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Baroreflex stimulation: A novel treatment option for resistant hypertension

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Abstract

Hypertension is a major public health problem in both developing and developed countries. Despite the increasing awareness of hypertension and its implications among patients and the treating physicians, the prevalence of resistant hypertension remains high and expected to increase. Many patients fail to reach their target blood pressure despite the wide availability of several antihypertensive agents and the continued recommendation of dietary and lifestyle modifications. Stimulation of the carotid sinus results in lowering of blood pressure by initiating the baroreflex and, in so doing, reducing sympathetic tone and increasing renal excretory function, in part, by exerting inhibitory effects on renin secretion. . Recent evidence from experimental studies suggests that the baroreflex may be more important in the setting of chronic hypertension than originally believed. In early phase clinical trials that did not include control arms, implantation of a baroreflex stimulator yielded a sustained decrease in blood pressure. An ongoing larger clinical trial with appropriate control arms is further exploring the safety and efficacy of the device. This article describes the history and potential mechanisms of action of this device including its extensive pre-clinical development and movement to human clinical trials.

Keywords

Baroreflex; resistant hypertension; carotid sinus

Background

Globally, in the year 2000, the total number of adults with hypertension was estimated to be 972 million and has been predicted to affect about 1.5 billion in 2025 (1, 2). Using the NHANES data (1999–2004), 29% of US population had BP >140/90 mm Hg in 2004 and this results in increased cardiovascular mortality (3, 4). Blood pressure reduction alone contributed to a 20% of decline in cardiovascular deaths (5). The therapeutic armamentarium for treating high BP grew at a fast pace in 1980s and 1990s. Unfortunately, with strict drug regulations, newer agents' entry into the market has slowed down and only one new class of agents has been introduced in the past decade. Several large clinical trials

and their meta-analysis have confirmed the fact that BP reduction with any antihypertensive agent or life style modification decreases the morbidity and mortality rates (6, 7).

Resistant hypertension is defined in the literature as a BP of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes or renal disease, despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic (8). The prevalence rates vary from 8–15% depending on the geographical location and several other factors and are often due to multifactorial reasons (9). The major endocrine causes of resistant hypertension such as hyperaldosteronism, Cushing's syndrome and pheochromocytoma and renovascular etiology should be excluded prior to establishing resistant hypertension. Usually, these patients are resistant to vasodilator therapy and warrant a specialist managing the BP with several antihypertensive agents. Many of these patients find the side-effects, expense, and inconvenience of numerous medications to be insurmountable barriers, and can also be viewed as people who are failing treatment using the available therapeutic approaches.

In this article, we review the physiology of baroreflex in patients with hypertension, controversies about its impact on long-term BP control, evolving evidence of the baroreflex stimulation in animal studies and the newer clinical trial evidence on carotid sinus stimulation in resistant hypertension.

Baroreflex and Hypertension

Normal Physiology

Arterial baroreceptors are located in the aortic arch and carotid sinuses, and are formed by small nerve endings present in the adventitia of these vessels. Baroreceptors are mechanosensors that are activated by pressure-induced stretch of the vessel wall (10). Although the mechanism is unclear, activation of baroreceptors results in an electrical signal (neural discharge) that is transmitted to the central nervous system. Baroreceptor afferents from the carotid sinus travel in the carotid sinus nerve (Hering's nerve) before joining the glossopharyngeal nerve (11). Primarily, in humans, the afferent fibers from aortic baroreceptors pass centrally via the vagus nerve (in other species, it might travel as a separate aortic nerve). Baroreceptor afferents in both the glossopharyngeal and vagus nerves terminate in the nucleus of the tractus solitarius (NTS) in the medulla of the brain. In turn, NTS neurons project to neurons in the dorsal and caudal lateral parts of the medullary reticular area, and activation of NTS neurons inhibits bulbospinal neurons in the medullary reticular area that provide tonic excitatory input to sympathetic preganglionic neurons that control sympathetic output to the peripheral circulation. Thus, activation of the baroreflex inhibits sympathetic outflow from the central nervous system. Other investigators have identified novel molecular mechanisms involved in the generation of this neural activity. Chapleau et al showed that action potential discharge and chemical autocrine and paracrine factors are important mechanisms contributing to changes in baroreceptor sensitivity during sustained increases in arterial pressure. Also prostacyclin might provide an autocrine feedback that restores and enhances the responsiveness of arterial baroreceptor neurons after their inhibition from excessive neuronal activation (12–14).

Because of the importance of the kidneys in long-term control of arterial pressure, renal sympathetic nerve activity may be an especially important determinant of the severity of hypertension. Postganglionic fibers to the kidneys innervate the vasculature, tubules, and renin containing juxtaglomerular cells. Increases in renal sympathetic nerve activity decrease sodium excretion by promoting sodium reabsorption, by decreasing renal blood flow and glomerular filtration rate, and by increasing renin release. In fact, increased renal sympathetic nerve activity is commonly present in subjects with primary hypertension (15).

However, while net sympathetic outflow is increased in primary hypertension, this does not necessarily exclude a sustained inhibitory influence of the baroreflex on sympathetic activity. Rather, this may indicate that central excitatory inputs predominate over the inhibitory effects of the baroreflex on sympathetic activity. If this notion is correct, however, the baroreflex must be chronically activated in hypertension.

Misconceptions in hypertension

In patients without hypertension, baroreflex role in long-term control of sympathetic activity and arterial pressure was under debate up until recently (16, 17). As BP rises, there is an initial increase in firing of baroreceptor afferents aiming to restore the BP to baseline (18). But, animal studies conducted several decades ago suggested that a sustained BP elevation results in diminished baroreceptor response and a new threshold for activation is established (19). This adaptive response occurs over minutes to days. Further, in chronic hypertensive state, baroreceptors also become less sensitive to any given change in BP. This effect is attributed to changes in vascular distensibility and altered activity in the brainstem portion of the reflex. This was first observed by Matton et al in 1954 and then demonstrated using electroneurographic techniques by McCubbin et al (20, 21). In essence, this resetting of the baroreceptors around the new prevailing BP forms the basis for the notion that the baroreflex is not important in modulating chronic hypertension.

Recent evidence on the role of baroreflex in chronic hypertension

Although technical limitations have largely precluded a quantitative evaluation of the degree of baroreflex resetting in hypertension, at the turn of the century, innovative approaches in chronically instrumented animals have provided novel insight into the role of the baroreflex in the chronic regulation of sympathetic activity and arterial pressure. These studies indicated that baroreflex resetting is incomplete in experimental hypertension. Further, these studies also indicated that baroreflex suppression of renal sympathetic activity and attendant increments in renal excretory function are sustained compensatory responses in hypertension (22, 23). Although quantification has not been established, these compensatory responses would be expected to attenuate the severity of hypertension.

More recently, a particularly insightful approach has been used by Lohmeier and associates to determine the mechanisms that mediate the long-term blood pressure lowering effects of the baroreflex. In these studies, the baroreflex has been chronically activated by electrical stimulation of the carotid sinuses. This technique bypasses mechanotransduction at the level of the baroreceptors and permits controlled electrical activation of the afferent limb of the carotid baroreflex. Their initial study was conducted in normotensive dogs (24, 25). Upon stimulation of the carotid sinuses, there was an immediate fall in mean arterial pressure (MAP) of ~ 25 mmHg in association with a modest reduction in heart rate, reflecting the reciprocal effects of baroreflex activation on the sympathetic and parasympathetic nervous systems. More importantly, this marked fall in MAP (and the reduction in heart rate) was sustained for the entire 7 days of baroreflex activation. On day 7 of baroreflex activation, MAP was 72 ± 5 , compared to 93 ± 3 mmHg during the control period. Reductions in MAP and plasma norepinephrine occurred in parallel, indicating that the fall in MAP was a result of sustained suppression of the sympathetic nervous system. Another important point was that there was no activation of the renin-angiotensin system during prolonged stimulation of the carotid sinuses, despite the large fall in MAP. This indicates the presence of a sustained inhibitory influence on renin secretion, presumably mediated by chronic suppression of renal sympathetic nerve activity. Based on these observations, Lohmeier and associates hypothesized that chronic activation of the baroreflex reduces arterial pressure by suppressing renal sympathetic nerve activity and promoting sodium excretion by both the

direct and indirect (via inhibition of renin release) effects of the renal nerves on sodium reabsorption.

Because Lohmeier and associates hypothesized that neurally-induced suppression of renin secretion plays an important role in preventing pressure-dependent renin release during prolonged stimulation of the carotid sinus, they also suggested that this response plays an important role in permitting chronic reductions in arterial pressure during baroreflex activation. More specifically, they suggested that if the renin-angiotensin system were activated concomitantly with the fall in arterial pressure induced by stimulation of the carotid sinus, this would significantly attenuate the blood pressure lowering effects of baroreflex activation. To test this hypothesis, the baroreflex was activated for 7 days in dogs with hypertension induced by chronic infusion of angiotensin II (26). The infusion rate of angiotensin used in this study increased MAP ~ 35 mmHg and is associated with only a 3-fold increase in circulating levels of the peptide. In this model of hypertension, there was a marked reduction (~ 75%) in the blood pressure lowering effects of the baroreflex activation. Presumably, this study emphasizes the importance of renal sympathoinhibition in suppressing renin secretion and offsetting pressure-dependent renin release, which otherwise would greatly diminish increments in renal excretory function and attendant reductions in blood pressure during carotid baroreflex activation. In addition, contribution from other aspects of sympathetic system might also play a role in this process.

Lohmeier and associates have also evaluated the antihypertensive effects of prolonged baroreflex activation in another model of experimental hypertension and one that is particularly relevant to primary hypertension in human subjects--hypertension associated with obesity (27, 28). Because activation of baroreflex has sustained effects to inhibit renal sympathetic nerve activity and because the renal nerves appear to play a critical role in mediating increases in arterial pressure in obesity, they hypothesized that prolonged baroreflex activation would lead to pronounced and sustained reductions in arterial pressure in dogs fed a high-fat diet. After 4 weeks on a high-fat diet, MAP was elevated ~ 15 mmHg in association with an increase in body weight of ~ 50%. Plasma NE, glucose, and insulin concentrations were elevated, but increases in plasma renin activity during the initial weeks of the high-fat diet were not sustained as the hypertension progressed. During week 5 of the high-fat diet, the carotid baroreflex was activated for 7 days. This resulted in reductions in plasma norepinephrine concentration and MAP to below control levels, but no changes in plasma glucose or insulin concentrations or plasma renin activity during baroreflex activation. These findings indicate that prolonged baroreflex electrical activation can chronically suppress the sympathoexcitation associated with obesity and abolish the attendant hypertension without activating the renin-angiotensin system and without affecting insulin resistance.

Because Lohmeier and associates reasoned that the renal nerves were important in mediating chronic reductions in arterial pressure during carotid sinus stimulation, they hypothesized that acute reductions in arterial pressure during baroreflex activation would not be sustained in dogs with denervated kidneys (29). Much to their surprise, and contrary to their hypothesis, the chronic blood pressure lowering effects of carotid sinus stimulation were equivalent in the same dogs before and after renal denervation. They provided several possible explanations for these unexpected observations, but the mechanisms that totally account for the fall in arterial pressure during chronic baroreflex activation are unclear and are under active investigation.

Thrasher et al showed that chronic baroreceptor unloading attained through ligation of the common carotid artery proximal to a single innervated sinus results in a rise in MAP of 20–30 mmHg. It was sustained for 7 days and returned to control levels after removal of the

ligature (30). Authors contended that the increase in MAP is due to a reflex increase in sympathetic activity to restore pressure in the innervated sinus distal to the ligature to control levels. Later, they extended the period of observation to 5 wk after ligation of the carotid (31). The increase in MAP during the first week following baroreceptor unloading was similar to their earlier study, but the increase was not sustained with a decline in MAP over the next few weeks and stabilized about 10 mmHg above control. Nonetheless, the final level of MAP was significantly greater than control, suggesting a sustained sympathetically-mediated increase in MAP. The reason for the temporal diminution in the severity of hypertension is unclear but could be attributed to partial resetting of the baroreceptors and vascular adaptations that improve delivery of the cardiac impulse to the carotid baroreceptors.

Evolution of baroreflex stimulators

Earlier devices

Studies dating back to 1950s focused on carotid sinus nerve stimulation as a therapeutic option in the treatment of hypertension. But, this was never considered as a front line treatment even in resistant hypertension secondary to its invasive nature. Electrical stimulation of the carotid sinus was first demonstrated in patients who underwent neck dissection for cancer. Carslten et al demonstrated that as the intensity of electrical stimulation increased, the MAP and the heart rate decreased and these responses returned to baseline upon cessation of stimulation of carotid sinus nerve (32).

This observation prompted Bilgutay and Colleagues to implant an electrical stimulator in a 40-year-old patient with BP of 260/165 (despite on four drugs) (33). Blood pressure promptly decreased to 150/90 mm Hg and the device was called as 'baropacer'. This device was placed under the pectoralis muscle and the leads were connected to the carotid sinuses and the device was turned on or off by placing a magnet over the device. A year later, Schwartz et al expanded this to eight patients. All patients had BP >190/110 mm Hg and underwent implantation of a bilateral carotid sinus nerve stimulator for about 5 months to 2.5 years (34). The BP reduced on average by about 48/42 mm Hg. Most importantly, 6 patients were able to completely discontinue their medications. But, as the device included an implanted pulse stimulator that was controlled by an external generator, it was difficult to operate from technical stand point. During the same year, Braunwald et al reported the use of carotid sinus nerve stimulation as a treatment option for refractory angina in two patients. Its ability to reduce the heart rate, BP and contractility of the heart was responsible for its effects on these patients (35).

The major limitations of these earlier devices were its lack of ability to individualize for each patient. Thus, some patients developed systemic symptoms such as orthostatic hypotension, bradycardia and some developed local irritation due to stimulator implantation. But, Tuckman et al addressed the limitations and implanted bilateral carotid sinus nerve stimulators in seven patients (36). This device did not result in hypotension, bradycardia, or local symptoms. Peters et al furthered the device and attempted to match stimulator frequency to heart rate as tachycardia could mean an increased sympathetic tone (37). They showed that the heart rate and BP did increase with exercise and thus the stimulators did not abolish the body's innate ability to increase the sympathetic activity at the time of exercise or increased demand. They further demonstrated that the BP lowering effect in these patients lasted at the end of 12 year follow-up (38).

Limitations

Despite the gradual improvement in the type and quality of carotid sinus stimulators and the implantation techniques, why did it fall out of favor? The two major reasons are: a) the

effectiveness and continued development of oral antihypertensive agents in reducing BP and the emergence newer agents in 1980s and 1990s and b) implantation of carotid sinus stimulator is an invasive procedure.

Resurgence and newer devices

Carotid sinus stimulator therapy has again come into focus as the entry of new agents has slowed and the prevalence of resistant hypertension is increasing. The device undergoing clinical trial is 'Rheos' (CVRx, Minneapolis, MN, USA) and it consists of an implanted pulse generator with leads attached to the carotid sinus bilaterally (39). In contrast to the older devices, the program in this device could be adjusted after the implantation as this was cited as a major limitation in the older devices and the electronics have been much miniaturized.

Clinical Trial evidence

Results of two clinical trials (one each in USA and Europe) assessing the role of baroreflex stimulation (using Rheos) in patients with resistant hypertension have been presented in international meetings as abstracts (40, 41). These studies were designed to establish the safety of the procedure and the device. In the US, ten patients with resistant hypertension who were taking a median of six antihypertensive medications underwent pulse generator with bilateral perivascular carotid sinus lead implantation. Implantation was performed bilaterally with patients under narcotic anesthesia in order to preserve the reflex for assessment of optimal lead placement. Dose-response testing at 0 to 6 V was assessed before discharge and at monthly intervals and the device was activated after 1 month recovery time. The SBP reduced by 41 mm Hg without any adverse events noted in these patients at the time of discharge. At 3 month follow up of these patients, SBP was reduced by a mean of 22 mmHg (from 180 ± 29 to 158 ± 32 , $P = 0.01$), and diastolic BP was reduced by a mean of 18 mmHg (from 105 ± 19 to 87 ± 21 , $P = 0.007$). Also, no increased incidence of hypotension, bradycardia or adverse renal effects has been noted.

Similar encouraging results were reported from an uncontrolled trial from Europe. Seventeen patients (on 5.2 ± 1.8 antihypertensive drugs) underwent bilateral perivascular carotid sinus electrodes (CSL) and a pulse generator (IPG) implantation. This resulted in a reduction of SBP (189 ± 33 to 165 ± 31 mmHg) ($P < 0.0011$), and diastolic BP (116 ± 22 to 99 ± 17 mmHg) ($P < 0.0010$). In these trials, the procedure time for implantation is relatively long and procedure related events such as tickling in throat, coughing, pain in teeth and jaws, pain in ears and tears were noted in few patients. Chest discomfort due to the placement of the device in the chest noted in these trials is also a concern. Two patients developed perioperative infection at the insertion site. Thus, modifications to the existing device should consider the above mentioned factors when redesigned.

Ongoing trials

A phase III multicenter randomized double blind clinical trial has started enrolling patients in United States (target of 300 patients) (42). The inclusion criteria includes: a) SBP of >160 mm Hg and a diastolic pressure of >85 mm Hg b) currently taking at least three different class of BP medication for at least for one month. Patients with atrial fibrillation, on dialysis and had prior neck surgery will be excluded. The primary outcomes measures include a) reduction of office cuff SBP at six months, b) sustained response to therapy through 12 months, c) system and procedure related adverse event free rate in the first 30 days, d) hypertension-related adverse event and serious device-related adverse event free rate more than 30 days post-implant to 13 months, e) serious therapy-related adverse event free-rate through 6 months.

Conclusion

Resistant hypertension is emerging as a bigger threat than previously anticipated and is a disease with significant morbidity and mortality. Do we have adequate therapies to protect and to treat our patients? The answer is both yes and no. With the present number of antihypertensive medications available seeing only slow growth, newer treatment options such as carotid sinus stimulators are promising therapies that are being vigorously tested as the preliminary data shows potential benefits.

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