Four decades ago, Trzebski et al in Warsaw reported an astonishing discovery, namely that hypersensitivity and augmented tonic activity of arterial chemoreceptors contribute to increased arterial pressure in young hypertensive men.1 This discovery has stood the test of time. In addition to increasing ventilation, activation of carotid chemoreceptors increases sympathetic nerve activity and arterial pressure. Young borderline hypertensive humans have a striking augmentation of the sympathetic nerve responses to chemoreceptor activation by hypoxemia.2 Conversely, suppression of arterial chemoreceptors by breathing 100% oxygen decreases sympathetic nerve activity and arterial pressure in hypertensive but not normotensive humans.3

Studies in spontaneously hypertensive rats and normotensive (Wistar) rats have paralleled and advanced these concepts.4,5 Spontaneously hypertensive rats display augmented increases in carotid sinus afferent activity during hypoxemia. In addition, carotid body denervation reduces the development and maintenance of increased sympathetic activity and arterial pressure in spontaneously hypertensive rats but not normotensive Wistar rats.6 The augmented sympathetic nerve response to hypoxemia is manifest in young prehypertensive spontaneously hypertensive rats and seems to result from a membrane abnormality that underlies the increased chemoreceptor sensitivity and activity.7 This suggests a primary genetic molecular mechanism for increased chemoreceptor sensitivity and tonic activity in spontaneous hypertension.

These and other studies in humans and rats have prompted interest in carotid body denervation as treatment for resistant, sympathetically mediated essential hypertension in humans.8

To this story of carotid chemoreceptors in spontaneous hypertension, Tom Lohmeier—a Mississippi master physiologist—and his colleagues add a new chapter in this issue of Hypertension.7 Lohmeier et al report that dogs with a secondary form of hypertension, namely obesity-induced hypertension, are hypoxemic and have augmented tonic activation of carotid chemoreceptors that contributes substantially to the obesity-induced hypertension. Bilateral carotid sinus denervation (denervation of carotid chemoreceptors and baro-receptors) produced a substantial antihypertensive response, attributed to carotid body chemoreceptor denervation and not to carotid baroreceptor denervation, which would be expected to increase arterial pressure.

The key characteristics highlighted by the Lohmeier study in dogs are obesity, hypoxemia, heightened chemoreflex sensitivity, tonic chemoreflex activation, increased sympathetic outflow, and hypertension (Figure). Although it is not known if the obese dogs had sleep apnea (T.E. Lohmeier, personal communication), the quintessential human equivalent of the phenotypic constellation in these dogs is obstructive sleep apnea (OSA). OSA patients are often obese, are exposed to repetitive nocturnal hypoxemia, and have increased peripheral chemoreflex sensitivity, high sympathetic drive, and increased risk of hypertension (Figure). Suppression of chemoreflex activity in OSA patients by breathing 100% oxygen (versus room air) elicits a reduction in sympathetic drive, heart rate, and arterial pressure.9 These findings support the concept that sympathetically mediated increases in arterial pressure in patients with OSA result substantially from chronic intermittent hypoxemia and tonic activation of arterial chemoreceptors.

Obesity adversely impacts lung function in humans. Lohmeier et al suggest that hypoxemia may be more common in obese humans than is currently recognized. We agree and have long held that some of the cardiovascular pathophysiology attributed to severe obesity may reflect effects of undiagnosed OSA. Nevertheless, many patients with obesity and hypertension are presumably normoxic. This prompts a question. Is hypoxemia the only contributor to chemoreceptor sensitivity in obesity? Surprisingly, there is a body of evidence for leptin signaling in carotid body glomus cells that translates into sensitization of carotid chemoreceptor afferent signaling.9 Increases in circulating and carotid body leptin are exaggerated by intermittent hypoxemia. In this regard, leptin is higher in patients with OSA and increased chemoreceptor activity than in comparably obese patients without OSA. These observations raise the possibility that in obesity and OSA, alterations in adipokines induced by hypoxemia might contribute to acquired sensitization of arterial chemoreceptors.

A second focus of the study by Lohmeier et al was an interaction of carotid baroreceptors and carotid chemoreceptors. Chronic baroreceptor activation produced by electric stimulation of the carotid sinuses attenuated tachypnea in obese dogs in addition to decreasing arterial pressure. Studies in experimental
animals and humans have demonstrated that acute activation of baroreceptors inhibits ventilatory and sympathetic responses to hypoxic stimulation of chemoreceptors. Lohmeier’s study suggests that carotid baroreceptor inhibition of chemoreceptor reflexes can be sustained and contribute to the decrease in sympathetic activity and arterial pressure during chronic baroreceptor activation in hypertensive states characterized by tonic activation of chemoreflexes (Figure). This reinforces the concept of carotid body denervation as a potential antihypertensive treatment for sympathetically mediated hypertension with tonic activation of chemoreceptor reflexes. It is noteworthy, however, that the putative reduction in sympathetic activity after carotid body denervation in the obese dogs was not accompanied by a decrease in circulating norepinephrine, whereas there was a pronounced fall in norepinephrine during carotid baroreflex activation. Alternative mechanisms could have contributed to the decrease in arterial pressure after chemoreceptor denervation. For example, chemoreceptor denervation was followed by significant hypoxemia (PaO2 of 65 mm Hg) and hypercapnia (PaCO2 of 53 mm Hg). Both hypoxemia and hypercapnia may elicit vasodilation and contribute to a fall in arterial pressure after chemoreceptor denervation.

What are the clinical implications of the Lohmeier study? Patients with OSA with heightened chemoreflex drive, increased sympathetic activity, and resistant hypertension would seem to be a target population for antihypertensive interventions, such as carotid body denervation. Insofar as carotid body denervation has been proposed for treatment of resistant, sympathetically mediated hypertension, it is relevant that patients with resistant hypertension have a very high likelihood of comorbid OSA, with some reports showing an OSA prevalence >70%. The antihypertensive effects of chronic positive airway pressure in patients with OSA and resistant hypertension have been modest with blood pressure reductions of $\approx 3$ mm Hg. Therefore, there is a need for alternative antihypertensive strategies in patients with OSA and resistant hypertension. However, chemoreceptor denervation has the theoretical potential for worsening apnea severity, given the role of chemoreflexes in driving breathing and terminating apneas. On the other hand, in a pilot study, we observed that renal denervation was accompanied by attenuation of OSA severity, findings supported by a subsequent meta-analysis. Although renal denervation has not met expectations as a treatment for resistant hypertension in general, it may conceivably be more effective in lowering blood pressure in those resistant hypertensives with comorbid OSA, perhaps in part by mitigation of OSA severity (Figure).

In summary, in an elegant tour de force, Lohmeier et al have added a new chapter to the unfolding story of the surprising contribution of tonic activation of arterial chemoreceptors in hypertensive states. They demonstrate that tonic activation of carotid chemoreceptors contributes to a secondary form of hypertension, namely obesity-induced hypertension, in dogs. These studies have implications for the development of new strategies for the treatment of patients with OSA, obesity, and resistant hypertension.

Sources of Funding
The authors’ research is supported by HL-84207 (A.L. Mark) and by HL-65176 (V.K. Somers) from the National Heart Lung and Blood Institute.

Disclosures

References


Obesity, Hypoxemia, and Hypertension: Mechanistic Insights and Therapeutic Implications
Allyn L. Mark and Virend K. Somers

Hypertension. published online May 9, 2016;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. 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/content/early/2016/05/09/HYPERTENSIONAHA.116.07338.citation

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/