limiting the power of our analyses and excluding the use of multivariate analyses. The general limitations of a retrospective design pertain also to the present work. Patients were recruited over a long period of time, and as Tables 1 and 3 specify, several important variables were not available for analyses in all patients. Representing retrospective observations, the responses of VTs to medical and invasive therapies cannot be considered more than suggestive. The classification of myocardial necrosis and fibrosis on biopsy was based on scoring that relied on visual scrutiny of the biopsy material. Even though an automated quantification method would be theoretically more ideal, the semiquantitative technique is widely used and endorsed by experts in the field. The use in risk assessment of LGE by cardiac MRI, although presentation with VT or VF was associated with the incidence of future arrhythmias, the incidence was considerable also in patients free of VT or VF on admission. Besides history of presentation, the extent of active and old myocardial injury may influence the susceptibility to arrhythmias as suggested by the relation of the end point events to circulating cTnT and to moderate-to-severe myocar-
mias as suggested by the relation of the end point events to myocardial injury may influence the susceptibility to arrhyth-
mias. A larger number of patients and quantitative LGE data are needed for proper analyses. In conclusion, our study shows that more than half of the patients with GCM experience life-threatening ventricular tachyarrhythmias during their transplant-free disease course. Although presentation with VT or VF was associated with the incidence of future arrhythmias, the incidence was considerable also in patients free of VT or VF on admission. Besides history of presentation, the extent of active and old myocardial injury may influence the susceptibility to arrhyth-
mias as suggested by the relation of the end point events to circulating cTnT and to moderate-to-severe myocardial fibrosis at presentation. A permanent ICD seems to constitute an effective modality for the treatment of ventricular tachyarrhythmias and the prevention of SCD in GCM.

Acknowledgments
We thank the medical and nursing staffs of the Division of Cardiology, Helsinki University Central Hospital, for their help in this study.

Sources of Funding
The study was supported by a Finnish government grant for medical research (EVO), the Finnish Foundation for Cardiovascular Research, and the Finnish Cultural Foundation; all Helsinki, Finland.

Disclosures
None.

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_Circ Arrhythm Electrophysiol._ 2016;9:
doi: 10.1161/CIRCEP.116.004559

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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