The Role of Left Ventricular Biopsy in the Management of Heart Disease

Running title: Cooper; Left ventricular biopsy and heart disease

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More than 50 years after the first description of transvenous endomyocardial heart biopsy (EMB),\textsuperscript{1} the role of EMB remains controversial. EMB is often essential for the diagnosis of allograft rejection and specific forms of native myocardial disease, including amyloidsis and giant cell myocarditis,\textsuperscript{2} yet expert consensus for the utility of EMB in more common scenarios is lacking. For example, a 2013 position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases recommends heart biopsy be performed for all cases of suspected myocarditis including most acute and chronic dilated cardiomyopathy.\textsuperscript{3}

In contrast, the 2013 ACCF/AHA Guideline for the Management of Heart Failure recommends that “endomyocardial biopsy should not be performed in the routine evaluation of patients with heart failure.” (class of recommendation III).\textsuperscript{4} The European Society of Cardiology Working Group and the AHA/ACCF recommendations are both based on expert opinion (Level of evidence C).

Most authorities in the field agree on the unique ability of EMB to diagnose specific viral heart infections and distinguish prognostically valuable histological patterns such as sarcoidosis or lymphocytic myocarditis.\textsuperscript{5,6} Lymphocytic myocarditis is a histological biomarker that predicts successful bridging to recovery after left ventricular assist device in adults\textsuperscript{7} and the long-term risk of allograft rejection in children.\textsuperscript{8} Furthermore, case series document that viral genomes (amplified from heart tissue) predict the risk of allograft rejection in children following heart transplantation\textsuperscript{9} and the risks of worsening left ventricular function and possibly heart transplantation or death in cardiomyopathy.\textsuperscript{10,11,12}

The major disagreements arise primarily from different perspectives of the ability of unique EMB data (histology, immunohistology, or molecular diagnostic tests such as viral genomes) to change therapy and thereby alter clinically meaningful outcomes. The data
supporting antiviral treatment for patients with virus positive cardiomyopathy are limited to experimental models, several small case series and single institution case reports.\textsuperscript{9,13} The data supporting the use of EMB to guide immunosuppressive therapy in chronic inflammatory cardiomyopathy are stronger, and include 2 single center trials of 84 and 85 subjects (both trials used immunohistochemical diagnostic criteria).\textsuperscript{14,15} In the setting of suspected myocarditis without high grade heart block or sustained ventricular arrhythmias, the value of EMB without viral genomes or immunohistology is likely low.\textsuperscript{16} What does EMB coupled with state-of-the-art molecular diagnostics offer beyond what is available from less invasive and less costly testing to meaningfully influence clinically important events in newly diagnosed or chronic cardiomyopathy?

In this context, Chimenti and Frustaci present safety and diagnostic data from the largest published case series of left ventricular biopsies.\textsuperscript{17} Their’s is an extraordinary experience that fills a major gap in our knowledge of a procedure that is rarely performed in US medical facilities. 4221 patients underwent EMB; 1153 LV EMB, 672 RV EMB, and 2369 both LV and RV EMB. The overall risk of major complications was remarkably low (.33\% for LV EMB and .45\% for RV EMB) and decreased over the 28 year study timeframe. Because all EMB procedures were performed by 2 operators (the co-authors), time of study enrollment can serve as a surrogate for operator experience. The risk of perforation was higher in RV than in LV EMB, probably because the thinner walled RV is more easily perforated by the bioptome. The low risk of perforation may be partially explained by the selective avoidance of patients with large, thin ventricles at highest risk. The risk of stroke was higher in LV EMB and numerically attenuated by the use of high dose aspirin compared to heparin.

Not surprisingly, disorders that primarily affect the LV, such as myocarditis, were more
frequently diagnosed by LV biopsy. Indeed the overall diagnostic yield of RV biopsy in patients with isolated LV involvement on imaging was only 53%. The diagnostic yield for myocarditis increased after 1990 when immunohistochemistry was added to hematoxylin and eosin to identify inflammation. It is surprising that ARVC/D, a disorder that primarily affects the RV “triangle of dysplasia”, was commonly diagnosed on LV EMB. These findings extend a smaller comparison study of LV and RV biopsy that found biventricular EMB has a superior diagnostic yield compared to RV EMB.

The strongest conclusion from these data and the other recently published LV EMB case series is that the risk of major complications from LV EMB is low, under 1%, when performed by experienced operators at centers with appropriate infrastructure support. Furthermore, it is safe to conclude that the diagnostic performance of LV EMB is superior to RV EMB when routine immunohistochemistry and viral genome amplification are used in the assessment of suspected LV myocarditis. Neither study specifically addresses the critical issue of how an increased rate of diagnosis affects patient management and outcome.

How should the present study affect clinical care? When EMB is considered clinically indicated for a primary LV disorder, LV biopsy should be strongly considered to maximize the overall value of the procedure to the patient. This recommendation depends on the availability of experienced operators and expert cardiovascular pathologists. But in the current state few cardiologists routinely perform LV EMB and likely lack the expertise required to achieve the lowest complication rates. Furthermore, the immunocytochemistry and viral genome analysis used in this study are not universally available. These and cost issues will contribute to an appropriate reluctance to adopt LV EMB. Nonetheless, heart failure referral centers where RV EMB is already performed should factor the Chimenti and Frustaci data into a patient-centered
value calculation when considering EMB.

A multidisciplinary initiative involving cardiac interventionalists, pathologists and possibly a separate molecular diagnostics lab will be required to perform routine LV EMB and the associated studies on heart biopsy tissue. Non-adopters can still defend their position by citing the remaining gaps in outcome data including a lack of specific EMB-guided outcome studies and cost effectiveness analyses. The current divergence of expert opinion suggests that equipoise exists in the routine use of EMB for “idiopathic” DCM. Therefore, given the global burden of idiopathic cardiomyopathy, a multicenter trial designed with features to minimize investigator bias to define the value of EMB is timely. The net value of EMB in the evaluation of cardiomyopathy will remain an area of unresolved disagreement without such a collaborative effort.

Conflict of Interest Disclosures: None.

References:


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