

EDITORIAL COMMENT

Unilateral Carotid Body Resection in Resistant Hypertension

An Exciting First Step Toward a New Therapy?*

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Hypertension is a highly prevalent condition and, when untreated, has myriad devastating consequences including myocardial infarction, cardiomyopathy, renal failure, and stroke. Extensive clinical data support the treatment of hypertension and demonstrates the reduction in cardiovascular events, stroke, and death in patients with hypertension whose blood pressure is controlled (1). Despite optimal medication management (concurrent use of 3 different medications of different classes, at maximally tolerated doses, 1 of which is a diuretic agent) and ruling out secondary causes of hypertension, up to 20% to 30% of patients with hypertension continue to have elevated blood pressure and are defined as having treatment-resistant hypertension. These patients are at a 3-fold increased risk of adverse cardiovascular outcomes compared with those with treatment-responsive hypertension (2). It is this subgroup of patients in whom additional therapies are needed to successfully control their hypertension and to reduce their risk of major adverse events. Only recently has the medical community begun to fully embrace that this population requires a special focus that goes beyond simple medical adherence, medication selection, and life-style modification approaches and that the cost of their comorbidities, both personal and financial, warrant the development of new approaches.

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In this issue of the *JACC: Basic to Translational Science*, Narkiewicz et al. (3) report the results of a proof-of-concept study of unilateral carotid body resection in patients with treatment-resistant hypertension. A total of 15 patients with office blood pressures of $179 \pm 7/106 \pm 4$ mm Hg on 5.7 ± 0.3 antihypertensive drugs were included in the trial and were followed for 12 months after unilateral carotid body resection. Successful carotid body resection was defined as pathological evidence of glomus cells in resected tissue, and this was confirmed in 14 of the 15 patients. Patients were monitored for changes in hypoxic ventilatory response, polysomnography,

SEE PAGE 313

muscle sympathetic nerve activity, blood pressure, and general adverse events. A total of 8 of the 14 patients with successful carotid body excision were found to be responders to the procedure, as evidenced by reduction in muscle sympathetic nerve activity and >10 mm Hg drop in ambulatory blood pressure at 3- and 6-month follow-up. Serious adverse events included 1 patient with pre-existing sleep apnea who had worsening of the apnea-hypopnea index, and 1 patient who was hospitalized after the procedure with difficult-to-control blood pressure. The procedure was otherwise deemed to be safe.

Resection of the carotid body aims to decrease blood pressure through reduction in afferent sympathetic tone originating from signals in the carotid body. In contrast, baroreflex activation therapy (BAT) stimulates the baroreflex, which subsequently leads to a decrease in sympathetic tone and increase in vagal tone. BAT has been studied most extensively in humans via implantation of an electrical stimulator (Rheos and Barostim Neo devices, CVRx,

Minneapolis, Minnesota) (4) and is also being targeted through dynamic shape change of the carotid sinus by a new stent (Mobiushd, Vascular Dynamics, Mountain View, California). BAT via electrical stimulation involves placement of a pacemaker-like generator under the skin in the chest and then tunneling a lead to the carotid sinus. An early device (Rheos) involved placement of a lead with 4 finger-like electrodes on each carotid bulb and wrapping these electrodes around the bilateral carotid bulbs. A newer device (Barostim Neo) involves a simpler placement of a single lead with a single electrode on a unilateral carotid bulb. BAT has started to accrue significant trial data to date and has 5-year follow-up data published, which continues to be promising. The procedure is generally well tolerated, although the earlier Rheos device carried a periprocedural event rate similar to open carotid endarterectomy. In contrast, the novel carotid sinus Mobiushd stent involves placement of an endovascular stent via percutaneous approach. The stent then induces a dynamic shape change in the carotid sinus leading to activation of the baroreflex. Although trial data have not yet been completed for the Mobiushd stent (CALM-FIM_US [Controlling and Lowering Blood Pressure With The MOBIUSHD], NCT01831895), it is appealing in its potential to have a less-invasive approach to activating the carotid baroreflex.

With regard to efficacy of unilateral versus bilateral therapy, baroreflex activation therapy was initially utilized by stimulating the bilateral carotid bulbs, but a subsequent device (Barostim Neo) applied stimulation only to a unilateral carotid body and achieved similar physiological effects; presumably, the same feedback mechanism affects the bilateral baroreceptors. It will be interesting to track the response of unilateral carotid body excision and determine whether the contralateral carotid body over extended time fully assumes the prior efficacy of both carotid bulbs or whether the fall in blood pressure remains durable. The dramatic fall in both office and ambulatory blood pressure seen in responders in the first months after surgery seems to attenuate at the 12-month follow-up in the current study, and further follow-up with more patients is certainly warranted.

Although more anatomically distant, renal sympathectomy also draws parallels with carotid body resection. In both, reduction in blood pressure is achieved through the reduction in sympathetic outflow through surgical removal of a stimulating region. Surgical renal sympathetic denervation was reported in humans dating back to the 1930s. Although it resulted in some impressive reductions in blood pressure, procedural morbidity and increased

medication options led to its abandonment. More recently, percutaneous renal sympathetic denervation has been studied with the Simplicity catheter system (Medtronic, Minneapolis, Minnesota) (5). With it, radiofrequency ablation is applied to the renal sympathetics via the renal artery. Initial positive results and minimal morbidity with this procedure led to much enthusiasm, which subsequently waned after a large prospective randomized trial of more than 500 patients failed to show significant efficacy in reduction of blood pressure compared with the control group (5). Whether the lack of efficacy was due to insufficient ablation of the renal sympathetics (suggesting a change in the technical aspect of the procedure could lead to more success) or whether renal denervation does not truly result in significant durable blood pressure change is not entirely clear. Nevertheless, applying a similar catheter-based ablation to the carotid body instead of surgical excision is another potential source of research. Although catheter-based treatment has an inherent appeal over surgery due to its less invasive nature, the lessons from catheter-based renal denervation give reason to ensure that catheter-based procedures can sufficiently match the efficacy of open surgery in terms of target tissue affected as well as clinical outcomes.

Compared with other procedural approaches to reducing hypertension via alteration in nervous system signaling, carotid body resection represents a novel approach. Surgical removal is an inherently permanent, nonpharmacological intervention that does not require placement of a foreign object in the patient. Although this has advantages of inherent compliance and removes the usual concerns with device implantation such as infection and device failure, it also has the disadvantage of being irreversible and requiring a significant surgical procedure. It is as yet unclear whether, in the event of severe hemodynamic stress, a patient would retain the capability to mount an appropriate response. Although the authors demonstrated glomus cells in resected tissue, it is also possible that only partial resection was achieved in some patients. Whether this makes a clinically significant difference in the rate of patients responding to treatment is not known.

In summary, Narkiewicz et al. (3) have nicely demonstrated the feasibility of a novel technique for surgical removal of the carotid body. Although not powered for efficacy, the results of this proof-of-concept study show a definite trend toward blood pressure lowering in patients who responded to the treatment. With the increasing recognition of the importance of treatment of resistant hypertension,

this demonstrates an interesting target for future nonpharmacological therapies. Whether these therapies are surgical excision, catheter-based ablation, or permanent device implantation remains to be seen, and it would be wonderful to see each of these procedures developed to yield efficacy for the wide variety of patients with this disease. Now that this technique is proven feasible, follow-up studies with larger numbers of patients will be needed to assess the efficacy and also hopefully determine which patients will respond significantly to the therapy. The authors' observation of elevated hypoxic ventilator response and respiratory frequency in responders suggest that this might be a fruitful tool for identifying patients who will be more likely to respond to the therapy before undergoing a procedure. Ideally, with additional research in this field, clinicians will have the tools to identify patients who are appropriate for a nonpharmacological intervention and

will be able to select between multiple procedures to tailor appropriate interventions to a given patient before he or she undergoes a procedure. Although controlling hypertension with a few easily tolerated and inexpensive medications benefits a large majority of patients, the continued high burden of myocardial infarction, heart failure, and stroke in patients with treatment-resistant hypertension shines a light on the need to continue to develop new treatments for this disease. Evolving invasive approaches to hypertension management, such as carotid body resection, offer an exciting potential to fill this need.

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