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When Should High-Grade Heart Block Trigger a Search for a Treatable Cardiomyopathy?

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High-degree heart block is an uncommon manifestation of acute myocarditis in adults. The rate of heart block requiring a pacemaker in biopsy-proven acute lymphocytic myocarditis generally is low but has been reported in up to 8.3% of cases.¹ Important exceptions include cardiac sarcoidosis and giant cell myocarditis (GCM), 2 uncommon and idiopathic disorders for which early immunosuppression may improve clinical outcomes. High-degree heart block occurs in the course of biopsy-proven cardiac sarcoidosis in 23% to 30% of cases (Table).² In GCM, second- or third-degree heart block requiring a pacemaker occurs in 25% of cases.³

This relatively high rate of heart block reflects the severity of the clinical course of cardiac sarcoidosis and GCM, which have a higher rate of death and heart transplantation than lymphocytic myocarditis.^{1,4} Unlike acute lymphocytic myocarditis, for which immunosuppression usually is not beneficial,⁵ GCM or cardiac sarcoidosis may improve with certain combinations of immunosuppressive drugs. In the case of acute GCM, cyclosporine combined with corticosteroids and usually a T-cell lytic agent like muromonab-CD3 improves transplant-free survival.⁶ Uncontrolled case series also suggested that left ventricular (LV) dysfunction due to cardiac sarcoidosis may improve with corticosteroid therapy.⁷

Because GCM and cardiac sarcoidosis are rare disorders, endomyocardial biopsy is not routinely recommended to detect them in the setting of complete heart block unless cardiomyopathy is present.⁸ Although a recommendation class was not assigned to this clinical scenario by the American Heart Association/American College of Cardiology Foundation/European Society of Cardiology (AHA/ACCF/ESC) Writing Group, the role of endomyocardial biopsy in idiopathic complete heart block was discussed in the text of the scientific statement. On the basis of expert opinion, the diagnostic yield of right ventricular

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None.

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septal endomyocardial biopsy in this clinical scenario would be quite low relative to the potential benefits. However, the frequency of specific and treatable disorders among young patients who present with heart block requiring a pacemaker only has been reported in a single Japanese case series⁹ until now.

In this issue of *Circulation: Arrhythmia & Electrophysiology*, Kandolin et al¹⁰ report a case series of 72 young adult patients aged 18 to 55 years with initially unexplained atrioventricular block in whom cardiac sarcoidosis or GCM was found in 14 (19%) and 4 (6%) patients, respectively. Consistent with prior reports, none of the patients had lymphocytic myocarditis. Over an average follow-up of 48 months, 7 (39%) of the 18 patients with cardiac sarcoidosis or GCM experienced cardiac death, cardiac transplantation, or ventricular fibrillation or were treated for sustained ventricular tachycardia. This rate compares to only 1 (2%) of the 54 patients in whom atrioventricular block remained idiopathic ($P<0.001$). This report is the first case series in which the rate of GCM and cardiac sarcoidosis is reported in a consecutive series of patients requiring pacemaker implantation.

Several aspects of the Kandolin et al study¹⁰ deserve comment. To what degree are their results generalizable to other adult populations with atrioventricular block? The authors' study population of young adults without clinically apparent causes for heart block represents a small fraction of the 6420 persons who received pacemakers during the 10-year study period. Only 212 (3.3%) were aged <55 years, whereas just slightly >1% (72/6420) had high-grade idiopathic heart block. The rate of cardiac sarcoidosis and GCM in an older cohort with established reasons for heart block certainly would be much lower.

The study cohort was from Finland, a country with a relatively high background rate of systemic sarcoidosis.¹¹ It is not known whether populations with different ethnic backgrounds and lower rates of systemic sarcoidosis would have similar findings. Most cases of GCM are described in whites, but this observation may reflect biases in diagnosis rate or variable presentations rather than a true difference in GCM incidence.⁴ In populations of African or Asian ancestry who have unexplained cardiomyopathy or heart block, the rates of cardiac biopsy-proven GCM or cardiac sarcoidosis are not known.

To identify the 18 cases of histologically proven GCM and cardiac sarcoidosis, the authors searched systematically for a specific cause of cardiomyopathy.¹⁰ Cardiac MRI, PET, and endomyocardial biopsy commonly were used. The 36 endomyocardial biopsy specimens (5 to 12 samples per session) of the LV, right ventricle, or both in 25 of 72 patients yielded 9 positive cases. Six cases of cardiac sarcoidosis and 1 case of GCM were diagnosed on initial biopsy, and 1 cardiac sarcoidosis case and 1 GCM case were diagnosed on second biopsy. This notably high rate of specific cardiomyopathy detection may reflect more diffuse myocardial disease at the time of heart block diagnosis. Indeed, the mean LV ejection fraction in the final cohort with unexplained heart block was mildly reduced at 50% (range, 25% to 70%), suggesting that about half of the cases had clear evidence of LV systolic dysfunction at the time of diagnosis. Interestingly, the 25% (9 of 36) rate of positive biopsy specimens is similar to the 28% (8 of 28) positive rate in a prospective GCM registry in

which the criteria for biopsy were an acute cardiomyopathy complicated by heart block, ventricular tachycardia, or failure to respond to usual care.⁶

The optimal initial and follow-up imaging strategy for patients with suspected GCM or cardiac sarcoidosis is not known. Several reports suggest that cardiac MRI may have specific features for cardiac sarcoidosis.^{12,13} The diagnosis of sarcoidosis by 18-fluorodeoxyglucose PET is less well established but, not infrequently, can identify a site of extracardiac sarcoidosis for biopsy.¹⁴ Endomyocardial voltage mapping has been used to guide biopsy to regions of low voltage in suspected cardiac sarcoidosis. Greater use of this and similar technologies may increase the sensitivity of biopsy, particularly in a disease with focal myocardial involvement like cardiac sarcoidosis. In those patients with normal cardiac function at the time of presentation with heart block, it would be reasonable to repeat an echocardiogram 6 to 12 months later to monitor for development of cardiomyopathy.

Should these findings affect the current AHA/ACCF/ESC scientific statement for use of endomyocardial biopsy? The 25% positive biopsy rate is high enough that endomyocardial biopsy should probably be recommended in populations at similar risk (based on ethnicity, age, and exclusion of more common causes). In select cases, the recommendation for endomyocardial biopsy probably should be class 2A (a reasonable procedure). However, to minimize risk and maximize the likelihood of a diagnostic sample, the medical center and operator should have experience in the procedure, as manifested by a low procedural complication rate, and timely and expert cardiac pathology consultation should be available.

From this and other studies, we know that a histological diagnosis of acute GCM will affect management and outcome. In the setting of cardiomyopathy, a biopsy-based diagnosis of sarcoidosis carries a poor prognosis.¹⁵ However, a remaining gap in our knowledge of cardiac sarcoidosis is whether treatment changes based on a histological diagnosis, or a probable diagnosis based on imaging abnormalities, will affect clinically meaningful outcomes in the clinical scenario of isolated heart block. Is the likelihood of recovery of atrioventricular conduction greater or risk of dilated cardiomyopathy lower with immunosuppressive therapy? In the Kandolin et al¹⁰ study, there was a trend toward less pacing on follow-up in the early immunosuppression group ($P=0.082$), but larger, multicenter prospective registries and trials are needed to adequately address the effect of a specific diagnosis-guided treatment on outcomes.

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Table

Prevalence of Various Cardiac Findings in Cardiac Sarcoidosis During the Course of Disease

	Prevalence in Study Series, %
Atrioventricular block	26–62
Bundle-branch block	12–61
Supraventricular tachycardia	0–15
Ventricular tachycardia	2–42
Congestive heart failure	10–30
Sudden death	12–65

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