

## EDITORIAL COMMENT

# Can We Now Find the Needle in the Haystack?\*



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Endomyocardial biopsy (EMB) is rarely performed today to determine the etiology of cardiomyopathies or to guide the therapy of patients who present with cardiomyopathies of unknown etiology. There are a number of reasons for this, including a lack of specific therapies for most cardiomyopathies, a low incidence of actually finding abnormal tissue with biopsy, and the advancement of other imaging technologies such as magnetic resonance imaging that although not diagnostic, can assist in ruling in or out specific disease processes. The Myocarditis Treatment Trial, which evaluated the use of immunosuppressive therapy in patients with biopsy-proven myocarditis, was one of the first steps in this resultant decrease (1). Patients with acute or chronic myocarditis were randomized to immunosuppressive therapy with prednisone plus either azathioprine or cyclosporine versus usual care. After 24 weeks of therapy, there was no difference in ejection fraction or survival between the 2 groups. However, many have reported differences in the prognosis of patients based on the specific etiology found on EMB, some of which might determine different therapeutic approaches. McCarthy et al. (2) identified differences in outcome in patients with fulminant myocarditis compared with those with acute myocarditis. One could argue that patients with fulminant myocarditis requiring acute ventricular assist device support should undergo placement of a temporary device instead of a long-term device because their chances of recovery appear to be

higher, knowledge only gained by biopsy. Additionally, specific diagnoses may help guide therapy based on prognosis. Felker et al. (3) reported the outcomes of 1,230 patients that underwent an extensive evaluation (history, cardiac catheterization, and EMB) to determine the etiology of patients with unexplained heart failure. They found significant differences in outcome based on etiology. However, despite this extensive evaluation, they were able to determine the etiology in 50% of the patients and EMB provided a specific histological diagnosis in only 15%.

To inform clinicians on the appropriate indications for performing an EMB, a consensus conference report from many societies on the risks and benefits of biopsy was published in 2007 (4). The risks of EMB were compared with the benefits for diagnosis, prognosis, and possible therapy. The authors presented 14 different clinical scenarios for which biopsies are performed. Class I indications were given for 2 different scenarios: patients with new-onset heart failure of <2 weeks' duration with hemodynamic compromise and patients with new-onset heart failure of 2 weeks to 3 months associated with a dilated left ventricle and new ventricular arrhythmias, advanced heart block, or failure to respond to usual medical therapy. For both of these groups of patients, giant cell myocarditis is a possible diagnosis. Although not studied in randomized clinical trials, there are reports of improved survival with immunosuppressive therapy for giant cell myocarditis (5). Other clinical scenarios received a class IIa recommendation for biopsy, including looking for myocarditis, eosinophilic infiltration, anthracycline-induced toxicity, unexplained restrictive cardiomyopathy, suspected cardiac tumors, and unexplained cardiomyopathy in children. Class IIb recommendations were given for performing biopsies in patients with new heart failure that

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responds to usual therapy, unexplained hypertrophic cardiomyopathy, suspected arrhythmogenic right ventricular cardiomyopathy (ARVC), and unexplained ventricular arrhythmias. The only Class III recommendation was for unexplained atrial fibrillation.

We recently reported the results of EMBs performed on patients with heart failure placed into these 14 clinical scenarios (6). Our aim was to evaluate if the biopsy was diagnostic and if therapy was changed based on the result. We found that for patients with a Class I indication for biopsy, the biopsy was diagnostic in 38.5% (<2 weeks) and 20% (>2 weeks to 3 months) of patients with new-onset heart failure not responding to medical therapy. Among others of the 14 clinical scenarios, the biopsy was diagnostic more than 20% of the time for patients with suspected eosinophilic infiltrate, anthracycline toxicity, unexplained restrictive cardiomyopathy, tumors, suspected ARVC, and ventricular arrhythmias. Despite these findings, the most common pathological diagnosis was mild, moderate, or severe fibrosis and/or hypertrophy. However, it is possible that patients without a diagnosis actually had the disease process and because of sampling and the patchy infiltration of many of these processes, the abnormal myocardium was not sampled. Without pathological evaluation of the entire heart, it would be impossible to determine if the biopsy, which takes 5 to 10 small pieces of tissue, was truly nondiagnostic or just missed the abnormal area completely. Clearly, methods to improve the diagnostic yield for this invasive procedure would be welcome.

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In this issue of *JACC: Heart Failure*, Liang et al. (7) reported their results of using electrogram-guided EMB in 11 patients for the evaluation of myocarditis and cardiac sarcoidosis. The researchers' hypothesized abnormal tissue would usually be associated with reduced voltage and/or abnormal electrograms. In contrast, normal tissue would have normal voltage and complete scar would have no voltage. They used a mapping catheter to find areas of abnormal tissue and then tried to place a biptome as close to that area as possible. They also biopsied tissue with normal voltage to use as controls. A total of 40 pieces of tissue were taken with corresponding electrograms. The researchers found a very high specificity and positive predictive value taking biopsies from areas with reduced voltage or abnormal electrograms. Five of the 11 patients were found to have

myocarditis or sarcoidosis, for an overall rate of diagnosis of nearly 50%. In contrast, areas of normal voltage or electrogram had normal tissue or mild fibrosis or hypertrophy. All, however, was not perfect. Even in areas with abnormal voltage or electrogram, the incidence of finding nondiagnostic tissue (fibrosis or myocyte hypertrophy) was still more than 50%. However, our previous study in similar patients found abnormal tissue in approximately 20%, and the use of these techniques to increase the yield to nearly 50% is certainly a significant step forward. Certainly, if others can confirm these results, the use of electrograms to guide the operator to the area to biopsy may become the standard of care.

This study has 2 significant limitations. First, standard biptomes used to perform biopsies have little flexibility to change position. Although one can attempt to position the biptome close to the area of abnormal tissue, directing the biptome to those areas can sometimes be difficult. Second, the researchers reported their experience in only 11 patients. They also did not take any random biopsies, and it is unclear what the rate of a positive diagnosis would be with "blind" biopsies. However, they should be credited for using electrograms in multiple patients, and further studies should be performed.

One other question is what to do with the results. The researchers found 1 patient with cardiac sarcoidosis, 2 with either sarcoidosis or giant cell, and 2 with myocarditis. One could debate for a long time about the proper therapies to use in some of these patients; for the patients with myocarditis, it is much harder to know if specific therapy is indicated. However, to treat a disease, one must reliably diagnose it; increasing the diagnostic yield of an EMB is the first step in that process. The use of intracardiac mapping at the time of biopsy appears to be a significant step forward.

EMB is a low-risk but usually low-yield procedure. Using a new tool to increase the chance of finding abnormal tissue in the haystack of the right ventricle is a significant step in the right direction. A direct comparison of usual biopsy versus electrogram-guided biopsy in the same patient should be performed to truly demonstrate the potential benefits of this procedure.

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