Resistant hypertension, as identified when administration of a thiazide diuretic plus ≥2 other antihypertensive drugs, all at full doses, fails to control an elevated blood pressure, is by no means a minor clinical problem. According to recent publications, the number of individuals falling into this category is ≈15% to 20% of the overall hypertensive population. Given the high prevalence of hypertension, this translates into a figure of several million patients per major country and of more than a hundred million patients worldwide.

Several therapeutic approaches have been proposed to enhance the size of blood pressure reduction in resistant hypertension and possibly to achieve, in a noticeable fraction, blood pressure control. One approach is to add to the existing multidrug regimen an antialdosterone agent, thereby more effectively blocking the sodium-retaining properties of this hormone, the release of which escapes to a significant degree the effect of the blockers of the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists) presently available. Another approach is to complement the usual multipharmacological treatment strategy with the vasodilator influence of the antagonists of endothelin receptors, which, indeed, seems capable of adding a further blood pressure reduction to any previous therapeutic effect.

A third approach is to resort to invasive procedures that can reduce the pressor or increase the depressor influences that physiologically modulate blood pressure. The invasiveness of this approach is ethically justified by the very high cardiovascular risk that characterizes the resistant hypertension condition. A reduction of the pressor influences can be obtained by denervating the kidneys through a radiofrequency generator positioned in the renal arteries through a percutaneously inserted catheter, because afferent fibers originating in the kidney exert sympathoexcitatory effects that can increase blood pressure, and removal of efferent sympathetic influences lowers overall total body norepinephrine spillover and reduces vasoconstriction in a region that accounts for a considerable proportion of systemic vascular resistance. An enhancement of the depressor influences can be obtained via the sympathoinhibitory effects of continuous “field” electric stimulation of the carotid baroreceptors via devices permanently placed around the carotid bifurcations.

For either approach, the pathophysiological rationale is made even more compelling by the evidence that sympathetic activity increases progressively with the increase in the severity of hypertension and that a sympathoexcitatory state is especially pronounced in individuals in whom blood pressure control is particularly difficult, such as in isolated systolic hypertension, and in hypertension associated with obesity, particularly when obesity is accompanied by obstructive sleep apnea. Furthermore, use of electric baroreceptor stimulation is supported by the evidence that, in hypertension, the baroreflex undergoes a “resetting” that avoids baroreceptor saturation, thus preserving the reflex ability to cause vasodilation and decrease blood pressure in response to an increase in its activity. This can be appreciated in the Figure, left panel, which shows the pressor and depressor responses (intra-arterial blood pressure measurements) to carotid baroreceptor deactivation and stimulation, respectively, obtained via the neck chamber technique in normotensive, moderate, and severe hypertensive patients. It can be further appreciated in the Figure, middle panel, which shows the sympathetic responses (microneurography) to arterial baroreceptor deactivation and stimulation obtained, in the same 3 conditions, by reducing and increasing blood pressure with vasoactive drug infusions.

Evidence that field electric stimulation of carotid baroreceptors can lower blood pressure on a chronic basis has been provided in dogs, and observations are available that a blood pressure reduction can also be obtained in resistant hypertensive patients after a use that spans over several months. This background information is expanded by the data reported in the article by Heusser et al published in this issue of Hypertension. Several findings of this article deserve to be emphasized. First, continuous electric stimulation of carotid baroreceptors over several months was accompanied by a reduction in 24-hour mean blood pressure. This expands on previous data regarding the persistent effectiveness of this stimulation procedure, the failure of which was responsible for the abandonment of this approach decades ago when it was first used for the treatment of resistant hypertension or intractable angina. It also provides evidence of a chronic depressor response on a variable such as daily life blood pressure that has special importance for patient prognosis. The size of the reduction (≈10/6 mm Hg systolic/diastolic blood pressure) was only apparently small if one considers that treatment-induced changes in 24-hour mean blood pressure are normally much smaller than the corresponding...
changes in clinic blood pressure. Second, the chronic blood pressure effect was related to the acute blood pressure fall obtained by electrical baroreceptor stimulation at a much earlier time, which gives hope that one might predict the long-term success of the procedure by earlier laboratory testing. Third, repeated acute stimulations, delivered 1 month after implantation of the devices, caused a clear-cut blood pressure reduction, as well as a marked inhibition of the outgoing sympathetic activity, as directly quantified in a peroneal nerve by microneurography. This is a relevant result because it shows that the surgical procedure by which the stimulating device is bilaterally implanted does not impair, through scarring, inflammation, or direct baroreceptor damage, the ability of the reflex to exert its sympathetic and vasomotor modulation. Additional support for this conclusion comes from the data provided by the sequence technique that, 1 month after the device implantation, the baroreflex was capable of modulating heart rate in response to spontaneous blood pressure changes, thereby subserving its role as a blood pressure stabilizer.

The study of Heusser et al has 2 additional intriguing results, as well as some limitations. It is intriguing that, although significant, the relationship between the reduction in blood pressure and the reduction in sympathetic activity induced by acute baroreceptor stimulation showed a relatively low correlation coefficient ($r^2=0.42$; $P<0.05$). This might mean that the sympathetic activity recorded in the peroneal nerve does not precisely represent the overall sympathetic influences of the baroreceptors. It may also mean, however, that nonsympathetic influences are involved in the blood pressure reduction. What these influences could be, however, it is not easy to imagine, because acute baroreceptor stimulation was associated with only a modest bradycardia and no significant changes in the spectral indices of heart rate variability, suggesting that a reduction in cardiac output was unlikely. There was, on the other hand, a significant, albeit not marked, reduction in plasma renin concentration, which is compatible with the possibility that a deactivation of the renin-angiotensin system plays a role. It is also intriguing that the baroreceptor stimulation had a much greater effect on sympathetic drive than on cardiac functions. As discussed by the authors, this may reflect an impairment of the baroreflex ability to modulate cardiac vagal, although not sympathetic, control. Indeed, this is supported by studies in experimental and human hypertension. Compared with Wistar Kyoto rats, in spontaneously hypertensive rats, an increase in blood pressure induced by infusion of norepinephrine was found to cause an equally marked sympathetic inhibition but a much smaller bradycardia. Similarly, compared with normotensive subjects, in moderate and severe essential hypertensive patients, increases and reductions in blood pressure induced by infusion of, respectively, vasopressor and vasodepressor drugs were found to be accompanied by progressively smaller changes in heart rate, whereas the changes in sympathetic activity were superimposable in the 3 conditions (Figure, middle and right panels). Incidentally, the reduced cardiac response to baroreflex stimulation is clinically advantageous, because a reduced cardiac output (eg, what happens with $\beta$-blockers) is associated with adverse effects, such as fatigue and limited exercise tolerance.

The limitations of the study by Heusser et al concern its small size and the timing of the acute baroreflex testing. Because the study included only 12 patients, generalization of the results to the effect of electrical baroreceptor stimulation in the large number of individuals with resistant hypertension is difficult. This is even more the case because the characteristics of the patients with resistant hypertension are extremely heterogeneous and, within the small group of patients included in the study, the responses to baroreceptor stimulation were so different as to range from a marked reduction to

![Figure](http://hyper.ahajournals.org/)

**Figure.** Left, Progressive reductions and increases in mean arterial pressure (MAP; intra-arterial measurements) in response to progressive increases and decreases in carotid transmural pressure (CTP) obtained via a neck chamber device. The central and right panels show the reductions and increases in muscle sympathetic nerve activity (MSNA) and heart rate (HR) in response to increases and decreases in MAP obtained via infusion of phenylephrine and nitroprussiate. Data refer to mean regression line or mean values ($\pm$SE) from normotensive subjects (N), moderate essential hypertensive subjects (MH), and severe essential hypertensive subjects (SH). Data are from References 10 and 13 by permission (modified).
an increase in blood pressure and sympathetic activity. Furthermore, because the baroreflex was not tested immediately after implantation of the stimulating devices, the study lacks a "control" response and, thus, cannot exclude that, although qualitatively preserved, the baroreflex function was somewhat quantitatively altered by the surgical procedure. Finally, because the baroreflex was not acutely tested after the electric stimulus had been applied for months, the study cannot provide information on whether a prolonged intense stimulation may not ultimately result in, via receptor desensitization, alterations in the central integrating processes and/or reduced responsiveness of effector neurons or effectors in deterioration and loss of its homeostatic role. It will be important to obtain this information in future studies that quantify the responses to acute baroreceptor stimulation before and at various times during the chronic stimulation procedure.

Disclosures

None.

References

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