Recent attention to the development of device-based neuromodulatory therapy increases expectations of a novel approach to the treatment of hypertension, as well as heart failure, in which sympathetic hyperactivity plays an important role in the pathophysiology.\(^1\) Chronic carotid sinus baroreflex activation therapy (BAT) is one of those options and clinical trials are ongoing in the USA and Europe.\(^2\) It should be noted, however, that the clinical trials are based on results obtained from carefully conducted experimental animal studies.\(^3\) Resetting the baroreceptor reflex toward a higher arterial pressure level is thought to be why high arterial blood pressure (AP) is not adjusted to the normal level in either hypertensive patients or experimental hypertensive animals.\(^4\) Many studies have been performed to elucidate the mechanisms involved in resetting of the baroreflex, which occurs at various levels, such as baroreceptors, afferent fiber activity, central nervous system, ganglia, and efferent sympathetic nerve activity (SNA), and in the vasculature.\(^5\) It remains unknown how and why resetting of the baroreflex occurs in hypertension despite these many studies. We need to keep in mind that there are differences in baroreflex control of SNA in both acute changes in AP and chronic hypertension, in addition to the terminology of adaptation and resetting (Figure), which makes it difficult for investigators to obtain clear mechanistic explanations.

In this issue of the Journal, Sata and coworkers\(^11\) demonstrate that the neural arc, but not the peripheral arc, shifted to a higher pressure range in spontaneously hypertensive rats (SHR) compared with Wistar-Kyoto (WKY) rats, suggesting that central sympathetic outflow is enhanced in SHR despite higher AP. Vascular structural changes in hypertension is one of the mechanisms.\(^12\) Another interesting point is that in a previous study the static characteristics of baroreflex control of SNA and AP showed an increased neural arc, although the dynamic characteristics regarding baroreflex control of SNA were preserved in SHR compared with WKY rats.\(^13\) The latter indicates that baroreflex control of SNA could function in the acute changes in AP in SHR. There are some important issues to consider when interpreting these findings. First, Sata et al used male SHR at approximately 20 weeks of age (adult). At this age, hypertension is established in SHR. It remains unknown whether the same phenomenon occurs at a much earlier or older age in SHR. The former suggests their observations might be related to a causative component because sympathetic activation is known to occur in the early stage of hypertension in SHR. The latter could demonstrate that the peripheral arc might also be altered in SHR because of apparent vascular structural changes. Sex differences with aging also might be associated. Second, the study was performed under acute and anesthetized conditions, which might be different from baroreflex control of SNA in the awake state, although I understand that the merit of their open-loop analysis is that it makes it possible to determine the neural arc and the peripheral arc (Figure). Third, the duration of stimulation of the carotid sinus was short, so it is uncertain whether their observations apply to long-term effectiveness of BAT. In their figure 1,\(^11\) it is difficult to see whether rapid adaptation might be different in SHR and WKY rats. It has been shown that central rapid adaptation is affected by central nitric oxide.\(^14\) We and others suggest that reduced central nitric oxide activity and increased reactive oxygen species enhance sympathetic outflow.\(^5,15\) As Sata et al discuss, increased oxidative stress in the rostral ventrolateral medulla via angiotensin type 1 receptors has been shown to increase the central sympathetic outflow, leading to hypertension. Finally, the effectiveness of BAT is expected to apply to other cardiovascular diseases with enhanced SNA, such as heart failure.\(^2,5\)

It is difficult to understand the concept of central resetting. The importance of baroreflex has been ignored in hypertension because it just resets to a higher pressure level and AP is not sustained after sinoaortic denervation, suggesting that the baroreflex system does not play a major role in sustained increase in AP.\(^6\) However, as described by Lohmeier and Iliescu, “if central resetting were a dominant process that counteracts changes in baroreceptor input into the brain, then chronic carotid sinus baroreceptor activation would not expected to produce sustained reduction of SNA and AP”.\(^4\) On the other hand, Chapleau and Abboud describe central resetting as involving neural-humoral interactions or an altered responsiveness.
Because it is technically difficult to apply open-loop analysis to humans, it is important to find appropriate methods by which we can analyze baroreflex function.

Nevertheless, in the study by Sata et al, they clearly show that the neural arc shifts toward a higher AP level in SHR using the baroreflex equilibrium diagram, indicating increased central sympathetic hyperactivity in SHR. Further studies will give us a better understanding of the neural mechanisms of hypertension and enable the development of novel autonomic modulatory therapies in the clinical setting.

Figure. (A) Illustration of baroreflex pathways from isolated carotid sinuses to the central nervous system (CNS) whereby reflex mediated sympathoinhibition and parasympathetic activation occurs. NTS, nucleus tractus solitaries; RVLM, rostral ventrolateral medulla; NO, nitric oxide; ROS, reactive oxygen species. (B) Schematic demonstrating adaptation of baroreflex control of sympathetic nerve activity (SNA) (Left) and central resetting of the baroreflex when isolated carotid sinus pressure is increased in a step-wise fashion. Note that these phenomena occur within a relatively rapid period (several minutes). In addition, these phenomena also occur at the baroreceptor level. (Modified and reproduced with permission from Chapleau MW, et al.) However, chronic carotid sinus baroreflex activation has been demonstrated to sustain a decrease in SNA and arterial pressure. (See Reference 4) (C) Schematic illustrating the baroreflex control of the SNA curve in hypertension. Circles indicate the operating point.
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