The International Endomyocardial Biopsy Position Paper: A Basis for Integration Into Modern Clinical Practice

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Recent years have seen an increase in global, multisociety, consensus-driven guidelines and position papers. These initiatives are a particularly important mechanism of providing a practical and broadly credible approach to common problems that have defied common description and to uncommon scenarios where a large heterogeneity of clinical practice occurs, even in highly specialized, tertiary care settings. The recently published Universal Definition of Heart Failure is a prime example of the former condition,[1] whereas the Position Statement of Endomyocardial Biopsy (EMB) published in this issue of the *Journal* is a corresponding example of the latter.[2] Here, we discuss the evolution of EMB from a single-indication test to its subsequent expansion and, more recently, to refinements of indication, performance and clinical value.

Endomyocardial Biopsy: The Beginning

The EMB was developed to allow early diagnosis and monitoring of acute cardiac allograft rejection through a joint Stanford University effort in 1973 led by Drs. Philip Caves and Margaret Billingham.[3] The ability to identify a key complication rapidly became a milestone for the improvement of clinical outcomes after heart transplantation.

This relatively safe and repeatable practice became the gold standard for cardiac-rejection monitoring and subsequently expanded to many other clinical indications. Consequently, Margaret Billingham became a founding member and, later, first female president (1990-91) of the International Society for Heart and Lung Transplantation (ISHLT), which also established the Philip K. Caves Award in 1982.[4] As the practice of EMB spread, an ISHLT classification of postcardiac transplant cellular rejection was developed in 1990, facilitating the standardization and management of graft rejection.[5] This classification was revised in 2004, adding early description of antibody-mediated rejection (AMR)[6] and, subsequently, a working formulation for pathologic diagnosis of AMR, including both morphologic and immunopathologic components.[7]

From Heart Transplant Pathology to Other Cardiac Diseases and Challenges Observed

In addition to cardiac transplantation, the Stanford group pioneered the use of endomyocardial biopsy to study doxorubicin cardiotoxicity.[8] In short succession, other indicated conditions were added, such as idiopathic dilated cardiomyopathy, rapidly progressive heart failure, suspected sarcoidosis, restrictive cardiomyopathy, metabolic cardiomyopathies, and acute myocarditis (especially the much-feared giant cell myocarditis). Nevertheless, usage worldwide was sporadic, highly variable and nonstandardized. Over time, it became apparent that the diagnostic yield of EMB varied greatly according to underlying diagnosis. For example, the diagnostic yield of EMB remained very high in conditions such as metabolic cardiomyopathies, eosinophilic, certain infiltrative conditions, and (the previously thought rare) amyloidosis, where cardiac involvement was relatively uniform. In other conditions such as lymphocytic myocarditis, pathologic identification did not necessarily lead to improved clinical outcomes, due primarily to lack of efficacious treatments. This led to some confusion regarding appropriate use of EMB outside of cardiac rejection. In addition, increased complication rates for the procedure in low-volume centers were noted, leading to less enthusiasm for the procedure and even greater inconsistency of use. As a result, expert white papers were published with the aim of defining clinical conditions in which use of EMB would be more likely to lend important input to clinical decision making.[9] Although helpful, these papers were applied primarily in a patchwork manner and did not

necessarily enjoy full international support. Meanwhile, advances in the diagnosis of several cardiac disorders, such as acute myocarditis, sarcoidosis, amyloidosis, and iron overload, using noninvasive means (particularly cardiac magnetic resonance and positron emission tomography) continued apace.[10,11]

EMB has, thus, been considered by many to be a curious and uncommon cardiac test limited to selected tertiary cardiac care centers and performed following cardiac transplantation or in a tiny number of obscure medical conditions. Due in part to misconceptions regarding the procedure itself, the complication rate and the diagnostic yield, referral for EMB remains low and highly variable among and within countries worldwide. The result is a catch-22 of sorts. Learning from studies involving EMB has suffered from the referral bias inherent in studies validating noninvasive cardiac testing as surrogates for pathological diagnosis using EMB-derived tissue, impacting the "true" diagnostic yields of noninvasive studies themselves. Nevertheless, slow progress in defining the technique, role and yield of EMB has occurred, making this position statement timely and welcome.

Challenges for EMB in Heart Transplantation and Potential Solutions

Poor interpathologist agreement in grading rejection has been a concern, with data from the Cardiac Allograft Rejection Gene Expression Observational Study (CARGO II) study demonstrating only 71% agreement for assessment of all grades, with most disagreements centering on the attribution of moderate (2R ISHLT) rejection, which often discriminates between increase in immunosuppression and outcomes observed in clinical trials.[12] Although the search for better standardization in diagnosis is still a challenge, automated computational-image analysis to grade cardiac allograft graft rejection may offer a solution of sorts.[13] In their 2472 archived EMB samples taken from 3 centers, a "hand-crafted approach" was used to build a Computer-Assisted Cardiac Histologic Evaluation grader using machine-learning methodology to reproduce the 4-grade clinical standard for acute cellular rejection diagnosis. This approach met the threshold for overall noninferiority in comparison to analysis by experienced independent pathologists, and it was superior for sensitivity in the high-grade rejection subgroup. Despite these promising results, several limitations remain, such as the lack of inclusion of AMR assessment in

the model and a more robust gold standard definition to train the model that would include a larger expert cohort consensus, key additional diagnostic tests and patient outcomes.[14]

The current development of molecular diagnostics for EMBs offers a great opportunity to reclassify disease states and improve the precision and accuracy of pathological information, and it also provides objectivity and mechanistic insights. In the INTERHEART study, a central biopsy microarray-based diagnostic system was used to assess heart transplant EMBs, based on rejection-associated transcripts (mRNA) and machine-learning derived algorithms (classifiers) to estimate the probability of T-cell-mediated rejection, AMR or injury other than rejection. The Molecular Microscope Diagnostic System (MMDx-Heart), in which the EMB is compared to standardized scores from a bank of EMB specimens, provides a molecular score report and its interpretation.[15,16] These advances are not yet mature enough to alter current clinical practice (and, hence, the position statement), but the applicability is very promising.[17]

Two other developments occurred in tandem. The first is the recognition that the occurrence of clinically important cardiac rejection in the absence of symptoms or left ventricular systolic dysfunction is very uncommon. This has led to a proposed reduction (where appropriate) in routine surveillance EMB and a suggested rational approach to surveillance EMB. This is a component of the position paper that many centers will welcome. The development of noninvasive tests, such as gene-expression profiling and donor-derived cell-free DNA for screening in stable patients, can reduce the number of protocol EMBs and has entered clinical practice in limited jurisdictions. However, access to these tests, as well as lower accuracy in the critical early period following cardiac transplantation, coupled with the de-emphasis of late routine EMB in low-risk individuals, has limited the impact of this technology.

Reframing the EMB: The Procedure, Professional Standards, and Hybrid Procedures

Several advances in the performance of EMB are highlighted in this article. They include well-described procedural details, discussion of newer bioptome technology and separate devices for each vascular approach. A rational explanation of the role of venous (antegrade) vs arterial (retrograde) approaches are discussed, with scenarios (repeated biopsies, shorter recovery time, fewer vascular complications) in which the venous

approach is preferred, and alternative scenarios (patchy myocardial involvement, thin right ventricular wall, risk of myocardial perforation) in which the arterial approach is preferred. A practical video link outlining the performance of a routine EMB will provide an important training tool for aspiring practitioners. Given the well-established link between higher center volume and lower procedural complication rate, this article appropriately states that EMB should be performed in centers with extensive experience and by operators with a minimum annual procedure volume and who are familiar with multiple approaches to and recognition and management of complications.

This article also takes aim at a major misconception regarding the low diagnostic yield of EMB, especially in conditions known to have patchy myocardial involvement--an Achilles heel of EMB. Recent studies have shown that imaging-guided EMB dramatically improves diagnostic yield to as high as 90% when performed in combination with other imaging tests, such as with **c**ardiac magnetic resonance (identification of fibrosis or inflammation/edema), by positron emission tomography (identification of hypermetabolic foci, as in sarcoidosis or myocarditis), and even for reduction of complications via identification of areas to avoid, such as fatty infiltration or myocardial thinning/aneurysm.[18,19] Further, introduction of electromyocardial mapping (via a separate system, as CARTO or combination bioptome/electrode) has greatly improved diagnostic yield through the identification of low-voltage areas to target for biopsy.[20] Finally, the emergence of various and effective therapies for several infiltrative conditions, such as hypertrophic cardiomyopathy, ATTr/AL amyloid and Fabry disease, coupled with the need to distinguish them from each other (even after noninvasive imaging has been exhausted), have led to a resurgence in the need for EMB.[21] As such, this article recognizes the increased utility of EMB for such patients.

The Position Paper in Context

EMB has long been a test misunderstood by many, and this has led to a large heterogeneity in its use and performance. Nevertheless, EMB is an valuable component of our increasingly powerful armamentarium of diagnostic tools. This position paper sets a timely and important standard by which cardiac centers around the world can incorporate this important procedure into their work flows. Key deliverables include description of clinical indications, performance of the EMB, including a welcome

suggested schedule revision of the transplant surveillance biopsy, which is still the most common indication for EMB. The paper clearly articulates who should perform this procedure and where it should be performed and suggests newer hybrid techniques that can be employed in order to maximize utility and minimize risk. With an increasing number of analytic techniques, including molecular diagnostics, proteomics, electron microscopy, and automated computational pathology, when translating from research to clinical practice, the key relationship will continue to center on an experienced operator/pathologist in close collaboration with the clinical cardiology team. The publication of the current international EMB position paper is a key tool to standardize and improve our ability to diagnose and treat many cardiac conditions.

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