For those who have comfortably accepted the mechanistic link between sympathetic nervous system activation and poor outcome in heart failure, the study by Brede et al in this issue of Circulation is a welcome confirmation. The authors appear to have demonstrated in a murine model that absence of sympathoinhibitory \( \alpha_2 \) adrenoceptors is associated with overactive catecholamine release, aggressive remodeling of the left ventricle, worsening signs of heart failure, and shortened life expectancy. Provocatively, deletion polymorphism of the \( \alpha_2 \) receptor in patients with heart failure also appears to be associated with worse heart failure and poorer outcome.

One may, of course, quibble with some experimental shortcomings. The number of animals is small, and surgical mortality is neither addressed nor accounted for. The magnitude of circulating norepinephrine increase in the at-risk receptor-deficient mice is surprisingly modest. The classic model has been assessed retrospectively from a database that is poorly described and not available for scrutiny. Furthermore, the experimental model of pressure overload from aortic banding bears little similarity to the syndrome of heart failure observed clinically. Nonetheless, the apparent link between poor outcome and \( \alpha_2 \) receptor dysfunction certainly provides support for an adverse effect of unthwarted sympathetic stimulation on the progression of the syndrome. Indeed, our early observations of a relationship between plasma norepinephrine and mortality in heart failure but stressed by the survival benefit of \( \beta \)-blocker therapy appear to have been mechanistically validated.

Or have they? Nothing is simple when dealing with the \( \alpha_2 \) receptor. It has traditionally been recognized to have at least two functions: to mediate vasoconstriction peripherally and to inhibit sympathetic nervous system activity centrally. Brede and his associates in Wurzburg remind us of a less well-known effect of \( \alpha_2 \) agonists; they inhibit presynaptic release of norepinephrine in the tissue, in this instance isolated atria. Added to this complexity is the recognition that there are at least two \( \alpha_2 \) receptors, and in these experiments activity of the \( \alpha_{2A} \) and \( \alpha_{2C} \) receptors, but not the \( \alpha_{2B} \) receptors, was critical to preventing progression of the disease. Some of these subtype issues are still in need of clarification. For example, adverse effects were noted in the \( \alpha_{2C} \) knockout mice, despite the authors’ acknowledgment that \( \alpha_{2C} \) receptors by themselves do not play a major role in central regulation of sympathetic tone. Deletion of the \( \alpha_{2C} \) receptor appears to contribute to sympathetic overactivity only when combined with \( \alpha_{2A} \) receptor deficiency. Therefore, how would isolated \( \alpha_{2C} \)-receptor knockout lead to heightened sympathetic drive? Is it a regional tissue effect? Or is the adverse response related to an independent compensatory mechanism developed by animals coping with lifelong absence of the receptor? Such potential mechanistic, regional, and species issues make translation of these observations into the clinical arena hazardous at best.

The most troubling threats to the comfortable hypothesis of a pathophysiological sympathetic role are recent clinical observations. If enhanced sympathetic activity is contributing to progression of heart failure, then inhibitors of that sympathetic activity should produce a favorable effect. Alpha\(_1\) receptor activation should be a manifestation of this unwanted adrenergic stimulation, but selective \( \alpha_1 \) blockers, such as prazosin and doxazosin, do not slow progression of heart failure and are less effective than diuretics in preventing heart failure in hypertensive patients. Imidazoline receptors inhibit sympathetic activity centrally, and moxonidine strikingly reduces plasma norepinephrine levels in heart failure but has an adverse effect on morbidity and mortality. Thus, clinical trials do not necessarily support the suggestion that sympathetic overactivity is an evil in heart failure. In our original observations of patients with heart failure, we concluded that plasma norepinephrine was a marker for the severity of the disease, but not necessarily a contributor to that severity.

What about \( \beta \)-blockers? These drugs (except perhaps bucindolol) exert a remarkably favorable effect on mortality and morbidity in heart failure. Don’t these clinical trials confirm the benefit of blocking at least one arm of the sympathetic nervous system? Perhaps not. \( \beta \)-blockers are potent inhibitors of renin production and produce profound reductions in plasma angiotensin II levels in patients with heart failure. The efficacy of inhibitors of the renin-angiotensin system in slowing progression of heart failure is now incontrovertible.

The concept of an adverse effect of chronic sympathetic stimulation on the progression of cardiovascular disease is therefore less secure today than it was a few years ago. The observations of Brede et al in receptor-deficient mice and in patients with heart failure should stimulate the study of additional experimental models and prospective clinical trials to confirm and extend these preliminary results. Indeed, if the clinical findings are confirmed, then \( \alpha_2 \) polymorphism could

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potentially serve as a guide to therapeutic decision-making. It is critical to future management and to research in heart failure to know which of the neurohormonal mechanisms implicated in cardiovascular disease progression should be inhibited. If the sympathetic nervous system is not one of them, then perhaps we should rejoice that the body’s design provided for down-regulation of adrenergic receptors during chronic stimulation to moderate its potential deleterious effects. A similar down-regulation of angiotensin II receptors might have spared us from the progressive cardiovascular disease syndromes that plague the world’s population.

References

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