Myocardial Infarction, Viral Infection, and the Cytoskeleton
Final Common Pathways of a Common Disease?*

Jeffrey A. Towbin, MD, FACC,†‡§
Matteo Vatta, PhD†
Houston, Texas

Myocardial infarction (MI) is a major cause of morbidity and mortality in adults worldwide and is believed to result from an acute coronary syndrome in most affected individuals (1). In subjects with MI caused by acute coronary syndrome, the coronary obstruction leads to ischemia, and the result is cell death, fibrosis, and ultimately an ischemic cardiomyopathy or a serious rhythm disturbance. The underlying etiologies leading to coronary obstruction are thought to include atherosclerosis in most instances, although infections have also been speculated to play a role (2). This includes chlamydia, viruses such as enteroviruses, and other agents. However, the exact mechanisms responsible for this form of MI are not well demonstrated.

In this issue of the *Journal*, Andréoletti et al. (3) provide evidence supporting the concept that infectious causes of acute MI and sudden death exist, are potentially common, and occur owing to disruption of a “final common pathway” of myocardial function (4). The authors investigated the endomyocardial tissues of 50 patients who died suddenly of acute MI and compared the results with samples obtained from 50 control subjects without evidence of cardiovascular disease and 50 matched subjects with nonischemic cardiomyopathy. Studies performed focused on the presence and occurrence of enteroviral ribonucleic acid genomes and VP1 capsid protein from coxsackievirus B in these tissues, as well as the effect of this virus on the protein structure of the myocardium. Specifically, the authors analyzed dystrophin protein in the myocardium as well as the structural integrity of the cardiomyocyte sarcolemma, the cell membrane of the myocardial cell, using immunohistochemistry. Their results showed that 40% of patients with acute MI had evidence of enteroviral infection of the myocardium compared with 4% of control subjects without heart disease and 8% of those with nonischemic cardiomyopathy. All patients with evidence of enteroviral ribonucleic acid in the heart exhibited VP1 protein as well, providing evidence of viral protein synthesis activity, and these sequences showed strong homology to coxsackievirus B2 and B3 serotypes (3). Furthermore, immunohistochemical analysis of the endomyocardial tissue using dystrophin antibody to the rod region demonstrated disruption of the sarcolemmal localization of dystrophin in the same tissue areas infected by these viruses. The authors conclude that active coxsackievirus in the heart significantly contributes to the pathogenesis of acute MI by focal disruption of dystrophin in the cardiomyocytes of these patients (3).

Does this make sense? Is there other supporting evidence for this claim? Let’s take a look. Dystrophin is a rod-shaped cytoplasmic protein in muscle that connects the cytoskeleton of a muscle fiber to the surrounding extracellular matrix through the sarcolemma at the carboxy-terminal end (C-terminus) and to the sarcomere, the contractile apparatus of muscle, at the amino-terminal end (N-terminus). This large protein, which has a molecular weight of 427 KDa and is composed of 3,684 amino acids, is encoded by one of the largest genes in humans, measuring 2.5 megabases of deoxyribonucleic acid. The protein has an N-terminus that binds to the sarcomere via an actin-binding domain, a rod region composed of spectrin-like repeat sequences with interspersed hinge regions, and a C-terminus that binds to the sarcolemma via a group of dystrophin-associated proteins, including syntrophin and beta-dystroglycan, as well as interacting with ion channels such as Nav1.5, the cardiac sodium channel encoded by the SCN5A gene (5–7). Dystrophin plays a variety of roles, including membrane stability, force transduction, and resistance to mechanical stress. When disrupted, dystrophin leads to skeletal muscle and cardiac dysfunction, as seen in such disorders as Duchenne and Becker muscular dystrophies and X-linked dilated cardiomyopathy, X-linked disorders caused by mutations in the dystrophin gene (7). Mutations in this gene lead to loss of dystrophin protein function, disruption of its binding to the dystrophin-associated proteins and sarcomeric proteins, membrane instability and permeability, and loss of force transduction. These disruptions in function are further disturbed by mechanical stress, ultimately leading to potentially irreversible skeletal myopathy and cardiomyopathy. In the latter case, heart failure and sudden death are common accompaniments. Interestingly, the same events occur when dystrophin is disrupted by acquired disease, especially viral-induced myocarditis. Badoff et al. (8) first showed that coxsackievirus B3 disrupts dystrophin in myocardial infec-
tion by cleavage of the rod region within the third hinge region due to the cleavage of dystrophin by entero viral protease 2A, which is encoded within the coxsackievirus B genome. This cleavage leads to the same pathophysiologic abnormalities seen in the genetic form of dystrophinopathy, with the resultant myocardial dysfunction and heart failure or sudden death ensuing. In some cases of Duchenne muscular dystrophy, Becker muscular dystrophy, X-linked dilated cardiomyopathy, and coxsackie-induced myocarditis, MI has been identified (9). In addition, ventricular arrhythmias and atrioventricular block also occur in these patients, and we have provided evidence that this is likely due to disturbed ion channel function, the “final common pathway” of arrhythmias (10). Thus, the work described by Andréoletti et al. (3) recapitulates these clinical disorders.

Previously, we have shown that this disruption in dystrophin may be reversible (11,12). Using left ventricular assist device (LVAD) therapy, which reduces mechanical stress and the inflammatory cascade, favorable remodeling of dystrophin was seen, and favorable remodeling of the heart with improvement in ventricular function and normalization of ventricular size and rhythm occurred. In addition, we have shown that coronary obstruction can occur in patients with myocardial viral infection and that some cases of coronary-induced ischemic cardiomyopathy have dystrophin disruption, and that it, too, is reversible in some LVAD-treated patients. Therefore, the elegant study by Andréoletti et al. (3) confirms these previously published studies and extends the findings to now include the common human disorder, MI, a leading cause of death and disability.

What does this mean? There are many “take-home messages” that this work provides. First, the concept that dystrophin plays a major role in cardiovascular function and dysfunction and that it is a key intermediary in the “final common pathway of cardiomyopathy” is further clarified and supported (4,13). In addition, these disorders, whether genetically inherited or acquired, appear to result via the same routes (14). Coronary arteries may become obstructed and lead to ischemia due to atherosclerosis based on cholesterol and lifestyle, but another significant etiology is infectious in nature. Whether this is due to genetic underpinnings such as mutations or polymorphisms in receptor proteins or other key “virulence factors” remains to be seen, but it is possible that these acquired diseases are genetically “predestined” (15). Further studies regarding this are warranted to risk-stratify and provide individualized medical advice to patients and families in this molecular era. Finally, could this work provide us with novel treatment strategies to improve the health and outcomes of humans? The data regarding LVAD therapy could give important insights and suggests that “mechanical stress” reduction therapies may be warranted (11,12). Could this be one of the actions of beta-blockers and angiotensin-converting enzyme inhibitors in the favorable outcomes of cardiomyopathy and heart failure patients? Could protease inhibitors be useful adjunctive therapies? Is this why human immunodeficiency virus (HIV)-infected subjects no longer appear to be at high risk for cardiovascular-related morbidity and mortality? We previously showed that the coxsackievirus genome was involved in the cardiomyopathy of HIV-infected patients and that the HIV genome was rarely seen (16). Would vaccination be useful, as it was for another enterovirus, poliovirus, or in mumps-induced endocardial fibroelastosis (17)? Finally, could medical therapies such as intravenous gamma-globulin or interferon be useful to treat patients with coronary syndromes and ischemic heart disease, as they have been in myocarditis (18,19)?

The work by Andréoletti et al. (3) opens many new doors in our understanding of MI, ischemic heart disease, heart failure, and sudden death and could become a classic paradigm-shifting concept that leads to better outcomes and reduction in the human burden related to coronary artery disease. It is time to start considering new care options for those with coronary syndromes and time to consider the development of preventive strategies based on this infectious process.

Reprint requests and correspondence: Dr. Jeffrey A. Towbin, Professor and Chief, Pediatric Cardiology, Texas Children’s Hospital, 6621 Fannin Street, MC 1945-C, Houston, Texas 77030. E-mail: jtowbin@bcm.tmc.edu.

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