Editorial Commentary

Is Very High Sympathetic Tone in Heart Failure a Result of Keeping Bad Company?

Murray Esler, David Kaye

The sympathetic nervous system is activated in patients with heart failure, with increase in the sympathetic outflows to the heart, kidneys, and the skeletal muscle vasculature having been clearly demonstrated through the use of isotope dilution-derived measures of norepinephrine spillover and the sympathetic nerve recording technique of clinical microneurography. Prognosis in cardiac failure (congestive heart failure, CHF) is directly linked to the level of activation of the sympathetic nervous system present, most strongly with that in the sympathetic outflow to the heart. One of the major advances in cardiology of the past 10 years has been the successful therapeutic targeting with β-adrenergic–blocking drugs of the defining neural pathophysiology of CHF, a pronounced and preferential stimulation of the cardiac sympathetic nerves, which has materially improved the clinical outcome in patients with heart failure.

The regulatory processes underlying the sympathetic nervous activation of CHF remain uncertain. In both experimental and human heart failure, there is evidence that rostral noradrenergic neuronal projections from the brain stem to hypothalamic nuclei, in particular the paraventricular nucleus of the hypothalamus, are important drivers of the increased sympathetic outflow. Whether the afferent mechanism for these CNS changes might perhaps involve hypoxia, arterial baroreflex impairment, or increased intracardiac pressure, or even combinations of all three, is disputed.

In the current issue of the Journal, Professor Grassi and colleagues from Milan, in an important paper provide intriguing results suggesting that another mechanism of sympathetic stimulation may also be operating, specifically that two conditions that importantly predispose to the development of heart failure, obesity and high blood pressure, both of which are characterized by the presence of high sympathetic tone, directly contribute to the level of sympathetic stimulation present in CHF. The authors’ results suggest that in CHF complicated by obesity, hypertension, or obesity-related hypertension, there is a direct summation of the sympathetic nervous activation characterizing heart failure with that of these other conditions. Among patients with heart failure, sympathetic nervous activity measured by microneurography was least in lean patients with CHF with normal blood pressure (although higher than in healthy people), intermediate in CHF accompanying hypertension or obesity, and highest in CHF accompanying obesity combined with hypertension.

What might be the mechanism underlying such an additive effect? For essential hypertension and some forms of experimental hypertension, the CNS mechanisms of sympathetic stimulation appear to be similar to those in CHF, involving activation of suprabulbar noradrenergic projections to the hypothalamus. Accordingly, it is easy to envisage a common, additive process jointly augmenting sympathetic outflow. In obesity accompanying CHF, the situation is not so straightforward in that in obesity the CNS mechanisms differ from those in CHF and essential hypertension, the sympathetic activation of obesity having variously been attributed to CNS actions of leptin or of insulin or perhaps to the influence of coexistent obstructive sleep apnea. Grassi and colleagues provide evidence that impairment of the arterial baroreflex, common to all conditions, is the mechanism of sympathetic nervous summation. This may be correct, but the theoretical difficulty here is that the arterial baroreflex is conventionally thought to primarily regulate phasic sympathetic outflow in response to short-term blood pressure change rather than ongoing, static sympathetic outflow.

One potential source of confounding in the present study is that the obesity or hypertension, which might be present at the initiation of the CHF and possibly contribute to its development, could disappear as the heart failure becomes established. Pathological loss of body weight, cardiac cachexia, sometimes occurs in CHF, whereas blood pressure may fall to even subnormal levels in patients with CHF who were previously hypertensive, as cardiac performance falters. Accordingly, lean patients with CHF with normal blood pressure at the time of the study might at an earlier stage have been hypertensive, obese, or both. It does seem clear, however, that it is current rather than antecedent hypertension and obesity that influences sympathetic tone in CHF. The authors’ finding that among patients with CHF, muscle sympathetic nerve activity was lowest in those with normal blood pressure and body weight at the time of study, despite some probable confounding of the type mentioned, establishes this.

Regional patterns of sympathetic activation in heart failure, hypertension, and obesity differ, most notably in that cardiac sympathetic activity is actually reduced in normotensive obesity. Of interest is whether there is a strict summation of sympathetic tone in the individual sympathetic outflows to different organs when CHF is associated with obesity or hypertension. The situation in the renal and cardiac sympa-
nervous system activation? The current high level of interest shown by many pharmaceutical companies in pharmacogenetics illustrates the pervasive influence of ideas such as this. Given our present state of knowledge, however, matching of antihypertensive therapy to the pathophysiology of the hypertension in an individual patient (or for that matter pharmacogenetic information) cannot be the primary therapeutic principle, in part because knowledge of both hypertension pathophysiology and the precise mechanisms of drug action remains imperfect. This point being made, and with reference to the remarkable benefits of β-adrenergic blockade in cardiac failure, the important, but to this stage not satisfactorily answered, question remains: of all antihypertensive therapies, might those inhibiting the sympathetic nervous system best reduce cardiovascular risk? The recent Losartan Intervention for Endpoint reduction in hypertension (LIFE) study, although not providing a definitive answer to this particular question, does suggest that this in fact may not be the case in demonstrating a survival benefit for an angiotensin receptor blocker (losartan) over a β-adrenergic blocker (atenolol) in hypertensive patients.

**References**


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