EDITORIAL COMMENT
Eradication of Viral Myocarditis
Is There Hope?*

Christina Baboonian, PhD,
William McKenna, MD, DSc, FRCP, FACC
London, United Kingdom

Adenoviruses acquired celebrity status when viral constructs began to be used as gene transfer vectors in man. Within a short period of time a virus ignored by all except dedicated virologists became known worldwide. A review of the current literature, however, reflects an omission. Adenoviruses as infectious agents are still very much ignored. In this issue of the Journal, Bowles et al. (1) attempt to address the imbalance and report on a multicenter study of adenovirus and enterovirus infections in patients with myocarditis and dilated cardiomyopathy (DCM). Their finding that adenoviral deoxyribonucleic acid (DNA) is present in 23% of myocarditis and 12% of DCM patients is a cause for concern and sufficient to justify the conclusions of the investigators that infections with these agents deserve attention, and that a treatment or prevention strategy must be considered.

COXSACKIE VIRUS INFECTION

Viral myocarditis has for almost 50 years been synonymous with Coxsackie B virus infection. Extensive attempts have been made to search for evidence of enteroviral involvement in the myocardium and study the pathogenesis of the disease (2). Why a common infection might be asymptomatic in most individuals and result in myocarditis in others is not known, but cardiotropic strains of Coxsackie viruses have been held to account for the virulence pattern observed in the community (3). Differences in the affinity of the virus for cellular receptors may also have a deciding role in infectivity and pathogenesis of enteroviruses, with some strains better able to spread in vivo (4). A significant breakthrough in understanding the mechanism of virus-induced disease came with the discovery that Coxsackie viral protease can cleave dystrophin and hence adversely affect myocyte structural integrity (5). Understanding the pathogenesis of enteroviral infection provided fresh incentive to continue the work. Case reports of Coxsackie viral myocarditis are still presented (6,7), and large-scale studies addressing the incidence of enteroviral involvement in disease continue to be of interest (8–10). Although viruses other than enteroviruses have periodically appeared in the literature, and influenza (11,12), parvoviruses (13,14), hepatitis C (15), and human immunodeficiency virus (16,17) among others (18) have all been related to myocardial disease, Coxsackie viruses have to date maintained the monopoly.

An observation long forgotten until re-instigated by Longberg-Holm et al. in 1976 (19) was a report published in the Journal of Bacteriology 10 years earlier (20) stating that two unrelated viruses, Coxsackie and adenoviruses, use common cellular receptors for entry. It took 12 more years before the common receptor for the two agents was characterized (21). In hindsight, the information is critical in understanding how two diverse agents, one a ribonucleic acid and one a DNA virus, with replication strategies that bear little resemblance to one another, are both capable of infecting the myocardium. Despite more than three decades of knowledge that both agents can enter the same cells and the understanding that adenoviruses are cardiotropic and able to induce myocarditis in mice (22), until recently no concerted effort had been made to look for adenoviruses in the heart tissue. Although case reports dating back to 1971 suggest an association between adenoviruses and myocarditis (23) and isolated incidences of infection leading to myocardial disease are recorded in the literature (24–28), the extent of the involvement of these agents in cardiomyopathy is unclear.

ADENOVIRAL MYOCARDITIS

Two early studies, one conducted in 1968 by Berkovich et al. (29) and one by Gardiner and Short in 1973 (30), present evidence of the scale of the problem with adenoviral myocarditis. The reports relate to both pediatric and adult cases of disease; using virus culture and serological markers of infection suggests that adenoviruses are associated with 17% of pediatric and 3% of adult cases of myocarditis. A 4% association of infection with adult disease was later confirmed by Vikerfors et al. in 1988 (31). Towbin’s laboratories started a systematic evaluation of human cardiac tissue for evidence of viral presence in 1994 and reported that 15 of 38 pediatric hearts taken from patients with myocarditis and examined by polymerase chain reaction (PCR) had adenoviral nucleic acids (32). Investigations in children continued, and the same team reported in 1999 that 9% of patients with myocarditis are infected with this agent (11). Two other studies relate to myocardial infection in children. One study carried out by Shimizu et al. (33) reported eight cases of sudden death in infants and found one infected child; the second was a study by Calabrese et al. (34) who, using PCR, found over a third of the pediatric myocarditis cases to be associated with adenoviruses. A review of the literature suggests that, although the number of reported studies in children is small and mainly presented as case

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From Department of Cardiological Sciences, St. George’s Hospital Medical School, Cranmer Terrace, London, United Kingdom.
Table 1. Association of Adenoviruses With Myocarditis and Cardiomyopathy in Adults

<table>
<thead>
<tr>
<th>Study, Year (Ref.)</th>
<th>Cases Investigated</th>
<th>Methods Used</th>
<th>No. of Patients</th>
<th>No. Found Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardiner and Short, 1973 (30)</td>
<td>Myocarditis or pericarditis</td>
<td>Serology</td>
<td>60</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Karjalainen et al., 1983 (46)</td>
<td>Military recruits/subclinical/ECG changes</td>
<td>Serology</td>
<td>126</td>
<td>19 (15.1%)</td>
</tr>
<tr>
<td>Karjalainen et al., 1986 (47)</td>
<td>Military recruits/subclinical/ECG changes</td>
<td>Serology</td>
<td>27</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>Drescher et al., 1987 (41)</td>
<td>Sudden death</td>
<td>Serumology</td>
<td>51</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vikerfors et al., 1988 (31)</td>
<td>Myocarditis</td>
<td>PCR</td>
<td>24</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Grumbach et al., 1999 (39)</td>
<td>Myocarditis/DCM</td>
<td>PCR</td>
<td>31</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pauschinger et al., 1999 (38)</td>
<td>Left ventricular dysfunction</td>
<td>PCR</td>
<td>94</td>
<td>12 (12.8%)</td>
</tr>
<tr>
<td>Fujioka et al., 2000 (40)</td>
<td>DCM</td>
<td>PCR</td>
<td>26</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Davydova et al., 2000 (36)</td>
<td>Myocarditis/DCM</td>
<td>PCR</td>
<td>33</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Hufnagel et al., 2000 (37)</td>
<td>Myocarditis</td>
<td>PCR</td>
<td>526</td>
<td>13 (2.5%)</td>
</tr>
<tr>
<td>Bowles et al., 2002 (35)</td>
<td>ARVD cardiomyopathy</td>
<td>PCR</td>
<td>12</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>Cioc et al., 2002 (25)</td>
<td>Myocarditis/sudden death</td>
<td>In situ hybridization</td>
<td>11</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td>1,021</td>
<td>62 (6.1%)</td>
</tr>
</tbody>
</table>

ARVD = arrhythmogenic right ventricular dysplasia/cardiomyopathy; DCM = dilated cardiomyopathy; PCR = polymerase chain reaction.

Table 2. Association of Adenoviruses With Myocarditis and Cardiomyopathy in Children

<table>
<thead>
<tr>
<th>Study, Year (Ref.)</th>
<th>Cases Investigated</th>
<th>Methods Used</th>
<th>No. of Patients</th>
<th>No. Found Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkovich et al., 1968 (29)</td>
<td>Myocarditis</td>
<td>Virus isolation (stool samples)</td>
<td>12</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Martin et al., 1994 (32)</td>
<td>Myocarditis</td>
<td>PCR</td>
<td>38</td>
<td>15 (39%)</td>
</tr>
<tr>
<td>Shimizu et al., 1995 (33)</td>
<td>Sudden infant death/myocarditis/pericarditis</td>
<td>PCR</td>
<td>8</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>Akhtar et al., 1999 (11)</td>
<td>Pneumonia and myocarditis</td>
<td>PCR</td>
<td>32</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Calabrese et al., 2002 (34)</td>
<td>Myocarditis</td>
<td>PCR</td>
<td>26</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td>116</td>
<td>30 (25.9%)</td>
</tr>
</tbody>
</table>

PCR = polymerase chain reaction.
conducted by Smith et al. (45), who have shown human cytotoxic T lymphocytes generated to react against one serotype of adenovirus are capable of lysing cells infected with other subgroups. Antigenic similarities between strains within one adenovirus subgroup may therefore influence outcome of an infection. Whether an infection remains subclinical or develops into full-blown disease could ultimately depend on which serotype one is exposed to first.

Adenovirus infections do not often result in disseminated disease. The presence of viral DNA in circulating and mucosal lymphocytes, however, suggests that the virus may not be confined to the site of infection (42). How frequently do respiratory and gastrointestinal infections culminate in viral entry into circulation is unknown. If this is a frequent event, the virus carried by lymphocytes will have access to myocytes with receptors encouraging viral entry. What proportion of such cases present as overt myocarditis is also uncertain. Some evidence suggests that myocardial involvement following acute infection may be frequent. Karjalainen et al. (46,47) assessed military recruits in two separate studies in 1983 and 1986 for evidence of recent infection using raised antibody levels as markers. In patients with adenovirus infection, serial electrocardiographic changes were noted, with ST-segment elevation and T-wave inversions lasting for four days or more.

Finally, whereas mortality is associated with some respiratory and gastrointestinal infections and disease in military recruits has proved to be a major inconvenience, adenoviruses have not been on top of the priority list for preventative measures. Involvement of these viruses in myocarditis alters our perspective and places adenoviruses alongside infectious agents such as measles and mumps. Hofling et al. (48) conclude a review article on progress toward vaccines against viruses that cause heart disease by expressing doubts that the marketplace will support the development of such vaccines. Our view is a little more optimistic. The pathogenic potential of agents that infect us all must not be ignored. Replication of defective adenoviruses, used as gene delivery vehicles, provide excitement and bring research in basic virology into focus. But there is a more sobering aspect to native adenoviruses that we must not forget: The consequences of infection, with cardiac involvement, can be death.

Reprint requests and correspondence: Dr. Christina Baboonian, St. George's Hospital Medical School, Department of Cardiological Sciences, Cranmer Terrace, London SW17 ORE, United Kingdom. E-mail: cbabooni@sghms.ac.uk.

REFERENCES


