REVIEW ARTICLE

More than 50 Years after Konno's Development of the Endomyocardial Biopsy

A Review from the Konno Memorial Laboratory and the Cardiac Biopsy Conference

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Summary

The endomyocardial biopsy (EMB) method was first developed by Japan's Dr. Souji Konno in 1962. Since then, this technique has been used worldwide in clinical cardiology for the recognition and diagnosis of cardiomyopathies, arrhythmias, and other heart conditions. Many studies relating to the EMB have been published at the global level, including a large review by Cooper, *et al.*,[1] wherein a limited selection of Japanese papers were cited despite considerable pioneering work on the EMB having been done in Japan. Following this, the Cardiac Biopsy Conference (CABIC) organization, which was founded in Japan in 1979, conducted a nationwide survey of the English language literature on the EMB. Among the collection of 500 studies compiled, approximately 40 abstracts have been selected by the co-editors in CABIC for further discussion. This report aims to supplement Cooper's work and bring to light other prominent contributions of Japanese researchers on the EMB.

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Key words: Cardiomyopathy, Histopathological diagnosis, Electric disturbance type cardiomyopathy, Japanese studies

Fifty years have passed since Dr. Souji Konno, a young cardiac surgeon, developed the catheter-type endomyocardial biopsy (EMB) method in 1962. As Professor Shigeru Sakakibara was the chairman of cardiac surgery at the Heart Institute of Japan at that time, Konno's paper was published by these two authors.[2,3] Although the use of this invention was considered to be a safe and dependable method, the EMB was not immediately adopted outside of Japan.[4] Eventually, however, the procedure was found to be clinically useful for the recognition of rejection phenomena by taking a tissue sample of the transplanted heart. This particular technique was introduced by the Stanford group, where heart transplantation was begun, using a short-sheath bioptome inserted into the internal jugular vein.[5] It was after then that modified methods with the use of a bioptome emerged and were more widely applied in clinical cardiology care for the recognition and diagnosis of cardiomyopathies, arrhythmias, and other cardiac conditions. The utility of Konno's EMB method through proper interpretation of biopsy findings was introduced into the English literature by Professor Morie Sekiguchi,[6-8] who had performed extensive basic studies to devise a practical guide on the systematic interpretation of biopsy results. During his stay in Germany in 1970-71, he promoted the EMB in Europe and became the chairman of the International Society and Federation of Cardiology (ISFC) Cardiomyopathy Section in 1987. Recently, a large review of the EMB was released by Cooper, *et al.*, entitled the role of endomyocardial biopsy in the management of cardiovascular disease, that was compiled following gatherings of the American Heart Association (AHA), the American College of Cardiology, and the European Society of Cardiology, which incorporated 13 Japanese papers into the list of 162 articles.[1] However, several essential findings published in English by Japanese investigators were not cited; it is for this reason that Japanese studies have been selected as the focus of this review so as to complete the global recognition of biopsy work to date.

Histopathological Diagnosis by EMB

Sekiguchi first reported his foundational work on the EMB method in 1969 in which he analyzed 126 cases and described that the EMB was capable of diagnosing several specific myocardial diseases, such as glycogen storage disease, sarcoidosis, and myocarditis.[6] As there had been so few reports on the EMB at the time, most specimens

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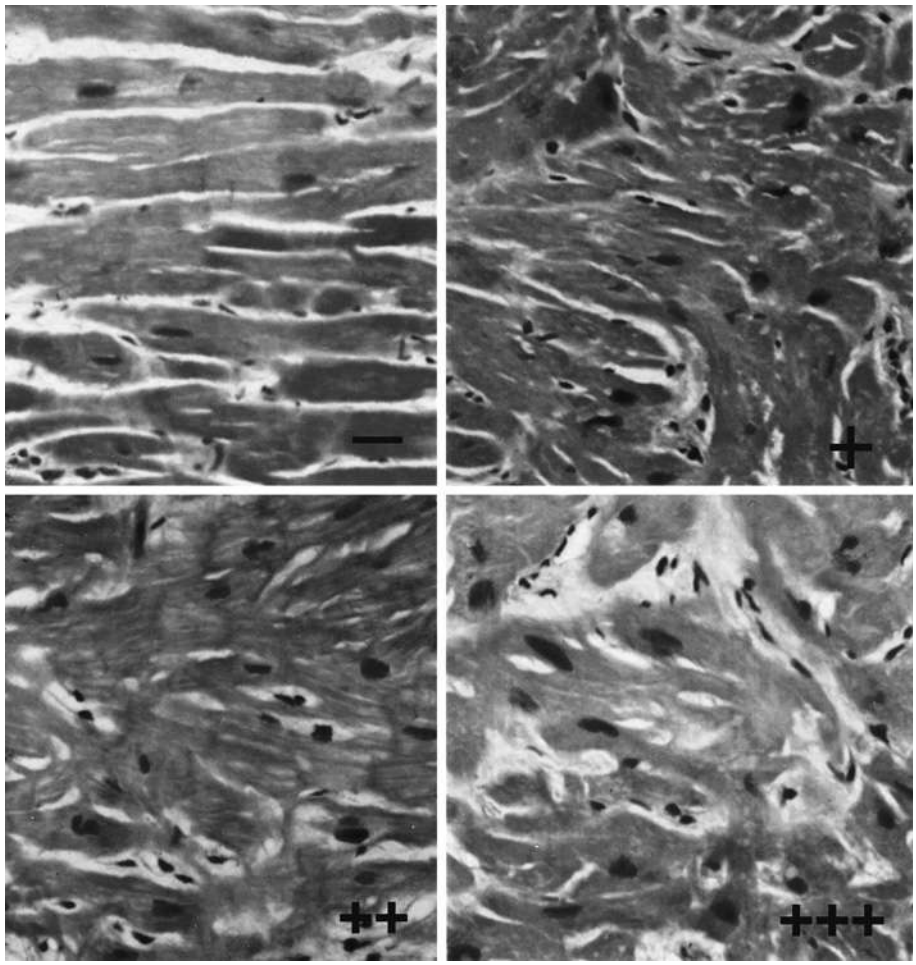

Figure 1. Representative micrographs of the bizarre myocardial hypertrophy with disorganization (BMHD) that characterizes hypertrophic cardiomyopathy. Grading of BMHD (-), (+), (++), and (+++) is presented.

showed non-contributory findings at first glance, but through his analysis, he developed a systemic histopathological classification system that considered hypertrophy of cardiomyocytes, degeneration, disarrangement and/or fragmentation of muscle bundles, interstitial fibrosis, and endocardial thickening.

Hypertrophic Cardiomyopathy (HCM)

It was firstly described by Sekiguchi, *et al.* that myocyte hypertrophy and disorganization of muscle bundles were frequently found in EMB specimens from patients with HCM and named this characteristic finding bizarre myocardial hypertrophy with disorganization (BMHD)[9] (Figure 1). Nunoda, *et al.* reported that while BMHD was observed in the EMB samples of 71% of HCM patients, this finding was rarely present in those of patients with hypertensive heart disease.[10] They calculated a sensitivity of 71%, predictive accuracy of 83%, and specificity of 89% of this finding in HCM patients. Takemura, *et al.* described that the expression of atrial natriuretic peptides in the EMB specimens of patients with HCM was related to myocyte hypertrophy, BMHD, and fibrosis.[11] Morimoto, *et al.* have presented several important concepts regarding the BMHD in apical hypertrophic cardiomyopathy (AH).[12] From the standpoint of clinical cardiology, AH differs from HCM with asymmetrical septal hypertrophy (ASH), and it is unclear whether AH represents a distinct form of HCM. The presence or absence and extent of BMHD were compared between patients with ASH or AH, in whom EMB was performed from the LV apex and from the interventricular septum. In the ASH group, BMHD of various degrees was observed in 86% of cases, whereas this finding was absent or at most limited to a very small area in the AH group ($P < 0.0001$). This comparative analysis led to the conclusion that AH differed from usual HCM with ASH from both clinical and EMB standpoints.[12]

Dilated Cardiomyopathy (DCM)

Sekiguchi, *et al.* evaluated numerous EMB specimens obtained from patients with DCM and developed a systematic method of histopathological assessment that in-

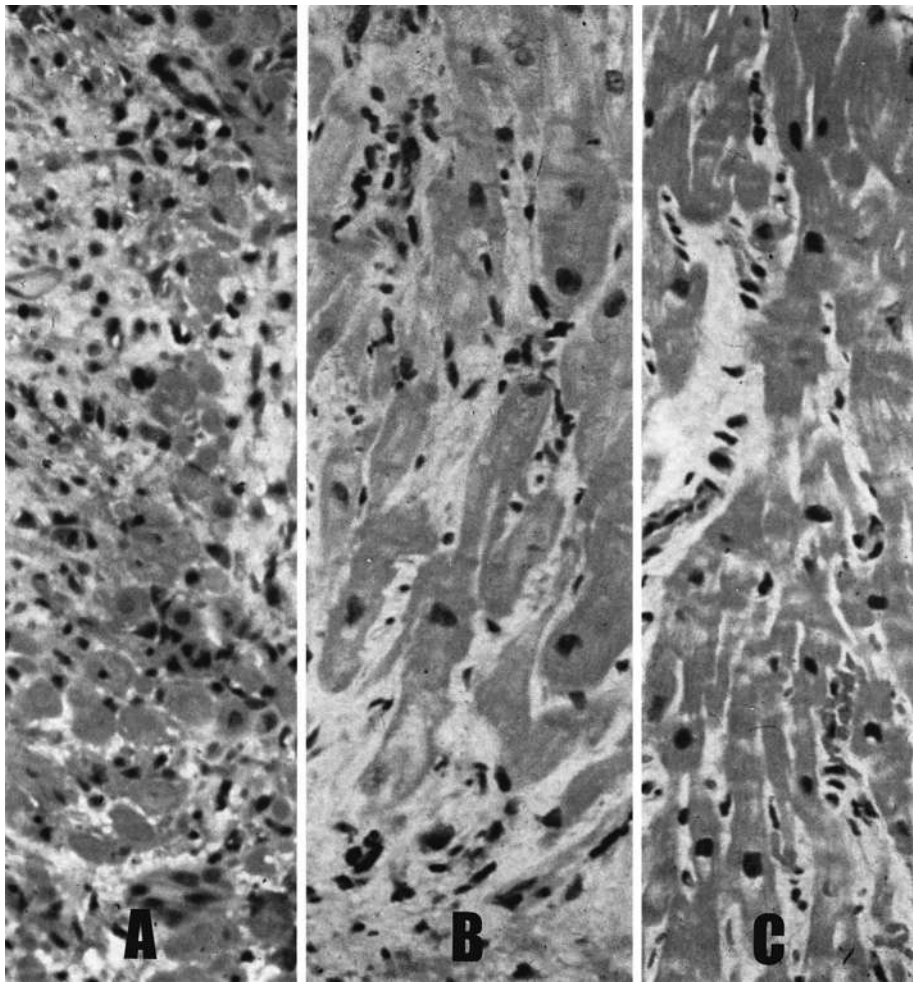

Figure 2. Examples of serial histopathologic endomyocardial biopsy findings. **A, B,** and **C** are taken from a case with acute myocarditis on whom serial biopsies were performed on the 9th (**A**), 17th (**B**), and 29th (**C**) day after disease onset.

cluded quantitative evaluation.[9] Ogasawara, *et al.* established the histopathologic contractility failure index (HCFI) through the EMB and evaluated the prognostic factors of DCM that included HCFI, ECG, and hemodynamics.[13] They concluded that a low HCFI score was related with a poor prognosis in DCM. The ultrastructural changes in EMB samples have also been analyzed by several investigators.[14,15] Mitochondrial degeneration, widening and increase in sarcotubular systems, fragmentation and scarcity of myofibrils, and widened intercalated discs are frequently disclosed in DCM.[14]

Electric Disturbance Type Cardiomyopathy (ECM)

There have been cases of cardiomyopathy that were not easily classifiable into hypertrophic or dilated types, that often showed ventricular arrhythmia, right or left bundle branch block, intraventricular conduction disturbance, atrioventricular conduction disturbance, or sinus node dysfunction (i.e., sick sinus syndrome).[16] The EMB in such cases revealed advanced myocardial degeneration or fibrosis. The description "arrhythmia-conduction disturbance type of cardiomyopathy" was considered to be appropriate for this category of myocardial disease. However, due to this finding appearing only in the monograph book entitled "Cardiomyopathy Update 3",[17-20] it was not included in Cooper's description but merits attention on a global level. Then, Sekiguchi, *et al.* published additional studies on this disease and proposed the simpler term of ECM.[21] In a series of 573 cardiomyopathy biopsies, 46% were hypertrophic, 30% were dilated, and 15% were classified as ECM.

Myocarditis

The histopathological diagnosis of acute, subacute, or convalescent myocarditis was established by Sekiguchi, *et al.* in accordance with the histopathological findings of myocarditis (HFMC) by the EMB.[22] They constructed a list of HFMC, in which it was noted the pertinent findings that characterized each stage of myocarditis development, i.e., acute, subacute, convalescent, and healed, through se-

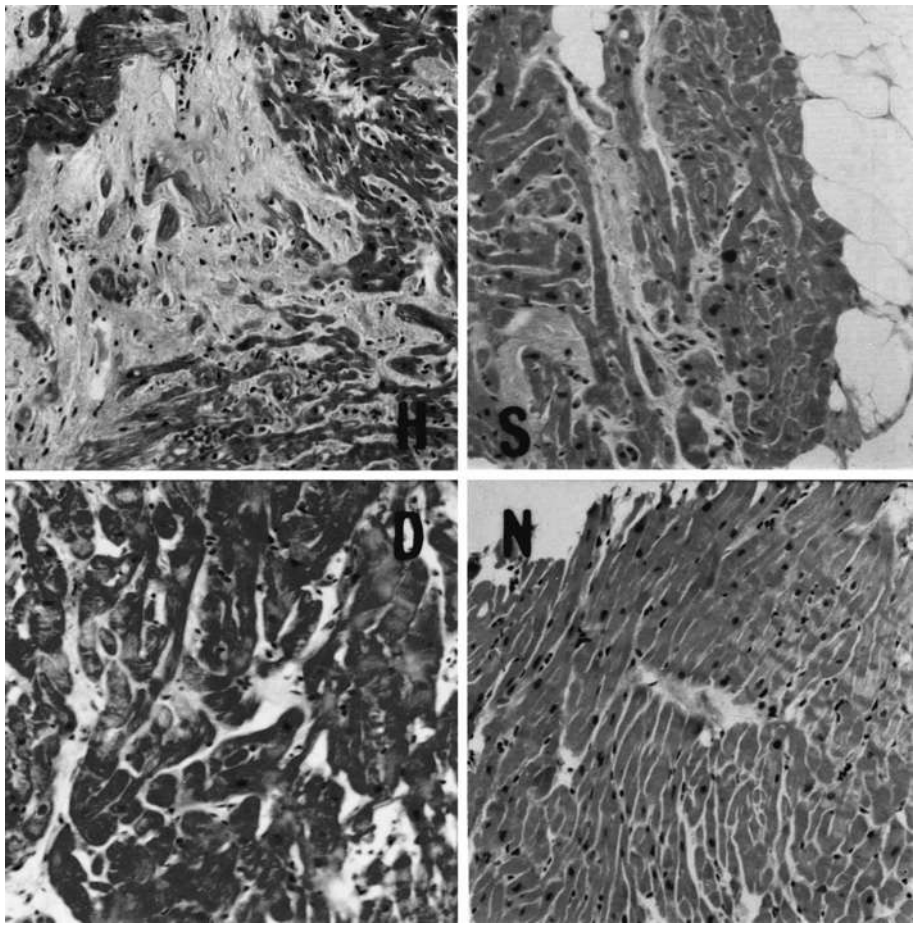

Figure 3. Model for histopathologic categorization of the presence or absence of postmyocarditic change. It is advisable to classify biopsy findings into the most appropriate category in the absence of any clinical information. **H** indicates highly suggestive; **S**, slightly suggestive; **D**, doubtful; and **N**, not suggestive.

rial endomyocardial biopsies (Figure 2). The Dallas criteria for the histopathological diagnosis of myocarditis, on the other hand, were created by pathologists dealing with myocarditis.[23,24] The important point in using the Dallas criteria is that the clinician must perform repeated EMB procedures to arrive at an appropriate diagnosis. However, this is not always feasible in routine practice, which is the reason why we have adopted the HFMC that can be utilized for patients receiving only one biopsy during the course of the disease[25] (Figure 3). Therefore, the terms "ongoing" and "healing" myocarditis have been replaced by "acute," "subacute", "convalescent", and "healed." Figure 3 represents a useful guide for determining HFMC.

Chronic Myocarditis

As chronic myocarditis lacks a concise definition, the term chronic myocarditis has been adopted to describe its various conditions. The Dallas criteria for myocarditis do not address this issue.[23,24] Thus, the Japanese Circulation Society organized a taskforce committee in order to establish appropriate guidelines.[26] EMB diagnosis of chronic myocarditis can be summarized as accumulation or infiltration of large and/or small round cells in the myocardium associated with myocytolysis or necrosis of adjacent myocytes. Diffuse interstitial fibrosis, irregular replacement of myocardial fibrosis, and fatty infiltration are also observed. It was the committee's hope that these definitions would be applied in both the clinical and histopathological recognition of this disease.

Sarcoidosis

It has been indicated that the ability for detecting non-caseating epithelioid granulomas by EMB is rather limited.[27] Only 22.2% of patients in whom the presence of cardiac sarcoidosis was strongly suspected due to other clinical features showed positive findings (granuloma) in their EMB samples.[28] Uemura, *et al.* revealed in a prospective analysis of 26 cases that the diagnostic settlement of cardiac sarcoidosis through the detection of granulomas amounted to approximately 19.2% of the cases studied.[29] Meanwhile, Yoshida, *et al.* reported that cardiac sarcoidosis was frequently found in patients with advanced atrioventricular block; 10 of 89 patients (11.2%), which could not be diagnosed without the EMB.[30] It was reported by Mikami, *et al.* that the electron microscopic study disclosed basal lamina layering (BLL) of the capillaries in the skeletal muscle of sarcoidosis patients.[31] Sekiguchi, *et al.* found BLL in EMB specimens from 77.8% of patients

with sarcoidosis.[28] They concluded that sarcoidosis with microangiopathic processes could exist and these were an important element of the disease. Morimoto, as a member of the Japanese Circulation Society Joint Working Group, established an EMB study team and has since postulated several key findings in the field of sarcoidosis.[32]

Electron Microscopic Studies

Sekiguchi described various findings of electron microscopy (EM) in the Bulletin of the Heart Institute during his pioneer work on the EMB.[33] Some characteristics, such as mitochondriosis, size variation, and degenerative changes, were noteworthy findings reflecting the metabolic retardation of the myocytes. Later, fibrillar disarray was considered to represent the nature of hypertrophic cardiomyopathy, which became a topic of EM work outside of Japan. The ultrastructural contractility failure index (UCFI) has been proposed for evaluating the hemodynamic disability and prognosis of patients.[34] As it is difficult to objectively evaluate the severity of interstitial pathology by means of ultrastructural evaluation, it can be said that intracellular, as well as capillary, changes can at least be assessed semi-quantitatively for EM evaluation of the diseased myocardium. According to the UCFI, there are six factors which interfere with the contraction of cardiac myocytes: 1) fragmentation of the myofibrils; 2) swelling of the mitochondria, and especially lysis of the cristae; 3) intracellular edema; 4) widening of the intercalated discs; 5) swelling of the capillary endothelium; and 6) accumulation of degenerating substance. When changes in the above-described 6 factors are semi-quantitatively evaluated, the sum of each grading may be regarded as an estimation of contractile phenomenon of cardiac mechanical performance. The UCFI was well correlated with left ventricular ejection fraction and mean circumferential shortening rate, and a high UCFI value was closely associated with increased mortality.[34] Some other EM papers were presented.[15,35,36]

EMB Recognition of Pediatric Diseases

We earlier described an infant in whom myocarditis was confirmed by EMB.[37] Sekiguchi, *et al.* analyzed the ultrastructural aspects of EMB samples from pediatric patients with endocardial fibroelastosis and identified a relationship with long-term prognosis.[38] Lastly, we proposed a grading system for the degree of myocyte hypertrophy in biopsy specimens at various pediatric ages, which may be useful for EMB assessment of pediatric cases.[39]

Cardiac Biopsy After Heart Transplantation

The EMB is a well-known an essential method in the evaluation of acute rejection following heart transplantation. As the first such transplant was not well received in Japan due to medico-legal reasons, the progress of heart transplantation was long delayed until 2008. Accordingly, Japanese reports on the subject are fewer in number.[40,41]

Complications of the EMB Procedure

Hiramitsu, *et al.* reported the results of a national survey concerning the EMB procedure conducted at Japanese health institutions, wherein 19,964 cardiac biopsies at 134 centers were assessed for major EMB complications.[42] The rate of right or left ventricular perforation was 0.7% (147 cases), while the mortality rate due to ventricular perforation was 0.05% (10 cases). Mortality showed no statistically significant difference between right and left ventricular perforations ($P = 0.22$).

A New Approach to analyze EMB Samples: Molecular Biological Investigation

Pathogenesis of cardiomyopathy has been elucidated by detection and analysis of some proteins or gene formation. Several investigators disclosed that virus genome was detected in EMB samples from DCM patients and suggested a link between viral myocarditis and DCM.[43,44] Moreover, Seko, *et al.* analyzed the expression of T cell receptor genes as well as enterovirus genomes by PCR using EMB samples from DCM patients.[45] They suggested that a cell-mediated autoimmune mechanism triggered by virus infection may play a role in the pathogenesis of DCM. Another several studies have been reported on the investigation of pathogenesis by analyzing some proteins or genes including dystrophin, tenacin C, troponin T, myosin heavy chain and glycolipid in EMB samples.[46-50]

The Difference Between Japan and Other Countries in the Attitude Toward EMB and Cardiomyopathies

As the EMB method was first developed in Japan, this technique has been widely used for the diagnosis of cardiomyopathies in clinical cardiology in our country.[2] The EMB is actively employed as a useful diagnostic tool for cardiomyopathies in Japan,[7,32] while it may be prudently applied for these diseases except for transplanted heart to recognize rejection phenomena in United States or European countries.[8,51] As regarding the differences of the disease concept, chronic myocarditis is defined in Japan and European countries as the condition which indicates chronic heart failure with prolonged inflammation of the myocardium,[26,52] but there is no notion of this disease in United States.[23,24] Further, the term "dilated-phase HCM" is used in Japan for the condition that indicates dilatation of cardiac ventricles in certain patients with HCM,[53] but this term is unused in United States and European countries in which "end stage HCM" is adopted.[54,55]

At any rate, however, it is common understanding that EMB is important for recognition of cardiomyopathies.

Forming a Nationwide Study Group on EMB

In 1979, Sekiguchi organized a study group on clinical cardiac biopsy, tentatively named the Clinical Biopsy

Study Group, and thereafter a Cardiac Biopsy Conference has been held every year in Japan. The name of this special conference is now called the Cardiac Biopsy Conference, abbreviated as CABIC. Approximately 200 participants from all over Japan attend the meeting, which covers all aspects of EMB study. Recently, the conference's format has been changed to not only describe the histopathological aspects of EMB, but also to analyze correlating work with the use of MRI and PET. CABIC now maintains its initial principle of cardiac biopsy study in addition to including the modern aspects of non-biopsy diagnosis and assessment of heart muscle disease. This group of professionals is now spreading to a wider field in that the diagnosis of cardiomyopathies should not be restricted to histopathological diagnosis; for example, the value of histopathological determination by EMB was only useful in 20% of cardiac sarcoidosis patients studied.[28] Indeed, CABIC members are involved in the study of many other categories of cardiomyopathic diseases, and numerous reviews have been made by the editing members of this review, as listed on the CABIC homepage.[56] We first began compiling English language EMB papers from Japan in 2008. As the total number of publications has exceeded 500, it was thought to be impossible to review the entirety, and so we selected approximately 40 essential reports in the current review. The titles of the remaining publications can be found on the CABIC homepage, which we expect to become a center for EMB-related information.

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