

# Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*<sup>SM</sup>

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

Murray Esler and David Kaye

*Hypertension* 2003;42;870-872; originally published online Oct 20, 2003;

DOI: 10.1161/01.HYP.0000098662.31444.13

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2003 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/42/5/870>

Subscriptions: Information about subscribing to Hypertension is online at  
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

# 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 spill-over and the sympathetic nerve recording technique of clinical microneurography.<sup>1-3</sup> Prognosis in cardiac failure (congestive heart failure, CHF) is directly linked to the level of activation of the sympathetic nervous system present,<sup>4</sup> most strongly with that in the sympathetic outflow to the heart.<sup>5</sup> One of the major advances in cardiology of the past 10 years has been the successful therapeutic targeting with  $\beta$ -adrenergic-blocking drugs of the defining neural pathophysiology of CHF, a pronounced and preferential stimulation of the cardiac sympathetic nerves,<sup>1</sup> which has materially improved the clinical outcome in patients with heart failure.<sup>6,7</sup>

The regulatory processes underlying the sympathetic nervous activation of CHF remain uncertain. In both experimental<sup>8</sup> and human<sup>9,10</sup> 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.<sup>9,11</sup>

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,<sup>2,3,12</sup> 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<sup>13</sup> and some forms of experimental hypertension,<sup>14</sup> 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<sup>15</sup> or of insulin<sup>16</sup> or perhaps to the influence of coexistent obstructive sleep apnea.<sup>17</sup> 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.<sup>18</sup>

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,<sup>19</sup> 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.<sup>12</sup> 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-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From Baker Heart Research Institute, Melbourne, Australia.

Correspondence to Prof Murray Esler, Baker Heart Research Institute, PO Box 6492, St Kilda Road Central, Melbourne, Victoria 8008, Australia. E-mail [murray.esler@baker.edu.au](mailto:murray.esler@baker.edu.au)

(*Hypertension*. 2003;42:870-872.)

© 2003 American Heart Association, Inc.

*Hypertension* is available at <http://www.hypertensionaha.org>  
DOI: 10.1161/01.HYP.0000098662.31444.13

thetic outflows would be of special relevance, given the contribution of renal sympathetic activation to sodium retention in CHF<sup>20</sup> and of cardiac sympathetic activation to the risk of death in patients with heart failure.<sup>5</sup> The measurements of venous plasma norepinephrine concentration and MSNA provided in the report of Grassi and coauthors cannot provide an answer to this question. Renal sympathetic activation is present in CHF, obesity, and hypertension,<sup>1,3,12</sup> and the general concordance of plasma renin activity values and MSNA found by Grassi and colleagues (given that renal renin release is importantly controlled by the renal sympathetic nerves) does suggest that sympathetic tone directed to the kidneys, as for MSNA, does summate. Whether this applies also to the sympathetic nerves of the heart is uncertain. If it did, paradoxically, the coexistence of normotensive obesity might even have a protective effect in CHF by lowering cardiac sympathetic tone.

Sympathetic tone does differ widely and inexplicably among patients with CHF.<sup>4,5</sup> This important study provides a probable explanation for this conundrum. Given the clearly established fact that the level of sympathetic activation present in a patient with CHF is a major determinant of their prognosis,<sup>4,5</sup> the study of Grassi and colleagues strongly suggests that the presence of accompanying obesity, hypertension, or their combination has an adverse effect in CHF, attributable to augmented sympathetic activity, which goes beyond any direct, adverse influence of these conditions. Furthermore, the value of  $\beta$ -adrenergic blockade might, perhaps, be greatest in patients with CHF with accompanying obesity or hypertension, although this remains to be tested. It could be anticipated that this interesting study, based primarily on phenotypes of sympathetic activation, might lead to a change in the dominant direction of contemporary research on heart failure therapy, which currently emphasizes specific molecular determinants of  $\beta$ -blocker response.<sup>21</sup>

The paper by Grassi and colleagues documents that coexisting hypertension in patients with CHF increases sympathetic nervous activity. This would be expected to increase their risk of death. Can these concepts of an adverse influence of excessive sympathetic nervous system stimulation be extended to patients who have essential hypertension without heart failure? Neurogenic mechanisms are dominant in pathogenesis in perhaps 40% of patients with essential hypertension.<sup>2,3,12</sup> This greater sympathetic activity could be expected to adversely affect prognosis. Can it therefore be inferred that in hypertensive patients without CHF in whom the hypertension is neurogenic, prognosis is particularly adverse? This question is at present unanswered. It might be that the level of cardiac sympathetic activation present in essential hypertension is insufficient for this. An adverse trophic effect of sympathetic activation in the human heart, however, is probable in hypertensive patients, as exemplified in the recent demonstration of a strong and direct relation of high cardiac sympathetic tone to left ventricular hypertrophy in patients with essential hypertension.<sup>22</sup>

Following this line of reasoning, might it be appropriate to specifically recommend antiadrenergic antihypertensive drugs in hypertensive patients? Perhaps this recommendation might be applied preferentially in patients with sympathetic

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  $\beta$ -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,<sup>23</sup> 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  $\beta$ -adrenergic blocker (atenolol) in hypertensive patients.

## References

1. Hasking G, Esler M, Jennings G, Burton D, Johns J, Korner P. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation*. 1986;73:615–621.
2. Grassi G, Colombo M, Seravalle G, Spaziani D, Mancia G. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension*. 1998;31:64–67.
3. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate and functions. *Physiol Rev*. 1990;70:963–985.
4. Cohn JN, Levine TB, Olivari MT, Garberg V, Tura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819–823.
5. Kaye DM, Lefkowitz J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol*. 1995;26:1257–1263.
6. Packer M, Bristow MR, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349–1355.
7. CIBIS II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS II). *Lancet*. 1999;353:9–13.
8. Patel KP, Zhang K. Neurohumoral activation in heart failure: role of paraventricular nucleus. *Clin Exp Pharmacol Physiol*. 1996;23:722–726.
9. Lambert GW, Kaye DM, Lefkowitz J, Jennings GL, Turner AG, Cox HS, Esler MD. Central nervous system monoamine neurotransmitter turnover and its association with sympathetic nervous activity in treated heart failure patients. *Circulation*. 1995;92:1813–1818.
10. Aggarwal A, Esler M, Lambert G, Hastings J, Johnston L, Kaye D. Norepinephrine turnover is increased in suprabulbar subcortical brain regions and is related to whole-body sympathetic activity in human heart failure. *Circulation*. 2002;105:1031–1033.
11. Grassi G, Seravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C, Del Bo A, Sala C, Bolla GB, Pozzi M, Mancia G. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation*. 1995;92:3206–3211.
12. Rumantir MS, Vaz M, Jennings GL, Collier G, Kaye DM, Seals DR, Wiesner GH, Brunner-La Rocca HP, Esler MD. Neural mechanisms in human obesity-related hypertension. *J Hypertens*. 1999;17:1125–1133.
13. Ferrier C, Esler M, Eisenhofer G, Wallin G, Horne M, Cox H, Lambert G, Jennings G. Increased norepinephrine spillover into the cerebrovascular circulation in essential hypertension: evidence of high central nervous system norepinephrine turnover? *Hypertension*. 1992;19:62–69.

14. Qualy JM, Westfall TC. Age-dependent overflow of endogenous norepinephrine from paraventricular hypothalamic nucleus of hypertensive rats. *Am J Physiol.* 1993;265:H39–H46.
15. Haynes WG, Sivitz WI, Morgan DA, Walsh SA, Mark AL. Sympathetic and cardiorenal actions of leptin. *Hypertension.* 1997;30:619–623.
16. Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. *Q J Med.* 1986;236:1081–1090.
17. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation.* 1998;98:772–776.
18. Korer PI. Integrative neural cardiovascular control. *Physiol Rev.* 1971;51:312–367.
19. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. *N Engl J Med.* 1964;271:403–409.
20. Di Bona GF, Herman PJ, Sawin LL. Neural control of renal function in edema-forming states. *Am J Physiol.* 1988;254:R1017–R1024.
21. Kaye DM, Smirk B, Williams C, Jennings G, Esler M, Holst D. Beta adrenoceptor genotype influences the response to carvedilol in patients with congestive heart failure. *Pharmacogenetics* 2003;13:379–382.
22. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Soctratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation.* 2003;108:560–565.
23. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:995–1003.