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Acute and chronic electrical activation of baroreceptor afferents in awake and anesthetized subjects

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Electrical stimulation of baroreceptor afferents was used in the 1960's in several species, including human beings, for the treatment of refractory hypertension. This approach bypasses the site of baroreceptor mechanosensory transduction. Chronic electrical stimulation of arterial baroreceptors, particularly of the carotid sinus nerve (Hering's nerve), was proposed as an ultimate effort to treat refractory hypertension and angina pectoris due to the limited nature of pharmacological therapy available at that time. Nevertheless, this approach was abandoned in the early 1970's due to technical limitations of implantable devices and to the development of better-tolerated antihypertensive medications. More recently, our laboratory developed the technique of electrical stimulation of the aortic depressor nerve in conscious rats, enabling access to hemodynamic responses without the undesirable effect of anesthesia. In addition, electrical stimulation of the aortic depressor nerve allows assessment of the hemodynamic responses and the sympathovagal balance of the heart in hypertensive rats, which exhibit a well-known decrease in baroreflex sensitivity, usually attributed to baroreceptor ending dysfunction. Recently, there has been renewed interest in using electrical stimulation of the carotid sinus, but not the carotid sinus nerve, to lower blood pressure in conscious hypertensive dogs as well as in hypertensive patients. Notably, previous undesirable technical outcomes associated with electrical stimulation of the carotid sinus nerve observed in the 1960's and 1970's have been overcome. Furthermore, promising data have been recently reported from clinical trials that evaluated the efficacy of carotid sinus stimulation in hypertensive patients with drug resistant hypertension.

Key words: Carotid sinus nerve; Aortic depressor nerve; Hemodynamics; Baroreceptor stimulation; Refractory hypertension

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Early studies of electrical stimulation of baroreceptor afferents

Derangement of the carotid sinus as a possible cause of the persistence of elevated blood pressure in hypertensive animals was first suggested by McCubbin et al. (1) in 1956. Using an electroneurographic approach, the authors demonstrated that in chronic renin-induced hypertensive dogs there were fewer impulses along the carotid sinus nerve than in the normotensive situation. The investigators hypothesized that there is an adaptation within the baroreceptor end organ, which perpetuates, rather than protects against, an elevation in blood pressure. However, in 1958, Warner (2) demonstrated that activation of the baroreflex by direct electrical stimulation of the carotid sinus nerve (Hering's nerve) reduced arterial pressure in anesthetized normotensive dogs for periods lasting up to 90 min. Subsequent work showed that electrical stimulation of the carotid sinus nerve for 10 to 20 s in patients undergoing head and neck surgery elicited similar results,

i.e., a rapid decrease in arterial pressure and heart rate with return to baseline levels within seconds after ending the stimulation (3). In 1964, Griffith and Schwartz (4) first reported the reversal of arterial hypertension by electrical stimulation of the carotid sinus nerve in anesthetized dogs. These investigators demonstrated a sustained reduction in systolic and diastolic pressure of approximately 60 mmHg in renal hypertensive animals submitted to unilateral stimulation of the carotid sinus nerve, with the opposite carotid sinus nerve left intact, for periods of up to 90 min. When the opposite nerve was transected, the animals responded maximally to the electrical stimulus, indicating that the opposite nerve, when left intact, buffered the hypotensive response to electrical stimulation of its counterpart.

Subsequent studies provided similar results with prolonged electrical stimulation of the carotid sinus nerve in dogs with chronic renal or acute neurogenic hypertension, as well as in dogs with arteriosclerosis. This trend indicates a return of arterial pressure to the prehypertensive control levels and persistence of this reduced pressure throughout the period of stimulation (5,6). Neistadt and Schwartz (6) observed a significant reduction in arterial pressure to electrical stimulation of the carotid sinus nerve in chronic renal hypertensive dogs. This response was accompanied by a reduction in cardiac output, with less reduction in renal blood flow. The decrease in arterial pressure was maintained for periods of up to 6 h of stimulation, and the response of the nerve to intermittent stimulation was effective 6 months after implantation of the stimulus device in the carotid sinus nerve. Therefore, electrical stimulation of baroreceptors was proposed as a supplementary treatment for refractory hypertension due to the limitations of pharmacological antihypertensive therapy available in the early 1960's (including undesirable side effects and lack of responsiveness to available medication).

Studies in patients with refractory hypertension using uni- or bilateral acute (3 min) and chronic (1 month to 2.5 years) electrical stimulation of the carotid sinus nerve produced comparable results, i.e., reduction of systemic arterial pressure and bradycardia (7-12). Bilgutay and Lillehei (13) reported successful treatment of a patient whose blood pressure was 260/165 mmHg despite the use of four antihypertensive medications. After chronic bilateral electrical stimulation of the carotid sinus, arterial pressure was reduced to 150/90 mmHg and was maintained at this level with continuation of baroreflex activation. In a report of 8 patients with refractory hypertension, Schwartz et al. (7) described a sustained reduction in blood pressure of 48/42 mmHg with bilateral carotid nerve stimulation over a period of 5 months to 2.5 years. Six patients were able to discontinue antihypertensive medications and two others required combined electrical stimulation of the carotid sinus nerve and pharmacological antihypertensive medication to achieve a marked reduction in arterial pressure. These studies revealed the efficacy of this technique to chronically counteract a sustained increase in arterial pressure by means of baroreflex activation.

In addition, electrical stimulation of the carotid sinus nerve involving acute (20 s to 3 min) and chronic (1 to 24 months) stimulation regimens was used to reduce episodes of refractory angina pectoris in patients with coronary artery disease, at rest and during exercise. Electrical stimulation resulted in the reflex reduction of heart rate, arterial pressure, myocardial contractility, tension time index, heart work, and myocardial oxygen demand (10,14-17). In a study of 21 patients with intractable angina pectoris, Braunwald et al. (14) demonstrated that activation of the baroreflex caused a substantial improvement in symptoms, leading to better physical performance in 16 patients during a period of 2 to 24 months postoperatively. Furthermore, electrical stimulation of the carotid sinus nerve was also used to treat paroxysmal supraventricular tachycardia refractory to the usual medications, which extremely debilitated the patients (18). Thus, the efficacy of chronic electrical activation of the baroreflex was extended beyond hypertensive states, improving the quality of life of patients suffering from intractable angina pectoris.

Despite these encouraging findings from early clinical studies, this approach was not pursued in the 1970s and 1980s owing to paramount limitations imposed by surgical approaches and implantable devices. In most of the early studies, the implantable device provided the current to electrodes implanted around the carotid sinus nerve. This protocol could damage the nerve during dissection and/or electrode implantation. In addition, chronic carotid sinus nerve stimulation itself could injure the nerve or promote substantial fibrosis. Furthermore, the frequency and intensity of stimulation required to achieve the desired hemodynamic effects were not clear due to variability among patients. When higher levels were required, stimulating tissues adjacent to the carotid sinus nerve caused pain and other painful symptoms. These symptoms included dysphonia, dysphagia, coughing, gagging, hyperpnea, tachypnea, dyspnea, hyperesthesias or paresthesias. In addition, the implantable stimulating devices were very bulky, battery capacity was sometimes insufficient and some devices presented no external current control.

Despite development of a system that allowed radiofrequency adjustment of the implanted devices and permitted customization of treatment for each individual (6,9,19), this approach to the treatment of hypertension was abandoned, presumably due to the technological

limitations mentioned above and to the development of new antihypertensive drugs. However, the electrical stimulation of baroreceptor afferents in anesthetized animals has been continued as a useful tool to investigate the reflex regulation of arterial pressure and heart rate in several species, such as dogs, cats, rabbits, swine, and rats (20-34).

Studies of baroreflex function by means of electrical stimulation of baroreceptor afferents

Electrical stimulation of baroreceptor afferents is a technique widely used in several species for studies of baroreflex control. In the rat, because the carotid sinus nerve is very small, difficult to manipulate and has baro- and chemoreceptor afferent fibers, the aortic depressor nerve (ADN) has been more conspicuously studied. In 1963, Krieger and Marseillan (35) identified the routes followed by the ADN fibers in the cervical region of anesthetized Wistar rats by means of electroneurographic recording combined with electrical stimulation. Further studies demonstrated, by means of electrical stimulation, that the Sprague-Dawley and Wistar rat ADN possessed almost exclusively baroreceptor afferent fibers and few, if any, functional chemoreceptor afferent fibers (33,36). These results established that electrical stimulation of the ADN in rats is a reliable method for triggering baroreflex activation in cardiovascular studies.

Electrical stimulation of the ADN or superior laryngeal nerve in rats under different types of anesthesia (e.g., pentobarbital, α-chloralose or urethane) induced reflex decreases in mean arterial pressure and heart rate that were frequency-dependent (36-39). During graded electrical activation of the ADN in rats, myelinated A fibers and unmyelinated C fibers are recruited, producing maximal decreases in mean arterial pressure at frequencies >10 Hz, and maximal bradycardia within 100-200 Hz (34,38,40). Nevertheless, the activation of these two subtypes of baroreceptor fibers appears to have distinct differences in sensory function related to the regulation of systemic arterial pressure and cardiac function. Activation of myelinated A fibers in the ADN evoked reflex changes in mean arterial pressure only at frequencies higher than 10 Hz, while activation of unmyelinated C fibers acted at lower frequencies, i.e., within 1-10 Hz. On the other hand, reflex control of heart rate throughout selective A- and C-fiber activation showed patterns of integration unexpectedly different from those of the reflex control of mean arterial pressure. Selective stimulation of myelinated A fibers at high frequencies, such as 200 Hz, was ineffective in producing bradycardia. However, low frequencies, which activated unmyelinated C fibers, produced substantial bradycardia, which became maximal at activation rates =10 Hz, just as observed for mean arterial pressure. Likewise, heart rate responses to supramaximal activation of A and C fibers of the ADN have an additive effect, whereas the hypotensive responses do not (34,40).

Baroreceptor stimulation in anesthetized rats indicated that electrical stimulation of the superior laryngeal nerve evoked a pronounced reduction in hindquarter vascular resistance. This type of stimulation produced a smaller, but significant, reduction in mesenteric and renal vascular resistance (37,39). On the other hand, Machado et al. (32) demonstrated that electrical stimulation of the ADN produced an important reduction in hindquarter vascular resistance with an increase in renal and mesenteric vascular resistance, suggesting that the aortic baroreceptors play a more important role in the regulation of blood flow in the hindquarter than in the renal and mesenteric vascular beds. In conscious rats, electrical stimulation of the ADN by means of fixed frequency (50 Hz) and progressive voltage (1 to 5 V) indicated that a decrease in mesenteric resistance, in contrast to hindquarter resistance, did not play a role in the hypotensive response (41). However, electrical stimulation of the ADN with a fixed current (1 mA) and progressive frequency (5 to 90 Hz) clearly demonstrated that a conspicuous decrease in both mesenteric and hindquarter resistance played a role in the hypotensive response (42). Until now, the role played by changes in vascular resistance in the hypotensive response during carotid sinus stimulation in conscious dogs or humans has not been reported.

Recently, Possas et al. (43) also demonstrated that electrical stimulation of the ADN in pentobarbital-anesthetized rats produced frequency-dependent decreases in mean arterial pressure that were accompanied by pronounced vasodilator responses in the hindquarter bed and less pronounced vasodilator responses in the mesenteric bed. According to these authors (43), this greater fall in hindquarter resistance induced by electrical stimulation of the ADN may involve the activation of postganglionic lumbar sympathetic vasodilator fibers, which release newly synthesized and preformed nitrosyl factors.

Electrical stimulation of the ADN was also used to examine the distribution of Fos protein-like immunoreactivity in the rat brain in order to characterize the central pathways involved in mediating the baroreceptor reflex (44). This study found labeling in several discrete brain nuclei, primarily on the ipsilateral side of stimulation. In the medulla, labeled nuclei were found in the nucleus tractus solitarii (NTS), area postrema, rostral and caudal ventro-

lateral medulla, nucleus ambiguous and medullary reticular formation. Other areas in the pons and in the forebrain were also labeled.

It is important to note that all previous studies that have examined the responses to aortic baroreceptor stimulation have been carried out in anesthetized rats, which may have been subject to the influence of anesthesia on basal parasympathetic and sympathetic tone, peripheral vascular resistance and central mediation of the baroreflex. Thus, our laboratory developed (41) a technique to electrically stimulate the ADN in conscious freely moving rats, which allowed us to examine hemodynamic responses such as reflex bradycardia, the fall in arterial pressure and changes in regional vascular resistance (mesenteric, renal and hindquarter) without the undesirable effects of anesthesia (41). In that study, electrical stimulation of the ADN for 5 s in normotensive Wistar rats produced a fall in pressure, bradycardia, and vasodilatation in the hindquarter, but no change in mesenteric vascular resistance. It is noteworthy that the progressive increase in randomly applied voltage elicited voltage-dependent reflex hypotension and bradycardia without causing any damage to ADN afferents. This was demonstrated by the remarkable reflex bradycardia caused by the increase in arterial pressure in response to intravenous injection of phenylephrine at the end of the set of electrical stimulation (Figure 1). In addition, the study demonstrated that methylatropine blocked the reflex bradycardia almost completely without affecting the degree of the hypotensive response. This finding indicates that the decrease in heart rate played no significant role in the reflex fall of arterial pressure, providing support for a conspicuous role played by the decrease in peripheral vascular resistance elicited by the sympathoinhibition during electrical stimulation of the ADN in conscious rats.

Furthermore, this technique also permitted researchers to investigate the role of different subtypes of ionotropic receptors in the NTS, N-methyl-D-aspartic acid (NMDA) and non-NMDA receptors, which are activated by the ubiquitous neurotransmitter L-glutamate, in the processing of reflex bradycardia (parasympathoexcitation) and hypotension (sympathoinhibition) (45). Inhibition of NMDA and non-NMDA receptors in the commissural NTS by microinjection of DL-2-amino-5-phosphonopentanoic acid (AP-5, a selective NMDA receptor antagonist) and 6,7-dinitroquinoxaline-2,3 dione (a selective non-NMDA receptor antagonist) produced complete blockade of the reflex bradycardia in response to electrical stimulation of the ADN, suggesting that the parasympathetic component of the activation is mediated by both receptors. On the other hand, the inhibition of NMDA and non-NMDA recep-

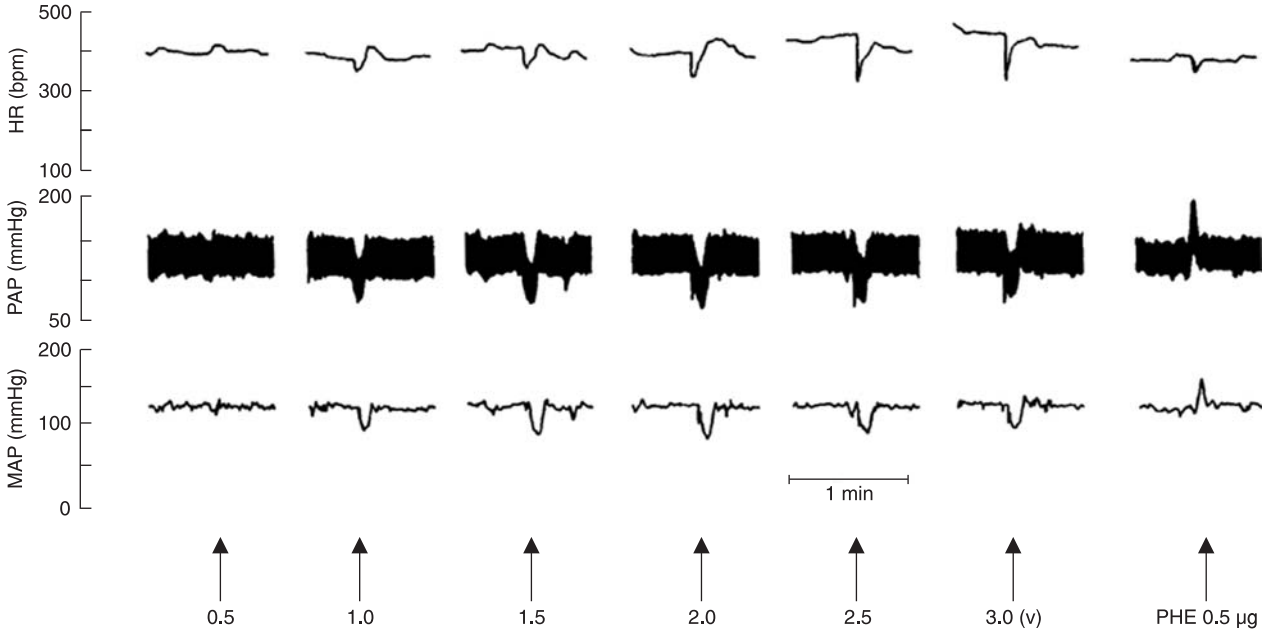

Figure 1. Electrical stimulation of the aortic depressor nerve in conscious normotensive rat. Typical tracings from conscious normotensive Wistar rat showing the responses of heart rate (HR), pulsatile arterial pressure (PAP), and mean arterial pressure (MAP) to electrical stimulation of the aortic depressor nerve, over a period of 5 s, with increasing voltage, and during intravenous injection of phenylephrine (PHE). [Modified with permission from *Am J Physiol Regul Integr Comp Physiol* 1999; 277 (1 Part 2): R31-R38].

tors reduced the reflex hypotensive response by only about 50%, suggesting that other metabotropic receptors, or neurotransmitters other than L-glutamate, may play a role in the neurotransmission of the sympathetic component of the reflex arch.

Recently, we used electrical stimulation of the ADN in conscious rats to investigate baroreflex function in normotensive and hypertensive rats (42). Electrical stimulation of the ADN for 5 s in conscious spontaneously hypertensive rats (SHR) produced significant frequency-dependent decreases in arterial pressure and heart rate, as well as decreases in hindquarter and mesenteric resistance (Figure 2). The absolute decrease in arterial pressure was similar when normotensive rats were compared to SHR at low frequencies. The decrease was significantly larger in SHR at high frequencies of stimulation. Hindquarter vasodilatation in SHR was larger than mesenteric vasodilation, while in normotensive rats the vasodilation exhibited by these regions was equivalent. Heart rate responses did not differ significantly between normotensive rats and SHR. These findings demonstrate a well-preserved, or even enhanced, baroreflex response in SHR that may reflect diverse central baroreflex control in hypertensive and normotensive rats. In addition, blockade of $ß_1$-adrenergic receptors with atenolol in normotensive rats did not affect baroreflex-mediated decreases in mean arterial pressure and heart rate elicited by electrical stimulation of the ADN. However, atenolol significantly blunted baroreflex-mediated bradycardia in SHR with no effect on baroreflex-mediated decreases in mean arterial pressure. These findings indicated that, in contrast to normotensive rats, withdrawal of sympathetic activity contributed significantly to baroreflex-mediated bradycardia in SHR. Thus, it can be hypothesized that this observation is probably related to the higher basal level of cardiac sympathetic tone in SHR.

In conscious chronically instrumented dogs, Lohmeier et al. (46,47) observed that activation of the arterial baroreflex for seven days by means of bilateral electrical stimulation of the carotid sinus produced a remarkable and sustained reduction in arterial pressure associated with mild bradycardia. These changes were associated with a decrease of ~35% in plasma norepinephrine concentration, indicating a conspicuous attenuation of the sympathetic drive elicited by electrical stimulation of the carotid sinus. Surprisingly, plasma renin levels did not change, as would be expected due to the pronounced fall in arterial pressure, suggesting that the baroreflex-mediated suppression of renin activity may play a role in the sustained hypotensive reflex response. After the discontinuation of baroreflex activation, the hemodynamic responses and plasma lev-

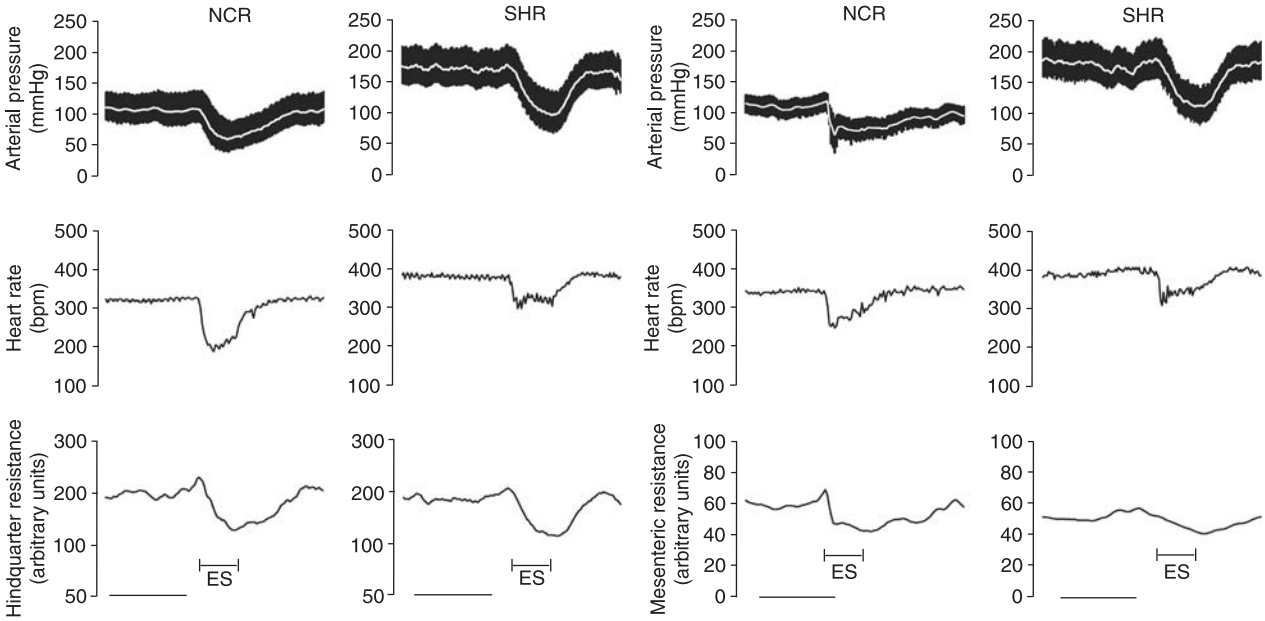

Figure 2. Hemodynamic responses to electrical stimulation of the aortic depressor nerve in conscious rats. Typical tracings from normotensive control rat (NCR) and spontaneously hypertensive rat (SHR) showing the responses of pulsatile arterial pressure (top), heart rate (middle) and vascular resistance (hindquarter and mesenteric) (bottom) to electrical stimulation (ES, 30 Hz, 1 mA, 2 ms) of the aortic depressor nerve over a period of 5 s. [Modified with permission from *Am J Physiol Heart Circ Physiol* 2007; 292 (1): H593-H600].

els of norepinephrine returned to basal levels.

Recent observations from the same group (48,49) provided similar results in conscious hypertensive dogs. Prolonged (seven-day) electrical activation of the carotid sinus decreased arterial pressure, attenuated the tachycardia, and reduced plasma norepinephrine concentration in dogs with obesity-induced hypertension (49). In contrast, there were no changes in the hyperinsulinemia and hyperglycemia of obesity or plasma renin activity during prolonged baroreflex activation. These findings indicated that baroreflex activation can chronically abolish sympathetic activation associated with obesity, as well as the concurrent hypertension. Although electrical activation of the baroreceptors reduced arterial pressure in conscious obese hypertensive dogs, in conscious angiotensin II-infused hypertensive dogs, this decrease in arterial pressure was markedly attenuated (75 to 80%), in conjunction with a lack of any significant change in heart rate. Therefore, Lohmeier et al. (48) suggested that the activity of the renin-angiotensin-aldosterone system is a major determinant of the arterial pressure-lowering effects of the baroreflex in different forms of hypertension. They also asserted that angiotensin II probably acts in the central nervous system to impair baroreflex control of renal sympathetic nerve activity and heart rate.

Moreover, the findings of Lohmeier et al. (48) strongly suggest that the mechanism by which carotid sinus stimulation reduces arterial pressure involves the attenuation of the renal sympathetic tone; furthermore, pre-existing levels of sympathetic activity probably affect this response. However, this mechanism is not entirely straightforward; in a recent study, Lohmeier et al. (50) demonstrated that after renal denervation the hemodynamic and neuro-humoral responses to electrical activation of the baroreflex were similar to those observed before renal denervation. Thus, the renal nerves are not necessary for achieving long-term reductions in arterial pressure during prolonged electrical baroreflex activation. Therefore, these recent findings not only support the notion that the baroreflex plays a role in long-term control of arterial pressure, but also encourage novel studies utilizing prolonged activation of the carotid sinus in hypertensive patients. This technique represents a feasible, adjunct, non-pharmacological approach to the treatment of hypertension.

Currently, electrical stimulation of the carotid sinus has been reconsidered for use in hypertensive patients, since the technical problems confronted in the early studies seem to have been overcome with the use of modern technologies involving electrodes and pulse-generating devices. In addition, the technique used to place electrodes has changed and nowadays the stimulating electrodes are implanted around the carotid sinus rather than around the carotid sinus nerve. This approach allows the use of conventional techniques for electrode implantation with a minimum probability of carotid sinus nerve damage, commonly applied in the treatment of atherosclerotic disease of the carotid bifurcation.

Clinical studies using electrical stimulation of the carotid baroreceptors are already in progress, especially for the treatment of patients with hypertension resistant to pharmacological therapy (51-55). In the US, ten patients with resistant hypertension after exposure to six antihypertensive medications were submitted to chronic bilateral electrical stimulation of the carotid sinus after successful implantation of a new electronic device (51). This technique produced a remarkable acute voltage-dependent decrease in systolic arterial pressure of 41 mmHg, in the range of 0 to 6 V. The peak response was observed at 4.8 V and no significant bradycardia or detectable side effects were detected during stimulation. Another study in eleven patients undergoing elective surgery for carotid artery disease demonstrated similar results during acute unilateral electrical activation of the carotid sinus wall (53). A voltage-dependent reduction in arterial pressure and heart rate was observed, with a peak response at 4.4 V. In addition, the authors demonstrated that the type of anesthesia used for the implantation of the electronic device and the anatomy of the carotid sinus appear to affect the hemodynamic response to baroreflex activation (53). Tordoir et al. (54) reported the findings of the European Multicenter Feasibility Study obtained from seventeen patients with drug-resistant hypertension. In that study, tests performed during a period of 1 to 3 days postoperatively resulted in a significant reduction in systolic and diastolic arterial pressure and heart rate. Repeated testing during 3 months of electrical activation demonstrated a long-lasting response and lower arterial pressure related to the therapeutic effects of electrical activation of the baroreflex.

As discussed above, these studies using acute or prolonged stimulation of the carotid sinus have demonstrated reductions in arterial pressure and heart rate after triggering the baroreflex and, accordingly, increasing cardiac parasympathetic activity and reduction of the sympathetic drive. Thus, electrical stimulation of the carotid sinus may represent a safe and effective therapeutic option for the treatment of resistant hypertension. Moreover, as electrical activation of the carotid baroreceptor reduces sympathetic outflow, recent studies have also applied this approach chronically to dogs (56). In dogs with chronic heart failure submitted to carotid sinus stimulation, researchers observed improved survival without enhanced ventricular function, combined with suppression of plasma

norepinephrine and plasma angiotensin II (56).

In conclusion, electrical activation of baroreceptor afferents has proven to be a reliable approach to examine baroreflex regulation in conscious normotensive and hypertensive animals (rats and dogs). The technique has been recently proposed and thoroughly tested, as an adjunct treatment of human refractory hypertension, currently representing a safe and effective therapeutic option.

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