Etiopathogenesis of AH

A large number of genes are associated with hypertension, but it is believed that there is a risk of development of this disease in these people but that exogenous factors nevertheless play a major role in driving the neurohumoral system (endogenous factors) changes, which remain a leading process in AH development [2].

Epidemiological studies worldwide indicate that, in spite of the use of powerful antihypertensive drugs, less than 30% of all AH patients fail to keep their blood pressure below the target levels <140/90 mmHg [4]. In some hypertensive patients, it can be difficult to keep BP under control, despite the use of combinations of antihypertensive drugs. These people are considered resistant to antihypertensive treatment. Resistant hypertension is the term used for patients who are tolerant to a maximum of three doses of antihypertensive drugs, where one of them is a diuretic. Resistant hypertension also covers patients who are unable to reach target blood pressure (<140/90 mmHg for the general population and <130/80 mmHg for patients with certain co-morbidities, such as diabetes mellitus, coronary heart disease and chronic kidney disease) [5-7]. Resistant hypertension includes patients whose pressure is controlled by the use of more than three medications, and patients whose pressure is controlled by four or more drugs to achieve the target BP values [8].

While the exact prevalence of resistant hypertension is unknown, clinical studies suggest that it is not rare, probably diagnosed in 20-30% of all AH patients. Considering the fact that senior citizens and obese people are at the highest risk for uncontrolled hypertension, the incidence of resistant hypertension increases as the population becomes older and more obese [8]. Estimated prevalence of resistant hypertension in ALLHAT, VALUE, CONVINCE and ASCOTT studies ranged from 7% to 15% [9,10]. Patients with resistant hypertension are at a higher risk of cardiovascular morbidity and mortality than those whose hypertension is controlled well [8,9,11]. The increased cardiovascular risk among patients with resistant hypertension depends on blood pressure [3] and the presence of powerful antihypertensive drugs.
associated co-morbidities, including diabetes mellitus, sleep apnea, obesity, left ventricular hypertrophy and renal disease [8,12-15].

Although the role of above factors in pathogenesis of essential hypertension is well established, their involvement in mechanisms responsible for treatment resistance has not been investigated thoroughly [16].

In the emergence of drug-resistant hypertension Tsiosifis et al. highlight the impact of increased activity of the sympathetic nervous system (SNS), which is particularly emphasized by co-morbidities such as hyper obesity (BMI 30 kg/m²), sleep apnea and aldosterone excess. The authors report that listed co-morbidities inducing insulin resistance, endothelial dysfunction and inflammation lead to increased sympathetic activity that causes increased activity of the RAAS and thus the emergence of drug-resistant hypertension [17,18].

More specifically, increased SNS activity has been documented in systolic-diastolic and isolated systolic AH [19,20], in white coat and masked AH [21], in dipping, extreme dipping, non-dipping and reverse dipping condition [22] and in pregnancy induced AH [19,23].

Given the above, the treatment of patients with resistant hypertension in the last decade has attracted growing attention. However, despite the use of the strongest antihypertensive drugs, blood pressure remains out of control in 5%-15% of patients. Therefore, the need for alternative treatment approach has been widely recognized in recent years. That is why an interventional treatment of hypertension, which was abandoned by the end of the twentieth century, was recently re-invented and gained intense scientific interest. In this respect, in the treatment of resistant hypertension, a special attention is paid to carotid baroreceptors stimulation and to vascular distension [27].

In response to a sensed "stretch", the baroreceptor sends a signal that travels from the carotid sinus nerve to join cranial nerve IX (CN IX), eventually signaling to the nucleus tractus solitarius in the medulla. Ultimately, this leads to an inhibition of sympathetic output, along with decrease in the release of renin and antiuretic hormone, which serve to reduce the intravascular volume and tone (Figure 1) [2.27-29].

Baroreceptors (pressoreceptors) in conjunction with the vasomotor center in the medulla oblongata and vagal nuclei are involved in maintaining the normal blood pressure.

In 1980 Peters et al. reported on experience with a device that matched a stimulator frequency to the patient heart rate, the idea being that heart rate elevations signaled increases in sympathetic tone that need to be controlled by greater activation of the baroreflex to achieve blood pressure control [36,37]. Patients implanted with this device achieved blood pressure lowering both at rest and during exercise. Effective blood pressure lowering was subsequently reported 12 years after the device implantation [36].

In the past decade, more sophisticated research has developed with the understanding that non-pharmacologic means of controlling blood pressure remains out of control in 5%-15% of patients. Therefore, the need for alternative treatment approach has been widely investigated [16].

In this respect, in the treatment of resistant hypertension, a special attention is paid to carotid baroreceptors stimulation and to sympathetic renal denervation, which show promising preliminary results [8,24].

**Cardiac Baroreceptors - Neurogenic Factor**

The adequate blood pressure control reduces cardiovascular risk independent of the drugclass [25,26] and any therapy that can reduce blood pressure in patients with resistant hypertension may be useful. Doctors have long recognized the importance of the carotid sinus in the modulation of autonomic tone and regulation of blood pressure [26].

Carotid sinus baroreceptors are located in the bifurcation of the common carotid artery and they are mechanoreceptors that respond to vascular distension [27].

Baroreceptors (pressoreceptors) in conjunction with the vasomotor center in the medulla oblongata and vagal nuclei are involved in maintaining the normal blood pressure.

In the past decade, more sophisticated research has developed with the understanding that non-pharmacologic means of controlling blood pressure remains out of control in 5%-15% of patients. Therefore, the need for alternative treatment approach has been widely investigated [16].

In this respect, in the treatment of resistant hypertension, a special attention is paid to carotid baroreceptors stimulation and to sympathetic renal denervation, which show promising preliminary results [8,24].

**Cardiac Baroreceptors - Neurogenic Factor**

The adequate blood pressure control reduces cardiovascular risk independent of the drugclass [25,26]. Any therapy that can reduce blood pressure in patients with resistant hypertension may be useful. Doctors have long recognized the importance of the carotid sinus in the modulation of autonomic tone and regulation of blood pressure [26].

Carotid sinus baroreceptors are located in the bifurcation of the common carotid artery and they are mechanoreceptors that respond to vascular distension [27].

Baroreceptors (pressoreceptors) in conjunction with the vasomotor center in the medulla oblongata and vagal nuclei are involved in maintaining the normal blood pressure.

In response to a sensed "stretch", the baroreceptor sends a signal that travels from the carotid sinus nerve to join cranial nerve IX (CN IX), eventually signaling to the nucleus tractus solitarius in the medulla. Ultimately, this leads to an inhibition of sympathetic output, along with decrease in the release of renin and antidiuretic hormone, which serve to reduce the intravascular volume and tone (Figure 1) [2.27-29].

Baroreceptors inhibit sympathetic output, reducing the release of renin and anti-diuretic hormone, which reduce the intravascular volume and tone [27]. The stimulation of carotid baroreceptors reduces kidney sympathetic tone and thus expresses their effects [30,31]. However, on the basis of his experimental work, Lohmeier has suggested that the levels of natriuretic a trial peptide (AMP) are increased under chronic baroreflex activation, which causes enlarged excretion through the kidneys, which in turn reduces the blood pressure [32].
pressure may be a realistic and necessary alternative. In 2004 Lohmeier examined normotensive dogs that underwent sustained electrical stimulation of their carotid sinuses over a 7-day period. They found an immediate fall in the mean arterial pressure (MAP) of 25 mmHg, and over the full 7 days the dogs sustained a decrease in MAP [38].

In 2005, Schmidli et al. reported results obtained on five patients who underwent chronic electrical activation of the baroreflex with a carotid stimulator [39]. The device produced a graded voltage dependent drop in blood pressure – a relationship that was sustained even with chronic activation of the baroreflex. Moreover, these patients were concurrently receiving maximum medical therapy including alpha and beta antagonist, suggesting that baroreflex activation provides incremental attenuation of sympathetic tone in the setting of oral anti-adrenergic therapy. This theory is supported by experiments conducted by Irwin et al. on anesthetized dogs [40].

Schimidli found that electrical carotid stimulation and esmolol infusion applied individually produced similar reduction in blood pressure and heart rate, but produced synergistic effect when applied simultaneously [41].

**Recent baroreceptor stimulation therapy**

The newest carotid sinus stimulator is a device called Rheos. It is manufactured by CVRx, Inc. (MN, USA) and consists of an implanted pulse generator with leads that tunnel subcutaneously and bilaterally attach to the carotid sinuses. The device requires surgical implantation under general anesthesia and is fully programmable after implantation to allow adjustment of the stimulation parameters [42].

Studies in humans have confirmed the efficacy of this interventional approach, which was observed in animals. Acute blood pressure reduction was noted by using the Rheos device during elective carotid surgery [31]. Several case reports in patient with resistant hypertension have shown the clinical utility and long-lasting reductions in blood pressure with carotid baroreceptor stimulation, setting the basis for proof-of-concept, properly designed clinical trials [43-45]. The device-based therapy of hypertension (DEBuT-HT) trial in 45 patients with resistant hypertension revealed a significant reduction in both systolic and diastolic blood pressures, which was evident from the beginning of the study and was maintained thereafter [46]. The 3-year efficacy was recently presented verifying the long-lasting effect of carotid baropacing. Recruitment for a large randomized study has been completed and results are still pending. Preliminary information suggests that some patients may not respond as well and a more careful selection process may need to be implemented.

Data from an early US trial, the Rheos feasibility trial, have shown some promising results. The trial followed up 10 patients taking a median of six blood pressure medications and follow-up at 3 months, showing sustained mean systolic pressure reductions of 22 mmHg (p=0.01) and mean diastolic pressure reductions of 18 mmHg (p<0.01) with no reports of orthostasis or adverse renal events [47].

The Baroreflex Activating System Study (BRASS) was conducted in 2003 at the Department of Cardiovascular Surgery at the University Hospital in Bern, Switzerland [48]. Eleven patients undergoing carotid endarterectomy were enrolled in the study. Under either local or general anesthesia, the carotid sinus was electrically stimulated, allowing acute activation of the carotid baroreflex over a range of clinically relevant intensities. This study demonstrated a reduction in systolic arterial pressure that was directly related to the intensity of stimulation of the carotid sinus. Thus, in this acute setting, activation of the carotid baroreflex produced dose dependent, controllable reduction in arterial pressure.

Stimulation of carotid baroreceptors is associated with heart rate variability and heart rate turbulence changes that are consistent with a decrease of sympathetic activity and an increase of the vagal tone. These changes are correlated with a significant blood pressure decrease. Thus, the data suggest that the modulation of the autonomic nervous system contributes to a better blood pressure control through stimulation of carotid baroreceptors in severely hypertensive patients [49].

**Conclusions**

Resistant hypertension affects a significant number of patients and carries a high risk of cardiovascular events. As such, any novel therapy for blood pressure control deserves our attention. Therapeutic lifestyle modification and intensive drug therapy for these patients have simply proven inadequate, leaving many patients at a drastically elevated risk from the cardiovascular complications associated with uncontrolled hypertension.

The carotid baroreflex represents an essential component of blood pressure regulation. The activation of the carotid baroreflex results in the attenuation of the sympathetic tone and subsequent blood pressure reduction. Carotid nerve activation has been used in the past for the treatment of severe hypertension, but it has been abandoned due to adverse events and several technical disadvantages. Recent technological advances have permitted the development of a new device that electrically stimulates carotid baroreceptors.

Since the current results are promising, further studies are needed to clarify the place of carotid baroreceptor stimulation in the management of patients with resistant hypertension.

**References**


