INVITED COMMENTARY

Myocardial Adrenergic Dysinnervation in Dilated Cardiomyopathy: Cornerstone or Epiphenomenon?

During the last few decades, interest in inflammatory cardiomyopathy has been growing. This interest has developed over the years because of substantial animal experimental data supporting the hypothesis that a pathogenetic link exists between infectious agents (usually viruses) and subsequent immune-mediated damage to the myocardium resulting in dilated cardiomyopathy (*1–3*) and because of human studies providing evidence of a significant prevalence of the viral genome in the heart of patients with dilated cardiomyopathy (*2*). These studies provided new insights into the immunologic mechanisms of the disease and into potential therapies for humans (*4*). Although a possible causal link between myocarditis and dilated cardiomyopathy has been suggested (*5,6*), definitive proof of such a link is still lacking. Dilated cardiomyopathy is an important cause of heart failure. A recent analysis of the data published between 1966 and 1997 showed a 21% incidence of progression to dilated cardiomyopathy over a mean of 3 y (*7*) in patients with a clinical or histologic diagnosis of acute myocarditis of viral or unknown origin.

Whatever the cause of heart failure, increased adrenergic activity plays a critical role in the evolution of the disease. Much experimental evidence has accumulated over the past few decades that shows that the failing human heart is adrenergically supported (*8–10*), and adrenergic support helps to maintain cardiac performance over the short term by modulating contractility and heart rate. A possibility is that it is the increase in cardiac adrenergic drive, leading to local release of the adrenergic neurotransmitter, rather than an increase in circulating norepinephrine (NE) that is both initially supportive and then ultimately deleterious to the failing heart (*11–13*). Catecholamines are actually cytotoxic substances. Oxidative metabolites of epinephrine have been shown to induce coronary spasm, arrhythmias, myocardial necrosis and ultrastructural damage, and ventricular dysfunction (*14,15*). Hydroxydopamine acts as a neurotoxin that causes degeneration of sympathetic nerve endings and leads to myocardial denervation lesions, which have been shown with ^{123}I-metaiodobenzylguanidine (MIBG) imaging (*16,17*). Specifically, chronic overexposure of the heart to norepinephrine causes hypertrophy, ischemia, and myocyte injury. Norepinephrine in concentrations found in the failing heart can induce myocyte damage (*18*). Some investigators have speculated that the sympathetic nerve endings are probably damaged by NE-derived free radicals (*19*). These toxic metabolites of NE were thought to be formed outside the neurons and taken up into the nerve terminals by the uptake-1 transporter (*19,20*). This speculation was confirmed by measurements of increased hydroxyl free-radical generation by nonenzymatic autooxidation of NE in the heart after NE administration (*21*) and after cardiac sympathetic nerve stimulation (*22*). The NE cardiotoxicity in isolated hearts was completely abolished by superoxide dismutase, supporting the hypothesis that the NE toxicity is mediated by NE-derived free radicals (*23*). Some reports on animal models have shown that exposure to high catecholamine levels could cause a loss of uptake-1 carrier site (*24–26*) in a way similar to that observed for β-adrenergic receptors. Because neuronal reuptake of NE is the major mechanism for terminating action of NE on the myocardial β-receptors, this impairment of uptake-1 can further accentuate myocyte hyperstimulation to the neurotransmitter (*27,28*), creating a vicious circle at the synaptic level and explaining, in part, why decreased MIBG uptake showed a potent prognostic value in heart failure (*29–31*).

The continuously increased adrenergic drive present in the failing heart delivers deleterious transducing signals to the myocyte through β- and, presumably, β2- and α1-adrenergic receptors. In the failing heart, β-adrenergic signal transduction is blunted secondary to desensitization, because of changes in β1 and β2 receptors, muscarinic receptor density, inhibitory G protein (an enzyme responsible for modulating receptor activity by phosphorylation), and even the expression of the adenylate cyclase enzyme itself (*32–34*).

In the end-stage failing heart, a 50%–60% reduction in the total signal-transducing potential is found, but substantial adrenergic neurotransmission capacity is preserved (*32*). These data suggest that the desensitization of the β-adrenergic receptor pathway present in the failing heart may serve a cardioprotective role (*35,36*).

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The concept that the adrenergic nervous system has a dysregulatory role in chronic heart failure was confirmed when the beneficial effects of β-blockade on both hemodynamic condition and clinical outcome were shown. Numerous clinical trials have shown multiple benefits of β-blocker therapy in patients with chronic congestive heart failure who remain symptomatic despite the use of optimal triple therapy (digoxin, diuretics, and angiotensin-converting enzyme [ACE] inhibitors). Three large, randomized, placebo-controlled trials (*37–39*) were stopped early because of substantial reductions in mortality in the active-treatment groups. On the basis of a metaanalysis of 22 trials involving 10,135 patients with heart failure, the use of β-blockers led to the saving of 3.8 lives and the avoidance of 4 hospitalizations for every 100 patients treated for 1 y (*40*).

Carvedilol is a third-generation β-blocker that combines nonselective β-blockade, α-blockade, and antioxidant effects (*41,42*). The unique pharmacologic profile of carvedilol may offer a particular advantage compared with other β-blockers in heart failure and may have caused the apparently better results observed with use of carvedilol in severe heart failure (*43*), compared with other β-blockers (*44*).

In this issue of *The Journal of Nuclear Medicine*, Watanabe et al. (*45*) report data showing cardioprotective effects of carvedilol on a rat model of dilated cardiomyopathy induced by autoimmune myocarditis. This model created autoimmune reactions in rats through injection of cardiac myosin, which leads to a constant morbidity and a 25% mortality from severe myocardiopericarditis. After 4 wk, the survivors were treated orally with either carvedilol solution or vehicle solution alone. The protective effect of carvedilol was estimated by its ability to improve hemodynamic variables such as heart rate and left ventricular end-diastolic pressure; mainly, to improve myocardial adrenergic status as assessed by MIBG uptake and clearance; and, finally, to decrease myocardial fibrosis.

The rationale for the choice of MIBG uptake and clearance to evaluate the effects of the treatment was based on previous experimental and clinical work on heart failure. Because the integrity of the sympathetic pathway determines myocardial fixation of MIBG, it is reduced in parallel with the alteration of norepinephrine uptake (*46*) and correlates with the myocardial content in norepinephrine in experimental heart failure (*47*) and with the degree of myocyte degeneration and necrosis in congestive heart failure (*48*). This factor contributes largely to the potent relationship reported between MIBG uptake and the unfavorable outcome in dilated cardiomyopathy (*29–31*). The washout rate of MIBG uptake may reflect norepinephrine spillover. Whether MIBG washout confers additional clinical information remains, however, uncertain (*31*).

The finding, reported by Watanabe et al. (*45*), that carvedilol exerts cardioprotective properties on myocardial adrenergic innervation is in line with previous clinical data. MIBG uptake was reported to increase after spironolactone (*49*) and ACE-inhibitor treatments (*50*). The effects of β-blocker treatment on MIBG uptake have also been investigated in some studies. No change in MIBG uptake was found after 3 mo of bucindolol administration (*51*). Conversely, an increase in MIBG uptake was reported after open-label metoprolol (*52,53*), carvedilol (*54,55*), or other agents (*56,57*) in either ischemic or nonischemic heart failure. Some reports indicated that MIBG imaging was also useful in predicting the response to therapy (*56,58*). These data suggest that the NE reuptake mechanism is improved with β-blockers, which may contribute to the improvement in cardiac function. Nevertheless, whether this effect is caused by β-blockers per se or is secondary to the overall improvement in hemodynamics remains unclear, although a report has shown that the changes in MIBG kinetics preceded the increase in left ventricular ejection fraction (*56*).

In the light of experimental data such as shown by Watanabe et al. (*45*) and in previous clinical reports, the myocardial adrenergic dysinnervation assessed by neuroimaging techniques in dilated cardiomyopathy has important clinical implications. MIBG imaging may thus help risk-stratify heart failure patients and monitor the effects of medical therapy, especially in patients treated with β-blockers. In patients who have heart failure from dilated cardiomyopathy but untreated by β-blockers, MIBG imaging and radionuclide left ventricular ejection fraction are likely challenged by the measurement of exercise capacity (maximal oxygen consumption, or peak VO_2) in assessing prognosis (*31*). However, these 2 nuclear medicine techniques are the best noninvasive indices to objectively evaluate the response to β-blocking agents. The value of peak VO_2 measurement in this situation remains controversial. Although patients generally report an improvement in functional status, peak exercise capacity remains unchanged or slightly reduced after carvedilol, with the reduction in peak exercise heart rate being the mechanism generally advocated to explain this discrepancy. Carvedilol seems to have lesser effects on exercise tolerance than does metoprolol (*59*). In controlled studies, carvedilol did not exhibit a significant effect on treadmill exercise capacity, compared with the effect of placebo (*60–64*). If the reality of the adverse effects of myocardial adrenergic dysinnervation on dilated cardiomyopathy is not questionable, some considerations may limit the practical consequences of this alteration. In the case of full anatomic denervation in cardiac transplantation, leading to dramatically decreased MIBG uptake in the heart (*65*), the only apparent physiologic consequence appears to be a prolongation of the action of β-receptor agonists, which are usually taken up through the uptake-1 carrier system (*12*). This can be explained by the fact that in the transplanted heart, NE concentration does not increase at the receptor site. Indeed, in a dog model associating experimental heart failure and ventricular denervation, significantly less catechol-

amine-induced desensitization was found in comparison with dogs having the same heart failure but intact myocardial adrenergic innervation (*66*). These data and others (*67*) indicate that the presence of normal ventricular innervation is required for physiologic expression of catecholamine overexposure.

The finding of Watanabe et al. (*45*) that carvedilol may prevent progression to dilated cardiomyopathy after myocardial injury is in accordance with a large body of evidence that β-blockers prevent deterioration in function and progression in remodeling (*68–72*) and even reverse remodeling (*70,72*). These data may encourage those who try to extend this experience to other types of myocardial injury, such as that present in anthracycline-induced cardiomyopathy (*73*).

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