EDITORIAL COMMENT
The Neurohormonal Paradigm: Have We Gone Too Far?*

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Following success with adrenergic blockade and inhibition of the renin-angiotensin-aldosterone axis, many physicians have believed that blockade of other neurohormonal systems will also prove to be beneficial in patients with heart failure (HF). However, recent data suggest that it is time to change our conception of how to improve survival and symptoms in these patients. We have seen that antagonizing activated neurohormonal systems may actually not only be advantageous, but may have adverse effects. The Randomized Intravenous TeZosentan (RITZ-4) study reported in this issue of the Journal continues the pattern (1).

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In 1984, Cohn et al. (2) reported the prognostic importance of elevated plasma concentrations of norepinephrine, and decades later we proved that beta-adrenergic blockade improves survival. Plasma renin activity also showed prognostic (3), and angiotensin-converting enzyme (ACE) inhibitors markedly improved survival. Therefore, it is not surprising that blockade of other systems also appeared tempting. Not only were the sickest patients found to have elevated concentrations of endothelin, arginine vasopressin, angiotensin, cytokines, and multiple other biomarkers, but animal physiology experiments have provided rationale as to why blockade might be important. In addition to causing vasoconstriction and endothelial abnormalities, many of these systems could theoretically exert direct negative myocardial actions. These systems have also been shown to affect apoptosis, fibrosis, and contractility. For example, both vasopressin and angiotensin stimulate protein synthesis within the myocyte (4). It has been proven that neurohormonal antagonism can decrease fibrosis in patients with HF. Therefore, it made sense to evaluate the consequences of antagonizing these systems.

Endothelin was a particularly appealing target. Plasma concentrations of endothelin-1 are elevated in patients with severe HF, and the concentration both correlates with severity of disease and is highly prognostic (5,6). Endothelin's actions are potentially deleterious. It causes vasoconstriction, induces smooth muscle proliferation, and affects myocardial contractility (7,8). It even promotes urinary sodium and water retention (9).

Small studies of endothelin receptor blockers were promising. In HF, endothelin receptor blockade improves hemodynamic parameters (10). It also improves endothelial function in models of atherosclerosis (11). By blocking endothelin's effects as a nitric oxide antagonist, endothelin blockers could even have beneficial effects on platelets and neutrophils (12,13).

Unfortunately, the data from large studies have been disappointing. In this issue of the Journal, we find out that a nonselective endothelin antagonist, tezosentan, did not acutely improve survival or reduce HF or myocardial infarction frequency in patients with acute decompensated HF associated with an acute coronary syndrome. Indeed, the tezosentan group tended to have a higher incidence of worsening failure and more renal failure. In addition, symptoms related to hypotension were greater in the active group. Despite theoretical benefits on both HF and coronary artery disease, administration of tezosentan resulted in no clinical benefit.

This study is consistent with other large studies of endothelin receptor antagonists. The ENdothelin Antagonism with Bosentan and Lowering of Events (ENABLE) investigators studied 1,613 patients with HF and demonstrated no improvement in mortality or HF hospitalizations (14). In the 419 patients evaluated in the ENrasentan COoperative Randomized (ENCOR) evaluation, fewer patients treated with enrasentan improved compared to placebo, and more patients were judged to worsen (15).

There are many possible explanations for these negative trials. O'Connor et al. (1) are, of course, correct in stating that the dose of tezosentan administered in RITZ-4 may have been too high and that the study was relatively small and underpowered. The authors should be congratulated on promptly publishing this negative study (a rarely accomplished deed), and one negative study does not eliminate the possibility that a drug might be beneficial. However, there is nothing in the completed clinical studies to lead us to the conclusion that lower doses of tezosentan would produce a better outcome.

It could be argued that a selective endothelin A (ET_A) antagonist would produce different results. Endothelin B receptor stimulation causes the potentially beneficial nitric oxide-mediated vasodilation, and a selective ET_A agent would not antagonize this. (Although some data suggest that in patients with HF ET_B stimulation causes vasoconstriction [16].) There are also data that a selective antagonist might be preferential by interfering less with endothelin clearance. However, in a study of 157 patients in which the selective agent darusentan caused hemodynamic improvement, there was no improvement in symptoms (with a trend towards more HF exacerbations and increased mortality). Furthermore, headaches were frequent, especially at higher concentrations, and many patients treated with darusentan improved compared to placebo, and more patients were judged to worsen (15).

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doses (17). Thus, the benefits of selective antagonism are theoretical at best.

The more likely hypothesis to explain recent clinical results is that we have reached a limit to observing important benefits with neurohormonal or cytokine antagonism. Antagonism of many activated systems associated with poor prognosis has proven disappointing. There were many reasons to believe that antagonism of tumor necrosis factor-alpha would be useful. Instead, studies of both etanercept and infliximab (18) suggest that antagonism might be detrimental. More complete antagonism of the adrenergic nervous system appeared tempting, but centrally acting moxonidine proved harmful (19) and peripherally acting alpha-blockers proved to result in more HF when given to patients for hypertension (20). Considering the observed escape from the actions of ACE inhibitors, more complete blockade with an angiotensin receptor blockers was predicted to be beneficial in chronic HF. Yet, when combined with beta-blockers and ACE inhibitors, the consequences appeared harmful (21).

So are there ways to improve the status of patients with HF? Perhaps part of the answer is to lower expectations. Not all medicines will improve survival (and, if they do, only very large studies will be able to detect it as the mortality rate decreases). Improvement in symptoms (if not accompanied by worse survival) is still an admirable goal. Thus, rather than arguing that arginine vasopressin antagonists will improve survival (22), the data suggesting benefits on fluid status should be explored (23,24). Agents that improve renal function might decrease hospitalizations and improve symptoms.

Even more important will be the development of new paradigms for the treatment of HF. Whether it is gene manipulation, cell transfer, or substantial improvements in mechanical devices, improvements comparable with those seen with beta-blockers and ACE inhibitors are possible. We must stop assuming that the body's compensatory actions to chronic HF are harmful; we do not understand enough physiology to know why they are often needed. We do know, however, that antagonism of endothelin receptors is unlikely to improve symptoms or survival in patients with HF.

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REFERENCES