PERSPECTIVE

Endomyocardial biopsy: the balance of success and failure

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ENDOMYOCARDIAL BIOPSY (EMB) has not fulfilled its promise. But, it may soon. It was a reasonable early expectation that the technique would provide an understanding of myocardial disease that would lead to effective treatment in most patients. This expectation has not been met. Instead, EMB has served an unforeseen medley of purposes, and has often found itself involved in odds and ends of cardiology. Yet, in circumscribed areas EMB has been successful in that it has benefited patients and clarified disease processes. In fact, the balance between successes and failures of EMB is close, and the ultimate place of EMB in cardiologic practice will be determined by the change in this balance in the near future.

Successes

Perhaps the greatest success of the technique is that it can be done remarkably safely and with excellent yield of tissue. In this regard, it is superior to most other solid-organ biopsy techniques. There are two areas of undeniable clinical utility of EMB that represent clear-cut indications for it: detection of cardiac transplant rejection and detection and quantitation of doxorubicin-induced myocardial disease. Each biopsy performed to evaluate these conditions gives clinically useful and usually critical information. Biopsy results can also identify certain specific myocardial diseases, but most biopsies performed for this indication do not provide useful information because of the low incidence of specific findings and the minimal clinical value of a nonspecific biopsy sample.

Cardiac transplant rejection. Early recognition of rejection has been attempted with numerous techniques, such as physical examination, standard electrocardiography, signal-averaged electrocardiography, cardiac scintigraphy, and a variety of immunologic studies. Cardiac biopsy remains the most reliable method, even though use of cyclosporine has modified biopsy findings in early rejection. Examination of EMB specimens also appears to be the best way to infer the existence of pulmonary allograft rejection in combined heart-lung transplantation.

Doxorubicin cardiotoxicity. Doxorubicin and other anthracyclines cause myocyte damage. This damage is usually not so extensive that it is clinically manifest when the dose is limited to 500 mg/m² or less. There are exceptions, however, especially in the presence of specific risk factors, and frequently it is desirable to extend dosing beyond the arbitrary limit. EMB is the most sensitive and accurate technique for determining the extent of doxorubicin-induced cardiomyopathy; furthermore, the information can be used, in combination with hemodynamic data obtained at the same time, to estimate tolerance to and monitor the result of subsequent doses of doxorubicin. Bristow et al. found that use of biopsy and hemodynamic data reduced the incidence of doxorubicin-induced heart failure in patients with risk factors from 17% to 6% and reduced the incidence of death due to heart failure from 10% to zero, when compared with monitoring without these invasive studies.

Noninvasive tests have been used for the same purpose, but they are not as accurate. There is no argument regarding the inadequacies of electrocardiography and echocardiography. These methods provide evidence of the cardiomyopathy only in its late stage, and even then specificity and reproducibility of the findings are insufficient. Recently radionuclide angiography has been described as a sensitive and specific measure of the extent of doxorubicin cardiotoxicity, even in its early stage. Comparison of this technique to EMB combined with right heart catheterization, however, has revealed discrepancies between the two methods. While the sensitivity of radionuclide angiography is good if both rest and exercise studies are performed, its specificity is poor. Serial studies improve specificity of radionuclide angiography, but increase the surveillance intensity and cost of delivering
cancer treatment. Angiography can be used as a screening test, but should not be used as a definitive determinant of prospective doxorubicin dosing. Patients with normal rest and exercise radionuclide studies need not undergo EMB, but those with abnormal studies are not necessarily at high risk of developing congestive heart failure and therefore should undergo EMB to determine their suitability for further anthracycline therapy.

Specific myocardial diseases. The list of specific myocardial diseases that can be diagnosed by EMB is lengthening. The first dozen entities shown in table 1 were listed 2 years ago. To that previous list we have added tumors of noncardiac origin, Kearns-Sayre syndrome (external ophthalmoplegia, retinal pigmentation, and atrioventricular block), cytomegalovirus infection, toxoplasmosis, cardiac involvement in Henoch-Schoenlein purpura, rheumatic carditis, and Chagas' disease of the heart. In addition, cardiac biopsy has recently been found to provide therapeutically useful information in patients with Kawasaki's disease and hypereosinophilic endomyocardial disease.

While the list of disorders being diagnosed by EMB grows, the net yield per biopsy may fall, because the likelihood of making any one of these new diagnoses may be less than the enthusiasm that the possibility generates among invasive cardiologists. It must be remembered that the huge majority of patients with myocardial disease of nonvascular and nonvalvular origin have idiopathic myocardial disease. Searching for needles in a haystack, even if there are nineteen of them, is a frustrating endeavor.

TABLE 1
Specific diagnoses made by endomyocardial biopsy

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<tr>
<th>Diagnosis</th>
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<tr>
<td>Cardiac allograft rejection</td>
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<tr>
<td>Myocarditis</td>
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<tr>
<td>Doxorubicin cardiotoxicity</td>
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<tr>
<td>Cardiac amyloidosis</td>
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<tr>
<td>Cardiac sarcoidosis</td>
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<tr>
<td>Cardiac hemochromatosis</td>
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<tr>
<td>Endocardial fibrosis</td>
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<td>Fabry's disease of the heart</td>
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<tr>
<td>Carcinoid disease</td>
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<tr>
<td>Irradiation injury</td>
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<tr>
<td>Glycogen storage disease</td>
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<tr>
<td>Cardiac tumors of cardiac origin</td>
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<tr>
<td>Cardiac tumors of noncardiac origin</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
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<tr>
<td>Toxoplasmosis</td>
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<tr>
<td>Henoch-Schoenlein purpura</td>
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<tr>
<td>Rheumatic carditis</td>
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<tr>
<td>Chagasic cardiomyopathy</td>
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Failures

The greatest failure of EMB is implied in the paragraph above. Little progress has been made toward a therapeutically useful classification or understanding of idiopathic congestive cardiomyopathy. Because of this failure, investigators have taken to quantitation of histologic and ultrastructural abnormalities to formulate a biopsy-based prognosis. This effort has led to confusion. About half of the recent literature on the subject demonstrates a good correlation between the extent of a variety of pathologic abnormalities and the extent of cardiac dysfunction and outcome in patients with idiopathic congestive cardiomyopathy. Histopathologic features, such as myocyte hypertrophy, nuclear abnormalities, fibrosis, and endocardial thickening, and ultrastructural features such as nucleolar morphology, myofiber diameter, myofibrillar mass, and mitochondrial morphology have been identified as useful indexes. But other authors find no such correlations and consider the sampling error too great to permit reliable biopsy-based prognostication.

Where does this leave us? Disappointed, of course, and perhaps with no good justification for performing a cardiac biopsy in the majority of patients who currently undergo the procedure. Not quite.

Future

The immediate future of EMB may lie with myocarditis. The technique will never have widespread, frequent application if its only clear-cut indication is monitoring of cardiac rejection and anthracycline therapy. All of the disorders listed in table 1, except for myocarditis, are rare, many can be diagnosed by other means, and only a few can be treated specifically. This being the case, it is hard to justify performing EMB in the standard case: the patient who presents with heart failure without previous myocardial infarction or valvular disease.

But, myocarditis is not rare. And, if it can be successfully treated, the attempt to identify it would constitute a proper indication for EMB in many "standard cases."

The evidence that myocarditis is not rare comes from several sources. Its incidence has ranged from 9% to 63% in unselected series. Although pathologic diagnosis of this entity has been severely hampered by varying and often incorrect histologic criteria, it seems that genuine cell-mediated myocarditis is sufficiently common to warrant searching for it, if it is susceptible to treatment.

There is no conclusive proof that immunosuppressive therapy (that with prednisone and azathioprine,
for example) eradicates the inflammatory cell infiltrate and thereby improves outcome in patients with myocarditis, but there is circumstantial evidence. The problem in interpreting available data is that myocarditis may resolve spontaneously. Do patients apparently "cured" by anti-inflammatory drugs simply improve spontaneously? The only way to answer this question is to perform a prospective, randomized trial. A potential trial design is described below and illustrated in figure 1.

A group of medical centers would be required to participate to guarantee recruitment of a sufficient number of patients to answer the question. Patients with unexplained congestive heart failure would undergo cardiac biopsy. Those with myocarditis would be asked to sign consent for a randomization study. They would be allocated to the three following treatment limbs:

1. Conventional therapy only. Standard therapy for congestive heart failure, including digoxin, diuretics, and vasodilators according to a rigid protocol.

2. Prednisone and azathioprine. Conventional therapy as in limb 1, as well as prednisone and azathioprine.


Patients would receive the therapy to which they were randomly assigned for 6 months, after which all would receive conventional therapy for congestive heart failure during an 18 month follow-up period. The results of therapy would be assessed by survival analysis, objective measures of cardiac performance, and repeat cardiac biopsies.

Such a study or one similar to it may determine if immunosuppressive therapy benefits patients with myocarditis. That determination could decide the ultimate fate of the EMB technique for the near future. Cardiomyopathy is one of the most common diagnoses made by the cardiologist. If a substantial proportion of patients with that diagnosis are candidates for EMB because they might have myocarditis, then use of the technique will increase substantially. If, however, we learn that myocarditis cannot be treated specifically, use of EMB will decline; it will be available only in centers at which cardiac transplantation is performed or at which large numbers of patients receive anthracycline therapy.

There are other potential future indications for EMB that might promote its use independent of the outcome of a myocarditis randomization trial. New anthracycline antibiotics are under development. Availability of these new drugs will increase use of EMB until a noncardiotoxic, yet effective, one is discovered. Morphometric analysis of EMB specimens raises the possibility that the myocardial effects of valvular insufficiency can be accurately quantitated and that the information might be used to properly time surgical intervention. Biochemical analysis of biopsy tissue, despite the small size of specimens, is now practical. This may be a most important development, since it offers the potential for an understanding of the causes of idiopathic myocardial diseases. Nothing substantial has come to light so far, but histologic and ultrastructural examination has provided no genuinely hopeful clues. Biochemical study of diseased tissue is the next obvious step and has in the past been a powerful approach to understanding of previously obscure noncardiac disorders.

**Place in practice**

EMB is still not widely available. It is performed frequently in only a few centers, and infrequently in a larger number of hospitals, but it is not available within short distance to patients everywhere in this country. The technique has not been practiced or taught in most training programs and the need for it has been properly perceived as small. In the context of current knowledge, this circumstance is appropriate. In a general cardiology practice, the clear-cut requirement for EMB arises only a few times a year. Since the technique, like other invasive procedures, cannot be performed safely on such an infrequent basis, it should not
be learned by all or even a substantial minority of cardiologists. Of course, new knowledge may change this recommendation.

Whom should the general cardiologist refer for biopsy? Patients in need of more than the usual amount of doxorubicin, or patients with risk factors such as prior mediastinal radiation, should undergo biopsy. Patients in whom there is a strong suspicion of cardiac sarcoidosis or eosinophilic endomyocardial disease are candidates for biopsy because effective therapy exists for both disorders. Aside from cardiac allograft rejection, there are no other disorders that require cardiac biopsy for diagnosis or for which there is a proven therapy. The largest potential referral group is patients with suspected myocarditis; however, until therapy is proven effective in this condition, biopsy should not be considered mandatory.

If use of EMB turns out to be successful in this latter group of patients, the balance will tip markedly in favor of EMB and it will assume a prominent position in cardiologic practice.

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