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Editorial

Call for action to establish standard diagnostic and therapeutic approaches for myocarditis☆

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> "*You can't connect the dots looking forward; you can only connect them looking backwards. So you have to trust that the dots will somehow connect in your future. You have to trust in something — your gut, destiny, life, karma, whatever. This approach has never let me down, and it has made all the difference in my life.*"
>
> [~Steve Jobs [1]]

Guideline-directed medical therapy (GDMT) improves the outcome of patients with the heart failure (HF) with reduced left ventricular ejection fraction (rEF). Taking the etiology of HF into account is important for reducing the heterogeneity of HF and assisting in identifying patients at risk of adverse outcomes among patients with HFrEF [2]. Pavlicek et al. showed that patients with chronic myocardial inflammation were at increased risk of receiving an implantable cardioverter defibrillator (ICD) for primary prevention and half of all ICD recipients experienced ventricular arrhythmias requiring ICD therapy [3]. This finding suggests the clinical significance of detecting myocardial inflammation. Persistent myocardial inflammation causes myocardial damage and lethal ventricular arrhythmia. Ongoing myocardial damage detected by creatinine kinase predicts deterioration in idiopathic dilated cardiomyopathy [4], and troponin measurement is more useful for predicting a poor outcome with ongoing myocardial damage [5]. However, approaches cannot be used to diagnose the etiology of HF. Pavlicek et al. suggested that endomyocardial biopsies (EMB) was important in diagnosing the etiology of HF and confirmed persistent myocardial inflammation for risk stratification [3]. The European Society of Cardiology HF guidelines state that EMB should be considered in patients with rapidly progressive HF despite GDMT, when there is a probability of a specific diagnosis that can be confirmed only in myocardial samples and specific therapy is available and effective [6]. Furthermore, EMB should be performed for patients with a life-threatening ventricular arrhythmia or its risk [7]. These guidelines recommend EMB as Class IIa, but there are several limitations. First, EBM is an invasive method, although it has few complications. Second, obtained histological findings are not necessarily appropriate because those findings depend on chosen EMB sites, which are technically limited. Therefore, we should develop non-invasive or minimally invasive methods to evaluate myocardial inflammation and diagnose the etiology of HF. Recently, cardiac magnetic resonance imaging was reported to be useful for diagnosing myocarditis using mapping techniques [8]. The progress of imaging technology in recent years is remarkable. We are currently becoming able to directly or indirectly detect myocardial inflammation, which involves immune cells and molecular mediators, using magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography [9]. The most important perspective is to perform precise comparison between these imaging data and immune-histological findings obtained by EMB as the gold standard. How to treat chronic myocarditis remains an unsolved important issue. Pavlicek et al. examined viral genomes by polymerase chain reaction, and these were detected in 39% of cases of myocarditis, which was defined by lymphocytic infiltrates and fibrosis without acute necrosis of myocytes. The most frequently detected viruses were parvovirus B19 in 61.2% of patients, followed by human herpesvirus 6 in 22.4% of patients. However, the rate of Enterovirus species, which used to be known as the most frequent virus that caused myocarditis, was only just 11.9%. Interestingly, there was no relationship between detection of the viral genome and transplantation of an ICD. This finding suggests that to improve the outcome, more effective immunosuppressive therapy should be developed than a specific viral therapy. In this study, only three patients were treated by immunosuppressive therapy. Therefore, the outcome data in this study suggested a natural course in patients with chronic myocarditis. In these patients, there was a significantly shorter median time after EMD to ICD implantation compared with that in patients with dilated cardiomyopathy. The independent predictor for ICD implantation was chronic myocardial inflammation (hazard ration 2.48 [95% confidence interval 1.02–5.5]).

Therefore, this important study suggests that future directions should be guided by the gold standard approach (EMB) for managing myocarditis. We cannot connect the dots looking forward. Therefore, we should develop appropriate management for myocarditis from multidisciplinary "dots", including inflammatory imaging, and molecular and pharmacological approaches. As quoted by Steve Jobs, we can

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only connect the dots by looking backwards to develop novel diagnostic and therapeutic approaches. There is an urgent need to establish diagnostic and therapeutic approaches for myocarditis.

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