Standardizing the role of endomyocardial biopsy in current clinical practice worldwide

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Introduction

In recent years, the use of advanced imaging modalities, including echocardiography with three-dimensional and myocardial strain analysis, cardiac magnetic resonance (CMR) and positron emission tomography (PET), has revolutionized the non-invasive approach to diagnosis and prognostic stratification of cardiac diseases. Along with a full morphological and functional cardiac assessment, CMR imaging provides *in vivo* characterization of the cardiac muscle composition.[1] In particular, the presence of late gadolinium enhancement (LGE) revealing myocardial fibrosis, the development of quantitative parameters (mapping technique) and extracellular volume (ECV) exploring the myocardial interstitium,[1,2] significantly restricted the role of endomyocardial biopsy (EMB) for the evaluation of heart diseases. An outstanding example is represented by the possibility of a non-invasive diagnosis in clinically suspected myocarditis with acute onset following the Lake Louise criteria by Friedrich *et al.* in 2009,[3] updated in 2018.[2] Furthermore, myocardial strain can reveal subtle systolic dysfunction in patients with clinically suspected myocarditis presenting with apparently normal ejection fraction.[4] Another setting of interest is represented by sarcoidosis where histological confirmation is mandatory to reach the diagnosis of cardiac and/or extracardiac involvement. In patients with cardiac sarcoidosis, 18F-fluorodeoxyglucose (18F-FDG) uptake at PET reflects the presence of tissue inflammation, representing a useful tool for suggesting myocardial involvement and monitoring specific treatment response.[5]

Therefore, it emerges the need to re-define the current role of EMB for diagnostic work-up and management of cardiovascular diseases. The recently published position statement on EMB by Seferović *et al.*[6] represents a milestone in this perspective and deserves important considerations.

Current role of endomyocardial biopsy

Endomyocardial biopsy still represents the gold-standard technique to reach a definite as well as an aetiological diagnosis, providing important prognostic implications and guiding aetiology-directed therapy.[7,8] Moreover, the development and application of immunohistochemistry and polymerase chain reaction (PCR) analysis to standard histologic evaluation has enhanced the diagnostic accuracy of this technique.[9] Viral search by PCR analysis on cardiac specimens is an essential step in the evaluation of candidates to immunosuppressive therapy, which currently lacks conclusive prognostic evidence and confers an increased risk of major complications if specific contraindications are not ruled out prior to treatment initiation (i.e. latent infections, lack of exclusion of ongoing infections in the target organ).

Endomyocardial biopsy is currently considered in the work-up of patients with acute heart failure (HF) or ventricular arrhythmias of unknown aetiology, non-ischaemic dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy, clinically suspected myocarditis, storage diseases, infiltrative diseases (amyloidosis), sarcoidosis and cardiac masses.[7,8] However, mostly due to its invasive nature and the lack of specific clinical trials and guidelines, clinical indications to perform EMB were based on expert opinions, often heterogeneous worldwide and changing over time so far. In a recent issue of this Journal, Seferović *et al.*[6] presented a position statement on EMB derived from the combined efforts of the Trilateral Cooperation Workshop of a multidisciplinary group of experts in cardiomyopathies and cardiovascular pathology of the Heart Failure Association (HFA) of the European Society of Cardiology, Heart Failure Society of America (HFSA) and Japanese Heart Failure Society (JHFS). This document harmonises previous expert opinion documents and position statements from single societies in a unique

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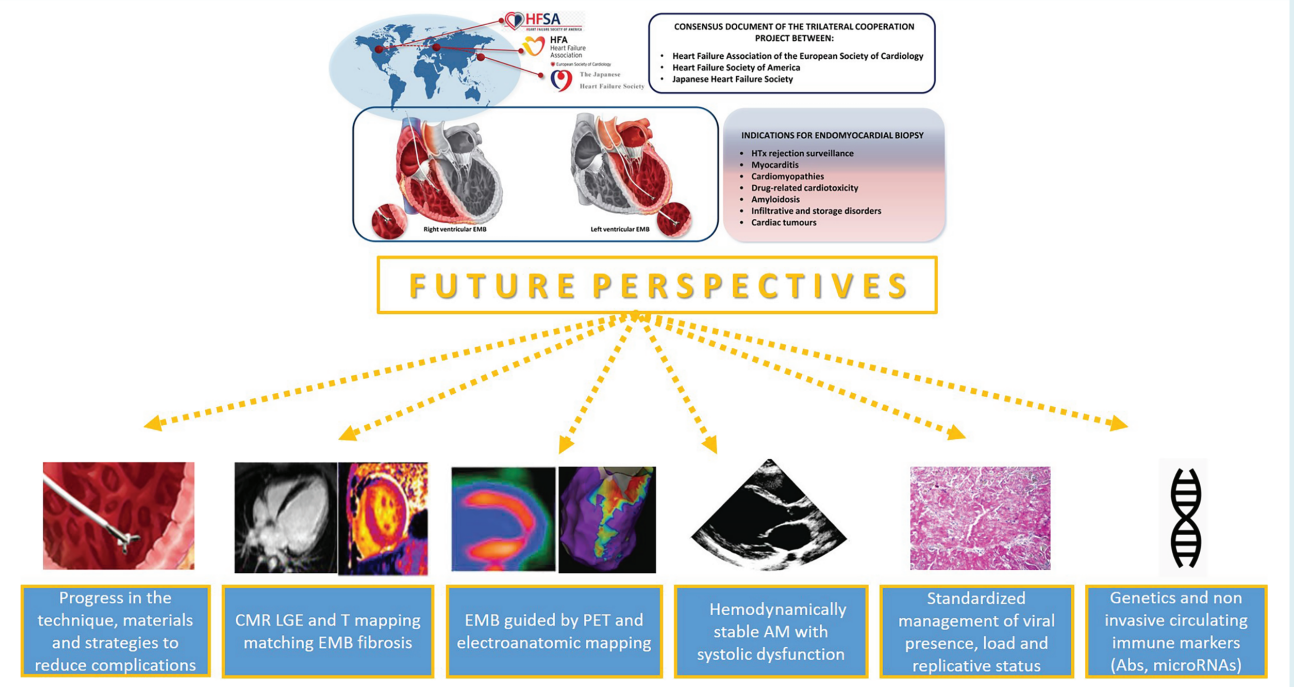

Figure 1 Clinical indications to endomyocardial biopsy (EMB) and future perspectives. Ab, antibodies; AM, acute myocarditis; CMR, cardiac magnetic resonance; HTx, heart transplantation; LGE, late gadolinium enhancement; PET, positron emission tomography. Modified from Seferović *et al.*[6]

perspective from the main international Societies of Cardiology. For the first time, this paper offers an updated reference for solid, shared clinical indications for EMB at a global level. This position statement has the merit of paving the way for a more standardized use of EMB in clinical practice and provides an opportunity to identify open issues to be addressed in future official intersociety guidelines with the acquisition of new dedicated evidence (*Figure 1*).

Endomyocardial biopsy: procedural issues

The most immediately evident issue related to EMB is how to select the best site of sample collection in the heart and whether biventricular EMB should be routinely considered to increase the diagnostic accuracy. It has been suggested that ≥5 samples should be taken from different sites in both ventricles in order to increase the diagnostic yield.[8,10] However, a patient-tailored approach based on the clinical suspicion and the pre-test probability of pathology remains a target to be addressed in the next future. While the diagnostic accuracy of EMB is high in diffuse cardiac diseases, such as cardiac amyloidosis, even when few cardiac samples are analysed, collection of specimens from multiple cardiac sites might be considered in focal diseases where the rate of false negative results is high (up to 75% in sarcoidosis).[11] Although this could be a valuable strategy to reduce the risk of sampling error, increasing the number of collected samples is paralleled by a higher risk of complications.[12] For this reason, third-level imaging techniques and intra-cardiac electro-anatomic mapping might be used in focal cardiac processes (e.g. sarcoidosis or myocarditis) to guide the best cardiac site and ventricle for EMB.[5] Pre-operative imaging may identify the sites with myocardial fibrosis (CMR LGE and T1 mapping), cardiac oedema and inflammation (CMR T2 mapping and 18F-FDG PET)[1] and the use of intra-procedural electroanatomic mapping may detect ventricular segments with fragmented or low voltages.[5] Although these findings are not disease-specific and reflect common responses to myocardial injury, they might help in selecting the best cardiac chamber (left vs. right ventricle) and site (most diseased area) for sample collection[5] and minimize the risk of complications with patient-tailored pre-procedural planning. Although promising, further studies on the ability of imaging techniques to guide EMB are required, including analysis of the improvement of diagnostic accuracy and cost-effectiveness compared to the current approach. Safety remains a major concern when performing EMB, patients may have large ventricles with thin walls and others are often very young patients, especially in the setting of myocarditis. While safety is also dependent on the experience of the centre and of the operator, miniaturization of bioptomes may improve the safety of left ventricular EMB. Smaller-sized (3 Fr) bioptomes allow for left ventricular EMB via 5 Fr sheaths also from radial approach in selected cases. Moreover, radial access has been shown to be associated with high success rates with the use of smaller sheaths, guiding catheters and bioptomes, possibly leading to fewer access-site bleeding complications compared to the femoral access.[13] Future prospective studies are warranted to assess the safety of performing EMB with modern technical approaches.

For the abovementioned reasons, patients with a potential indication for EMB should be referred to high-volume centres with specific expertise in the collection of cardiac samples to minimize the risk of complications. Moreover, tissue analysis should be performed by an experienced cardiac pathologist in order to provide high-quality interpretation of histological findings. The clinical indications for EMB should be carefully evaluated by referral centres, guided also by the position statement by Seferović *et al.*[6] This approach may reasonably increase the appropriateness and safety of the procedure and promote the diffusion of EMB as a fundamental tool to reach a diagnosis of certainty.

Endomyocardial biopsy: clinical indications and controversial scenarios

One of the most important aspects of the position statement by Seferović *et al.*[6] is the worldwide identification of nine specific clinical scenarios in which EMB should be considered to reach the final diagnosis and/or to guide decision-making and therapeutic options. Among all indications, clinically suspected myocarditis and non-ischaemic DCM represent particularly challenging settings due to their polymorphic clinical presentation and evolution.[12] In our opinion, in these patients, a careful candidate selection with a stepwise approach is essential. In detail, we do support a comprehensive approach including a careful patient's history collection, clinical examination and non-invasive imaging exams including electrocardiography, echocardiography, CMR, and, in specific cases, genetic testing, PET, or cardiac scintigraphy with bone tracers. This approach to EMB indications is also recommended by the 2021 guidelines for the diagnosis and treatment of acute and chronic HF from the European Society of Cardiology.[14] In case of inconclusive results from non-invasive tests, we consider haemodynamically stable non-ischaemic DCM patients without significant improvements in terms of left ventricular reverse remodelling under optimal medical therapy, as potential candidates for EMB. In haemodynamically stable patients with clinically suspected myocarditis and normal left ventricular function, we suggest to consider EMB if persistently or relapsing increased serum troponin values or frequent ventricular arrhythmias are present. In those contexts, the value of EMB lies in the ability to guide diagnosis and immunomodulation strategies based on histopathological and immunohistochemical analyses, combined with the evaluation of viral presence in the heart via PCR analysis.[9] However, in the past, routine search for viral genome presence was debated with controversial recommendations among Japanese, American and European Societies of Cardiology. Of note, the new intersocietary document[6] underlines the need to investigate viral presence in cardiomyocytes to guide therapeutic strategies. Finally, EMB can be the only tool able to reach a final diagnosis in haemodynamically stable patients with a hypertrophic phenotype and HF having clinical and instrumental features suggesting the presence of hypertrophic cardiomyopathy 'phenocopies' such as cardiac amyloidosis.[15]

In all abovementioned scenarios, EMB is expected to be highly informative towards ongoing mechanisms of cardiac damage such as the presence, magnitude and type of inflammatory infiltrates potentially amenable to specific treatments (i.e. giant-cell myocarditis), active viral replication, infiltrative or storage conditions, toxic injuries, ventricular derangement and alterations of cardiomyocytes.

Finally, despite being a valuable tool, EMB should be used in selected cases with solid clinical indication for a number of reasons: (i) its accuracy is not 100% and inconclusive results are encountered in clinical practice, (ii) EMB is associated with a modest, but still relevant, risk of potential major procedural complications, (iii) the presence of mild myocardial histological changes is not always clinically relevant and does not address a specific therapeutic approach, and (iv) the lack of cardiac pathologists with experience in the interpretation of histological findings restricts EMB diffusion. Therefore, EMB results should be integrated and interpreted in light of medical history, clinical features and a thoughtful non-invasive assessment of patients to derive the highest clinical benefit from histological findings.

Future perspectives

Although a consensus exists about the need for EMB in clinically suspected myocarditis with fulminant onset with cardiogenic shock or acute HF and left ventricular dysfunction or life-threatening arrhythmias,[10] many uncertainties remain concerning the optimal management of haemodynamically stable patients with non-ischaemic left ventricular systolic dysfunction and clinically suspected first episode of myocarditis, recurrent myocarditis, or persistently elevated troponin values. In those clinical settings, whether EMB should be performed and its best timing are still unclear, and need to be further investigated.

In our opinion, EMB gains particular relevance (i) in acute cardiac settings, refractory to standard therapies, (ii) in patients who cannot undergo non-invasive assessments (i.e. CMR not feasible because of frequent arrhythmias, etc.), (iii) for surveillance indications (i.e. reject after heart transplantation), and (iv) in selected cases of chronic haemodynamically stable patients with inconclusive non-invasive approaches and suspicion of inflammatory disease (i.e. persistently or relapsing increased serum troponin values, frequent ventricular arrhythmias, development of new-onset severe systolic dysfunction) or hypertrophic cardiomyopathy 'phenocopies'. This approach translates into a lower number of patients who are potential candidates for EMB, avoiding taking unnecessary procedural risks, and into the identification of clinical settings where this procedure has the most favourable risk–benefit balance.

The potential combination of tissue characterization with LGE or increased T values/ECV at CMR with the knowledge of the genetic background might be a further promising field to explore in the future. Indeed, the combined role of inflammation and genetics in inducing cardiac remodelling need to be further investigated. Some genetic variants seem to be associated with specific patterns of myocardial inflammation/fibrosis and cardiomyocyte injury.[5] In this perspective, further studies are required to investigate the correlation between myocardial fibrosis identified

by CMR and EMB. This is an intriguing field, especially in presence of specific mutations that can be found in overlap with different cardiomyopathies and affect clinical management.[16] Novel insights into disease-specific mechanisms of cardiac injury might come from circulating microRNAs and analysis of T-cell responses that have recently proven useful in differentiating clinically suspected myocarditis with acute infarct-like onset from myocardial infarction.[17] Although they cannot provide aetiological information (i.e. virus-positive vs. virus-negative myocarditis), circulating microRNAs might serve as future non-invasive test to guide the diagnosis, especially in patients with pseudo-infarct presentation.

Finally, it has been acknowledged that a team-based approach is fundamental when managing patients with an indication for EMB and should include centres with specific expertise in evaluating patients with cardiomyopathies, performing EMB and interpreting the immunohistopathological and bio-molecular results. Reference centres play a key role in selecting EMB candidates and guiding the final diagnosis and subsequent clinical and therapeutic choices. Therefore, the creation of a 'hub–spoke' network should be fully supported in the near future.

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