Resistant Hypertension Treatment through Carotid Baroreceptor Stimulation

Gino Seravalle and Guido Grassi

Affiliations: 1Cardiology Department, Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy and 2Clinica Medica, Ospedale San Gerardo, Università Milano-Bicocca, Monza, Italy

ABSTRACT

A significant number of hypertensive subjects fail to achieve adequate blood pressure control despite adherence to maximal doses of several antihypertensive drugs. Electrical stimulation of the carotid sinus is a new and interesting approach to the treatment of resistant hypertension. The purpose of this paper is to overview the argument starting from the historical physiological background to potential therapeutical applications through the recent advances in technology regarding electrical baroreceptor stimulators.

Keywords: resistant hypertension, carotid baroreflex, baroreceptor stimulation, sympathetic nervous system, therapy, surgery

INTRODUCTION

Despite growing awareness of the linear relationship between the level of blood pressure (BP) and the risk of cardiovascular events [1] and the importance of blood pressure goals, blood pressure control worldwide remains poor [2, 3]. Several trials have clearly shown a failure to achieve BP goals despite receiving more than three antihypertensive drugs [4–7] (Figure 1). A significant number of hypertensive subjects fail to achieve adequate BP control despite adherence to maximal doses of several antihypertensive drugs. These patients are regarded as having resistant hypertension, defined as failure to achieve a BP of \(<140/90\) mmHg despite taking three antihypertensive medications, including a diuretic agent [2, 3, 8, 9]. To this end, the investigation of new approaches in the drug treatment of resistant hypertension is increasing with the addition to the existing multidrug regimen of an antialdosterone agent [10], thereby more effectively blocking the sodium-retaining properties of this hormone, or adding an antagonist of endothelin receptors, which is able to induce a further BP reduction as a result of its vasodilatory properties [11].

More intriguing is the interest in invasive procedures capable of reducing the pressor or increasing the depressor influences that physiologically modulate BP. Long-term control of arterial pressure has been attributed to the kidney because of its ability to couple regulation of blood volume with the maintenance of sodium and water balance by the mechanisms of pressure natriuresis and diuresis. There is evidence that an important cause of the defect in renal excretory function in hypertension is an increase in renal sympathetic nerve activity (RSNA) resulting from the direct action of angiotensin II on brain stem nuclei, increasing the basal level of RSNA and impairing its arterial baroreflex regulation [12]. A reduction in the pressor influences can be obtained by denervating the renal arteries through a percutaneously inserted catheter capable of removing efferent sympathetic influences, thus lowering overall total-body norepinephrine spillover, and reducing vasoconstriction in an a that accounts for a considerable proportion of systemic vascular resistance [13]. An enhancement of the depressor influences can be obtained via the sympathoinhibitory effects of continuous electric stimulation of the carotid baroreceptor [14]. The renewed interest in electrical stimulation of the carotid sinus will be the central argument of this review.

HISTORICAL BACKGROUND

The influence of arterial reflex in BP control has been known from ancient Rome where it was observed that manual compression of the arteries anatomically located in the neck of animals was able to induce sedation. In 1799, Parry observed for the first time in humans that, along with bradycardia, carotid compression induced hypotension. At the beginning of the twentieth century, it was found that the carotid bifurcation region is particularly sensitive to pressor and depressor stimuli and has a role in BP control. Carotid baroreceptors are stretch receptors that transmit signals to the medullary vasomotor centers through the carotid nerves. The impulses are processed in the central nervous system and inhibit the discharge of the sympathetic nervous system (Figure 2). As the arterial baroreflex represents a major inhibiting mechanism of the sympathetic nervous system, it seemed rational to assume that an alteration in baroreflex activity is implicated in the pathogenesis of hypertension [15–17].
Figure 1. Effects of antihypertensive drug treatment on systolic blood pressure (SBP) in trials on essential hypertensive (left) and diabetic hypertensive (right) patients. Values at trial entry (B) and during treatment (T) are shown for each trial. Dashed horizontal lines refer to goal BP values indicated by international guidelines to be achieved during treatment. Modified with permission from [4]

Figure 2. Scheme illustrating the main reflex mechanisms that, through central integration, are responsible for the cardiovascular homeostasis. NTS, nucleus tractis solitari; CNS, central nervous system; Ach, acetylcholine; NE, norepinephrine; GI, gastrointestinal
BAROREFLEX CARDIOVASCULAR CONTROL

As BP increases, baroreceptor triggering leads to diminished sympathetic outflow to the heart, kidneys, and peripheral vasculature, as well as heightened parasympathetic tone in the heart. The result is a fall in peripheral vascular resistance, heart rate, stroke volume, and BP. The decrease in renal sympathetic tone reduces the activity of the renin–angiotensin–aldosterone system (RAAS), with a resultant decrease in renal salt and water retention as well as diminished angiotensin II-mediated vasoconstriction [15–19]. Decreased arginine vasopressin secretion is also observed during increased baroreceptor activity, contributing to reduce systemic vasoconstriction and renal water retention [15–18].

It is well established that the arterial baroreflex buffers short-term fluctuations in BP, whereas arterial baroreceptors are rapidly reset in response to sustained BP elevations [16, 17].

BARORECEPTOR ACTIVATION

The concept of carotid baroreceptor activation is actually based on the idea that increased nerve traffic from the carotid sinus to brainstem cardiovascular centers would result in a sustained fall in BP. This continuous neural signal evokes a subsequent decrease in BP and heart rate. The manipulation of BP levels by electrical stimulation of the carotid baroreceptors could “re-set” the baroreflexes, and thus hypertension could be controlled more easily.

The goal of lowering BP in humans by activating carotid baroreceptors is not a new approach. The first studies in the late 1950s performed in experimental animals [19–21] showed that a significant reduction in BP was achieved in normotensive dogs for periods of up to 90 min following direct electrical stimulation of the carotid sinus nerve. A consistent BP reduction lasting for the whole year of evaluation was observed by Schwartz et al [22] in studies performed both in normotensive and hypertensive dogs.

The hemodynamic effects of bilateral electrical stimulation of the carotid sinus nerves in humans have been evaluated in several studies. In the study by Tuckman et al [23], the acute carotid stimulation of supine hypertensive patients reduced cardiac output by 11%, peripheral resistance by 10%, mean arterial pressure by 21%, and heart rate by 16%. Similar results were also reported in other studies [24–26].

Another important issue is whether unilateral or bilateral baroreceptor activation is required to obtain the optimal response. Parsonnet et al [27] have noted that, although maximum BP reduction was obtained by simultaneous bilateral application, this response was similar to that obtained by stimulation of the more responsive of the two carotid sinus nerves. In contrast, Schwartz et al [22] demonstrated that simultaneous bilateral stimulation is much better than the stimulation of either nerve, and usually more effective than the summation of the unilateral stimulation.

However, the use of these early devices was not devoid of adverse events and technical difficulties. Adverse events included: (1) paralysis of the hypoglossal nerve with dysarthria and hemiatrophy of the tongue; (2) blurring of vision and dizziness in the standing position; (3) perioperative death attributed to the fact that the surgical approach to the carotid baroreceptor area was in its infancy. Technical difficulties included: (1) current spread around the inserted electrode with discomfort and pain; (2) difficulties in communication between the external antenna and the inserted receiver; (3) nerve damage; and (4) stimulation of the nearby chemoreceptor afferents leading to sympathoexcitation. The above-mentioned disadvantages have been overcome by recent advances in technology.

Despite the early successes with an implantable carotid simulator system, the appeal of a surgical approach to hypertension declined as the armamentarium of effective antihypertensive drugs increased and because of the invasiveness of carotid baroreceptor therapy. Although recent decades have seen a dramatic improvement in the treatment of hypertension, we remain limited in our ability to treat the most resistant patients effectively.

NEW APPEAL OF CAROTID STIMULATION

In the last two or three decades, significant evidence has accumulated suggesting a causative or accessory role of sympathetic nerve activity in the pathogenesis of essential hypertension [28–31]. Findings indicate that a sympathoexcitatory state is especially pronounced in individuals in whom BP control is particularly difficult, as in isolated systolic hypertension [32], in hypertension associated with obesity [33, 34] and obstructive sleep apnea [35], and in subjects with an altered dipping profile [36] (Figure 3). These studies suggest that suppression of sympathetic activity should be one of the major goals of hypertensive therapy [36]. In the setting of progressively lowering BP targets needed to prevent end-organ disease and continued refinements in implantable medical technology, this has led to a renewal of interest in carotid sinus stimulation. The use of electrical carotid baroreceptor stimulation is also supported by the evidence that, in hypertension, the baroreflex undergoes a “resetting” that avoids baroreceptor saturation, thus preserving the reflex ability to cause vasodilation and decrease BP in response to an increase in its activity [15].

In the first years of the millennium, studies by Lohmeier et al [37, 38] and Barrett et al [39] showed that, in animals with angiotensin II-induced acute and chronic hypertension, this treatment produced a decrease in renal sympathetic nerve activity in animals with an intact baroreflex but not in animals that had undergone sinoaortic denervation. These data suggest that the baroreflex is important in chronic hypertension and that renal sympathoinhibition, with a resultant increase in natriuresis, may be the mechanism by which the baroreflex participates in long-term BP control [18, 40]. A further step was evaluation of the effect of long-term stimulation on the baroreflex using electrodes implanted around both carotid sinuses of dogs [38]. Baroreflex activation for 7 days produced a rapid and sustained reduction in heart rate and BP as well a significant reduction in plasma

www.slm-asia.com
norepinephrine levels, but plasma renin levels did not increase, suggesting that baroreflex-mediated suppression of renin activity played a role in the sustained hypotensive response. More recently, the same group evaluated the effects of prolonged electrical carotid baroreflex stimulation in dogs with obesity-induced hypertension, showing a significant reduction in mean arterial pressure and plasma catecholamines without a concomitant increase in plasma renin activity [40]. Thus, in obesity, baroreflex activation can suppress the endogenous activation of the sympathetic nervous system and reduce high BP. These data also support the hypothesis that baroreflex-mediated suppression of renal sympathetic nerve activity and renin secretion is an important mechanism by which the carotid stimulation exerts its antihypertensive effect.

As far as human studies are concerned, carotid baroreceptor stimulation was first studied in the 1960s. After less than optimal results resulting from technical problems and symptoms related to local tissue and nerve stimulation (dysphagia, coughing, gagging, hyperpnea, dyspnea), the development of systems that permitted radiofrequency adjustment of implanted devices allowed tailored stimulation of parameters to individual patients. Thanks to these innovations, Tuckman et al [23] implanted bilateral carotid sinus nerve stimulators, permitting fine regulation of the stimulus in achieving BP reduction and avoiding undesirable effects over a period of 2–18 months. Peters et al [24] used a device that matched stimulator frequency to patient heart rate, based on the hypothesis that heart rate elevations signaled increases in sympathetic tone that would need to be answered with greater activation of the baroreflex to achieve BP control. Patients fitted with these stimulators were able to increase their heart rate and BP with exercise, thus avoiding the inability to increase sympathetic tone during physiologic demands as seen with previous devices. Schmidli et al [41, 42] reported results on the acute and chronic effects of carotid stimulation showing a voltage-dependent reduction in BP levels.

To date, several studies are under way with a Rheos device for chronic electrical stimulation of the carotid sinus (CVRx, MN, USA): the European and US Feasibility studies and the Rheos Pivotal trial. In the Device Based Therapy of Hypertension (DEBuT-HT) study, 16 patients completed the 2-year follow-up [43]. Both systolic and diastolic BP were significantly lowered by 35 ± 8 mmHg and 24 ± 6 mmHg, respectively. These reductions were comparable to those observed at 3 and 12 months after activation of the device. More than 75% of these patients showed a reduction of >20 mmHg in systolic BP, and 31% showed BP control. In the European/US study [44], the Rheos device applied to 16 resistant hypertensive patients was able to induce statistically significant reductions in BP values at 3 months accompanied by reduction in left ventricular mass index (−24.1 ± 18.7 g/m²), septal wall thickness (−1.3 ± 1.8 mm), and left ventricular posterior wall thickness (−1.4 ± 1.1 mm). These results were also accompanied by a reduction in the number of antihypertensive drugs. A study of 12 patients with resistant hypertension fitted with the Rheos device did not show an impairment in renal function after a 1-year follow-up [45]. In this study, glomerular filtration rate was unchanged, while the effective plasma flow tended to decrease, thus resulting in a significant rise in filtration fraction. A recent study of 12 resistant hypertensive patients by Heusser et al [46] showed that acute electric baroreflex stimulation decreased systolic BP by 32 ± 10 mmHg, and this was correlated with a reduction in muscle sympathetic nerve activity, heart rate, and plasma renin concentration. This result is relevant because it shows that the surgical procedure by which the stimulating device is bilaterally implanted does not impair, through scarring, inflammation, or direct baroreceptor damage, the ability of the reflex to exert its sympathetic and vasomotor modulation.
CONCLUSIONS

Although intriguing, the results obtained with carotid baroreceptor stimulation for the treatment of resistant hypertension leave a number of clinically relevant questions. First, are the favorable effects of this intervention maintained over time? Is there any evidence of a time-dependent baroreflex desensitization to the electrical stimuli? What about the long-term safety of the procedure? How much can the baroreflex function be quantitatively altered by the surgical procedure? What about the battery’s half-life and the necessity of several changes after implantation? Taking into account these problems, what is the economic impact of this procedure in the treatment of resistant hypertension?

Taken together, these questions demonstrate that much needs to be learned about this procedure, which nevertheless opens new options for the treatment of resistant hypertension.

Disclosure: The author declares no conflict of interest.

REFERENCES