Virus and the Heart

By Walter H. Abelmann, M.D.

SUMMARY

Viral infections may overload the heart by altering pulmonary or systemic vascular resistance, may induce congenital malformations, or may invade the mature heart muscle and provoke acute and possibly chronic myocarditis. The nature of the association of myocarditis with known viral infections and the pathophysiologic effects of myocardial involvement are analyzed. Although viral myocarditis of clinical significance is relatively rare, recent advances in diagnosis and therapy warrant greater dissemination and application of existing knowledge as well as further clinical investigation.

Additional Indexing Words:
Myocarditis

The nature of cardiac involvement in viral diseases has been the subject of several recent reviews.1-4 Viral infections may affect the heart in one of three ways:

(1) The infection may result in systemic or pulmonary hypertension (poliomyelitis) or systemic vasodilatation, which in turn may lead to heart failure or circulatory collapse, especially in patients with underlying chronic cardiac or pulmonary disease. These circulatory effects may account for much of the cardiovascular morbidity of viral etiology and for most of the excess mortality of patients with chronic cardiopulmonary disease during influenza outbreaks.

(2) Infection during fetal life by viruses that cross the placenta may induce congenital malformations. This relationship has been well established for rubella.5 About 50% of children exposed to maternal rubella during the first month of fetal life have congenital anomalies, two thirds of which involve the heart. The risk lessens subsequently but persists through the fourth month. The most frequent anomalies are patent ductus arteriosus and peripheral pulmonary stenosis. Efforts at wider exposure of prepubertal girls to rubella or rubella vaccination appear justified.

In addition, evidence for an association between maternal Coxsackie B virus infection and congenital heart disease has been presented by Brown and Evans.6 Analysis of paired, maternal sera revealed a significantly higher incidence of infection with Coxsackie B virus, types 3 and 4, during pregnancy in the mothers of 43 infants with congenital heart disease than in matched controls. It is of note that half of the infections were subclinical.

Mumps virus has been assigned an etiologic role in congenital endocardial fibroelastosis. In a study by Shone and associates7 42 of 50 cases had a positive reaction to intradermal killed mumps virus antigen, compared to 9% of 138 controls. Gersony, Katz, and Nadas,8 however, were unable to confirm this in a series of 16 cases.

(3) Viruses may invade the mature heart directly, inducing structural and functional alterations.

Which Viruses Cause Myocarditis?

Table 1 lists 18 of the more common viruses or viral diseases generally accepted as potential causes of myocarditis. Yet, we may legitimately ask how many of these are
established causes. Only influenza, Coxsackie, and poliomyelitis viruses have been isolated from heart tissue with any regularity. Myocarditis in animals infected experimentally has been reported only for Coxsackie, vaccinia, pseudorabies, and encephalomyocarditis viruses.

**Table 1**

<table>
<thead>
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<th>Viral Diseases Associated with Myocarditis</th>
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<tr>
<td>Rubeola</td>
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<td>Rubella</td>
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<td>Variola</td>
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<td>Vaccinia</td>
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<td>Varicella</td>
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<tr>
<td>Herpes zoster</td>
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<tr>
<td>Mumps</td>
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<td>Influenza</td>
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<td>Psittacosis</td>
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What are the Structural and Functional Effects of Myocardial Invasion by Virus?

The viruses associated with myocarditis are blood borne and are thought to reach the heart with the more than 360 liters of blood that daily perfuse this organ even in inactive man. Presumably virus leaves the capillaries and, via the perivascular interstitium, enters the myofibrils, in which it replicates. Myocytolysis, necrosis, and edema are thought to be the direct effects of intracellular replication of virus. Autoimmune reactions have also been postulated but not proven. An inflammatory response is usually—but not necessarily—provoked, resulting in accumulation of cellular infiltrates, generally interstitial, often perivascular. These infiltrates are capable of healing without residua. Such microscopic lesions may be either focal or diffuse, without evident abnormality upon gross inspection of the heart. Virus has also been isolated from hearts showing no structural abnormalities on light microscopy. On the other hand, the severely and diffusely involved heart may display pallor, flabbiness, dilatation, and even increase in weight.

I am not aware of any systematic hemodynamic observations in proven viral myocarditis—or myocarditis of any etiology. Hemodynamic observations made in this laboratory in acute experimental Chagasic myocarditis in C3H mice due to *Trypanosoma cruzi* revealed a significant decrease in left ventricular systolic pressure, no significant change in right ventricular systolic pressure, and significant

![Figure 1](http://circ.ahajournals.org/)

*Figure 1*

Pressure-volume curves of isolated right and left ventricle of a normal C3H mouse (left) and a mouse with acute Chagasic myocarditis (right). LV = left ventricular; RV = right ventricular. Compliance of both right and left ventricles, indicated by the slope of the curves, is increased in myocarditis.
increases in both right and left ventricular end-diastolic pressures. These findings are compatible with biventricular heart failure. The few isolated hemodynamic observations in clinical cases of severe myocarditis that have come to my attention are in agreement with this hemodynamic pattern. Does this pattern represent true myocardial failure or decreased compliance as in constrictive pericarditis, endocardial fibroelastosis, interstitial fibrosis, or amyloidosis? To answer this question, we are currently studying ventricular pressure-volume characteristics at various stages of experimental Chagasic myocarditis. Figure 1 depicts the left and right ventricular pressure-volume curves of a healthy control mouse and a Chagasic mouse 80 days after inoculation. The slopes of these curves reflect compliance. The right ventricle is more compliant than the left in the healthy as well as the diseased mouse. In myocarditis, both right and left ventricles appear more compliant. Thus, it would seem, at least in this form of myocarditis, that inflammation and necrosis increase compliance and lead to dilatation of the ventricles. The increased diameter of the diseased ventricle, according to the law of Laplace, results in an increase in wall tension which may lead to further dilatation.

So far we have addressed ourselves to general and hemodynamic effects of diffuse myocarditis. We have already stated that myocarditis may be focal, without effect upon gross appearance and heart weight and presumably without hemodynamic effects. Focal myocarditis may cause atrial or ventricular irritability, atrial or ventricular tachyarrhythmias, or partial or complete heart block. Focal lesions most frequently affect repolarization and result in S-T abnormalities of the electrocardiogram. There is nothing specific about any of these electrophysiologic effects. However, these changes tend to be variable, transient, and often completely reversible.

**What Factors are Known to Modify Acute Myocarditis?**

A number of factors have been identified as potential modifiers of the incidence, nature, severity, and course of acute myocarditis. Pearce has shown that intravenous injection of pitressin, a powerful coronary vasoconstrictor, as well as other means of inducing myocardial hypoxia, increases the incidence and severity of myocarditis in experimental vaccinia and pseudorabies. The severity of myocarditis associated with a given infection may thus be determined by the extent to which the disease and its complications enhance or decrease myocardial hypoxia. Hypoxia has been considered especially important in the pathogenesis of myocarditis accompanying poliomyelitis and influenza.

Hypoxia may also, in part, be responsible for the enhancing effect of exercise upon experimental Coxsackie myocarditis first demonstrated in 1964 by Tilles and associates in our laboratory. When C3H mice infected with a cardiotropic strain of Coxsackie A9 virus were exercised daily by swimming, virus was isolated from 46% of the hearts of 24 exercised animals but only from 8% of hearts of 24 control animals. Furthermore, virus was isolated in higher titer from the exercised animals. Recently, Lerner and associates have confirmed the myocarditis-enhancing effect of exercise for Coxsackie virus B3. When mice infected with this more virulent strain were made to swim, most animals died in acute congestive failure.

In 1956, Kilbourne and collaborators reported evidence of a synergistic effect of cortisone and a cardiotropic virus. Their strain of Coxsackie B3 virus by itself resulted in but minimal focal lesions in mice. In the presence of cortisone, however, disseminated myocardial necrosis was produced.

Pearce also reported that the incidence of myocarditis associated with experimental virus III infection in rabbits was increased after intravenous administration of *Streptococcus pyogenes* toxin. It is possible that respiratory infections of bacterial etiology, by means of both hypoxic and toxic effects, may precipitate or enhance myocarditis due to viral infections. It may thus be of interest to search for viral etiology of aseptic myocardial inflammatory lesions associated with bacterial infections.
The above pathophysiologic considerations make it reasonable to postulate that increased volume or pressure loads upon either ventricle have the potential not only of decreasing cardiac reserve, but also of enhancing the viral pathologic process and its consequences. Among possible factors that should be mentioned are fever, systemic and pulmonary hypertension (e.g. in poliomyelitis), pregnancy, preexistent heart disease, and coexistent systemic disease (e.g. anemia). No systematic exploration of the role of these factors has yet been carried out.

In What Manner Does Myocarditis Present Clinically?

The manner of clinical presentation (table 2) logically follows from the above considerations. A wide spectrum is evident, ranging from total absence of clinical manifestations to sudden unexpected death. The extent to which the presence of myocarditis will be suspected is a function of the severity of the overt manifestations, on the one hand, and the alertness of the clinician on the other. It must also be kept in mind that the cardiovascular manifestations may be overshadowed by the systemic manifestations of the viral illness. The details of symptoms, signs, and laboratory findings in viral myocarditis have often been reviewed.1,3,4 Myocarditis should be suspected when an individual without prior heart disease and without evidence of ischemic heart disease develops atrial or ventricular arrhythmias or conduction disturbances (especially if transient), changing electrocardiographic abnormalities (especially of repolarization), cardiac enlargement, pericardial friction rub or effusion, heart failure, or cardiac arrest. Tachycardia is the rule, but bradycardia has been observed. Gallop rhythms may constitute the only evidence of heart failure. In more severe failure, the pulse tends to be small, and blood and pulse pressure low. Whereas signs and symptoms of left ventricular failure may predominate, the picture is usually one of right or biventricular failure. Dilatation of atrioventricular valve rings and ventricles may result in mitral or tricuspid insufficiency. Myocarditis may, however, develop rapidly and progress to circulatory collapse, before congestive heart failure has become manifest.

How is the Diagnosis of Viral Myocarditis Established for the Individual Patient?

When a patient is seen early during the course of illness, it may be possible to isolate virus from throat washings, stool, blood, or myocardium. This is most likely to be successful within the first week. Isolation of a virus establishes its presence, but does not necessarily prove its etiologic role in the illness under consideration.

Detection of rising antibody titer in the serum during the second and third weeks of convalescence may be considered evidence of a recent infection likely to be related to recent symptoms. To this end, tests for complement fixation, virus neutralizing antibody, and hemagglutination inhibition are becoming increasingly available. A fourfold increase is the generally accepted criterion for a current infection. Recently, identification of antigen in tissue or body fluids by immunofluorescent methods and demonstration of virus in tissue by means of electron microscopy have become possible and promise to become clinically useful.3

What is the True Incidence of and Mortality from Myocarditis?

Careful search by Gore and Saphir14 revealed an incidence of 1,402 cases of myocarditis among more than 40,000 autopsies at the Armed Forces Institute of Pathology.

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Table 2
Presentation of Viral Myocarditis

<table>
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<th>No clinical manifestations</th>
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<tr>
<td>Unexplained sinus tachycardia</td>
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<tr>
<td>Atrial or ventricular premature beats</td>
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<tr>
<td>Atrial or ventricular tachycardia</td>
</tr>
<tr>
<td>Ventricular fibrillation/cardiac arrest</td>
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<tr>
<td>Partial or complete heart block</td>
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<tr>
<td>Gallop rhythms</td>
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<tr>
<td>Pericardial rub</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Circulatory collapse (shock)</td>
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<tr>
<td>Abnormal ECG or X-ray</td>
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<td>Incidental autopsy finding</td>
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Table 3

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<th>Therapy of Acute Myocarditis</th>
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<tr>
<td>Specific therapy</td>
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<tr>
<td>Restriction of activity</td>
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<tr>
<td>Oxygen</td>
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<tr>
<td>Monitoring</td>
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<tr>
<td>Antiarrhythmic drugs</td>
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<tr>
<td>Artificial pacemaker</td>
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<tr>
<td>Digitalis</td>
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<td>Diuretics</td>
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Of these, 70 were found in association with viral diseases, and 84 cases of isolated myocarditis might have been of viral etiology. If these two groups are combined, an incidence of 0.38% is obtained. During 1967, 860 deaths or 0.4 per 100,000 population were attributed to acute, nonrheumatic myocarditis in the United States. The validity of these estimates is open to question.

Morbidity is equally difficult to assess. For most viral diseases, involvement of the heart appears to be rare. Although it has been estimated that in outbreaks of Coxsackie viral disease cardiac involvement occurred in about 5% of cases, we really do not know the size of the population infected. Furthermore, reliable criteria for cardiac involvement have not been established. Thus, the validity of nonspecific electrocardiographic abnormalities of the T wave and S-T segment in the diagnosis of acute myocarditis has recently been questioned by Scott and collaborators, who find that while 1.49% of 737 children with acute respiratory infection had such electrocardiographic abnormalities, 1.85% of a control group of 108 children exhibited similar changes. Laboratory evidence of recent viral infection was encountered just as often in patients with normal as in patients with abnormal electrocardiograms (49.5 vs. 42.6%). On the other hand, an interesting recent report suggests that asymptomatic myocarditis may be quite frequent. Stevens and Ground, on the basis of studies of the hearts of 263 pilots killed in aircraft accidents, concluded that the incidence of asymptomatic, isolated, focal myocarditis may be as high as 5% in British males aged 18 to 50 years, and cite evidence that the incidence in Australia may be even higher.

What are the Principal Therapeutic Considerations?

Therapy is influenced by the etiology of the disease, as well as by its manifestations. The principal therapeutic modalities are presented in Table 3. In myocarditis associated with psittacosis, lymphogranuloma venereum, or primary atypical pneumonia, specific therapy with tetracycline is indicated. Restriction of activity during the acute phase of illness would appear appropriate on clinical grounds alone. The aim should be to keep cardiac work at a minimum. The evidence that exercise enhances the severity of experimental Coxsackie myocarditis bears upon this point.

The concern that hypoxia may aggravate viral myocarditis may be taken as indication for oxygen therapy, especially in the presence of an irritable or failing heart. The repeated observation of life-threatening arrhythmias and the risk of sudden, unexpected death would seem to indicate the need for electrocardiographic monitoring. Would it not seem reasonable to extend to the patient with acute myocarditis the potential benefits of intensive care units? Defibrillation and resuscitation may be lifesaving. In second- or third-degree heart block, the insertion of a temporary pacemaker may be desirable.

Patients in congestive heart failure tend to respond well to digitalis and diuretics, especially in childhood. A relatively low threshold for digitalis toxicity, however, has repeatedly been observed, although precise studies are lacking.

Adrenal steroids have been used but never proven to be effective. Some patients treated with steroids have recovered. There have been no controlled trials. Inasmuch as experimental Coxsackie myocarditis is clearly enhanced by cortisone, as mentioned above, this therapeutic approach cannot be recommended.

Are There Late Sequelae of Viral Myocarditis?

It has been known for some time that rheumatic carditis may become chronic and eventually lead to residual fibrosis, and that both Chagas’ disease and toxoplasmosis may...
lead to a chronic cardiomyopathy. Such a possibility has been entertained for viral myocarditis, but never proven. The fact that most cases of chronic cardiomyopathy are idiopathic has fostered the speculation that they represent end stages of viral myocarditis. Bengtsson and Lamberger followed 90 patients with presumptive acute myocarditis for 5 years and found that 20% still had cardiac symptoms, 15–20% had abnormal electrocardiograms, and about 30% had abnormal exercise electrocardiograms.

In 1969, Wilson and associates studied the natural history of experimental murine infection with Coxsackie virus B3 and demonstrated persistent inflammation progressing to myocardial fibrosis. These residual scars involved about one fifth of the myocardium. In man, by means of fluorescent antibody techniques, Burch and associates demonstrated Coxsackie B virus antigens in myocardium, associated with chronic, focal, interstitial myocarditis. In three cases, antigen was also demonstrated in the leaflets of the mitral valve; one of these was a 55-year-old man with unexplained cardiomegaly.

Conclusions

Acute viral myocarditis may be associated with most of the common viral diseases in small but significant proportions of cases; the myocarditis often remains unrecognized. The course is usually benign, but may be highlighted by life-threatening arrhythmias, heart failure, or circulatory collapse. Therapy not only holds promise of acute survival, but may reduce later sequelae. Chronic cardiomyopathy—still an unproven sequel in man—has now been documented after experimental Coxsackie myocarditis.

Clinically evident heart disease of viral etiology is of low prevalence in any individual medical center, but in the aggregate accounts for an appreciable number of severely ill patients. Existing knowledge with regard to diagnosis, treatment, and prevention might well be more widely applied. Systematic study of clinical and experimental forms of myocarditis would provide answers to many of the questions posed here. Because of the low incidence, interhospital studies should be considered. Existing clinical and research units devoted to the intensive study and care of patients with ischemic heart disease would seem eminently suited for further clinical investigation of acute myocarditis in man.

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