VIRAL MYOCARDITIS – CLINICAL ISSUES AND CONTROVERSIES: QUESTIONS TO BE ANSWERED

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Abstract

Suspected viral myocarditis is an important cause of cardiomyopathy that presents diagnostic and therapeutic challenges. One might say it is a disease of a thousand faces, still challenging for diagnosis and treatment. There are still lot of controversies in the field of myocarditis and questions to be answered. The exact incidence of myocarditis is difficult to be estimated. Pathophysiology of the viral myocarditis is today well studied, but still not elucidated in all stages. The clinical presentation of viral myocarditis varies from non-specific electrocardiographic abnormalities and mild viral illness to acute hemodynamic compromise and acute heart failure or even sudden cardiac death in case of diffuse myocarditis. The initial evaluation should include electrocardiography, echocardiography, and, if possible, contrast-enhanced cardiac MRI. Recent advances in the diagnosis of myocarditis have centered on the development of newer technologies to more precisely identification of the cardiac inflammation.

The treatment of viral myocarditis varies by clinical presentation. The most severe presentation, acute heart failure, should be managed according to the current guidelines of the ACCF/AHA/ESC and the Heart Failure Society of America. Extracorporeal membrane oxygenation (ECMO) has also been used as a short-term bridge to transplant or recovery, but usually in patients with sustained ventricular arrhythmias, in whom support with ventricular assist devices would be less effective.

Definition and Diagnosis

Myocarditis is defined as inflammation of the heart muscle – myocardium. The diagnosis may be established by clinical or histopathologic criteria, although the gold standard for diagnosis has been the Dallas criteria based on histopathology from an endomyocardial biopsy (4). The need for an invasive procedure required to obtain a sample of the myocardium and histopathologic analysis complicate practical clinical approach to the diagnosis and treatment. Furthermore, the Dallas criteria are not any more sensitive...
for myocarditis since it has been shown that they do not consider the presence of viral genome in the heart (5).

Besides viral infection, myocarditis can also be caused by bacterial as well as spirochetal agents, mycotic disorders, rickettsial diseases, protozoal diseases, helminthic agents, cardiotoxins, causes of hypersensitivity reactions and systemic disorders (6). However, the viral myocarditis is the most common in the developed countries including Serbia. There is a huge number of different viruses causing myocarditis. The most common viruses causing viral myocarditis are listed in Table 1. Recent influence H1N1 pandemy revealed that influenza H1N1 infection followed by severe myocarditis has been reported mainly in children but some studies implicated that it was not rare also in adults (7).

<table>
<thead>
<tr>
<th>Viral agents commonly causing myocarditis</th>
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<tr>
<td>1. Adenovirus</td>
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<td>2. Arbovirus</td>
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<td>3. Coxackievirus B</td>
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<td>4. Cytomegalovirus</td>
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<td>5. Dengue virus</td>
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<td>6. Echovirus</td>
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<td>7. Epstein-Barr virus</td>
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<td>8. Hepatitis C</td>
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<td>9. Herpesvirus</td>
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<td>10. HIV</td>
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<td>11. Influenza virus</td>
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<td>12. Mumps</td>
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<td>13. Parvovirus B19</td>
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<td>14. Poliomyelitis</td>
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<td>18. Varicella</td>
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<td>19. Variola</td>
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<td>20. Yellow fever</td>
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Table 1. The most common viruses causing viral myocarditis

**Epidemiology**

The exact incidence of myocarditis is difficult to be estimated. The study of Fabre et al. (8) revealed myocarditis to be the cause of sudden cardiac death in 8.6% of cases and it was identified in up to 9% of routine postmortem examinations. There are also some gender differences. Most studies of myocarditis report a slight male predominance, suggesting the important role of the estrogen hormones (9,10). Enteroviruses have traditionally been linked to viral myocarditis, mainly due to the co-occurrence of increased enterovirus titers and a clinical syndrome of acute heart failure (11). In the era of new molecular techniques and invasive, one could say, aggressive strategy in endomyocardial tissue examination, many other viruses and viral co-infections have been recognized as the important cause of the viral myocarditis (12,13).

Nowadays there are more than 30 viruses associated with DCM. The prevalence of enteroviruses decreased after 1995, followed by the increase in the prevalence of adenoviruses (14). More recently, parvovirus B19 has been the most commonly detected viral genome in patients with severe myocarditis (15,16). So, the pathogenic role of enteroviruses in myocarditis and chronic DCM is well established. Nevertheless, it can be said that there still some questions about pathogenetic role of the parvovirus B19 in acute myocarditis – there is a high prevalence of parvovirus B19 DNA in the heart of patients with no evidence of dilated cardiomyopathy or myocarditis (17,18). There are also some specific virus distribution according to the different geographic parts: in Japan, hepatitis C virus has been associated with myocarditis, while influenza virus, cytomegalovirus, and Epstein- Barr virus have been identified in some patients with acute and chronic myocarditis (6).

**Pathophysiology**

Pathophysiology of the viral myocarditis is today well studied, but still not elucidated in all stages. The myocarditis characteristically develops after a lag period of several weeks following the initial systemic infection, suggesting the involvement of immunological mechanisms. Viremia is followed by cardiomyocyte infection. Viruses enter cardiac myocytes and macrophages through specific receptors, inciting a cytotoxic effect (19,20).

There are four phases of the viral myocarditis. In the first phase, acute infection of cardiac myocytes results in myocardial death and activation of the innate immune response, including interferon gamma, natural killer cells, and nitric oxide (21,22). Antigen-presenting cells phagocytize released viral particles and cardiac proteins and migrate out of the heart to regional lymph nodes. This is the most important phase for the development of the consequences and further DCM. Most of the patients recover, but few of them have progression to a second phase - an adaptive immune response. This response leads to the production of the antibodies to viral proteins. This production is favourable for the patient. But, the problem lies in the changed immune response and the production of the antibodies to some cardiac proteins (including cardiac myosin or muscarinic receptors), followed by effector T cells proliferation. Macrophages are innate immune cells that play an important role in activation of the immune response and wound healing. Viral infections requiring Th1-type responses may induce M2 as a strategy to evade the immune system. M2 are particularly efficient at scavenging self tissues following injury through receptors like the mannose receptor and scavenger receptor-A. Thus, M2 may increase autoimmune disease by presenting self-tissue to T cells. M2 may also exacerbate immune complex (IC)-mediated pathology and fibrosis, a hallmark of autoimmune disease in women, due to the release of profibrotic factors such as interleukin (IL)-1α, transforming growth factor-α, fibronectin and matrix metalloproteinases. Fairweather and Cihakova (23) have found that M2 comprise anywhere from 30% to 70% of the infiltrate during acute viral or experimental autoimmune myocarditis and shifts in M2 populations correlate with increased IC-deposition, fibrosis and chronic autoimmune pathology. Thus, women may be at an increased risk of M2-mediated autoimmunity due to estrogen’s ability to increase Th2 responses.

In the third phase, the immune response is down-regulated, and fibrosis replaces a cellular infiltrate in the myocardium. In this phase the main problem is left ventricular remodel-
eling caused by the unproprie neurohumoral stimulation and hemodynamic stress: the both ventricles dilate (left ventricle especially), the heart develops heart failure, leading to the chronic dilative cardiomyopathy. Viral genome may persist in the heart or inflammatory mechanisms may persist and contribute to ventricular dysfunction, or even both (24).

Some new investigations confess that myocarditis might be a defect in central immune tolerance. Metzger et al. showed that myocarditis is a T cell-mediated autoimmune disease that occurs due to insufficient thymic negative selection of α-myosin-reactive T cells (25). It is also well documented that some environmental conditions influence the course of the viral myocarditis: selenium deficiency contributes to the acute, subacute and chronic myocarditis in coxsackievirus-infected mice, by fostering the active virus replication in the myocardial tissue, that shoule be kept on mind in myocarditis prevention as well as in treating (26).

Clinical Presentation and Diagnosis

One could say myocarditis is a disease of a thousand faces. Indeed, the clinical presentation of viral myocarditis varies from nonspecific electrocardiographic abnormalities and mild viral illness to acute hemodynamic compromise and acute heart failure or even sudden cardiac death in cases of diffuse myocarditis (27). Development of the dilative cardiomyopathy is an important clinical problem, arising after an initial episode of viral myocarditis, perhaps unrecognized and forgotten (28). However, most of the patients are quite asymptomatic, leading to the problem of myocarditis misdiagnosis. Viral myocarditis may be particularly virulent in infants and in pregnant women leading to sudden acute heart failure (29-32). Sometimes, myocarditis is diagnosed as “by-stander” of some other manifested disease (33,34). Its focal presentation may mimic, but also trigger (in the case of coronaritis) acute myocardial infarction (34).

Symptoms

The symptoms are nonspecific, including fatigue, dyspnea, palpitations and precordial discomfort (35,36). Most frequent symptoms are: dyspnea (72%), chest pain (32%), and arrhythmias (18%) (27). Chest pain usually reflects associated pericarditis, but precordial discomfort suggestive of myocardial ischemia is occasionally observed (35,36). Acute focal myocarditis mimics a diagnosis of myocardial infarction, with acute onset of chest pain, tachyarrhythmia, regional wall motion abnormalities or even sudden death (37-39).

Signs

Physical examination findings are variable and nonspecific. The findings can include tachycardia, laterally displaced point of maximal impulse, soft S1 sound, S3 or S4 gallop. Tachycardia is probably the most important sing or “conditio sine qua non” in acute myocarditis, an characteristically is out of proportion to the temperature elevation. A transient apical systolic murmur may appear, as a consequence of the functional mitral regurgitation (39,40). Clinically proved congested heart failure can be seen in the more severe cases (29,37). Pulmonary and systemic emboli may occur in the most severe cases.

Laboratory Findings

Inflammatory syndrome is positive, sedimentation rate and CRP, in acute phase. Leucocytes are usually within physiological ranges, sometimes with typical lymphocyte predomination. CRP is frequently present in the myocardium of patients suffering also from DCM and correlates with C5b-9 and macrophages in myocardial tissue. Zimmermann et al. suggest that CRP contributes to myocardial damage not only in acute phase, but also in chronic myocardial inflammation in DCM via activation of the complement system and chemotaxis of macrophages (41,42).

Levels of cardiac biomarkers, including CK-MB, troponin I, and troponin T, are not always elevated, but its elevation indicates myocardial damage and there is a strong positive correlation between myocardial injury and their level. Elevated troponin T levels were found just in 35% of patients with suspected myocarditis providing a sensitivity of 53%.30 The serum concentration of troponin I is increased more frequently than that of CK-MB fractions in patients with acute myocarditis (24).

Serological analyses of viral infection in suspected myocarditis are still widely used, although convincing evidence for their value is lacking (43). It is important to emphasize that viruses rarely could be cultured from the heart tissue of patients with fatal acute myocarditis. Mahfoud et al. proved that only in 5 out of 124 patients (4%), there was serological evidence of an infection with the same virus that was detected by EMB. Sensitivity and specificity of virus serology were only 9 and 77%, respectively, the positive predictive value 25% and the negative predictive value 49%.

It can be said that for patients with suspected myocarditis, virus serology has no relevance for the diagnosis of myocardial infection.

Electrocardiography

Electrocardiography may be quite normal or show nonspecific ST-T wave changes, ST elevation mimicking acute myocardial infarction, or various degrees of blockade of the atrioventricular node. The presence of Q waves or bundle branch block is associated with large myocardial damage and increased rates of heart transplant or death (9,44). Complete AV block is a rare situation and usually transient, resolving without sequelae, but, occasionally may be the cause of the sudden death (45,46). Intraventricular conduction abnormalities are associated with more severe myocardial damage and a worse prognosis (45-47).

Echocardiography

Echocardiography plays the crucial role in the non-invasive diagnosis of the viral myocarditis. Echocardiography is a non-invasive method, widely used and feasible method for the quantification of the left ventricular dimensions, function and existence of the segmental and global hypokinesia. Classic echocardiographic findings include global hypokinesis with or without pericardial effusion (48). Decreased left ventricular systolic function without segmental hypokinesia and akinesia are highly indicative for myocarditis. Diastolic dysfunction is also an important echocardiographic sign for suspected myocarditis and sometimes it is the only, but very

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important echocardiographic sign, especially in younger population. Echocardiography should also be used to rule out other causes of heart failure, such as valvular, congenital, or amyloid heart disease.

Felker et al. (48) concluded that in there are almost normal LV diastolic dimension with significant deterioration of the systolic function in fulminant myocarditis. Surprisingly, right ventricular systolic function was found to be an independent predictor of death or myocardial transplant in patients with acute myocarditis (49). Left ventricular thrombi can be seen in the most severe cases, linked to highly deteriorated left ventricular function (40).

**Coronary Angiography**

Coronary arteries imaging (invasive or non-invasive) in myocarditis reveals almost always normal coronary arteries, although myocarditis may affect patients with coronary artery disease, but the culprit lesion cannot be identified, since the heart problems are not caused by compromise in coronary circulation. Coronary angiography (CA) is not the first choice diagnostic tool in acute myocarditis. In some patients there may be coexistence of myocarditis and coronary artery disease (CAD). In these patients, with ST elevation and high probability for CAD, CA could be done in order to exclude underlying CAD. Recent development of the multidetector computed tomography (MDCT) coronaryography has introduced this fast and non-invasive diagnostic tool for diagnostic use in patients with ST elevation and low probability for CAD.

**New Diagnostic Technologies**

Recent advances in the diagnosis of myocarditis have centered on the development of newer technologies to more precisely identification of the cardiac inflammation. An article by Skouri et al. (50) reviewed noninvasive imaging studies for detecting myocardial inflammation. The importance of noninvasive cardiac imaging is so important mainly due to the low sensitivity of the Dallas criteria in histological diagnosing of myocarditis. An estimated number of 17 endomyocardial biopsies is necessary to diagnose myocarditis with 80% sensitivity, leading many experts to believe there is a real need for practical noninvasive imaging studies to aid in diagnosing and managing of the acute DCM (51). Cardiac MRI is very useful weapon in diagnosing of myocarditis (52,53).

Newer techniques, including segmented inversion recovery gradient echocardiography pulse sequences, have improved contrast enhancement of the myocardium and allowed visualization of small myocardial injuries, increasing the sensitivity of detecting active myocarditis. Mahrholdt et al. found that contrast enhancement was present in 88% of patients in a study of 32 patients with suspected myocarditis., and biopsy samples from the area of enhancement showed active acute or chronic myocarditis in 90% of patients (54). The overall study findings concluded that focal myocardial gadolinium enhancement, coupled with regional wall motion abnormalities on echocardiography, yielded a positive predictive value of 71% and a negative predictive value of 100% (55).

**Endomyocardial Biopsy**

Histologic examination of heart tissue is required to confirm the diagnosis of myocarditis. However, endomyocardial biopsy (EB) is an invasive procedure and its utility is limited because of sampling error from patchy inflammatory infiltrates and variability in observer interpretation (56). In a large case series, the sensitivity of endomyocardial biopsy was only 35% compared to a clinical criterion standard that included recovery of myocardial function (57). Immunostains for cell specific markers such as T lymphocytes (CD3) or macrophages (CD68) or human leukocyte antigens have a sensitivity of up to 50%, which is much better than routine histologic techniques. (58,59). This is also very important in risk prediction: recent series suggest that the presence of inflammation as defined by immunoperoxidase stains may predict the subsequent risk of death or heart transplant (16).

The presence of viral genomes in heart tissue from patients with acute myocarditis may predict adverse events. The absence of viral genomes in patients with chronic myocarditis may identify a subset of patients who will respond to a short course of immunosuppression (60,61). The current recommendations from an American College of Cardiology Foundation/American Heart Association/European Society of Cardiology (ACCF/AHA/ESC) scientific statement support a limited role for EB in the evaluation of patients with cardiomyopathy. The class I indications are limited to patients with newonset heart failure (<2 weeks) associated with a normal or dilated left ventricle with hemodynamic compromise and to patients with new-onset heart failure of 2 weeks to 3 months’ duration with a dilated left ventricle, ventricular arrhythmia, or high degree atrioventricular blockade or to patients whose condition fails to respond to treatment in 1 to 2 weeks (62).

**Treatment**

The treatment of viral myocarditis varies by clinical presentation. The most severe presentation, acute heart failure, should be managed according to the current guidelines of the ACCF/AHA/ESC and the Heart Failure Society of America (63-66). Experimental models of murine myocarditis generally support the guideline based treatment recommendations that apply to forms of noninflammatory DCM and that have been studied in clinical trials. Hemodynamically stable patients with DCM and symptomatic heart failure may benefit from angiotensin-converting enzyme inhibition or angiotensin receptor blockade. Trials have shown that in euolemic patients with DCM, beta-adrenergic blockade may improve LV function, heart failure symptoms, and decrease inflammation, with improvement in survival. Patients with persistent heart failure symptoms despite optimal management with angiotensin and adrenergic pathway inhibition may benefit from aldosterone antagonists, such as eplerenone or spironolactone. Diuretics should be carefully used to optimize intravascular volume. The use of anticoagulation is similar to that in patients with non-ischemic DCM - it is usually indicated in the setting of concomitant atrial fibrillation or arterial or venous thromboembolism. In patients with severe myocarditis and symptomatic hypotension, parenteral inotropes, including phos-
phodiesterase inhibitors (milrinone) or adrenergic agonists (dobutamine or dopamine) may be required. Despite maximal oral and parenteral medical therapy, patients with the most severe form of acute myocarditis may require mechanical circulatory support. Data from case series suggest that ventricular assist devices may provide a bridge to transplant or to recovery in patients with acute myocarditis (67,68). Extracorporeal membrane oxygenation (ECMO) has also been used as a short-term bridge to transplant or recovery, but usually in patients with sustained ventricular arrhythmias, in whom support with ventricular assist devices would be less effective. In a case series, Chen et al. reported that 80% of patients who received ECMO therapy were bridged to recovery (69).

Because patients generally present days to weeks after the initial viral infection, antiviral therapy has limited applicability in patients with acute viral myocarditis. Also, the sensitivity of endomyocardial biopsy for the diagnosis of viral genomes in the myocardium has not been reported. Nonetheless, antiviral agents have been evaluated for the treatment of acute myocarditis in animal models and in a few small case series. Ribavirin and interferon alpha improved survival in mice with acute myocarditis when administered at the time of virus inoculation (70,71). Antiviral therapy cannot be recommended for the treatment of acute myocarditis at this time; however, the role of antiviral therapy for more chronic myocarditis associated with persistent viral genomes is a matter of active clinical investigation.

A large body of experimental evidence suggests that acute and some chronic myocardial injury in myocarditis is due to an immune response involving T lymphocytes and autoreactive antibodies. However, data from the few randomized clinical trials suggest that on average patients with acute myocarditis do not benefit from immunosuppression. For example, the US Myocarditis Treatment Trial, in which 111 patients with histologically confirmed myocarditis were randomised to immunosuppression and immunomodulation trials suggested that a symptom duration of less than 6 months was associated with a lack of active treatment benefit, and yet trials of DCM in which patients had symptoms for more than 6 months were generally positive. The difference in response was due largely to spontaneous improvement in the placebo arm participants who had symptoms for less than 6 months (72). In a trial of immunosuppression in patients with myocarditis and symptoms for more than 6 months, LVEF and New York Heart Association functional class improved after treatment with azathioprine and prednisone (73). In a recent trial of patients who had chronic myocarditis, no viral genomes, and symptomatic heart failure, treatment with azathioprine and prednisone also improved cardiac function and New York Heart Association functional class (60). After recovery from acute myocarditis, patients should be cautioned to refrain from aerobic activity for several months. Timing of resumption of aerobic exercise should be guided by the severity of acute injury and the degree of ongoing LV systolic dysfunction. For patients with ongoing systolic dysfunction, counseling on lifestyle modifications is vital, including a low-sodium diet, fluid restriction, and avoidance of nonsteroidal anti-inflammatory medications.

**Prognosis and Outcome**

The prognosis for patients with acute myocarditis varies. It depends on clinical presentation, ejection fraction (EF), and pulmonary artery pressure (74,75). Surprisingly, several studies suggest that patients with fulminant myocarditis and hemodynamic compromise at presentation have better outcomes, if they receive aggressive hemodynamic support early, have better survival than some of those with acute nonfulminant myocarditis (76-79). In a prospective study, McCarthy et al. used clinical features to classify patients with biopsy-proven myocarditis and found that 93% of those with fulminant myocarditis were alive at 11-year follow-up compared with 45% of those with acute nonfulminant myocarditis (80).

The results of these studies have shown the necessity of early recognition of risk factors for fulminant myocarditis and subsequent aggressive early hemodynamic support. Lee et al. found that, in general, the group of patients with fulminant myocarditis and acute myocarditis had higher pulse rates, lower blood pressure levels, higher C-reactive protein levels, lower cardiac biomarker levels, wider QRS complexes, and decreased LVEFs on admission compared with the nonfulminant group and also the higher in-hospital mortality rate (81). The results of other studies have shown excellent long-term prognosis for patients who are treated with aggressive hemodynamic support (82).

Several mechanisms have been identified by which fulminant myocarditis results in persistent LV dysfunction less frequently than acute nonfulminant myocarditis (82). Kühl et al. postulated that persistence of viral genome leads to chronic inflammation, thus diminishing the recovery of LV function (13). They found that, in patients with clearance of viral genome, EF improved from 50% to 58%, and in patients with persistence of viral genome, EF decreased from 54% to 51%, both findings are statistically significant. These results underscore the importance of immunohistochemical findings on endomyocardial biopsy that are suggestive of chronic inflammation as a negative prognostic indicator. In contrast with patients who have acute myocarditis, patients who have evidence of chronic inflammation may respond to immunomodulatory therapy. At the end, it can be said that the prognosis in acute myocarditis is generally good except in patients with giant cell myocarditis, but persistent, chronic myocarditis usually has a progressive course but may respond to immunosuppression.

**CONCLUSION**

Suspected viral myocarditis is an important cause of cardiomyopathy that presents diagnostic and therapeutic challenges. The initial evaluation should include electrocardiography, echocardiography, and, if possible, contrast-enhanced cardiac MRI. Patients with presentations suggestive of ischemia should usually undergo coronary angiography if they have high probability for coronary artery disease or MDCT coronaryography, in case of low probability for CAD. Patients with ventricular tachycardia, hemodynamic instability, or high-grade AV block should be treated in coronary care unit and usually endomyocardial biopsy should be advised. Polymerase chain reaction techniques may facilitate precise viral genomic diagnosis, which may guide future
therapies. Patients with a fulminant presentation should be aggressively supported therapeutically because outcomes are particularly favorable if they survive the initial injury. All patients should receive standard heart failure care as outlined in the ACC/AHA/ESC guidelines. Ongoing trials of antiviral treatment such as the use of interferon beta may lead to the use of specific antiviral treatment in the future. Conversely, it is still not clear if patients with chronic DCM and no evidence of viral genome in the heart tissue may benefit from immunosuppressive therapy.

A recent viral infection should always be considered as a cause of acute DCM, being mindful that the spectrum of viruses that cause myocarditis continues to change. Cardiac MRI is useful for diagnosing acute myocarditis. Finally, endomyocardial biopsy is indicated in patients with hemodynamic compromise, heart block, or ventricular tachycardia or those whose condition fails to respond to standard care.

Apstrakt

Virushni miokarditis može biti akutnog, subakutnog i hroničnog toka. Akutni virusni miokarditis je oboljenje najčešće asimptomatskog toka, ali može biti praćen i nastankom akutne srčane insuficijencije, komplikovanim poremećajima srčanog ritma i sprovođenja, a retko, u najtežim slučajevima komplikovan je i nastankom iznenadne srčane smrtri. Rana dijagnoza i terapija su vrlo važne za tok i sprečavanje nastanka komplikacija, ali nespecifičan tok ovog oboljenja često usporava pravovremenu dijagnozu i terapiju. Fulminantni miokarditis, neoečekivano, može imati dobro prognozu ukoliko se pravovremeno primeni mehanička ventilacija i po potrebi ekstrakorporalna membranska oksigenacija, koja je vrlo efikasna kod bolesnika sa malignim ventrikularnim poremećajima srčanog ritma. Nažalost, još uvek su nedovoljno jasni faktori sprečavanja nastanka hroničnog miokarditisa i dilatativne kardiomiopatije. U navedenom radu izloženi su savremeni stavovi o dijagnozi i terapiji virusnog miokarditisa.

REFERENCES


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