# The role of endomyocardial biopsy in the diagnosis of cardiomyopathies

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**Though many publications in the field of myocarditis and cardiomyopathies have renewed interest in the value of endomyocardial biopsy, its role in the work-up of patients with cardiomyopathies, idiopathic arrhythmias and even ischemic heart disease, is still debated. Since its introduction in 1963 the technique has been developed with current routine use of a biventricular and even atrial approach. At the same time immunohistochemistry and molecular biology studies have greatly enhanced the information obtainable from myocardial samples. The authors report their experience and briefly review the pertinent literature on the current use of endomyocardial biopsy in the diagnosis and treatment of dilated, hypertrophic and restrictive cardiomyopathy, of idiopathic arrhythmias and in ischemic heart disease.**

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## Introduction

Endomyocardial biopsy (EMB) was introduced into clinical practice by Konno and Sakakibara in 1963[1,2], and gradually became a recognized, valuable diagnostic investigation. These developments were made possible by its application not only to the right but also to the left ventricle[3,4] and to the atrial septum[5,6] and by the analysis of biopsy specimens by immunohistochemical and molecular biology techniques[7,8]. Actually different types of cell death, i.e. necrosis and apoptosis, and the presence of myocyte proliferation, can be histologically recognized[9-11] and specific infectious agents, not revealed by serologic tests, detected by polymerase chain reaction (PCR)[12-15].

Familial and sporadic forms of cardiomyopathies due to structural abnormalities of sarcomeric or cytoskeletal proteins have been recognized[16,17]. Unsuspected storage diseases mimicking hypertrophic cardiomyopathy (HCM) and due to either mitochondrial or lysosomal enzyme deficiency, are increasingly identified and now treated[18-21].

Recently many publications in the field of myocarditis and cardiomyopathies have renewed interest in the use of EMB to diagnose specific and potentially treatable diseases; however, the role of EMB in the work-up of patients with cardiomyopathies, idiopathic arrhythmias and even ischemic heart disease, is still not well defined. In fact doubts are still raised about its poor diagnostic accuracy, due to high sampling error, and the risks of major complications like free-wall perforations and cardiac tamponade[22]. On the other hand the development of new therapies for specific myocardial disease, administrable on the basis of histological diagnosis, has given adjunctive value to the diagnostic contribution of EMB.

In this article we report the experience of our group in the performance and analysis of EMB, with a concise review of the pertinent literature.

## Personal experience

From 1983 to March 2002 we have performed 2747 EMB procedures: 1481 from the right ventricle, 1144 from the left ventricle, and 122 from the atrial septum (Fig. 1). The rate of complications has been very low with 10 right ventricular free-wall perforations (0.4%), all resolved by spontaneous (6 cases) or surgical (4 cases) repair, and no death. In most cases the initial diagnosis has been changed or specified through the histological examination accompanied by immunohistochemical, molecular biology analysis, electron microscopy evaluation, and by immunologic studies (Fig. 2).

Four to six endomyocardial samples obtained from each patient were processed for histological and immunohistochemical studies. For histology, multiple 5-μ thick

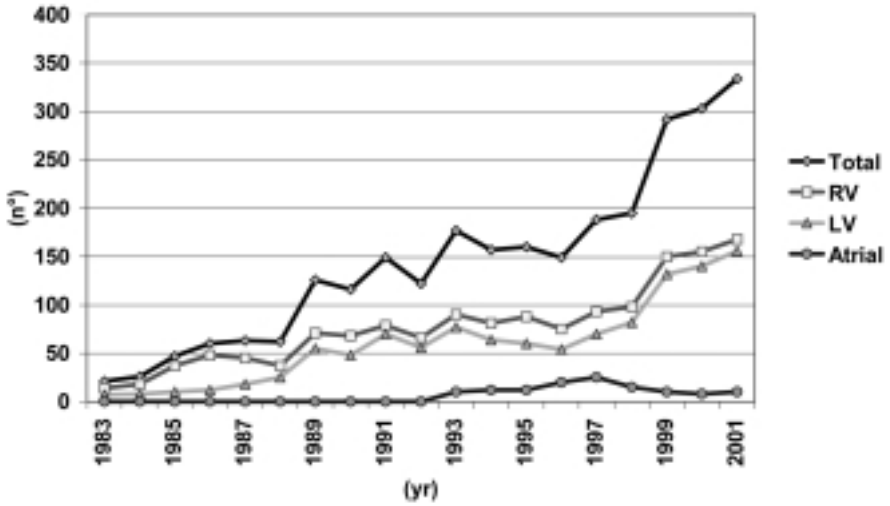


**Figure 1.** *Number of endomyocardial biopsies performed per year. LV = left ventricular; RV = right ventricular.*

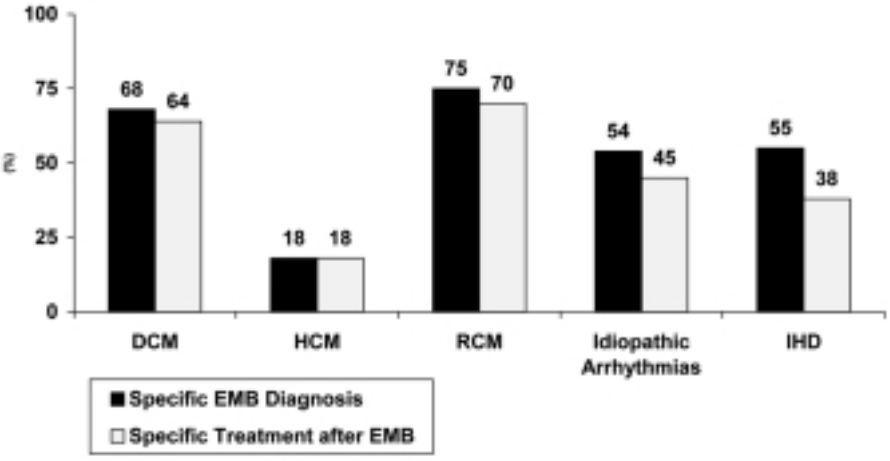


**Figure 2.** *Impact of endomyocardial biopsy (EMB) in the diagnosis and treatment of cardiomyopathies, idiopathic arrhythmias and ischemic heart disease (IHD). DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; RCM = restrictive cardiomyopathy.*

sections were cut, processed with standard staining (hematoxylin-eosin, Miller's elastic Van Gieson, Masson's trichrome) and examined at light microscopy. For the histological diagnosis of myocarditis the Dallas criteria[23] were employed, integrated by immunohistochemical analysis for the characterization of the inflammatory infiltrates. Two frozen myocardial specimens for each patient were used for molecular biology studies, in particular PCR and reverse transcriptase-PCR analysis, in order to detect RNA and DNA genomes of the most common cardiotropic viruses in patients with evidence of myocarditis[15].

One sample has been processed for electron microscopy studies.

## Endomyocardial biopsy in dilated cardiomyopathy

We studied 1028 patients with a diagnosis of dilated cardiomyopathy (DCM) on the basis of clinical data and non-invasive studies. All had normal coronary arteries, no valve disease and no systemic disease that could explain the cardiac dilation and dysfunction. In 67% of these patients EMB allowed to reach a specific diagnosis and in 64% to define a more appropriate treatment (Fig. 3). In particular myocarditis was diagnosed in 57% of patients, DCM due to hormonal imbalance (growth hormone deficiency or hypothyroidism) in 5%[24,25], alcoholic DCM in 3%, and catecholamine cardiomyopathy (occult pheochromocytoma, cocaine abuse) in 2% of the cases[26].

The diagnosis of myocarditis was obtained on the basis of the histological Dallas criteria, and lately by immunohistochemistry of inflammatory infiltrates and PCR for the most common cardiotropic viruses (Fig. 4). The systematic application of this approach contributed to the diagnostic accuracy of EMB and to the treatment of myocarditis: in fact specific therapies could now be administered to myocarditis patients on the basis of their virologic and immunologic profile[27-36].

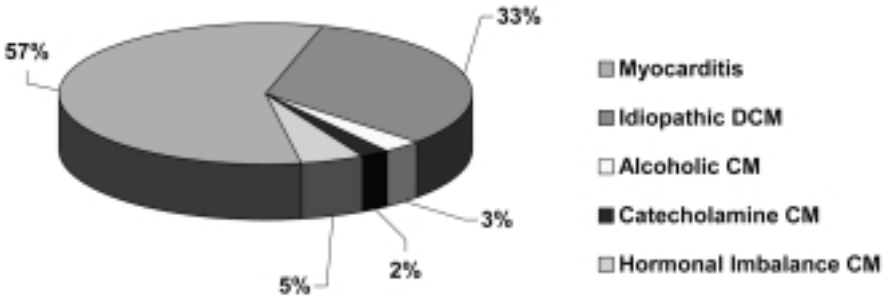


**Figure 3.** *Endomyocardial biopsy diagnosis in patients with dilated cardiomyopathy (DCM). CM = cardiomyopathy.*

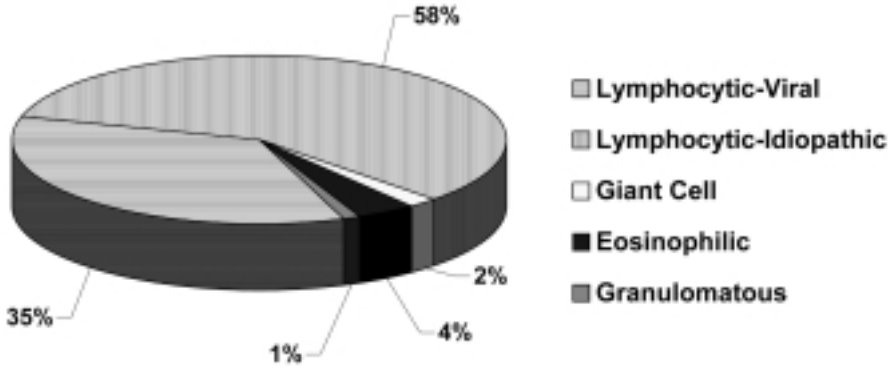


**Figure 4.** *Prevalence of myocarditis revealed by endomyocardial biopsy.*

## Endomyocardial biopsy in hypertrophic cardiomyopathy

The diagnosis of HCM is actually made by non-invasive tools including cardiac two-dimensional echocardiography and magnetic resonance imaging. Nevertheless several entities such as infiltrative (i.e. amyloidosis and granulomatous myocarditis)[37] and storage (i.e. glycogenosis, mucopolysaccharidosis, etc.)[38,39] diseases may mimic HCM. Fabry disease, particularly in the "cardiac variant" where the heart is the sole organ involved, can be clinically and morphologically indistinguishable from a HCM, as increased ECG voltages with repolarization abnormalities and cardiac two-dimensional echo and magnetic resonance imaging changes, consistent with either symmetric or even asymmetric left ventricular hypertrophy, are commonly observed[40-42]. Large studies report Fabry disease contributing to 3% of patients with idiopathic left ventricular hypertrophy[43] and up to 9% of patients with non-obstructive HCM[44]. Assessment of α-galactosidase A activity in the peripheral lymphocytes should be obtained in all patients with idiopathic left ventricular hypertrophy or with a first diagnosis of HCM, in particular in adult age[45,46]: in cases with low enzymatic levels an EMB is required for a definite evaluation. The suspect of non-HCM may rise from the evidence of a concomitant prominent thickening of the atrial septum and the right ventricular free wall in addition to the hypertrophy of left ventricular walls commonly observed in HCM patients.

In the 102 patients with suspected HCM studied through a biventricular EMB, in 18 (17.6%) histology revealed a different diagnosis: Fabry disease in 10 patients (9.8%), and granulomatous myocarditis in 8 (7.8%). The last two entities, even if relatively rare, are both treatable as enzyme-replacement therapy is now available for Fabry disease[19,20,47] and granulomatous myocarditis can benefit from steroids and immunosuppressive agents[48].

## Endomyocardial biopsy in restrictive cardiomyopathy

Various entities can be recognized as restrictive cardiomyopathies as they may combine the characteristic hemodynamic pattern of diastolic deep-plateau with thickened ventricular walls, atrial dilation and preserved cardiac contractility. In fact non-infiltrative (such as idiopathic restrictive cardiomyopathy, HCM, scleroderma), and infiltrative (such as amyloidosis, sarcoidosis) disorders, endomyocardial (endomyocardial fibrosis, hypereosinophilic syndrome, carcinoid heart syndrome) and storage (hemochromatosis, Fabry disease, glycogen storage disease) diseases and even metastatic cancers can give rise in their course to a restrictive cardiomyopathy[49].

In addition, whenever a biventricular compromise occurs, despite the introduction of new echocardiographic methods[50], restrictive cardiomyopathy can become difficult to differentiate from a constrictive pericarditis.

In our experience EMB has been often required to clarify the organic substrate of a restrictive cardiomyopathy and the differentiation from the various entities has been crucial toward the definition of appropriate treatment and prognosis. We have performed biventricular EMB in 60 patients with suspected restrictive cardiomyopathy: amyloidosis was the final diagnosis in 25 patients (41%), eosinophilic endomyocardial disease (including endomyocardial fibrosis and Churg-Strauss syndrome) in 18 patients (30%), HCM with right ventricular involvement in 6 patients (10%), sarcoidosis and hemochromatosis in 4 patients (7%), scleroderma in 3 patients (5%)[51-54].

## Endomyocardial biopsy for lone cardiac arrhythmias

Severe supraventricular or ventricular arrhythmias may manifest as unpleasant or life-threatening clinical problem in patients with an otherwise normal heart. Even sophisticated non-invasive tools such as two-dimensional echocardiography with tissue Doppler imaging and cardiac nuclear magnetic resonance are usually unable to identify the underlying organic substrate, while invasive procedures including cardiac catheterization and coronary angiography give usually normal results. We have studied 263 patients with idiopathic ventricular arrhythmias or lone atrial fibrillation through a biventricular and, in 89 patients, even an atrial biopsy with no complication. Results of EMB have provided consistent impact on the identification of myocardial pathology and in defining the appropriate treatment and the likely prognosis. In particular focal myocarditis or cardiomyopathies localized to the atrial myocardium has emerged in patients with lone atrial fibrillation[5,6,55], myocarditis or ignored hypertrophic, dilated or right ventricular arrhythmogenic cardiomyopathies have been recognized in patients with idiopathic ventricular arrhythmias or aborted sudden death[4,15,56,57]. In this regard it is important to remind the implications that a specific diagnosis may have even on patients' relatives.

## Endomyocardial biopsy in ischemic heart disease

Ischemic heart disease can be associated with a substantial myocyte loss, giving rise to acute or chronic heart failure. Left ventricular dysfunction is usually correlated with the severity and the extension of coronary artery lesions so that from the analysis of segmental wall motion a presumptive localization of the vascular territory involved can be made. However some patients exhibit a strong functional/anatomic mismatch that raises questions on the occurrence of post-ischemic events or overlapping pathologies. Various hypotheses have been forwarded including change in the gene expression and then in the synthesis of contractile proteins[58]. We have submitted to a biventricular EMB 25 patients with severe coronary artery disease, presenting with heart failure and biventricular dilation and dysfunction: in 12 patients we were able to document an autoimmune myocarditis, responsive to immunosuppressive therapy[59]. We suggested the possibility of a Dressler-like myocarditis as a sequelae of an occult intramural or a limited transmural myocardial infarction that may elicit a hypersensitivity reaction to myocardial segregated antigens in patients with specific HLA profile.

EMB may be helpful even in the differential diagnosis of patients with apparent myocardial infarction and a normal coronary angiogram[60]. In 48 patients we have found an acute myocarditis or myocardial necrosis due to cocaine abuse mimicking an acute myocardial infarction. The last entity must be suspected in particular in younger patients and can be easily recognized by the presence at optical microscopy of myocardial contraction band necrosis[61].

## Perspective role of endomyocardial biopsy in the post-genomic era

In the recent years the development of DNA microarray technology has changed the approach to the genetic component of cardiac diseases. The decrease in costs and more affordable techniques even in the presence of small amount of DNA, have made its use widespread[62,63]. The possibility to apply DNA microarray analysis on myocardial samples obtained from EMB is a new important tool in the study of familial cardiomyopathies[64] and of the genetic component of multifactorial (i.e. myocardial infarction)[58,65] or infectious (i.e. myocarditis)[66] cardiac diseases. The possibility to assess, by tissue analysis, transcriptional and post-transcriptional regulation of gene expression may be of great importance in clarifying the pathways of gene activation and of gene modifiers implied in the mechanisms that lead from a specific genotype to a specific phenotype in familial HCM and DCM. Furthermore different patterns of gene activation and expression could be responsible for the variability in the response to initial damage and subsequent treatment in both myocardial infarction and myocarditis.

A new role for EMB is also depicted by recent studies on myocardial tissue regeneration and stem cells[11,67,68]. In fact EMB may represent the fundamental approach to test the possible transposition in humans of the stem cell utilization and the subsequent results obtained in animals.

## Conclusions

In conclusion, the diagnostic value of EMB depends on the increases with right ventricular, biventricular, atrial septal sampling, with the number of samples obtained and with the number of analysis performed on the samples. The histological diagnosis should be complemented by immunohistochemical and molecular biology studies and by ultrastructural analysis. The risk of complications in expert hands is low even when several samples are obtained.

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