Editorial

Sympathetic Nervous System in Heart Failure

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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 al1 in this issue of Circulation is a welcome confirmation. The authors appear to have demonstrated in a murine model that absence of sympathoinhibitory α2 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 α2 receptor in patients with heart failure also appears to be associated with worse heart failure and poorer outcome.

See p 2491

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 clinical material 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 α2 receptor dysfunction certainly provides support for an adverse effect of unfettered sympathetic stimulation on the progression of the syndrome. Indeed, our early observations of a relationship between plasma norepinephrine and mortality in heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less effective than diuretics in preventing heart failure6 and are less 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These subtype issues are still in need of clarification. For example, adverse effects were noted in the αc knockout mice, despite the authors' acknowledgment that αc receptors by themselves do not play a major role in central regulation of sympathetic tone. Deletion of the αc receptor appears to contribute to sympathetic overactivity only when combined with α3 receptor deficiency.5 Therefore, how would isolated αc-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 mechanism, 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. Alpha2-receptor activation should be a manifestation of this unwanted adrenergic stimulation, but selective α1 blockers, such as prazosin and doxazosin, do not slow progression of heart failure6 and are less effective than diuretics in preventing heart failure in hypertensive patients.7 Imidazoline receptors inhibit sympathetic activity centrally, and moxonidine strikingly reduces plasma norepinephrine levels in heart failure8 but has an adverse effect on morbidity and mortality.9 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.2

What about β-blockers? These drugs (except perhaps bucindolol)10 exert a remarkably favorable effect on mortality and morbidity in heart failure.3,4,11,12 Don't these clinical trials confirm the benefit of blocking at least one arm of the sympathetic nervous system? Perhaps not. β-blockers are potent inhibitors of renin production and produce profound reductions in plasma angiotensin II levels in patients with heart failure.11 The efficacy of inhibitors of the renin-angiotensin system in slowing progression of heart failure,14 renal failure,15 cerebrovascular disease,16 and atherosclerosis16 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 al1 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 α3 polymorphism could...
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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