

## Antiadrenergic Therapy of Chronic Heart Failure Surprises and New Opportunities

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The great British-American scientist-philosopher Alfred North Whitehead divided progress into three stages, the second of which was termed precision, in which the “right ways and wrong ways” of an original idea are elucidated.<sup>1</sup> During this period, reinterpretation of the basic idea occurs and is essential to progress. Whitehead’s message is that important ideas are dynamic instruments that are constantly changing as new and usually unexpected information becomes available. This is why tests of particular hypotheses, including those tested in Phase III clinical trials, are often unresponsive, and why therapeutic paradigms constantly change. Within such an ephemeral milieu, the key to ultimate success is to view each unexpected or negative result as an opportunity for constructing and testing even more novel and valuable hypotheses within the framework of the general idea, to ascend to the final stage where progress can be “generalized.”<sup>1</sup>

Whitehead’s philosophical legacy is impressively in play in the area of antiadrenergic therapy of chronic heart failure (CHF). The unarguable basic idea is that the biologically powerful adrenergic compensatory mechanism plays a critical role in the natural history of CHF. It is the details or nuances within the general paradigm that continue to change, and lately, surprisingly so. As recently reviewed,<sup>2</sup> the importance of dysfunctional adrenergic activation in CHF was first elucidated by work performed by Braunwald’s group at the National Institutes of Health in the 1960s. Among other things, this early work provided the first evidence of marked adrenergic activation in CHF. However, on the basis of reduction in myocardial tissue norepinephrine, and the short-term effects of large doses of antiadrenergic agents,<sup>3</sup> the overall interpretation was that adrenergic support was deficient in CHF. This view prevailed for 10 to 15 years, and it contributed to the original logic behind developing Type III phosphodiesterase inhibitors as a treatment for CHF. In the late 1970s and early 1980s, three separate lines of evidence contributed to a 180-degree turn in the role of adrenergic mechanisms in CHF. As recently summarized,<sup>4</sup> these paradigm-changing observations were: (1) the apparently favorable clinical response to  $\beta$ -blocking agents when administered chronically to subjects with idiopathic dilated cardiomyopathies; (2) the evidence that the failing human heart exhibited  $\beta$ -adrenergic receptor downregulation and pathway

desensitization, which are typical responses to excessive exposure to adrenergic drive; and (3) the demonstration that coronary sinus norepinephrine levels were elevated in CHF patients, reflecting an increase in interstitial levels despite the decrease in tissue stores. For the next 15 to 20 years, the prevailing view was that excessively and incessantly increased adrenergic drive is uniformly harmful to the natural history of primary or secondary dilated cardiomyopathies and to the CHF clinical syndrome.<sup>4</sup> This refinement predicts that any treatment that reduces adrenergic activation would produce favorable effects on CHF natural history.

However, results of recently completed clinical trials are not consistent with this general paradigm. An agent that powerfully lowers norepinephrine through central imidazoline and/or  $\alpha_2$ -adrenergic receptor activation plus possible presynaptic  $\alpha_2$ -receptor agonism, moxonidine, increased mortality by >50% in the Moxonidine Congestive Heart Failure (MOXCON) Trial, with the study being terminated for safety concerns after  $\approx$ 1000 patients were enrolled.<sup>5</sup> In phase II this compound was powerfully sympatholytic, and the degree of systemic norepinephrine reduction was directly associated with an increase in serious adverse events despite evidence for reverse remodeling, the signature of favorable antiadrenergic effects on the failing heart.<sup>6</sup> Because sympatholysis is the only known important pharmacological property of moxonidine, these data seriously challenged the uniform dogma that antiadrenergic therapy is beneficial. That sympatholysis is a harmful pharmacological property in a therapeutic agent used to treat CHF is further supported by data from the  $\beta$ -Blocker Evaluation of Survival (BEST) Trial, in which the unique  $\beta$ -blocker/sympatholytic agent bucindolol increased mortality in 14% of the treated population through a pronounced sympatholytic effect that was not observed in placebo-treated patients.<sup>7</sup> The BEST Trial was stopped for benefit in the majority of the study population examined (non-black New York Heart Association Class III), with the degree of mortality reduction consistent with the results of other large  $\beta$ -blocker trials just reported in these populations.<sup>8,9</sup> In addition, in the entire BEST cohort, nearly all secondary end points were favorably affected by bucindolol.<sup>8</sup> Dilution of efficacy to a statistically insignificant reduction (by 10%) in mortality in the larger cohort of BEST was due to the lack of efficacy in Class IV and black patients,<sup>8,9</sup> which

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has in turn been ascribed to the unique sympatholytic properties of bucindolol.<sup>7</sup> Therefore, the harmful effects of sympatholysis are observed when a “pure” agent, such as moxonidine, is used to treat advanced heart failure patients, as well as when an otherwise beneficial, mixed action agent, such as bucindolol, is used in subpopulations who are predisposed to adverse effects of adrenergic withdrawal. The likely explanation for the polar difference in the response of these two general classes of antiadrenergic agents is that during the crucial early period of adrenergic inhibition, sympatholytic agents produce an irreversible removal of adrenergic support with the inability to recruit adrenergic drive when needed to support cardiac function. In contrast,  $\beta$ -blockers are mass-action agents whose inhibition can be easily reversed by norepinephrine competition, which allows for the retention and recruitment of the powerful adrenergic support mechanism on an as needed basis. Extensions of these observations include the potentially favorable effects of therapeutic approaches that allow the beneficial aspects of adrenergic inotropic support to be maintained in the presence of  $\beta$ -blockade,<sup>10</sup> or the addition to  $\beta$ -blockade of positively inotropic device therapy.

Powerful sympatholysis, conferred in a third-generation  $\beta$ -blocker by presynaptic  $\beta_2$ -receptor blockade unopposed by potent  $\alpha$ -blockade, is unique to bucindolol, and is not present in carvedilol or  $\beta_1$ -receptor selective second-generation antagonists.<sup>11</sup> Therefore, pharmacological heterogeneity among  $\beta$ -blocking agents can translate into differences in clinical response, in contrast to the rather unvarying pharmacological properties and clinical responses to angiotensin-converting enzyme inhibitors. Another pharmacological property that can influence clinical outcomes is intrinsic sympathomimetic activity (ISA).  $\beta_1$ -receptor ISA to the extent possessed by xamoterol is clearly harmful,<sup>12</sup> consistent with the myopathic and cytotoxic potential of  $\beta_1$ -adrenergic signaling in model myocardial systems. Analogous to work in transgenic models,  $\beta_1$ -receptor intrinsic activity appears to be more clinically harmful than  $\beta_2$ , because the  $\beta_2$  ISA-containing agent celiprolol is well tolerated in CHF.<sup>13</sup> There has been controversy about bucindolol possessing ISA on the basis of evidence of this property in functioning rat myocardium<sup>14</sup> and perhaps in nonfunctioning human myocardial tissue cultures.<sup>15</sup> However, three independent studies in functioning isolated human nonfailing or failing human myocardial preparations have demonstrated no ISA for bucindolol, even under conditions of augmented signal transduction.<sup>16–18</sup> Moreover, in the most sensitive method of ISA detection, Holter Monitoring of 24-hour heart rate, xamoterol, and celiprolol demonstrate ISA, but bucindolol does not.<sup>19</sup> In fact, recent data from my laboratory indicate that under well-controlled conditions of augmented signal transduction in functioning isolated human right ventricular preparations, carvedilol, but not bucindolol, exhibits ISA<sup>17</sup> (unpublished data). The small amounts of carvedilol ISA detectable in experimental conditions of artificially augmented signal amplification are similar to those recently reported in transgenic mice overexpressing human  $\beta_1$ -adrenergic receptors.<sup>20</sup> In view of the excellent clinical results with carvedilol, subpharmacological ISA detected by

these methods is not likely to produce adverse effects, but it could contribute to the beneficial results of carvedilol.

In contrast to the above-noted pharmacological properties that create heterogeneity of response in CHF, blockade of myocardial  $\beta_1$ -adrenergic receptors versus additional pathological growth-coupled adrenergic receptor pathways has not produced evidence of the superiority of one approach versus another, for left ventricular functional,<sup>21,22</sup> clinical,<sup>23</sup> or molecular<sup>24</sup> responses. As discussed previously,<sup>23</sup> this is likely due to the  $\beta_1$ -receptor selectivity of norepinephrine and, to a greater degree of myocardial pathogenicity of the  $\beta_1$  versus  $\beta_2$  or  $\alpha_1$ -receptor pathways. The soon-to-be reported Carvedilol Or Metoprolol European Trial (COMET) Trial comparing metoprolol to carvedilol should provide the ultimate answer as to whether blockade of additional myocardial adrenergic receptors adds incremental clinical benefit to  $\beta_1$ -blockade in CHF.

Of major relevance to antiadrenergic strategies in CHF is the recent report by Small et al<sup>24</sup> that a double adrenergic receptor polymorphism, an  $\alpha_{2C}$  deletion-loss of function genotype ( $\alpha_{2C}$ Del322 to 325), combined with a high-functioning  $\beta_1$ -receptor genotype ( $\beta_1$ Arg389), confers a 10-fold risk for the development of heart failure. The  $\alpha_{2C}$  polymorphism likely leads to a reduction in the natural brake on norepinephrine release provided by  $\alpha_2$ -receptors, and the increased adrenergic drive in these individuals then presumably damages the heart to a greater extent in individuals with the high function  $\beta_1$ -receptor polymorphism. Importantly, the  $\alpha_{2C}$  polymorphism is enriched in blacks,<sup>24</sup> and it provides a potential explanation for certain characteristics of CHF in this population, including worse cardiac function and prognosis per a given degree of functional incapacity. How can this information be reconciled with the antiadrenergic treatment data? Merging of these two bodies of data provides a unique opportunity to tailor antiadrenergic therapy to patient populations who may be more likely to respond, and to move beyond the outdated and soon-to-be economically untenable approach of treating large numbers of patients to capture the minority who actually respond to a specific therapy. For example, the  $\alpha_{2C}$  polymorphism subjects may well be the ones in BEST who predisposed bucindolol to the adverse effects in blacks, via exorbitant sympatholysis at a point in the natural history in which their severely failing myocardium had become completely dependent on high levels of adrenergic support. But what if a sympatholytic agent had been given much earlier in these patients' CHF course to prevent the increased potential for adrenergic damage? Moreover, if this were to be combined with  $\beta_1$ -receptor blockade in subjects who also possess the  $\beta_1$ Arg389 high-functioning  $\beta_1$ -receptor polymorphism, then a study in left ventricular dysfunction or mild heart failure might well be able to detect an efficacy signal in a relatively small sample size. It has already been shown that a pharmacogenetic profile can predict response to  $\beta$ -blocking agents,<sup>25</sup> and the recent data of Small et al<sup>24</sup> suggest that responders to this form of therapy can be even further refined.

In summary, recent clinical trial data with antiadrenergic agents in advanced CHF populations reveal a surprisingly marked heterogeneity of clinical response between sympa-

tholytic and  $\beta$ -receptor blocking compounds, with sympatholysis being harmful and receptor blockade being beneficial. These observations nudge current adrenergic theory back toward the original interpretation of the importance of adrenergic support to survival in at least some advanced heart failure patients, and they suggest that more attention needs to be given to the maintenance of such support in the development of the next generation of therapy. Moreover, new information on the effects of adrenergic receptor polymorphisms provides the rationale for pharmacogenetically tailored antiadrenergic therapy, which may include agents that would not be effective in the entire advanced heart failure population.

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