Influenza-related Viral Myocarditis

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ABSTRACT
Seasonal influenza outbreak is responsible for significant morbidity and mortality around the world. The disease can be severe, leading to rapid worsening of breathing and culminating in death. The pulmonary manifestations are prominent and may mask the involvement of other organs, such as the heart. This review will focus on the incidence, pathophysiology, clinical manifestations, and management of viral myocarditis.

INCIDENCE
In addition to the occasional epidemic of influenza A, there have been 3 major pandemics in the past century. The Spanish flu in 1918, caused by the H1N1 strain, appears to have been the most devastating, affecting about one-third of the world population and resulting in 50 million deaths. It affected mostly young healthy individuals. The Asian flu in 1957 was caused by the H2N2 strain, and the Hong Kong flu in 1968 was caused by the H3N3 strain. The recent swine flu pandemic was caused by the H1N2 strain, and the Hong Kong flu in 1968 was caused by the H3N3 strain. The recent swine flu pandemic was caused by the H1N1 strain. While similar to the 1918 pandemic, it had less impact, since it appears that the strain was genetically different and less virulent. The current vaccination and other preventive measures, as well as treatment, are equally different and designed to mitigate the complications of the infection. Needless to say, the world is now very different from the post-World War I era, and most countries are at high alert to combat this pandemic. The media and the widespread dissemination of information on the Internet enhance awareness of the disease, limits its spread, and hopefully has a positive impact on its morbidity and mortality.

In severe cases of infection, clinicians pay utmost attention to the pulmonary symptoms that ensue, yet the infection may affect other organs such as the heart, causing acute myocarditis. Cases of acute myocarditis may result in shortness of breath, left ventricular dysfunction, and even death.

During the Sheffield, England influenza epidemic from 1972 to 1973, the cases of 50 consecutive patients who were initially diagnosed as mild cases and were treated on an outpatient basis were followed. Transient electrocardiogram (ECG) changes were seen in 18 patients, and long-lasting changes were seen in 5 patients. The ECG changes were non-specific:
S-T abnormality, nodal rhythm, atrial fibrillation, and atrio-ventricular dissociation. Four of the patients died, and autopsy revealed abnormal myocardium with changes ranging from inflammatory cellular infiltration to interstitial edema and petechial hemorrhages.

During the influenza epidemic in 1978 in Finland, 104 consecutive military recruits who presented with sudden respiratory illness were prospectively studied. Forty-one patients tested positive for influenza A. Six patients had, in addition to electrocardiographic abnormalities, regional wall motion abnormalities on 2-D echocardiography. The chance of coronary artery disease in young military recruits should be very low, and it is highly probable that these regional wall motion abnormalities represent cases of acute myocarditis, with an incidence close to 15%. Other publications have also reported acute myocarditis during viral illness.

In a landmark study conducted during the Asian influenza pandemic of 1957, 33 cases of sudden or unexpected death occurred in the United States in the influenza pandemic of 1957. All cases underwent autopsy. During the epidemic of 1918, Locke et al performed autopsies on 126 fatal cases of influenza. In the majority of cases, the heart was affected. Frequently, both the left and right sides of the heart were dilated. Microscopic examination revealed loss of cardiac striations; the nuclei of the cardiac muscle cells were pale, swollen, or fragmented; and the interstitium was filled with hemorrhage, edema, and cellular infiltration. The pericardium frequently showed inflammatory changes, and, rarely, the endocardium revealed subendocardial petechial hemorrhages.

**CLINICAL MANIFESTATION**

Each year, 3 million to 5 million patients suffer from seasonal influenza, with an annual mortality rate of 300,000. During influenza pandemics, morbidity and mortality are expected to increase, and since pulmonary involvement is more universal and frequently severe, it may conceal the diagnosis of viral myocarditis. A heightened awareness of cardiac involvement is essential in a disease that affects at least 10% of the infected population.

The onset of acute carditis starts on day 4 to 7 of the onset of viral symptoms. Patients may have worsening shortness of breath or recurrence after initial improvement. Patients may present with other cardiac symptoms such as chest pain or palpitations. On examination, patients may have sinus tachycardia out of proportion to the degree of fever, signs of cardiomegaly, and, when significant, left ventricular dysfunction and signs of congestive heart failure are evident.

In a patient with suspected acute carditis, a 12-lead ECG should be acquired. Changes such as sinus tachycardia, atrial or ventricular arrhythmias, conduction abnormalities, and non-specific S and T wave abnormalities raise the degree of suspicion and prompt the need for further diagnostic testing. Morimoto et al were able to show that patients with significant conduction abnormality demonstrated myocardial interstitial edema using myocardial biopsies. Lewes et al, in 1974, suggested that patients with significant myalgias are more likely to develop acute myocarditis during a viral illness and may develop significant electrocardiographic abnormalities.

Echocardiography is the mainstay in making the diagnosis of acute myocarditis. It may show diffuse...
left ventricular dysfunction, but occasionally it demonstrates regional wall motion abnormalities. These areas of regional wall motion abnormalities are usually involved with the mononuclear inflammatory cells and interstitial fibrosis.\textsuperscript{16} When cardiac necrosis ensues, cardiac biomarkers may be detected in the blood, particularly troponin.\textsuperscript{17} Serum interleukin-10 is elevated in patients with severe acute myocarditis and may predict the need for mechanical cardiopulmonary support.\textsuperscript{18} Acute and convalescent viral titers may aid in the diagnosis.

While the majority of cases of viral myocarditis are of mild to moderate severity, some cases may be fatal,\textsuperscript{19,20} particularly during epidemics.\textsuperscript{21} Lee et al\textsuperscript{22} showed that prolongation of the QRS complex and depressed left ventricular function on admission were predictive signs of fulminant myocarditis and were associated with increased mortality.

Acute myocarditis may have unusual presentations, such as acute myocardial infarction and can also precipitate acute myocardial infarction in patients with known coronary artery disease.\textsuperscript{23, 24} This is due to inflammation of epicardial coronaries or microvascular inflammation.

**MANAGEMENT**

The majority of cases of acute myocarditis may be mild and result in spontaneous improvement, but some cases may be fatal. Many cases not recognized during the acute episode may develop into dilated cardiomyopathy later and may require cardiac transplantation.\textsuperscript{25} Therefore, recognition and early treatment are of paramount importance, particularly during influenza pandemics.

In addition to bed rest and the standard management of patients with congestive heart failure, special attention needs to be focused on the use of angiotensin converting enzyme inhibitors (ACEI) in myocarditis.\textsuperscript{26} There is a paucity of controlled studies using ACEI in human myocarditis. With the incidence of the disease being low during non-epidemic times, often mild or moderate in severity, and occasionally missed clinically, conducting human controlled studies to test the efficacy of various medications in human myocarditis is a challenge. It has been shown, however, that the disease process in a murine model of coxsackievirus myocarditis closely parallels that of human myocarditis.\textsuperscript{27}

With the ACEI captopril's role in the treatment of left ventricular dysfunction and congestive heart failure well-established in humans, we sought to test its effect in the treatment of experimental murine myocarditis. Ninety 3-week-old cesarean-derived mice (Charles...

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Figure 1A. Microphotograph of animal heart infected with coxsackievirus B3, showing extensive inflammation and necrosis.

Figure 1B. Captopril treated animal. Low power magnification, hematoxylin, and eosin. (Courtesy of Circulation. Rezkalla et al., Circulation. 1990;81(3):1039-1046.)
River Laboratory, Wilmington, Massachusetts) were infected with coxsackievirus B3 and divided into 2 groups. The first group of mice was started on treatment on day 1 of the infection, while a second group started treatment on day 10 of the experimental infection. In each group, treatment was then randomized to captopril at a dose of 0.05 mg/g administered intraperitoneally twice daily or normal saline. The group given captopril had less cardiac mass and less evidence of congestive heart failure as measured by liver to body weight ratio. These effects were expected in the face of the known effects of captopril. The surprising finding was the significant reduction in inflammation, cardiac necrosis, and dystrophic calcification in the group treated with captopril starting on day 1 of the infection (Figure 1A and 1B). We hypothesized that perhaps, besides the ACEI properties, the oxygen radical scavenging properties of captopril may be responsible for such a dramatic benefit. Enalapril was not effective in treating the infected group, while captopril was, and resulted in improved survival.

The effect of beta blockers on acute myocarditis has been somewhat controversial. While metoprolol was not found to be favorable during acute myocarditis, carvedilol was clearly beneficial. In the experimental model of coxsackievirus-induced murine myocarditis, carvedilol treatment resulted in decreased expression of the proinflammatory cytokines as well as matrix metalloproteinases. This resulted in improved left ventricular function in treated animals. There is no role or benefit for corticosteroid therapy in acute viral myocarditis. Their use in animal model studies has resulted in increased mortality. Their use in human studies has been disappointing, and currently there is no clear role for their use, particularly during the acute phase. The role of antiviral therapy is even less clear, suggesting a need for controlled randomized trials. A simple diagram to help clinicians manage cases of acute myocarditis is depicted in Figure 2.

CONCLUSION

During any influenza outbreak, a significant number of patients may be infected and suffer the consequences of this widespread disease. The spectrum of illness associated with influenza infection is broad, ranging from several days of headache, fever, and generalized malaise to secondary pulmonary infections that may be life threatening. And it may include acute carditis, whose early signs and symptoms may be subtle and are frequently overlooked. Acute myocarditis has been directly attributed to the influenza infection and has contributed to the fatalities associated with the infection. Thus, it is imperative that early recognition and prompt therapeutic intervention with effective agents (ie, captopril or carvedilol) be instituted to achieve a favorable outcome and avoid the long-term complications that have been associated with the infection.

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Figure 2. Diagram for diagnosis and treatment of acute viral myocarditis.