News and Views from the Literature

Heart Failure

Dilated Cardiomyopathy Can Result from Mutations in Sarcomere Protein Genes

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Dilated cardiomyopathy is a group of disorders characterized by decreased systolic function, ventricular dilatation, and myocyte hypertrophy, which result in heart failure and premature death. A variety of distinct pathologic processes may initiate myocyte injury, ventricular dilation, and myocardial dysfunction. Inherited genetic defects are thought to account for 25% to 30% of cases of dilated cardiomyopathy. The genetic mutations previously identified as causes of dilated cardiomyopathy have involved molecular defects in cytoskeletal proteins, such as the dystrophin-dystroglycan-laminin transmembrane complex that connects the cytoskeleton of the myocyte to the structural proteins that surround the cell.[1] It has been reported that disruption of the dystrophin complex also occurs in viral myocarditis.[2] The shared defect in the dystrophin-glycoprotein complex between an acquired (viral) form of dilated cardiomyopathy and rarer genetic forms suggests this might be an important common mechanism in the pathophysiology of cardiomyopathy. Elucidation of other genetic defects that result in dilated cardiomyopathy would be expected to provide further insights into the pathogenetic mechanisms of this disease.

Mutations in Sarcomere Protein Genes as a Cause of Dilated Cardiomyopathy

Kamisago M, Sharma SD, DePalma SR, et al.
N Engl J Med. 2000;343:1688-1696.

A recent study by Kamisago et al. utilized a genome-wide linkage analysis on 21 kindreds with familial dilated cardiomyopathy.[3] This prompted a search of the genes encoding the sarcomere proteins ß-myosin heavy chain, cardiac troponin T, cardiac troponin I, and (α-tropomyosin for disease-causing mutations. A genetic locus for mutations associated with dilated cardiomyopathy was identified where the gene for cardiac ß-myosin heavy chain is encoded in 4 kindreds (maximal lod score 5.1). A mutation resulting in a deletion in the cardiac troponin T gene was also identified. These mutations were particularly prevalent in families with early-onset ventricular dilation and systolic dysfunction. The sarcomere mutations found in this study to cause dilated cardiomyopathy appeared in regions that could be expected to diminish the mechanical function of cardiac myocytes. The troponin T deletion was in the domain that is responsible for calcium-sensitive troponin C binding. The location of the cardiac myosin mutations was in a region that contributes to the tight binding of actin and could also impair contractile function. It appears that mutant sarcomere proteins can trigger two distinct series of pathologic events that remodel the heart, one pathway resulting in hypertrophy and increased contractility and the other in ventricular dilation and decreased contractile function (see Figure 1). It can be estimated on the basis of this study that mutations in sarcomere protein genes may account for approximately 10% of cases of familial dilated cardiomyopathy.

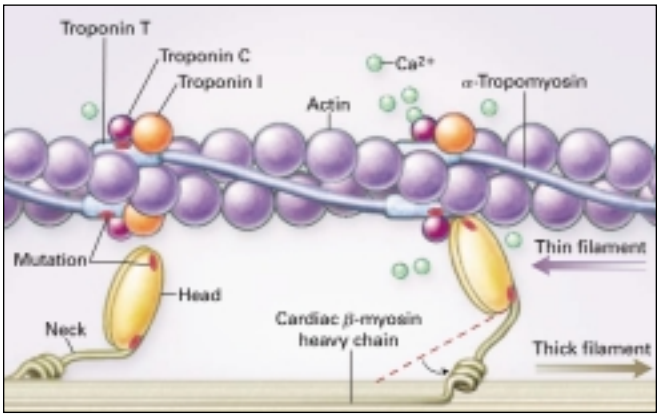

Figure 1. *From Kamisago M, Sharma SD, DePalma SR, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. N Engl J Med. 2000;343:1688-1696. Copyright © 2000 Massachusetts Medical Society. All rights reserved.*

Distinct mutations in sarcomere proteins have now been shown to result in dilated cardiomyopathy and hypertrophic cardiomyopathy. Identification of these and other genetic defects causing dilated cardiomyopathy holds promise to lead to a better understanding of the mechanisms involved in the initiation and progression of this disease. Genetic testing will in the near future allow early and specific diagnosis of patients, as well as screening of family members.

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Vasopeptidase Inhibition in Patients with Heart Failure

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Neurohumoral activation plays a key role in the initiation and progression of heart failure. Neurohumoral inhibition with angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, and aldosterone antagonists has been shown to decrease symptoms, reduce hospitalizations, and prolong survival in patients with heart failure. Despite the benefits of these agents, alone or in combination, patients with heart failure still face substantial risks. Vasopeptidase inhibitors are a new class of pharmaceutical agents that have been shown to increase the activity of endogenous vasodilators.[1] Vasopeptidase inhibitors inhibit the activity of the enzyme neutral endopeptidase, which degrades the natriuretic peptides (atrial, brain, and calcium-activated), bradykinin, and adrenomedullin. These inhibitors may provide additional benefit in heart failure, since they target the imbalance between endogenous vasoconstrictors and vasodilators in heart failure more than ACE inhibition alone.[2]

Comparison of Vasopeptdase Inhibitor, Omapatrilat, and Lisinopril on Exercise Tolerance and Morbidity in Patients with Heart Failure: IMPRESS Randomized Trial

Rouleau JL, Pfeffer MA, Stewart DJ, et al.
Lancet. 2000;356:615-620.

Omapatrilat is a recently developed drug that provides dual inhibition of neutral endopeptidase and ACE. The recently published IMPRESS clinical trial compared the effects of this vasopeptidase inhibitor to those of the ACE inhibitor lisinopril on functional capacity and clinical outcomes in 573 patients with NYHA class II-IV congestive heart failure.[3] Patients were randomly assigned to receive omapatrilat at a daily target dose of 40 mg or lisinopril at a daily target dose of 20 mg for 24 weeks. This study showed that both agents were well tolerated but that there were fewer cardiovascular system adverse events with omapatrilat. Omapatrilat treatment was associated with more frequent dizziness. One case of angioedema occurred with lisinopril, none with omapatrilat. Time on exercise treadmill tests done at week 12 increased similarly in the omapatrilat and lisinopril patient groups (24 vs 31 seconds, P = .45). There was a significant benefit of omapatrilat in the composite of death, hospitalization, and discontinuation of study drug for worsening heart failure (odds ratio, 0.52, 95% confidence interval [CI], 0.28 to 0.96, P = .035). Of patients randomized to lisinopril, 6.1% developed significant elevations in serum creatinine, compared to 1.8% of those receiving omapatrilat (P = .009). This finding that fewer of the patients given omapatrilat developed impaired renal function than of those given lisinopril is compatible with a protective effect of natriuretic peptides on glomerular filtration rate. The major limitations of this study are that the number of patients studied was small and the length of follow-up was short, so that the results are suggestive of benefit but require further confirmation.

This clinical trial suggests that omapatrilat may have some advantages over ACE inhibitors in the treatment of patients with congestive heart failure. The use of vasopeptidase inhibitors could represent a treatment approach that further reduces the morbidity and mortality in patients with heart failure. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, a large multicenter clinical trial comparing the effects of omapatrilat and enalapril on mortality in 4420 heart failure patients, will provide more definitive data.

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Acute Coronary Events as a Trigger of Sudden Death in Heart Failure

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Sudden unexpected death constitutes 25% to 83% of deaths in patients with heart failure.[1] Primary arrhythmias have been believed to be the predominant mechanism of sudden death in these patients.[1] In contrast, sudden death in patients without heart failure but with coronary artery disease (CAD) is often accompanied by acute coronary findings. In autopsy studies, plaque rupture, a fresh thrombus, or recent acute myocardial infarction (MI) was found in 57% to 73% of CAD patients without heart failure who died suddenly.[2] Since CAD is present in 50% to 75% of patients with heart failure, it is possible that acute coronary events contribute significantly to sudden death. The importance of these events in triggering sudden death in patients with heart failure has not been clear or well studied previously.

Acute Coronary Findings at Autopsy in Heart Failure Patients with Sudden Death: Results from the Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial

Uretsky BF, Thygesen K, Armstrong PW, et al.
Circulation. 2000;102:611-616.

A recent study by Uretsky and associates evaluated autopsy results in patients in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, a randomized clinical trial that compared low doses of angiotensin-converting enzyme (ACE) inhibitors with high doses in patients with class II-IV heart failure.[3] The prevalence of acute coronary findings (coronary thrombus, ruptured plaque, or acute MI) and their relation to sudden death was analyzed. Acute coronary findings were present in 33% of the 171 patients in whom autopsies were obtained. Of patients with significant CAD, 54% who died suddenly had acute coronary findings. The percentage of patients classified as dying of MI was 28% in the autopsy group versus only 4% in the nonautopsy group ($P < .0001$). Of the autopsy patients with acute MI who died suddenly, acute MI was not suspected or diagnosed clinically before autopsy in 97% (31 of 32 patients).

Acute coronary findings were also present in a significant number of patients who died of progressive heart failure. Of patients with CAD, there were acute coronary findings in 32% who were classified as having died of myocardial failure. Of these, 40% (6 of 15 patients) with myocardial failure did not receive a diagnosis of MI during life.

This analysis indicates that acute coronary findings are frequent in patients with heart failure who die and are often not diagnosed clinically. This is especially true in patients with CAD who sustain sudden cardiac death. Therapies that have been demonstrated to reduce the risk of acute coronary syndromes in patients with established CAD include antiplatelet therapy with aspirin or clopidogrel, ß-blockers, ACE inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.[3] These therapies would be expected to have significant clinical benefit for patients with heart failure. The reduction in sudden death seen with ACE inhibitors and ß-blockers in heart failure clinical trials may have resulted as much from a reduction in atherosclerotic events as other previously ascribed mechanisms (antiarrhythmic, hemodynamic, and antiremodeling effects).[4,5]

This study by Uretsky and colleagues represents an important advance in understanding the mechanisms of sudden death in patients with heart failure. It indicates that acute coronary events appear to be a major trigger for sudden death in these patients. As such, improved utilization of strategies to prevent the progression of CAD and atherosclerotic plaque rupture in patients with heart failure may substantially reduce the incidence of sudden cardiac death and overall mortality.

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