What do we really know about sympathetic outflow and blood pressure in humans? For example, in healthy normotensive young subjects, baseline sympathetic outflow can vary 2-fold to 3-fold. We also know that in healthy aging subjects, baseline sympathetic outflow can be increased dramatically with only a modest impact on vascular resistance and little or no impact on blood pressure. Additionally, there is no clear evidence for dramatic increases in baseline sympathetic outflow in “garden variety” essential hypertension. If we stop here, a position of “nihilism” about sympathetic outflow and blood pressure seems reasonable.

However, when the sympathetic nervous system is destroyed by disease or surgery, blood pressure is highly labile. We also know that many “stressors” that evoke a pressor response also evoke marked sympathetic activation, and that the magnitude of these pressor responses can be a harbinger of future hypertension. Finally, in disease states like congestive heart failure, excessive sympathetic activation is a “bad thing.” If we emphasize these points, sympathetic vasconstriction seems more important to blood pressure and perhaps survival.

In the middle of this confusion about sympathetic activity and blood pressure lie the baroreflexes that sense changes in arterial pressure and evoke increases in heart rate and sympathetic outflow when blood pressure is “low” and reciprocal responses when blood pressure is “high.” Together with their allies in the brain stem and kidney, they make the needed physiological adjustments so that in “normotension” there is an appropriate blood pressure for any given behavioral state.

One mechanism that is essential to this flexible regulatory pattern is baroreflex “resetting.” During physiological conditions that require acute changes in blood pressure the baroreceptors quickly reset to things like “defend” a higher arterial pressure during exercise or let pressure fall during sleep. However, in hypertension, chronic resetting of baroreflexes occurs so that a higher pressure is defended and the hypertensive state is maintained or even reinforced. If we are lucky, perhaps treatment of hypertension will reduce arterial pressure and reset the baroreflexes so that a more normal blood pressure is defended. In other words, we might get a 2-for-1 “physiological bargain” when hypertension is treated.

Does This Happen?
In this edition of Hypertension, Fu et al. working with Ben Levine in Dallas, provide evidence that such a physiological bargain is not so easy to come by. They carefully studied the impact of antihypertensive therapy (combined losartan and hydrochlorothiazide) on short-term and long-term blood pressure control in newly diagnosed hypertension in middle-aged patients. Although their therapeutic regimen clearly caused sustained reductions in arterial pressure from 160/100 to 135/80, there was a marked increase in muscle sympathetic nerve activity (but not heart rate) seen in the first weeks after starting therapy that continued when repeat measurements were made after 3 months.

Further, maneuvers that caused blood pressure to change, indicated that while baroreflex control of heart rate was reset around a lower operating point, there were persistent changes in the relationship (gain) between pressure and heart rate that did not change over the course of therapy. More importantly, baroreflex control of sympathetic outflow was unchanged by treatment, and the elevated sympathetic outflow after weeks and months of treatment suggests that the arterial baroreflexes were behaving as if they were continuously unloaded and not reset.

What are the implications of this startling observation of persistent elevations in sympathetic activity after antihypertensive treatment? First, as the authors note, whereas lowering blood pressure in hypertensive patients clearly reduces their risk for a variety of cardiovascular events and other complications, it does not normalize them. Could this be caused by the persistent sympathetic activation? Is this situation at all parallel to the importance of sympathetic activation as predictor and provoker of bad outcomes in congestive heart failure? Second, are all common antihypertensive drugs alike and will this persistent sympathetic activation be seen no matter what drugs are used? In this context, older classes of drugs that act centrally to reduce sympathetic outflow will likely not be associated with persistent sympathetic outflow after treatment. Additionally, perhaps other more commonly used drugs like β-blockers do a better job of resetting baroreflex function. Third, are large outcome studies and treatment trials needed comparing the efficacy of hypertension treatment strategies that lower sympathetic outflow with strategies that do not? Can previous results be interpreted post-hoc in the context of emerging data about how different drugs affect both sympathetic outflow and blood pressure?
Finally, the observations of Fu et al, although in a limited number of subjects, reinforce the ongoing need for detailed physiologically based phenotyping that has recently been discussed as research priorities for hypertension emerge in the 21st century. Simple phenotyping is no longer enough if we are going to understand the complex effects of treatments on complex diseases like hypertension. In this context, the more we understand about the integrative physiology of blood pressure regulation and the integrative pathophysiology of hypertension, the easier it will be to understand and interpret treatment trials, outcome studies, and meta-analyses. In the modern era, we are bombarded with information that ranges from population studies to molecular biology. Well-conceived and executed integrative physiology studies will help us to better define and understand successful treatment of hypertension.

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Hypertension. 2005;45:487-488; originally published online February 21, 2005;
doi: 10.1161/01.HYP.0000158405.04387.bf

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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