Impact of Global Versus Renal-Specific Sympathoinhibition in Aldosterone-Induced Hypertension

Implications for Medical Device-Based Treatment of Resistant Hypertension

Casey Y. Carmichael, Richard D. Wainford

In this issue, Lohmeier et al1 present a series of elegant studies that seek to determine the impact of chronic electric activation of the carotid baroreflex2 or renal nerve ablation3 on aldosterone-induced hypertension in a conscious dog model. These studies have direct relevance to the application of carotid artery and renal nerve device-based treatments for resistant hypertension owing to our current lack of understanding of the mechanisms that determine patient responsiveness to these interventions. The authors provide the first evidence that carotid baroreflex activation (BA), which induces global suppression of sympathetic activity and blood pressure reduction,4,5 evokes an attenuated but persistent reduction in blood pressure during aldosterone-induced hypertension. Significantly, the authors observed no impact of renal-specific sympathoinhibition, achieved via renal denervation, on aldosterone-induced hypertension. The presented data suggest resistant hypertension featuring excess aldosterone may be more successfully targeted therapeutically via BA versus renal nerve ablation, and that the beneficial effect of BA will be reduced in this patient population.

Chronic electric activation of the carotid baroreflex and radiofrequency renal nerve ablation evoke global and renal-specific sympathoinhibition, respectively, and lead to persistent reductions in blood pressure in patients with resistant hypertension.6,7 However, these approaches are not efficacious in all resistant hypertensive patients. Primary aldosteronism is an exclusion criterion in ongoing trials, but the extent of assessment of patient aldosterone levels in these trials is unclear. This raises the possibility that elevations in aldosterone, a feature common in resistant hypertension,8,9 may contribute to the variability observed in the clinical trials conducted using the device-based therapies. Another potential factor accounting for the observed variability in patient responses to these interventions is the level of sympathetic activity. Both BA and renal denervation evoke sympathoinhibition,2,3 and as such, it is reasonable to assume these interventions will evoke greater reductions in blood pressure when sympathoexcitation is a major contributing factor to resistant hypertension. The role of sympathetic activation in aldosterone-induced hypertension remains controversial,1 leading Lohmeier et al1 to postulate that if aldosterone does not evoke sympathetic activation, medical device-based interventions that suppress sympathetic outflow will be less efficacious in this setting.1 Previous studies by Lohmeier et al1 have established that (1) BA chronically suppresses blood pressure and sympathetic activity in a non–renal nerve-dependent manner1 and (2) BA and renal denervation abolish obesity-related hypertension.4,9 The current studies presented in this issue of Hypertension examine the impact of BA and renal denervation on aldosterone-induced hypertension.

A key finding of the current work is that chronic BA evokes an attenuated reduction in blood pressure in animals with aldosterone-induced hypertension versus control normotensive animals, despite evoking comparable and sustained suppression of sympathetic activity across treatment groups. The initial acute BA evoked reduction in arterial blood pressure was comparable in aldosterone-infused and control dogs. This acute hypertensive response reflects the impact of BA on the suppression of global sympathetic outflow. However, the chronic impact of BA on reducing blood pressure was significantly attenuated in animals with aldosterone-induced hypertension. The differences between the acute and chronic effects of BA on blood pressure reduction across treatment groups reflect the time course of rapid sympathetic effects versus slower renal mechanisms. Significantly, the authors did not observe aldosterone-induced increases in sympathetic activity, suggesting sympathoexcitation does not contribute to aldosterone-induced hypertension. These data suggest that in the presence of elevated aldosterone levels, BA-evoked suppression of global sympathetic outflow is not able to compensate for the antinatriuretic effects of aldosterone that drive hypertension. Supporting a diminished role of BA as an antihypertensive treatment in non–neurogenically-mediated forms of hypertension is the attenuated effect of BA in the canine angiotensin-II infusion model.4,9

The second novel finding of the current studies is that BA, which suppressed global sympathetic outflow, did not act centrally to inhibit vasopressin secretion during normotensive control conditions or to reduce the increases in vasopressin secretion and water intake triggered by aldosterone excess. This observation is in contrast to acute pressure–induced changes in
baroreflex activity that suppress vasopressin secretion. These data highlight differential effects of chronic BA on central sympathetic outflow (inhibition) and osmotic stimulation of vasopressin (no effect) during normotensive and hypertensive conditions. Physiologically, the lack of effect of chronic BA on osmotically stimulated vasopressin secretion and water intake is likely functioning to prevent exacerbation of hyponatremia in the setting of aldosterone-induced hypertension.

The third major finding is that in contrast to BA, renal denervation did not evoke a reduction in blood pressure in aldosterone-induced hypertension. These data are conflicted with the previous data from this group that both BA and renal denervation attenuate obesity-induced canine hypertension, a model featuring profound sympathoexcitation. This finding of a lack of effect of renal denervation in aldosterone-induced hypertension supports (1) the hypothesis that the effects of renal denervation will be diminished/absent in a setting not featuring marked sympathoexcitation and (2) the growing body of evidence that indicates the renal nerves are not required to mediate the chronic lowering of blood pressure during BA. Furthermore, these data collectively suggest that baroreflex-evoked natriuresis, and subsequent reductions in blood pressure, will be attenuated in hypertensive states not exhibiting increased renal-specific sympathoexcitation. A question not addressed by the current investigation is the mechanism(s) by which BA increases renal excretory capacity to reduce long-term blood pressure independent of actions affecting renal sympathetic nerve activity. An additional caveat is the relatively short duration of the current studies that does not include determination of the effects of BA during prolonged hypertension, in which excess aldosterone can result in end organ damage via inflammatory and fibrotic mechanisms.

Collectively, these data suggest that the presence of excess aldosterone, which in support of previous studies does not evoke sympathoexcitation, will result in an attenuated or abolished hypotensive response to BA (global sympathoinhibition) and renal nerve ablation (renal-specific sympathoinhibition), respectively (Figure). The current studies also strengthen the previous studies of this research group that reported the blood pressure reductions evoked by chronic BA are not exclusively renal nerve dependent. Owing to the prevalence of excess aldosterone in resistant hypertension, these preclinical data predict that BA and particularly renal nerve ablation will have reduced efficacy in patients with elevated aldosterone. This hypothesis is supported by evidence that aldosterone antagonist administration was a positive predictor for a reduction in blood pressure in response to renal nerve ablation in the Symplicity HTN-3 trial. The current studies and previous work by this group also suggest that the use of BA and renal nerve ablation will be enhanced in patients with elevated sympathetic tone. Overall, these findings highlight the need for the identification of predictors of the likely success of currently used device-based interventions (ie, BA and renal nerve ablation). Furthermore, they suggest that assessment of global sympathetic activity and aldosterone content may represent an initial starting point for patient screening before treatment with these surgical interventions.

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

**Figure.** Impact of baroreflex activation (BA) and renal denervation (RDNX) in the setting of aldosterone-induced hypertension (ALDO-HTN) on heart rate, blood pressure, and neurohumoral factors. AVP indicates plasma arginine-vasopressin content; CVLM, caudal ventrolateral medulla; IML, intermediolateral cell column; ND, not determined; NE, plasma norepinephrine content; NTS, nucleus tractus solitarius; and RVLM, rostral ventrolateral medulla.
Sources of Funding
R.D. Wainford is supported by National Institutes of Health grants R01HL107330 and K02HL112718.

Disclosures
None.

References
Impact of Global Versus Renal-Specific Sympathoinhibition in Aldosterone-Induced Hypertension: Implications for Medical Device-Based Treatment of Resistant Hypertension
Casey Y Carmichael and Richard D Wainford

Hypertension. 2015;65:1160-1162; originally published online April 20, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.05228

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/65/6/1160

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

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

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