Cardiac Sarcoidosis and Giant Cell Myocarditis as Causes of Atrioventricular Block in Young and Middle-Aged Adults

Riina Kandolin, MD; Jukka Lehtonen, MD, PhD; Markku Kupari, MD, PhD

Background—Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) may present as high-degree atrioventricular block (AVB), but their proportion of the causal spectrum of AVB is not well-known. We investigated the prevalence of biopsy-verified CS and GCM in young and middle-aged adults undergoing pacemaker (PM) implantation for AVB.

Methods and Results—We used the PM registry of Helsinki University Central Hospital to identify all patients aged 18 to 55 years who underwent PM implantation for AVB between January 1999 and April 2009 and reviewed their medical records. In total, 133 patients had either second- or third-degree AVB as an indication for PM. Of them, 61 had a known cause for AVB, and they were excluded from further analyses. Among the remaining 72 patients with initially unexplained AVB, biopsy-verified CS or GCM was found in 14 (19%) and 4 (6%) patients, respectively. The majority (16/18, 89%) were women. Among the adult patients aged <55 years, the prevalence of CS and GCM combined was 14% (95% CI, 7.7% to 19.3%) of the whole AVB population and 25% (95% CI, 15% to 35%) of those with an initially unexplained AVB. Over an average of 48 months of follow-up, 7 (39%) of 18 patients with CS or GCM versus 1 of the 54 patients in whom AVB remained idiopathic, experienced either cardiac death, cardiac transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia (P<0.001).

Conclusions—CS and GCM explain ≥25% of initially unexplained AVB in young and middle-aged adults. These patients are at high risk for adverse cardiac events.

Key Words: cardiomyopathy ■ heart block ■ myocarditis ■ nuclear medicine ■ pacemakers

Atrioventricular conduction block can result from diverse local or diffuse cardiac diseases or injuries like myocardial ischemia or infarction, cardiomyopathies, infectious or noninfectious myocarditis, invasive procedures, and idioopathic degeneration of the conduction tissue. The underlying condition strongly influences both the age of onset and the prognosis of atrioventricular block (AVB).1–4 Cardiac sarcoidosis (CS) is a granulomatous inflammatory myocarditis with AVB as the most common clinical manifestation along with ventricular arrhythmias and heart failure.5,6 The diagnosis of CS is based on endomyocardial biopsy (EMB) that demonstrates granulomatous inflammation or, alternatively, on histologically confirmed extra cardiac sarcoidosis combined with cardiac imaging indicative of myocardial involvement.7,8 The diagnosis of isolated CS (ie, sarcoidosis confined to the heart) is particularly difficult because its confirmation depends solely on EMB, the sensitivity of which is notoriously limited.9–11 Although CS commonly results in AVB, it is a rare disease, and the proportion it constitutes of the total etiologic spectrum of AVB is not well-known. An earlier Japanese study found a prevalence of 11.2% for clinically or histologically diagnosed CS among consecutive patients aged 69±13 years with high-degree AVB.5

Editorial see p 260

Clinical Perspective on p 309

Giant cell myocarditis (GCM) is a fulminant cardiac disease that shares some clinical and histological characteristics with CS but usually runs a more aggressive course. Most typically, it presents as rapidly progressive heart failure and ventricular tachyarrhythmias, but it may also cause AVB. Rarely, a slower progression or even a self-limiting course has been described.12–14 EMB is more sensitive in detecting GCM than CS because of the more widespread myocardial inflammation in the former.

In this observational study, we assessed the prevalence and significance of CS and GCM as causes of AVB in young and middle-aged adults. To that end, we reviewed the diagnoses and clinical course of all adult patients aged <55 years who received a permanent pacemaker (PM) for AVB over the past decade. We found that in this age group, CS and GCM combined are responsible for at least one fourth of otherwise unexplained AVB and predict a high rate of life-threatening cardiac events postimplantation.

Methods

Study Population and Data Collection

We used the PM registry of Helsinki University Central Hospital, a tertiary medical center with a referral population of 1.45 million, to...
identify all patients aged 18 to 55 years who underwent their first PM implantation between January 1999 and April 2009. The registry covers all PM implantations within our catchment area. The PM registry information and the medical records were scrutinized, and the subgroup of individuals with a second- or third-degree AVB as an indication for PM implantation were selected to comprise the present study population. Their diagnoses, including details of all diagnostic procedures conducted before and after PM implantation, were reviewed, and the causes of AVB were retrospectively evaluated and confirmed. All patients had regular postimplantation PM control visits at our hospital. Serious cardiac events during follow-up were identified from the electronic medical records that also contain up-to-date mortality data up to the end of April 2009. The study protocol was approved by the institutional review board.

Initial Etiologic Classification of AVB

For the purposes of the present work, the cause of AVB at the time of PM implantation was classified as either known or unexplained on the basis of clinical data and results of diagnostic studies available at the time of implantation. The cause was considered known if the patient either had a history or was given a new diagnosis of any condition known to cause AVB, such as intracardiac surgical or catheter-based intervention, ischemic heart disease, infectious endocarditis, acute myocarditis, autoimmune disease, cardiomyopathy, congenital heart disease, mediastinal irradiation, or cardiac transplantation. The remaining patients were classified as having an initially unexplained AVB.

Myocardial Imaging

During the primary admission and selectively later postimplantation, the patients underwent diagnostic examinations that always included routine laboratory tests and a complete echocardiographic study (Vivid 7 echocardiograph; GE Healthcare). Coronary angiography with contrast left and right ventricular cineangiography was performed when clinically indicated or if myocardial imaging showed evidence of myocardial infarction. In 2005, 18F-2-deoxyglucose (18F-FDG) PET and gadolinium-enhanced cardiac MRI (Gd-MRI) became available at our institution, and either of these imaging studies since was commonly used in patients with unexplained AVB.

Figure 1. Representative histological findings in endomyocardial biopsy samples (hematoxylin-eosin, original magnification ×40). A, Granulomas and giant cells consistent with cardiac sarcoidosis. B, Multinucleated giant cells with fibrosis, inflammatory cells, and necrotic cardiomyocytes consistent with giant cell myocarditis.

Figure 2. A summary of patient selection and classification. AVB indicates atrioventricular block; CS, cardiac sarcoidosis; GCM, giant cell myocarditis; PM, pacemaker.
Fasting cardiac \(^{18}\text{F}-\text{FDG}\) PET always was done in association with technetium-\(^{99}\text{mTc}\) myocardial scintigraphy. Blood glucose level was controlled, and if it was <7 mmol/L (<120 mg/dL), the study was performed. After an intravenous injection of \(^{18}\text{F}-\text{FDG}\) (303±57 MBq), patients rested for 60 minutes in a semidarkened, quiet room. PET images were acquired with a Philips Gemini PET/CT scanner. Within 1 week from the PET/CT scan, a \(^{99}\text{mTc}-\text{tetrofosmin}\) myocardial perfusion imaging at rest was performed. The myocardial perfusion was compared with the FDG uptake in the left ventricle. An area where myocardial perfusion was decreased and FDG accumulation was focally enhanced was interpreted as suggestive of an inflammatory process.\(^{20,21}\) Initially, PET scan was focused on the heart, but since late 2008, whole-body \(^{18}\text{F}-\text{FDG}\) PET suggestive of an inflammatory process.\(^{20,21}\) Initially, PET scan was focused on the heart, but since late 2008, whole-body \(^{18}\text{F}-\text{FDG}\) PET images have been acquired.

MRI was performed with 1.5-T imager (Avanto; Siemens; Erlangen, Germany). Breath-hold cine MRI was performed using ECG-gated segmented true fast imaging with steady-state precession. Five to 15 minutes after injection of a contrast agent (gadodaterol meglumine 0.1 mmol/kg), late-enhancement images were acquired in the same views as for cine images, using inversion recovery turbo fast low-angle shot sequence. On cine MRI, CS may exhibit segmental contraction abnormalities or focal myocardial thickening or thinning. CS typically entails patchy subepicardial enhancement isolated to the midmyocardial wall or epicardium with right and left ventricular involvement.\(^{22}\) The segmental extent of delayed contrast enhancement was recorded.

### Endomyocardial Biopsy

Right or left ventricular endomyocardial biopsy (EMB) were performed if any of the imaging modalities showed abnormalities suggestive of myocardial inflammation or infiltration. Typically, 5 to 12 samples per session were taken under fluoroscopic and ultrasound guidance. The diagnosis of CS or GCM was based on histopathology. The diagnosis of CS required the presence of well-formed nonnecrotizing granulomas, with or without isolated giant cells, and special staining to rule out other causes of granulomatous inflammation (Figure 1A). The diagnosis of GCM required the presence of a widespread inflammatory infiltrate with multinucleated giant cells in association with myocyte necrosis and eosinophils\(^{12}\) (Figure 1B). If EMB was not diagnostic but the clinical picture and cardiac imaging was strongly suggestive of CS, either a repeated EMB or a biopsy of possible \(^{18}\text{F}-\text{FDG}\)-positive mediastinal lymph nodes was performed.

### Statistical Analysis

The differences between patient group characteristics were assessed using the Mann–Whitney \(U\) test and the \(x^2\) or Fisher exact tests. The survival curves were analyzed and plotted by the Kaplan–Meier method. The primary end point in these analyzes was a composite of cardiac death, cardiac transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia. In all tests, a 2-tailed \(p<0.05\) was considered statistically significant. The analyses were performed using SPSS version 17 for Windows (SPSS Inc; Chicago, IL).

### Results

#### Patient Classification

Figure 2 summarizes the process of patient selection and classification. A total of 212 patients aged 18 to 55 years had a PM implanted between January 1999 and April 2009, representing 3.3% of all PM implantations (N=6420) at our center over this period. A total of 133 patients aged 18 to 55 had either second- or third-degree AVB. Of these, 61 (median age, 48 years; 51% women) had a known cause of AVB, with prior heart surgery, cardiomyopathy, ischemic heart disease, and congenital heart disease as the most common etiologic conditions (Table 1); these patients were excluded from further analyses. The remaining 72 patients (median age, 47 years; 61% women) had an initially unexplained AVB. Their medical records were reviewed and clinical courses followed until the end of April 2009 (median, 48 months; range, 1 to 123 months).

### Patients With Initially Unexplained AVB

For the evaluation of the etiology of AVB, the 72 patients with initially unexplained AVB underwent 147 diagnostic studies, including echocardiography (n=72), cardiac \(^{18}\text{F}-\text{FDG}\) PET combined with \(^{99}\text{mTc}\) myocardial scintigraphy (n=24) (of which 10 were whole-body PET), cardiac catheterization and angiography (n=13), and cardiac Gd-MRI (n=13). All together, 25 patients underwent 36 separate right or left ventricular EMB sessions prompted by deterioration of left ventricular function or abnormalities in wall thickness on echocardiography and signs suggestive of myocardial inflammation on \(^{18}\text{F}-\text{FDG}\) PET or Gd-MRI. The first EMB exposed CS in 6 patients and GCM in 1. Repeat EMBs were taken due to deterioration of left ventricular systolic function and emergence of ventricular tachycardias (exposed CS in 1 and GCM in 1) or because of extensive imaging abnormalities (exposed CS in 1). Two patients with negative EMB finding despite \(^{18}\text{F}-\text{FDG}\) PET indicative of myocardial inflammation underwent biopsy of PET-positive mediastinal lymph nodes, and sarcoidosis was confirmed in both of these cases. Further, sarcoid histology was confirmed from extracardiac tissue (lungs, skin, extrathoracic lymph nodes) in 3 patients. GCM was diagnosed in 2 patients on autopsy, and 1 case of CS from the explanted heart. Thus, 18 of the 72 patients (25%, 95% CI, 15% to 35%) had either CS (n=14; 95% CI, 10 to 29) or GCM (n=4; 95% CI, 0.3 to 11). Nine (64%) of the 14 patients with CS had an isolated cardiac involvement, whereas 5 also had clinical manifestations of extra-CS (lungs, skin, extrathoracic lymph nodes). In patients with a positive EMB, 42% (range, 14% to 75%) of biopsy samples had

#### Table 1. Etiologies for Atrioventricular Block With a Known Etiology at the Time of Pacemaker Implantation (n=61)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Value (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprocedural</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Open heart surgery</td>
<td>14</td>
</tr>
<tr>
<td>EP procedure</td>
<td>4</td>
</tr>
<tr>
<td>Myopathy</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>8 (13)*</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other†</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or n. EP, electrophysiology.

*With prior myocardial infarction of whom 4 patients had undergone coronary artery bypass surgery and 4 coronary angioplasty (2 had Q waves on ECG).
†Two patients with calcified aortic valve disease and 1 with spinal fracture with quadriparesis.
CS was treated with oral prednisone for
Treatment and Events During Follow-Up
findings consistent with CS. In addition to these 18 patients with either CS or GCM, 4 patients had echocardiographic septal abnormalities (thinning or thickening) combined with a septal perfusion defect at 99mTc myocardial scintigraphy and a hot spot at 18F-FDG PET (Figure 3) (ie, a constellation suggestive of CS20). However, their EMBs remained negative and, for the purposes of this study, they were classified as having probable CS within the group of idiopathic AVB.
Table 2 shows selected characteristics of the 18 patients with CS or GCM compared with the 54 patients in whom AVB remained idiopathic. None of the patients had significant valvular disease. Of note, patients with CS or GCM more often were women and had a statistically significantly higher prevalence of left ventricular systolic dysfunction and echocardiographically abnormal septum. Recovery of atrioventricular conduction, defined as <10% ventricular pacing during follow-up, was found in 2 (13%) of 16 patients with CS or GCM versus 13 (25%) of 52 patients in the idiopathic group, but this difference was statistically nonsignificant (P=0.49). There were no statistically significant differences in any of the characteristics in Table 2 between patients with CS and GCM.

Treatment and Events During Follow-Up
CS was treated with oral prednisone for ≥1 year in 13 of 14 patients, 6 of whom also received azathioprine. Two of 4 patients with GCM received a combination of prednisone, azathioprine, and cyclosporine. Four patients with CS and 2 with GCM received an intracardiac defibrillator (n=4) or cardiac resynchronization therapy defibrillator (n=2). On clinical grounds, steroids also were given to the 4 patients with probable cardiac sarcoidosis (ie, with high-degree atrioventricular block and findings in cardiac imaging typical for cardiac sarcoidosis despite negative endomyocardial biopsy findings. In each part, the top row of images shows a technetium-99m-tetrofosmin myocardial perfusion image, and the bottom row shows the corresponding 18F-2-deoxyglucose uptake. Every patient had a localized septal perfusion defect (*) with a superimposable hot spot on PET imaging suggestive of active inflammation. FDG F-18 indicates 18F-2-deoxyglucose; Tc, technetium-99m.

Table 3 summarizes the adverse cardiac events during follow-up, and Figure 4 shows the Kaplan–Meier curves for survival free of the composite end point. From the 18 patients with CS or GCM, 4 died, 4 had ventricular fibrillation, 6 had documented sustained ventricular tachycardia, and 3 underwent cardiac transplantation because of terminal heart failure (n=2) or recurrent uncontrollable ventricular tachycardia.
In the GCM group, 3 patients had ventricular fibrillation compared to 1 patient in the CS group (P=0.019). With regard to other events during follow-up, CS versus GCM differences remained insignificant. In the group of 54 patients in whom AVB remained idiopathic, 1 patient had ventricular tachycardia leading to defibrillator discharge; none died. The frequency of the composite end point was much higher in patients with CS and GCM than in the idiopathic group (39% versus 2%, P<0.001). Furthermore, the only patient in the idiopathic AVB group reaching the end point was 1 of the 4 having probable CS (see earlier discussion).

### Discussion

The key finding of this study is that CS and GCM are more common causes of AVB in young and middle-aged adults than usually thought. Thus, they were found in 14% of adults aged <55 years requiring a PM for AVB, and in ≥25% of patients in the same age group with an initially unexplained AVB, 3.3% of all patients undergoing PM implantation at our institution were aged 18 to 55 years. This finding is similar to that of a recent study in which 5% of patients undergoing PM implantation (74.3% for AVB) were aged <53 years. One reason for these high-prevalence figures could be the known high prevalence of sarcoidosis in the Nordic countries, including Finland. Another likely reason is that myocardial imaging and cardiac biopsies were actively used in the routine diagnostic assessment of patients with high-degree AVB. Our findings accord with the 11.2% prevalence of CS in Japanese patients with AVB, although in the present study, histological confirmation of sarcoidosis was required.

Another important finding of our work is the female predominance among patients with CS or GCM. This finding might reflect the sex-dependent differences in immune response in myocarditis. A large prior study in which 38% of cases were diagnosed at autopsy or from explanted heart, showed a slight male predominance in CS (62%) and GCM (52%). Several other studies indicated a female dominance of 60% to 80% in CS. One could speculate that the female predominance in our study could be due to a difference in disease presentation. It is possible that CS and GCM manifest more often as heart failure in men and as AVB or ventricular tachycardias in women. The third major finding of the present study is the frequency of impaired left ventricular function already at the time of AVB manifestation in patients with CS and GCM and, in particular, their high incidence of serious cardiac events after PM implantation.

Table 3. Adverse Cardiac Events on Follow-Up in Patients in Whom AVB Remained Idiopathic, AVB Due to Confirmed CS/GCM, and AVB Due to Confirmed or Probable CS/GCM

<table>
<thead>
<tr>
<th>Event</th>
<th>Idiopathic (n=54)</th>
<th>Confirmed CS/GCM (n=18)</th>
<th>Confirmed or Probable CS/GCM (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
<td>4 (22)‡</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
<td>9 (17)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Nonsustained*</td>
<td>1 (2)</td>
<td>6 (33)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Sustained†</td>
<td></td>
<td>3 (17)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0</td>
<td>4 (22)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>1 (2)</td>
<td>7 (39)</td>
<td>8 (36)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). MACE indicates major adverse cardiac event (cardiac death, transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia). Other abbreviations as in Table 2.

*Six or more ventricular beats with a duration <30 s.
†Ventricular tachycardia with a duration ≥30 s.
‡Intergroup comparison between CS and GCM was significant (P=0.019).
The diagnosis of CS is positive when an EMB sample shows unequivocal sarcoid histopathology. The diagnosis also can be made by identifying sarcoidosis in an extracardiac tissue sample in a patient with clinical presentation and findings from a 12-lead ECG and on one or more modalities of cardiac imaging indicative of myocardial involvement. Either way, the diagnosis is difficult, and many of our cases of CS (or GCM) were identified only after repeated imaging-guided EMB or sampling of mediastinal lymph nodes after negative EMB findings. Yet, even despite an active biopsy policy, sarcoidosis isolated to the heart may escape detection because of the limited sensitivity of EMB. Our cohort had 4 patients with echocardiography, myocardial scintigraphy, and 18F-FDG PET findings sufficiently characteristic of CS to warrant steroid therapy despite negative EMB results (Figure 3). Had these patients been analyzed in the CS group, 31% of initially unexplained AVB would have been attributable to CS or GCM in our study population. Yet, although Gd-MRI and 18F-FDG PET appear to be sensitive in detecting active myocardial inflammation and fibrosis in CS, the findings are not specific for sarcoïd involvement.

In the present series, 7 (39%) of 18 patients with AVB due to CS or GCM had a major adverse cardiac event over an average of 2 years after PM implantation. This finding is in keeping with the generally poor prognosis of these forms of myocarditis.

Furthermore, among the 72 patients with an initially unexplained AVB, all primary composite end points were recorded in individuals with either verified (n=7) or probable (n=1) CS or GCM. Similarly, Ardehali et al recently showed that in patients with initially unexplained dilated cardiomyopathy, EMB-verified sarcoidosis portends a particularly poor outlook.

Some data suggest that corticosteroid therapy may improve left ventricular function in CS and that it may occasionally correct the AVB in CS. On the other hand, immunosuppression may have little or no effect on ventricular arrhythmias, which in CS are probably related more to fibrotic areas promoting reentry mechanisms than to areas of myocardial edema and active inflammation. In the present study, AVB was reversible in 2 (13%) of 16 patients after institution of corticosteroid therapy. Although immunosuppression is considered important in both CS and GCM, all evidence is based on small observational case series or registries. Therefore, the dosing of steroids and other immunosuppressive agents, the duration of treatment, the best follow-up methods and measurements, and the criteria for a positive response have not been defined and vary from center to center. The only treatment trial attempted hitherto failed to recruit patients.

The present work is limited by the relatively small patient cohort, the observational and retrospective study design, and the lack of a systematic and identical diagnostic work-up (eg, only 42% of patients who underwent 18F-FDG PET had the whole body screened) for AVB over the entire decade of interest. Based on this study, we cannot tell what proportion of all AVBs CS or GCM cause, yet our findings strongly suggest that CS and GCM are not uncommon causes of AVB in young and middle-aged adults. Our data also show that the prognosis in CS and GCM is poor even when the main presenting manifestation is AVB. All together, our results support a policy of active and systematic screening for CS and GCM in all adults aged <55 years presenting with unexplained second- or third-degree AVB. We hypothesize that early diagnosis of CS or GCM with proper treatment and close surveillance has a favorable impact on prognosis.

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References

Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) are rare inflammatory myocardial diseases that may have atrioventricular block (AVB) as their presenting clinical manifestation. This study involved 133 consecutive patients aged 18 to 55 years who underwent pacemaker implantation for second- or third-degree AVB at our institution. Use of modern cardiac imaging methods and an active biopsy policy revealed CS and GCM in 14 and 4 patients, respectively, of the 72 with an initially unexplained AVB. The majority (16/18, 89%) of these patients were women. Thus, in this age group, the prevalence of CS and GCM combined was 14% of the whole AVB population (95% CI, 7.7% to 19.3%) and 25% of those with an initially unexplained AVB (95% CI, 15% to 35%). Over an average of 48 months of follow-up, 7 (39%) of 18 patients with CS or GCM experienced a major cardiac event, including transplantation, cardiac death, ventricular fibrillation, or treated sustained ventricular tachycardia. These data suggest that CS and GCM are not uncommon causes of AVB in young and middle-aged adults and that the prognosis of CS and GCM is poor even when the first manifestation is AVB. We encourage a policy of active and systematic screening for CS and GCM in all adults aged <55 presenting with unexplained high-degree AVB.
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