Diagnostic Approach to Cardiac Involvement in Idiopathic Inflammatory Myopathies
A Strategy Combining Cardiac Troponin I but not T Assay with Other Methods

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Summary
Cardiac involvement in idiopathic inflammatory myopathies (IIMs) attracts more attention than it ever did because of its morbidity and impact on worse prognosis, although the accurate information needs further epidemiological studies. Early identification and intervention for the diseased heart may help improve the clinical outcomes of IIMs with cardiac involvement. Cardiac troponin assays, allowing for sensitive detection of minor myocardium injury, may provide a new way for early detection for heart involvement in IIMs. While elevated cardiac troponin I (cTnI) specifically indicates cardiomyocyte injury, the elevation of cardiac troponin T (cTnT) levels may not only derive from damaged heart but also diseased adult skeletal muscles in which cTnT could re-express in patients with IIMs. cTnI is the biomarker of choice for diagnosis of cardiac involvement and may also be a prognostic factor in IIMs. Meanwhile, electrocardiography (ECG), cardiac imaging (e.g., echocardiography, cardiac magnetic resonance) and histopathological techniques (e.g., endomyocardial biopsy) take on different degrees of importance for the diagnosis of cardiac involvement. We propose a diagnostic strategy combining the routine use of cTnI assay with other techniques (routine ECG and echocardiography, cardiac magnetic resonance, and or endomyocardial biopsy in necessity) and clinical investigation for early detection of heart involvement in IIMs. Future researches are required to validate the algorithm for performance.

Key words: IIMs, cTnI, cTnT, Diseased Heart, Diagnosis

Idiopathic inflammatory myopathies (IIMs), including polymyositis, dermatomyositis, inclusion body myositis, and immune-mediated necrotizing myositis, are a group of systematic autoimmune disorders characterized by inflammation of muscle resulting in muscle weakness, muscle enzyme elevation, and extra-muscular manifestation.1,2 The heart is just a muscle, and cardiac involvement is not uncommon in patients with IIMs. In recent years, the number of reports concerning heart involvement in IIMs have increased as more sensitive, invasive, or noninvasive techniques were used to detect this extra-skeletal muscular involvement.3,4 A few observational studies based on objective evidence of diseased heart have demonstrated that the incidence for cardiac involvement approximately was 9% to 72%, and those patients with diseased heart had worse prognosis, and cardiac manifestation was a major cause of deaths.4,5 Hence, early identification for cardiac involvement may help improve the management and clinical outcomes of these patients, but currently, the diagnostic strategy is lacking. Cardiac troponin I and T (cTnI and cTnT) assays, which could sensitively and specifically detect myocardium injury, are crucial tools in acute cardiac care, especially for the management of acute coronary syndrome (ACS),6,15 and have also been proposed to detect cardiac involvement in IIMs since their introduction for detecting ischemic myocardial injury,13,14 although cTnI and cTnT assays showed varying performance.6,15,16 Meanwhile, other methods, such as electrocardiography (ECG), cardiac imaging, and histopathological techniques, also take on different degrees of importance for the diagnosis. In this article, we briefly introduce the present status and pathogenesis of cardiac involvement in IIMs, and review the roles of cardiac troponin assays and other methods for the diagnosis, and finally propose a strategy using these methods for early detection of heart involvement in IIMs.

Cardiac Involvement in IIMs
Oppenheim first reported heart involvement in polymyositis and dermatomyositis in 1899.17 In the early years, physicians once thought that cardiac involvement was rare in inflammatory myopathies,18,19 however, in recent years, observational studies have shown that morbid-
Cardiac Troponin in Patients with IIMs

Cardiac troponin I and T, the more sensitive and specific biochemical markers compared with CK-MB for myocardial injury, had revolutionized the management of ACS since the early 1990s. It was believed that the detection of elevated cTnI or cTnT in peripheral blood indicated cardiomyocyte injury and the new high-sensitivity assays could examine very minor damage on heart muscle. Kobayashi, et al. first proposed the use of cTnT for detecting cardiac involvement in IIMs in 1992, thereafter cTn assays were also empirically applied in this condition. However, researchers found that 41%-78% of general IIMs patients with increased cTnT and only 2%-2.5% of them with elevated cTnT in three relatively large-scale investigations, the significantly discrepant results, also occurring in some case reports, led to challenge for the specificity of cTnT for myocardial injury in IIMs.

Troponin I, T, and C are the three subunits of troponin complex that is the thin-filament regulatory protein in skeletal and cardiac muscle. Different forms of troponin I and troponin T are encoded by individual genes and have been identified in cardiac, fast twitch, and slow twitch skeletal muscles. Cardiac troponin I is only expressed in adult cardiac tissues and is not expressed in skeletal muscle or fetal heart muscle, and the detectable cTnI in blood only derive from myocardium. Conversely, cTnT gene is expressed at low concentration during the early development in fetal skeletal muscle, and the expression is suppressed from the mid-fetal stage. Early research in patients with chronic renal diseases revealed that the second generation cTnT assay, using monoclonal antibodies M7 as capture antibody recognizing an epitope at residues 125-131, and M11.7 as detection antibody recognizing an epitope at residues 136-147, would not detect the isoform of cTnT released from diseased skeletal muscle. Nevertheless, the subsequent data from real world suggested that the elevation of cTnT, which was also detected by M7 and M11.7, or M7 and 5D8 recognizing the same epitopes as M11.7 did, was more frequent than the elevation of cTnT in patients with IIMs. Moreover, Jaffe, et al. recently documented that there were re-expressed cTnT isoforms in diseased
skeletal muscle from myopathies including IIMs that could cause elevation in circulation levels of cTnT by western blot analysis using the capture and detection antibodies from both fourth-generation and high-sensitivity cTnT assays.

Overall, the elevation of cTnT levels in peripheral blood may derive from diseased heart muscles or diseased adult skeletal muscles, or early fetal skeletal muscles, whereas elevated cTnT levels in circulation specifically indicate myocardium injury; therefore, cTnI is the biomarker of choice for detecting and quantifying cardiomyocyte damage for patients with IIMs.

In current clinical practice, a vast majority of point-of-care, sensitive, high-sensitivity cTnI and cTnT assays run on automated platforms, and the guidelines recommended the high-sensitivity ones for management of ACS but did not recommend routine assays for nonischemic conditions unless for special objectives. For cardiac involvement in IIMs, unlike myocardial infarction in which necrosis or injury of cardiomyocytes occur quickly after ischemia attack and the rapidly elevated cardiac troponins disappear after several days, the histopathological changes of the heart tend to be slow and diffused according to previous studies, and the elevation of cardiac troponins may persist due to continuous damage induced by inflammatory activity. Theoretically, it is reasonable that the routine use of cTnI assay for early detection of heart involvement, preferable to high-sensitivity ones allowing for detection of minor myocardium damage, especially in the early stage when ECG and cardiac imaging prefer to be negative and patients are more likely to be asymptomatic, and normal levels of cTnI make the diagnosis unlikely.

In addition, as cTnI is a quantitative biomarker for myocardial injury, the dynamic changes of cTnI levels could help to improve the monitoring of disease progress and therapeutic success in IIMs with heart involvement, and the cTnI levels at diagnosis may be a prognostic indicator for clinical outcomes while elevated cardiac troponin is associated with increased rate of cardiac event and mortality in many acute and chronic diseases even general population. However, no studies have focused on these topics, further investigations are required.

**Other Diagnostic Tools for Detecting Cardiac Involvement in IIMs**

The measurement of plasma natriuretic peptide level, especially for B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), was supposed to be a sensitive method to detect preclinical hemodynamic and structural cardiovascular changes. The diagnostic and prognostic values of natriuretic peptides have been confirmed in heart failure and some other cardiovascular disease, and even higher level of natriuretic peptide could predict the increased risk of death and cardiovascular events in general population. Theoretically, the diseased heart may be associated with higher natriuretic peptide level compared with healthy one in IIMs, and the elevated natriuretic peptide could predict poorer outcome. However, few studies have discussed this topic, and only two small-sample researches demonstrated that higher BNP or NT-proBNP was correlated with reduced cardiac function in IIMs. Natriuretic peptide remains to be further studied in IIMs.

Histopathological studies, endomyocardial biopsy (EMB), and postmortem examination are gold standard methods to diagnose cardiac involvement in patients with IIMs. The characteristic histological findings in myocardium suggest cardiac involvement in these patients; however, nondiagnostic findings, which may be resulted by unoptimized specimen procurement and triage, nonstandard pathological analysis as well as impermanent inactivity of autoimmune-mediated inflammation, could not define the inexistence of heart involvement. Moreover, the invasive EMB is associated with some immediate risks and delayed complications and the overall complication rate of which depends on the experience of the operator, and postmortem examination is too late to change the clinical prognosis of those patients. Whatever the limitations, EMB should be performed for improving outcomes when the setting of a patient is applicable to indications endorsed by professional societies of cardiology, and postmortem examination may need to be considered in some special conditions to identify the leading cause of death.

ECG could trace cardiac electric activities, and it is the basic method to detect arrhythmias in patients with IIMs. It is reasonable that all these patients should have short-term ECG at diagnosis because of its cost-benefit ratio, and continuous ECG monitoring is needed for the detection and characterization of arrhythmias when the result of short-term ECG is inconclusive. Nevertheless, it should be noted that the abnormalities of ECG in these patients are not disease-specific and without diagnostic values for etiology, unlike the ECG findings of some inherited primary arrhythmia syndrome such as Brugada syndrome, and a normal ECG would not make the diagnosis unlikely because of the sensitivity for involvement of cardiomyocyte and cardiac conduction system.

Cardiac imaging could supply the data of cardiac structure and function in IIMs, and abnormal imaging findings add the likelihood of heart involvement in these patients, whereas normal findings in imaging may not rule out the early stage of diseased heart when biochemical changes tend to appear at first.

Echocardiography is the method of choice for basic cardiac imaging assessment for reasons of accuracy, availability, safety, and cost. The tissue Doppler imaging modality allows early detection of cardiac impairment by assessing long-axis strain and mitral annual velocity above and beyond traditional echocardiography. Hence, routine echocardiography should be considered in IIMs, particularly in those with suspicion of cardiac involvement, and this was also recommended by the guideline endorsed by professional societies of echocardiography. Previous studies had reported variant frequency of echocardiographic abnormalities in IIMs and some defined the abnormalities as indicators for cardiac involvement; however, it was not considered that not all aberrant findings were results of heart involvement due to myocardial inflammatory followed by heart remodeling and the relative specific echocardiography indicator need to be de-
fined for heart involvement in IIMs.

Cardiac magnetic resonance (CMR) possesses several advantages compared with echocardiography, and this flexible imaging modality provides a noninvasive measure to determine not just conventional parameters of anatomy and function but also the tissue composition of myocardium. Its unique capability allowed early detection of tissue changes, including inflammation, necrosis, fibrosis, and increased water content, which mean the high likelihood of diseased heart in these patients, and it may also help to identify whether these changes induced by myocarditis associated with IIMs or other etiologies. Moreover, a recent study enrolling 53 patients reported that CMR seems to provide a measurable and quantifiable tool for evaluating cardiac involvement in IIMs and can thus be used for follow-up purposes in these patients, and an earlier case series had concluded a similar result. Nevertheless, the clinical implications of routine CMR for diagnosis and follow-up need further evaluation because of the lack of evidence for cost-benefit ratio, and CMR may be considered in patients with inconclusive diagnostic findings according to other methods.

**Strategy Combining cTnI Assay with Other Methods for Early Detection of Cardiac Involvement in IIMs**

We propose a strategy for early detection of heart involvement in patients with IIMs. All these patients should have assessments for cTnI assay (prefer to high-sensitivity ones), ECG, and echocardiography, followed by screening other common causes, rather than cardiac involvement for abnormal findings in these assessments; meanwhile, CMR and or EMB may be required for further evaluation depending on clinical scenarios (Figure).

If the concentration of cTnI is below the upper limit of normal (ULN) and there are no abnormal findings in ECG and echocardiography assessments, the patient is unlikely to show cardiac involvement. If patient has normal cTnI but aberrant findings in ECG and echocardiography, these findings are more likely caused by other etiologies because high-sensitivity assays would detect cTnI chronically released by damaged heart in IIMs; however, CMR and or EMB may be considered for further evaluation due to the low possibility for normal cTnI with inactivity of myocardial inflammation in cardiac involvement. In general, patients with normal cTnI levels are more likely to be without cardiac involvement because myocardial injury induced by abnormal autoimmune response tends to be persistent and diffused in IIMs and the high-sensitivity cTnI assays used in current clinical practice can detect very minor myocardium damage, although sometimes, further investigations and/or clinical observation are required to ensure that.

Conversely, the elevated cTnI could not identify the high likelihood of cardiac involvement when many other underlying cardiac and noncardiac diseases may be associ-
associated with the elevation (Table II). The situation becomes more complicated when abnormal findings of ECG and echocardiography are present. It should be noted that some aberrant findings in electric activity, structure, and function of the heart unlikely occur in cardiac involvement of IIMs and suggest definite etiology of disease, such as long or short QT syndrome, Brugada syndrome, hypertrophic or restrictive cardiomyopathy, rheumatic or hypertensive heart disease, and more nondiagnostic abnormalities may be resulted by diverse causes including IIMs. Therefore, it is necessary to interpret the elevated cTnI and possible abnormalities of ECG and echocardiography according to clinical history, physical examination, and other laboratory studies, and screening for other common etiologies is important. If these could be explained by other etiologies, patient is more likely without cardiac involvement, but further clinical observations are needed. CMR and or EMB (if clinical scenario is applicable to the indications) should be considered when the elevation and abnormalities (if present) could not be explained by other etiologies or the condition is uncertain.

However, due to limited researches in this interdisciplinary field nowadays, this algorithm is developed according to limited evidences and clinical experience, future application in clinical practice will verify its performance. Furthermore, high quality studies are required to address the diagnostic and prognostic value of cTnI, as well as the value of cTnI for monitoring disease progress in IIMs with cardiac involvement.

**Conclusion**

Cardiac involvement in IIMs attracts more attention than before because of its morbidity rates and its impact on worse prognosis, although accurate information needs further investigation. The myocardial biomarker, cTnI, not cTnT which could be re-expressed in adult diseased skeletal muscle, has an important role in detecting diseased heart following the myopathies, moreover, elevated cTnI may be a prognostic factor and improve the monitoring of disease progress. Other laboratory studies, such as ECG, echocardiography, CMR, and EMB are also crucial for the diagnosis of heart involvement. A strategy combining routine use of cTnI with those techniques (routine ECG and echocardiography) and or EMB in necessity) and clinical investigation may contribute to early diagnosis for cardiac involvement and improvement for prognosis in IIMs, and further researches are needed to validate its performance.

**Disclosures**

**Conflicts of interest:** The authors declare no potential conflicts of interest.

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**Table II.** Other Conditions Associated with Elevated Cardiac Troponin I Levels

| Conditions |
|------------|
| Myocardial injury related to coronary artery disease |
| Plaque rupture, intraluminal thrombus formation |
| Coronary artery spasm, dissection, embolism or vasculitis |
| Coronary endothelial dysfunction |
| Myocardial injury related to other causes for imbalance of oxygen supply/demand |
| Tachy-/brady-arythmia |
| Hypertrophic cardiomyopathy, hypertension with or without left ventricle hypertrophy |
| Aortic dissection or severe aortic valve disease |
| Pulmonary embolism, pulmonary hypertension |
| Shock, severe anemia or respiratory failure |
| Myocardial injury basically not related to ischemia |
| Myocarditis, cardiomyopathy (e.g. Stress, Dilated) |
| Infiltrative disease (e.g. Amyloidosis, haemochromatosis, sarcoidosis) |
| Cardiotoxicity agents or poisoning (e.g. Anthracyclines, cocaine, snake venoms) |
| Cardiac contusion or cardiac procedures (e.g. CABG, ablation, cardioversion) |
| Rhabdomyolysis with cardiac involvement |
| Hypo- and hyperthyroidism |
| Heart failure |
| Renal dysfunction and associated cardiac disease |
| Sepsis and critically illness |
| Severe acute neurological disease (e.g. Stroke, subarachnoid hemorrhage) |
| Extreme endurance efforts |
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