

## Review Article

**Epidemiology and Diagnosis of Viral Myocarditis**SHICHAO LV<sup>1</sup>, JIE RONG<sup>1</sup>, SHUNV REN<sup>1</sup>, MEIFANG WU<sup>1</sup>, MENG LI<sup>1</sup>, YAPING ZHU<sup>2</sup>, JUNPING ZHANG<sup>2</sup><sup>1</sup>Tianjin University of Traditional Chinese Medicine, <sup>2</sup>First Teaching Hospital, Tianjin University of Traditional Chinese Medicine, Tianjin, China

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**V**iral myocarditis (VMC), which consists of localized or diffuse myocarditis lesions caused by a viral infection, is one of the common clinical heart diseases. Since the 1970s, the incidence of VMC in China, Japan and other countries has continued to grow, and large quantities of clinical data concerning the disease have been reported. However, its pathogenesis is not yet clear, and Europe and America have devoted a great deal of attention to the study of this aspect of the disease. Due to the rapid development of molecular biology in recent years, much progress has been made with the disease, though there have been no breakthroughs in its treatment. As the disease spectrum changes and viruses are spreading, viral disease is increasing. VMC is becoming a common heart disease, after coronary heart disease, whose incidence is tending to increase further in the 21st century. Therefore, it is particularly important to grasp the epidemiological characteristics and diagnostic methods associated with VMC.

**Epidemiology**

VMC can occur in all age groups, from infants to the elderly, but it is mainly found in children and adults under the age of 40, with 35% of patients being between 10 and 30 years old. Due to the variety of VMC viruses and their epidemic law,

there are differences in the predominant viruses of different regions and in different years within the same region. Virological examinations have not been widely used, with the result that there are few representative, high-value epidemiological reports, while the exact incidence and prevalence of VMC are still unknown. At present, the incidence of VMC is mainly based on the following three types of evidence:

1. The detection rate at myocardial autopsy or biopsy. In 1986, Wakafuji et al analyzed 377,841 cases of autopsy from the Japanese Pathology Society for the 20 years between 1958 and 1977. The results showed that 434 cases were nonspecific myocarditis and tuberculoid myocarditis (0.11% and 0.007%, respectively), while the incidence increased significantly after 1974, despite the fluctuations among different years.<sup>1</sup> Passarino et al reviewed and analyzed 17,162 autopsy cases in a general hospital in Italy between 1965 and 1994 and found that myocarditis accounted for 0.53% of these cases.<sup>2</sup> The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) demonstrated that, from August 1993 to June 1999, 526 cases in 3055 patients were diagnosed as acute or chronic myocarditis, of which 74 cases were consistent with acute myocardi-

tis and 452 were consistent with chronic or borderline myocarditis in terms of clinical and histological findings.<sup>3</sup>

2. The frequency of patients clinically diagnosed with myocarditis during the period of virus infection prevalence. About 5% of patients can have heart involvement, especially when Coxsackie virus, influenza virus or polio virus is prevalent, and the percentage may reach more than 10% in certain areas. In 1981, during the period when influenza was prevalent during the summer in Shanghai, China, virus antibody was positive in 78 of 183 patients with fever (42.6%), 13 cases of which were consistent with a clinical diagnosis of VMC, with an incidence of about 7.1%, accounting for 16.7% of infected patients.<sup>4</sup> In addition, paired virus serum antibody was positive in 581 of 1426 cases who were VMC-suspected patients from the years 1978 to 1986 (40.7%), similar to the year 1981; 393 cases were confirmed as VMC, with the incidence increasing to 27.6%.<sup>5</sup>
3. The proportion of VMC patients out of all patients in a certain region and a certain group of people. A collaborative group was organized in nine provinces and cities (Shanghai, Fujian, Guangdong, Yunnan, Hubei, Gansu, Shaanxi, Heilongjiang, and Beijing) in China from 1978 to 1980 to investigate the incidence of VMC, finding 1709 pediatric patients with VMC (1455 cases in acute stage, 74 cases in recovery stage, 133 cases in chronic stage, and 47 cases in sequelae stage), 136 VMC-suspected cases, and 90 cardiomyopathy cases; the incidence of VMC was 6.88-29.15 per 100,000, and the prevalence was 8.03-41.86 per 100,000.<sup>6</sup> Kytö et al reviewed the statistical data for fatal myocarditis in Finland from 1970 to 1998 and found that, among 1,349,824 deaths from all causes, 639 deaths were recorded as potential myocarditis deaths: namely, 0.47 per 1000 deaths were caused by myocarditis. The incidence of fatal myocarditis with clear pathogeny remained roughly constant in the 1970s and 1980s, but there was a slight rise in the 1990s.<sup>7</sup> VMC in Yunnan China has significant local characteristics, also known as “unexplained sudden cardiac death of Yunnan”, “local fulminant myocarditis of Yunnan”, etc. It appeared in the poor and mid-level mountainous areas of Yunnan province and mainly involved young farmers. Eighty-seven cases of fulminant myocarditis were recorded in Yunnan Province during 1978-2004,

involving 634 people and leading to 267 deaths; the average incidence was relatively low (1.2%), with part of the incidence slightly higher (6.7%), the average fatality rate approximately 42%, and the highest mortality 100%.<sup>8</sup> At present, the incidence of VMC presents an upward trend, and heart disease statistics of Shanghai show that, from 10th place in the 1950s, VMC has risen to the 4th heart disease in terms of patients hospitalized for heart disease in the region.<sup>9</sup>

### Virus spectrum

Since the virus antibody titer may decrease or even disappear with time, the sensitivity and specificity of serological examinations are low after the acute stage. It is hard to identify the relationship between virus infection found by serological examination and myocarditis onset, except during the virus epidemic period. In addition, the virus cannot always be detected in adults with symptoms of myocarditis. Almost all human virus infections can involve the heart. It has been found that more than 30 kinds of virus can cause myocarditis, the intestinal virus being most common. The most common viruses are Coxsackie B-2~6,9 and A-9, and the former is the virus most widely reported to cause myocarditis. Next comes ECHO virus, especially type 6, and adenovirus, types 3 and 7. Furthermore, myocarditis caused by flu and poliomyelitis is also common. Recently, with the rising VMC prevalence rate and continuous improvement in virus detection methods (paired serum antibody test, *in situ* hybridization with nucleic acid probe, polymerase chain reaction [PCR], serum IgM examination, etc.), research shows that the virus spectrum of VMC has greatly changed since the 1970s and 1980s (Table 1). The viruses that have been found continue to increase. VMC caused by multiple viruses is also more common than before. It has attracted more and more attention to the further exploration of the pathogenesis of VMC, taking multiple virus infection factors into account.

Most researchers believe that VMC is mainly caused by enterovirus, and VMC caused by Coxsackie virus is the most reported; this virus is also used in experimental animal and cell models. However, Griffin found that myocardial specimens from autopsies of 58 VMC patients confirmed by pathologic examination were mostly adenovirus infections (18 cases), followed by enterovirus (12 cases), as well as cytomegalovirus (2 cases) and herpes simplex virus (2 cases).<sup>10</sup>

**Table 1.** Evolution of the virus spectrum of VMC.

Report title	Journal name	Year of publication	Virus	Infection rate	Country
Griffin 1995	Cardiovasc Pathol	1995	enterovirus	20.7% (12/58)	USA
Griffin 1995	Cardiovasc Pathol	1995	adenovirus	31.0% (18/58)	USA
Kühl 2005	Circulation	2005	Parvovirus B19	51.4% (126/245)	Germany
Matsumori 2006	J Card Fail	2006	hepatitis C virus	4.4% (59/1355)	Japan
Bratincsák 2010	J Am Coll Cardiol	2010	H1N1 influenza A virus	4 of 80 children infected by HAN1 A influenza virus were confirmed as HAN1 A influenza virus related myocarditis	Portugal

In addition, Okabe reported that hepatitis-C virus (HCV) plus strand RNA was detected using PCR in the heart and liver tissues of 3 chronic active myocarditis patients who died of heart failure, suggesting that hepatitis virus may cause myocardial infection.<sup>11</sup> In Japan, reports about myocarditis caused by hepatitis C virus are common. Matsumori et al detected anti-HCV antibody from 1355 patients who had heart failure without clear etiology; 59 cases (4.4%) were positive for anti-HCV antibody, a significantly higher rate than in the United States.<sup>12</sup> In Germany, Kühl reported that parvovirus B19 genome could be found by the gene amplification method in about 51.4% of cases.<sup>13</sup> Papadogiannakis et al believed that current diagnostic procedures had underestimated the myocarditis morbidity caused by parvovirus infection, and suggested using PCR technology to improve the detection rate of infection, so as to achieve a correct diagnosis.<sup>14</sup> Bratincsák et al also reported 4 children who suffered from acute myocarditis after H1N1 A influenza virus infection, and emphasized the relevance of H1N1 influenza A virus to severe myocarditis.<sup>15</sup> Thus, the virus spectrum of VMC has already changed, and if we only test for Coxsackie virus in clinical practice, it is certain to cause confusion in diagnosis. It is necessary to study the characteristics and prognosis of myocarditis caused by different viruses.

### Gold standard of diagnosis

Endomyocardial biopsy (EMB) is considered as the “gold standard” for VMC diagnosis, and also forms the basis for histology diagnosis. However, it is an invasive examination whose safety remains to be evaluated, which limits its clinical application. The inconsistencies in sampling time, region error and diagnosis standard limit the accuracy of the diagnosis. Because of the existence of error in myocardial biopsy,

4 to 6 samples are usually needed in order to make a diagnosis. However, autopsy reports indicate that at least 17 biopsy specimens are needed to achieve a correct diagnosis rate more than 80%.<sup>16</sup> In order to define the status of EMB, which remains in dispute in the diagnosis of cardiovascular diseases, the AHA/ACC/ESC jointly issued a scientific statement. The statement puts forward guidelines for the application of EMB in clinical practice, through analyzing 14 kinds of clinical conditions. However, it does not explicitly state the recommendation class or level of evidence for the application of EMB to VMC.<sup>17</sup>

During 1977-1979, 10 universities of the Japanese Ministry of Health, Labour and Welfare established a standard classification for the pathologic diagnosis of pediatric myocarditis:<sup>18</sup> acute and subacute myocarditis; chronic interstitial myocarditis; giant cell myocarditis. In 1982, Edwards proposed a myocarditis pathologic diagnosis standard in clinical research and development of cardiology:<sup>19</sup> myocardial damage, manifesting as granular degeneration of myocardial cells; coagulation and dissolution of sarcoplasm with small focal lesions; inflammatory cell infiltration, mostly lymphocyte and monocyte infiltration, with  $\geq 5$  cells per high-power field presenting diffusion or focal shape. In 1984, at a meeting in Dallas, Texas, 8 experienced pathologists put forward the Dallas Standard, which is still in use today.<sup>20</sup> This classifies the disease according to the first result of EMB (myocarditis, with or without myocardial interstitial fibrosis; borderline myocarditis; without myocarditis) and according to the serial biopsy (progressive myocarditis, with or without myocardial interstitial fibrosis; curing myocarditis; cured myocarditis, with or without myocardial interstitial fibrosis). (Table 2).

The different standards above each have their own emphasis. By comparison, the Japanese standard classifies myocarditis into acute and subacute myo-

**Table 2.** Comparison among histological diagnosis standards.

Japanese standard	Edwards standard	Dallas standard	
		Classifying according to the first result of EMB	Classifying according to the serial biopsy
Acute and subacute myocarditis	Myocardial damage	Myocarditis	Progressive myocarditis
Chronic interstitial myocarditis	Inflammatory cell infiltration	Borderline myocarditis	Curing myocarditis
Giant cell myocarditis		Without myocarditis	Cured myocarditis

carditis, chronic interstitial myocarditis, and giant cell myocarditis; the Edwards Standard defines myocarditis in terms of myocardial damage and inflammatory cell infiltration; while the Dallas Standard emphasizes repeated histology biopsy and points out that it is hard to make a correct diagnosis based on a single EMB. However, in practice, the pathological myocardial changes are difficult to detect by a single light microscope examination. Therefore, the immunohistochemical method is in common use now to corroborate myocardial damage, and is able to complement the above standards.

### Clinical diagnostic standard

It's difficult to make a diagnosis of VMC without a unified international standard, because of (1) the various symptoms and conditions, (2) the non-specific symptoms and auxiliary examinations, (3) the difficulty in viral isolation and unclear viral infection history, and (4) the huge differences in histopathologic diagnosis standards. "Suggestions on clinical diagnosis index of VMC" was first prompted by a pedo-myocarditis cooperation group in the 1970s in nine provinces and cities in China.<sup>21</sup> After being refined several times, it was finalized in 1983 and was adopted by Chinese researchers (Table 3). It was further refined at the Sixth China Pediatric Cardiology conference in May 1994, forming "The diagnostic standard of pediatric viral myocarditis",<sup>22</sup> which was refined still more at the Pediatrics Myocarditis and Cardiomyopathy conference in September 1999, forming the present diagnostic standard of pediatric myocarditis: "The diagnostic standard of viral myocarditis (revised protocol)".<sup>23</sup>

At the national myocarditis and cardiomyopathy symposium in May 1987, referring to the diagnostic standard of pediatric viral myocarditis in nine cities, Chinese researchers initially created "The diagnostic reference standard of adult acute viral myocarditis (protocol)",<sup>24</sup> which was revised in both 1995 and 1999 and became the diagnostic reference for adult acute viral myocarditis at the present time.<sup>25,26</sup>

In a survey of the diagnostic standards of myocarditis established in China, diagnostic standards for adults in 1987, 1995 and 1999 were unconcerned with stages, while diagnostic standards for children varied in stages among three times, based primarily on the severity changes, and course lengths, as shown in Table 4. In addition, some academics also recommended, according to the characteristics of disease stages, that the disease could be divided into the virus infection stage, immune activation stage, and dilated cardiomyopathy stage; however, objective indicators for stage division were lacking (Table 5).<sup>27</sup>

During 1977-1979, ten universities of the Japanese Ministry of Health, Labor and Welfare set out a trial scheme for the clinical diagnosis of pediatric myocarditis,<sup>18</sup> and the Japanese circulation academe published "Guidance on diagnosis and treatment of myocarditis" in 2009,<sup>28</sup> which was more rigorous and finer than the previous diagnostic standards before, as shown in Table 6.

**Auxiliary examinations**

Given the limitations of EMB, cardiac magnetic resonance (CMR) has gradually come to receive great attention as a noninvasive inspection method. With features including multi-parameter and multi-directional imaging, good soft-tissue contrast and high spatial resolution, CMR can show not only the region of myocardial injury, but also the degree of myocardial edema, having potential diagnostic value for VMC. With EMB as the diagnostic gold standard for VMC, CMR was evaluated in 319 patients, and showed high sensitivity (94%) in the diagnosis of VMC with a medium level of specificity (69%).<sup>29</sup> Cardiac tissue changes can be reflected using the T1 and T2 re-

**Table 3.** Comparison among diagnostic standards for pediatric viral myocarditis (China).

Diagnostic index	Standard in 1983	Standard in 1994	Standard in 1999
Etiological diagnostic evidence	<p>Virus can be isolated from pericardium puncture fluid, pericardium, myocardium, endocardium or specificity fluorescein-labeled antibody exam (+);</p> <p>Virus can be isolated from excrement, pharynx swab or blood, elevation or descending of homotype virus neutralizing antibody titer in a sample collected in the convalescent phase to at least four times than that in the first serum sample.</p>	<p>Specificity IgM antibody titer in blood is higher than 1:128; Viral nucleic acid can be detected in myocardium or blood.</p>	<p>Index for final diagnosis: Virus or viral nucleic can be isolated from endocardium, myocardium, pericardium or pericardium puncture fluid, specificity virus antibody exam (+).</p> <p>Reference: Virus can be isolated from excrement, pharynx swab or blood, and homotype antibody titer in a sample collected in the convalescent phase increases or reduces over four times than that in the first serum sample. Specificity of IgM antibody titer in blood is (+); Viral nucleic acid can be detected in blood.</p>
Clinical diagnostic evidence	Main index		<p>Heart insufficiency, cardiogenic shock or heart-brain syndrome;</p> <p>Cardiac dilatation (X-ray or echocardiogram);</p> <p>ECG changes: ST-T change on 2 or more main leads with R wave (I, II, aVF, V<sub>3</sub>) lasting more than 4 days with dynamic change, sinoauricular block, atrioventricular block, completely right or left branch block, coupling, multiform, multisource, conjugating or parallel premature beats, non atrioventricular nodal or atrioventricular reentrant induced ectopic tachycardia, low voltage (except neonates) and abnormal Q wave;</p> <p>CK-MB rising or cardiac troponin (cTnI or cTnT) (+).</p>
	<p>Acute or chronic heart insufficiency or heart-brain syndrome with any one of cardiac dilatation, gallop rhythm or gallop rhythm. ECG with any one of evident arrhythmia, ST-T change (last longer than 4 days with dynamic changes), myocardial infarction type graph or exercise test (+).</p>	<p>Increased CK-MB in one month;</p> <p>Abnormal heart isotope scanning.</p>	
	Secondary index		
	<p>Evident acratia, pale, hydrosis, palpitation, short breath, dyspnea, dizziness, precordial discomfort, cold hands and feet, muscle pain or abdominal pain, etc. (with at least two of those symptoms);</p> <p>Low first heart sound at apex area of heart, or tachycardia in rest state;</p> <p>Slight abnormality of ECG.</p>	<p>Viral infection at onset time or 1-3 weeks before;</p> <p>CPK, GOT, LDH, CKMB increase, and anti-myocardial antibody (AHA, HRA) increase in the course of disease.</p>	
Ruling out to diagnose	Ruling out other heart diseases, such as rheumatic myocarditis, congenital heart disease, Kawasaki disease, etc.		
Hard to diagnose	Considering as "suspected myocarditis", and giving necessary treatment and long-term follow up.		Giving necessary treatment or follow up.

laxation times, spin density, and early and late gadolinium enhancement method, while edema, hyperemia and capillary seepage, necrosis and fibrosis are the three main kinds of cardiac tissue change seen in myocarditis. Thus, CMR can distinguish between normal myocardial cells and those with myocarditis, providing a more accurate diagnosis of myocarditis. According to the Myocarditis CMR international consensus group, when three classification markers (early

myocardial gadolinium enhancement, T2 weighted imaging, and delayed gadolinium enhancement) are combined, the predictive value for myocarditis can be up to 78% if 2 or more of the 3 kinds of cardiac tissue changes of myocarditis are present, but may be only 68% if there is just cardiac tissue necrosis or fiber. Therefore, CMR is currently just an auxiliary examination for aiding diagnosis instead of confirming or excluding myocarditis.<sup>30</sup>

**Table 4.** Comparison among diagnostic standards of adult acute viral myocarditis (China).

Diagnostic index	Standard in 1987	Standard in 1995	Standard in 1999
History and signs	Virus infection history and cardiac manifestations		
ECG	Atrioventricular block, sinoatrial block or bundle branch block; atrial or ventricular flutter or fibrillation; level or oblique ST-segment depression $\geq 0.05$ mV in more than 2 leads; abnormal ST-segment elevation or abnormal Q waves in multiple leads.		
	Frequently multiform, multisource, conjugating or parallel premature beats.	Multisource, conjugating ventricular premature beats.	
	Short paroxysmal, paroxysmal supraventricular tachycardia or ventricular tachycardia	Autonomic atrial or junctional tachycardia, sustained or non-sustained paroxysmal ventricular tachycardia, frequent atrial premature beats.	Nodal tachycardia, autonomic atrial or junctional tachycardia, paroxysmal or non-paroxysmal ventricular tachycardia.
	T-wave inversion, flat or reducing $< 1/10$ of R wave in more than 2 leads with R wave		—
	CPK-MB, SGOT, LDH rising or 50% higher than the normal value.	CK, CK-MB, AST, LDH rising or with dynamic changes. Troponin I/T, myosin light chain or heavy chain should be checked if possible.	Troponin I/T (quantitative examination), CK-MB rising evidently.
Myocardial damage	Decreasing left ventricular systolic function.		Echocardiogram showing enlargement of heart chambers or ventricular wall motion abnormality, and/or nuclide heart function examination proving decreasing left ventricular systolic or diastolic function.
Etiological examination	Viral antibodies; virus being isolated from endocardium, myocardium, pericardium or pericardium puncture fluid, or specificity fluorescein-labeled antibody exam (+).	Viral antibodies, virus-specific IgM; intestines viral or other viral gene fragment being detected from pericardium or pericardium puncture fluid.	Virus, viral gene fragment or viral proteantigen being detected from pericardium or pericardium puncture fluid; viral antibodies, virus-specify IgM.
Ruling out to diagnose	Ruling out other heart diseases, such as $\beta$ -receptor hyperfunction, rheumatic myocarditis, etc.		
Hard to diagnose	Long-term follow up, endomyocardial biopsy if possible.		

Since viral antibody titer can decrease and disappear as time goes on, the sensitivity and specificity of serological examinations are low after the acute stage. It is hard to identify the relationship between virus infection found by serological examination and myocarditis onset, except during the virus epidemic period. What is more, with the rising prevalence of VMC and continuous improvements in virus detection methods, research has shown that the virus spectrum of VMC has changed greatly from before. The viruses that have been found continue to increase and VMC caused by multiple viruses is also more common than before. Our concept of diagnosis needs change from separating and finding the virus to paying attention to

impaired cardiac muscle. The pathogenesis of VMC consists of two phases: the early phase, with the virus directly violating myocardium and causing myocardial damage and dysfunction, and the later period, with a secondary autoimmune reaction. Virus infection may only be the cause of cardiomyopathy, while the persistence of the autoimmune reaction is the key to viral myocarditis developing into myocardial fibrosis and further transferring to cardiomyopathy. Anti-myocardial antibody is a kind of autoimmune antibody against some particular antigenic determinant, having organ specificity and disease specificity. Many kinds of anti-myocardial auto-antibodies can be detected in VMC patients, four kinds of which – MHC,

**Table 5.** Comparison among clinical stages of viral myocarditis (China).

Stages	Reference diagnostic standards for pediatric viral myocarditis		
	1983	1994	1999
Acute stage	Neopathy, evident and changeable symptoms, with less than 6 months' course.	Neopathy, evident and changeable symptoms and examination, with less than 6 months' course.	Neopathy, evident and changeable symptoms and abnormal examination, with less than 6 months' course.
Recovery stage	Symptoms and ECG, etc., improving but not healing, with more than 6 months' course.	Symptoms and objective examination improving but not healing, with more than 1 year's course.	—
Chronic stage	Symptoms, ECG and X-ray recurrent or protracted, active condition in terms of laboratory examination, with more than 1 year's course.	Conditions recurrent and aggregated at times, progressive cardiac enlargement or recurrent heart failure, with more than 1 year's course.	Progressive cardiac enlargement, recurrent heart failure or changes in arrhythmia conditions, with more than 1 year's course.
Lag stage	—	Symptoms recurrent, examination index protracted, with more than 1 year's course.	Symptoms recurrent, examination index protracted, with more than half year's course.
Sequelae stage	Once suffered from myocarditis, and without symptoms but ECG abnormality.	—	—

ANT,  $\beta$ 1, and M2—have high sensitivity, showing that autoimmune lesions of the myocardium are part of the pathogenesis of VMC.<sup>31</sup> According to an analysis of 20,351 serums in clinical diagnosed VMC patients during the decade 1992-2001, with 200 normal serums as control, the positive rate of myocardial antibody for viral myocarditis patients was 37.8%, while for healthy individuals it was 6.5%; the difference was statistically significant ( $p < 0.01$ ).<sup>32</sup> Thus, anti-myocardial antibody detection can serve as an important indicator of cardiac muscle damage and can help monitor the course of the disease.

### Diagnostic status and strategy

The diverse clinical symptoms of VMC, together with differences in severity and the lack of specific tests, have led to a lack of conformity between clinical diagnosis and pathological diagnosis. Only 17-29% of patients who were clinically diagnosed with myocarditis had the diagnosis confirmed by myocardial biopsy, while 71-83% of cases showed normal cardiac tissue or general chronic changes by light microscopy. Similarly, only 11% of VMC patients who were diagnosed by myocardial biopsy were diagnosed clinically, while in the remaining 89% it was difficult to make a clinic diagnosis of VMC.<sup>33</sup> In addition, in some patients without any symptoms or with just respiratory or gastrointestinal symptoms VMC can be ruled out, leading to a missed diagnosis. Acute severe VMC

with critical clinical symptoms might show symptoms of severe heart failure, arrhythmias, and could mimic acute myocardial infarction; thus it could often be misdiagnosed as myocardial infarction, resulting in adverse consequences if treated with thrombolytic therapy.<sup>34</sup> On the other hand, diagnostic expansion should also possibly be avoided: for example, only chest pain, palpitation and ECG abnormalities failing to be diagnosed as VMC. Symptoms such as palpitations, chest tightness, mild weakness, sinus tachycardia on the ECG, increased serum CVB-IgM antibodies and CVB neutralizing antibodies and (or) positive EVs-RNA, with normal echocardiography, chest X-ray, serum troponin, and CK-MB, seen in some patients shortly after an upper respiratory tract infection, may be diagnosed as just the cardiac response after virus infection instead of VMC.<sup>35</sup> A hundred twenty patients who showed unexplained recurrent sighing respiration, anisorhythmia, paroxysmal precordial discomfort, dizziness, palpitation, panic, chest tightness, suffocation, and weakness, having been misdiagnosed as VMC, were analyzed and finally diagnosed by examination as cardiac neurosis in 41 cases, functional premature beat in 38 cases, left ventricular false tendons in 2 cases, pre-excitation syndrome and paroxysmal supraventricular tachycardia in 30 cases, idiopathic ventricular tachycardia in 1 case, and beta-receptor hyperfunctioning in 8 cases.<sup>36</sup>

The symptoms of VMC often depend on the extent of lesions, with different severities, from no subjective

**Table 6.** Comparison between clinical diagnostic standards of viral myocarditis (Japan).

Trial scheme of clinical diagnosis of pediatric myocarditis (1981)	Guidance on diagnosis and treatment of myocarditis (JCS 2009)
Prodrome: flu-like signs and symptoms, gastrointestinal signs and symptoms; and heart signs and symptoms in ten days.	In acute myocarditis, flu-like signs and symptoms, gastrointestinal signs and symptoms, skin rash, joint pain, or muscle pain may occur before cardiac signs and symptoms. However, sudden death may occur without preceding clinical signs.
Cardiac auscultation: weakened heart sounds, gallop rhythm and systolic murmur.	Cardiac findings such as tachycardia, bradycardia, arrhythmia, weakened heart sounds, gallop rhythm (III, IV), pericardial rub, and systolic murmur occur.
Chest X-ray: podoid enlargement.	—
ECG: ST-T segment changes, Q-T elongation, low voltage, QRS electrical axis changes, abnormal Q waves, bundle branches/atrioventricular block and extra systole.	Generally, an abnormal ECG is observed during the course of myocarditis. ECG manifestations are diverse, and include atrioventricular block (I to III degree), intraventricular conduction delay (widened QRS complex), reduced R wave height, abnormal Q waves, ST-T segment changes, low voltage, frequent premature beats, supraventricular tachycardia, atrial fibrillation, sinus arrest, ventricular tachycardia, ventricular fibrillation, and asystole.
Echocardiogram: heart hypofunction, pericardial effusion.	Localized or diffuse wall thickening, reduced wall motion, reduced cardiac chamber size, and pericardial effusion are found on echocardiography.
AST, CPK, LDH, etc. rise in the early stage.	In myocarditis, myocardial constitutive proteins (cardiac troponin T and creatine kinase-MB) are detected in serum. C-reactive protein and white blood cell count are elevated. Early detection of troponin T using whole blood enables immediate diagnosis of myocarditis.
—	Since the conditions in items 2 and 5 above may progress within a few hours, changes over time in these conditions should be followed. If a patient has bradycardia, widened QRS complex, frequent premature beats, wall thickening, exacerbation of reduced wall motion, elevated troponin T, and continuous increase in troponin T level, the patient may have a cardiopulmonary emergency.
—	Definitive diagnosis of myocarditis requires that acute myocardial infarction be excluded.
—	The presence of abnormal histological findings on endomyocardial biopsy makes the diagnosis of myocarditis definite. However, the absence of such findings does not exclude the possibility of myocarditis.
Elevation of viral antibody titer in a serum sample collected two to three weeks later to at least four times that in a sample obtained the first time.	Elevation of viral titer in a sample collected in the acute phase to at least four times that in a sample obtained in remission is useful for identify viral infection as the cause. Polymerase chain reaction is often used to demonstrate the presence of viral infection and to detect the viral genome. Separation of virus or identification of virus by antibody titer in throat swabs, urine, feces, blood, and especially pericardial effusion or cardiac muscle tissue provides direct evidence of myocarditis.

symptom to sudden death. At present, the ECG is still one of the important indicators of VMC, but with low specificity. ECG can only get recording data of 20-50 cardiac cycles at one time, whereas Holter monitoring can obtain data for 100-140 thousand cardiac cycles, which can be used to comprehensively assess arrhythmia and ST-T changes, and provide a reliable basis for the early screening, diagnosis and treatment of VMC. As the increase in myocardial enzymes is non-specific, a rise in cardiac enzymes does not necessarily mean myocardial injury. The increase in myocardial enzymes may be due to a variety of reasons, including organic disease, and also exercise, tension, etc.<sup>37</sup> In view of this,

more sensitive and more specific indicators remain to be found to determine the myocardial injury.

At present, cardiac troponins (cTn) are considered to be the best indicators of myocardial injury, unrelated to factors such as age and sex, with a high degree of sensitivity and specificity.<sup>38</sup> Cardiac troponin is a protein complex composed of three subunits controlled by different genes, including cTnI, cTnT and cTnC. In the myocardial cell, most cTnI and cTnT are fixed to myofibrils in the form of troponin complex, and a lesser quantity are free in the sarcoplasm. In the early stage of myocardial damage, free cTnI and cTnT are released quickly, leading to



a rise in serum cTnI and cTnT levels. As myofibrils are constantly being disintegrated and fractured, cTnI and cTnT fixed on myofibrils are also constantly released, so serum cTnI and cTnT continue to rise. Studies showed that cTnT can be detected in serum within 3 hours of myocardium damage and lasts up to 15 days;<sup>39</sup> cTnT in serum in patients with acute viral myocarditis is significantly higher than that in healthy individuals, and can be still higher after 2 weeks' treatment, with a significant decline, suggesting that the concentration of cTnT is closely related to cardiac damage.<sup>40</sup> In addition, patients suspected of having myocarditis with cTnI and/or cTnT-positive can be diagnosed as VMC by myocardial biopsy of endocardium at a high level.<sup>41</sup> Therefore, cTnI and cTnT are considered to be the new gold standard of regional myocardial ischemia damage. cTnI is currently a promising biochemical marker for diagnosing myocardial damage, with good specificity and high sensitivity. However, cardiac troponin in serum is not stable, easily degrading and forming compounds, and can be affected by endogenous material. Moreover, cardiac troponin detection has not been standardized, and most detection products are not able to reach the required sensitivity. Therefore, in the future we should establish a relatively fixed detection system, set up a cardiac troponin database for different types of heart disease, set reference values for diagnosis, and pay attention to the trend of cTn changes in patients.<sup>42-43</sup>

With the rapid development of molecular biology techniques, virus detection methods are continually improving—for example, synthetic peptides instead of viruses are used to detect CVB-IgM antibodies in serum, not only avoiding live virus infection, but also getting the etiology judgment early and specifically.<sup>35</sup> However, the majority of patients do not show symptoms in the early stage of infection, and it is difficult to take the specimen in time, resulting in a low positive rate of virus isolation. With the application of new detection methods and the accumulation of experience in clinical practice, we need to constantly revise and improve the diagnostic criteria, in order to gradually reduce the number of misdiagnoses and missed diagnoses. We recommend that the patient who does not fully meet the VMC diagnostic criteria can be given a “suspected” diagnosis, treated as myocarditis with long-term follow up, and given staging diagnosis and treatment. In addition, clinicians should make the diagnosis carefully, so as not to increase patients' economic or mental burden, or waste

medical resources. Meanwhile, the diagnosis should be made on the basis of a comprehensive analysis of clinical data and the exclusion of other diseases.<sup>44</sup> Ruling out possible diseases, diagnostic treatment, evidence-based medicine, and the response to treatment can help indirectly determine the VMC diagnosis, which provides a better way for diagnosing suspected VMC and makes up for the lack of medical history, symptoms and laboratory examination for diagnosis, avoiding missed diagnosis or misdiagnosis of patients with atypical VMC. Since myocardial biopsy has not been popular, patients cannot be definitely diagnosed as VMC in the initial stage; however, they should still be observed and treated in terms of myocarditis, and followed up for 6 to 12 months or even longer in order to determine the diagnosis. In addition, long-term follow up is one of the effective ways to estimate therapeutic effect and prognosis.

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