AMPD1 Gene Mutation in Congestive Heart Failure
New Insights Into the Pathobiology of Disease Progression

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In the late 19th century, Sir William Osler noted that patients with myocardial damage due to valvular heart disease had a highly variable clinical course. Some patients remained free of symptoms for a relatively prolonged period of time, whereas others rapidly decompensated. More recently, the presence of cardiac dilatation has been found to be a robust predictor of the development of symptomatic congestive heart failure. However, in large populations of patients with asymptomatic and nonischemic myocardial dilatation, only a relatively modest percentage developed symptomatic congestive failure during 11 years of follow-up. This marked variability in the progression of disease in different individuals led investigators to suspect that these differences might be attributable to variations in genetic background. This hypothesis was further supported by recent evidence suggesting that (1) dilated cardiomyopathy is familial in a larger percentage of cases than was originally recognized, (2) specific loci are associated with adult-onset autosomal dominant dilated cardiomyopathy, and (3) mutations affecting cytoskeletal proteins are associated with the development of dilated cardiomyopathy. However, investigators have not found molecular markers that would predict the development of congestive heart failure in the general population, nor have they identified genetic determinants that might affect the progression of the disease in individual patients.

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In this issue of Circulation, Loh and colleagues provide the first evidence of a correlation between the presence of a genetic marker and the progression of heart failure in patients with dilated cardiomyopathies. Patients having a relatively common mutation in at least 1 allele of the adenosine monophosphate deaminase 1 (AMPD1) gene experienced a significantly longer duration of heart failure symptoms before referral for transplantation evaluation and had a greater chance of surviving without a cardiac transplant than patients heterozygous or homozygous for the wild-type allele. If confirmed in a larger and more heterogeneous patient population, these results could have important implications in the diagnosis and treatment of patients with heart failure.

AMP deaminase is the rate-limiting step for entry into the purine nucleotide cycle and catalyzes the conversion of AMP to IMP. Alternatively, AMP is converted to adenosine by nucleotidase. In the presence of diminished AMP deaminase activity, the stoichiometry of the reaction in the skeletal muscle would be expected to shift toward increased production of adenosine. Indeed, previous studies in patients with AMP deaminase deficiency and individuals homozygous for the AMPD1 mutant allele have demonstrated increased adenosine production in the skeletal muscle. Although Loh et al suggested that the increase in skeletal muscle adenosine production might be responsible in part for the increased circulating levels of adenosine seen in patients with congestive heart failure, the short half-life of adenosine in the peripheral circulation suggests that the major effects of adenosine are local. Thus, it is also possible that adenosine levels might be increased in the cardiac muscle of patients with congestive heart failure who are heterozygous or homozygous for the mutant allele. This hypothesis is consistent with previous studies that demonstrated that myocytes from a variety of species, including humans, are able to release adenosine during ischemic stress.

That an increase in intracellular adenosine could have a beneficial effect in the failing myocardium is supported by a series of studies in which adenosine has been associated with a variety of cardioprotective effects, such as induction of vasodilation, inhibition of platelet aggregation, attenuation of neutrophil adhesion to endothelial cells, inhibition of neutrophil-induced endothelial cell damage, inhibition of renin release and noradrenergic neurotransmission, stimulation of nitric oxide release and prevention of oxygen free radical–induced injury, and inhibition of cardiac fibroblast growth. Furthermore, adenosine plays a central role as an endogenous mediator of ischemic preconditioning.

The complex nature of the myocardial response to adenosine is due at least in part to the presence of at least 3 adenosine receptors on the myocardium. The A1 and A3 adenosine receptors are negatively coupled to adenylyl cyclase and exert an antiadrenergic action with a resultant decrease in adrenergically induced contractility. These actions, mediated via inhibitory G proteins, provide an effective protection for the ischemic myocardium yet might have a deleterious effect in patients with idiopathic cardiac dilatation. By contrast, the A2 adenosine receptor is coupled to enhanced coronary vessel vasodilation and increased myocardial contractility via cAMP-dependent and -independent mechanisms. Thus, activation of the A2 receptor might...
balance these negative inotropic effects of $A_2$ activation while at the same time reducing cardiac afterload.\textsuperscript{11,14}

Recently, investigators have demonstrated the ability of adenosine to attenuate the expression of the proinflammatory cytokine tumor necrosis factor-$\alpha$ (TNF-$\alpha$) by activated inflammatory cells, effects that were mediated by the $A_2$ receptor.\textsuperscript{15–17} Similarly, adenosine can attenuate the expression of TNF-$\alpha$ by lipopolysaccharide-stimulated neonatal rat cardiomyocytes, adult rat ventricular myocytes, rat papillary muscle, and the failing human heart, effects that are also $A_2$ receptor dependent.\textsuperscript{18,19} In addition, adenosine decreased the postischemic production of TNF-$\alpha$ by isolated rat hearts.\textsuperscript{20}

The relevance of the anti–TNF-$\alpha$ effects of adenosine to human heart failure is suggested by recent studies demonstrating that the failing human heart reexpresses TNF-$\alpha$\textsuperscript{21} and that there is a direct relationship between severity of disease and plasma TNF-$\alpha$ levels.\textsuperscript{22} Indeed, TNF-$\alpha$ levels appear to be preferentially elevated in patients with relatively severe symptoms, and this might participate in the transition from cardiac compensation to decompensation and end-stage failure. Furthermore, TNF-$\alpha$ is able to recapitulate many of the biological features of dilated cardiomyopathy in in vitro preparations,\textsuperscript{23} and the cardiac-specific overexpression of TNF-$\alpha$ in transgenic mice elicits the development of cardiac hypertrophy, dilatation, interstitial infiltrates, fibrosis, ventricular dysrhythmias, reexpression of fetal genes, and early death.\textsuperscript{24} In addition, inhibition of bioactive TNF-$\alpha$ by overexpression of soluble TNF-$\alpha$ receptors abrogates the development of interstitial infiltrates and improves abnormalities in cardiac gene expression.\textsuperscript{25} Thus, increased production of adenosine with subsequent inhibition of TNF-$\alpha$ expression might provide an attractive explanation for the prolonged event-free survival seen by Loh et al\textsuperscript{6} in patients harboring the mutation in the $\text{AMPD1}$ gene. Neither myocardial nor skeletal muscle adenosine levels were measured in the study by Loh et al\textsuperscript{6}; therefore, the adenosine hypothesis remains speculative. However, this hypothesis certainly warrants further investigation.

Our enthusiasm regarding the study reported by Loh et al\textsuperscript{6} must be tempered by the recognition that studies in populations of patients with idiopathic dilated cardiomyopathy share a common limitation: an inability to define the denominator. That is, it is not possible to determine the time at which the myocardium underwent the initial insult that activated the process of ventricular remodeling and dilatation. Thus, individuals inheriting a gene polymorphism or mutation that was maladaptive might die before they reach medical attention or referral to a specialist, whereas patients who have an adaptive genotype might never come to medical attention or never be referred to a tertiary center because they remain asymptomatic. These inherent biases may be responsible for the large disparity amongst the numerous studies that have assessed the prognostic importance of polymorphisms in the $\text{ACE}$ gene in populations of patients with heart failure.\textsuperscript{26,27} One approach that would avoid many of these pitfalls would be to assess the association between genotype and outcome in a large population of patients with diminished left ventricular function after a myocardial infarction. Not only would it be possible to definitively identify the date of the damage to the myocardi-

um, but patients could be recruited from community hospitals as well as tertiary centers, thus providing a more heterogeneous population. Furthermore, genotyping could be performed before the development of symptomatic heart failure, thus allowing for prospective rather than retrospective analysis.

Another important challenge in designing studies that assess the ability of genotype to predict the development of a phenotype in a population of patients with congestive heart failure is selection of appropriate study outcomes. Loh et al\textsuperscript{6} assessed a combined end point of transplantation and death. Although such an analysis may be useful in a single-center study, marked variation in donor organ availability and allocation at different centers precludes the value of pooling these 2 outcomes in a multicenter study. The prospective analysis of worsening heart failure or death would be relevant outcomes.

Over the last decade, there has been an exponential growth in the number of DNA markers potentially available for clinical studies. The US National Human Genome Research Institute recently unveiled a 5-year-plan that promises a “working draft” of the human genome by the year 2001 and the completion of the sequence of the entire human genome by the year 2003.\textsuperscript{28} This will clearly result in an increase in the number of clinical investigations that seek to use genetic polymorphisms to predict clinical outcomes. Because much of the variation in the human genome may be background noise without functional significance, it is important for such studies to demonstrate that the mutation of interest modifies the expression or function of mediators of human disease in a way that fits the clinical hypothesis. The importance of the $\text{AMPD1}$ mutation has been demonstrated previously in patients with skeletal muscle disease. Thus, it provides an important target for additional evaluation in patients with heart muscle disease.

Despite the limitations associated with any study assessing the relationship between genotype and phenotype in a population of patients with congestive heart failure, the study by Loh et al\textsuperscript{6} is of great interest in that it is the first to demonstrate a direct relationship between a genetic variant and disease progression in patients with congestive heart failure. Our ability to provide new and innovative strategies for the treatment of congestive heart failure will depend on the development of a better understanding of the relationship between genetic background and outcomes in patients with this condition. Thus, it will be important to confirm the study by Loh et al\textsuperscript{6} in a larger and more heterogeneous population of patients and to pursue identification of the specific cellular and molecular mechanisms responsible for the benefits associated with altered $\text{AMPD1}$ activity in these patients. Such an understanding of the genetics of dilated cardiomyopathy will afford clinicians the ability to tailor pharmacological and/or mechanical therapy to individual patients on the basis of their genetic backgrounds and to more accurately assess prognosis.

References


**Key Words:** Editorials ■ genes ■ heart failure ■ transplantation
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Circulation. 1999;99:1397-1399
doi: 10.1161/01.CIR.99.11.1397

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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