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Insights into pathophysiology of carotid baroreceptor stimulation as a method for treatment of resistant hypertension

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Abstract

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 applies to patients who are unable to reach the target blood pressure. Patients with resistant hypertension are at a higher risk of cardiovascular morbidity and mortality than those whose hypertension is controlled well. Evidence suggests that baroreceptors play an important role in a long-term blood pressure regulation. Previous studies in animals and humans have demonstrated safe and effective blood pressure decrease with chronic electrical stimulation of the carotid sinus. Electrical baroreflex stimulation appears safe and effective and may be a useful adjunct to medical treatment in patients with resistant hypertension. This review discusses the evolution and patophysiological basis of carotid baroreceptor stimulation as well as the current data available from ongoing trials.

Keywords: resistant hypertension, baroreceptors, carotid baroreceptor stimulation

Introduction

Arterial hypertension (AH) is a major health problem worldwide, with a high prevalence in general population. It is also an important risk factor for cardiovascular (CVD) and renal (RD) diseases. According to WHO data, about 30 - 50% of the adult population suffer from AH. The prevalence of AH in 2025 is expected to rise by 60% (29.2% - 1.56 billion people) from the current 26.4% (972 million people in year 2000) [1, 2].

Hypertension remains a major risk factor for early renal failure, stroke, heart failure and heart attack. The risk of end-stage chronic kidney disease and myocardial infarction is four times higher in persons with systolic blood pressure above 160 mmHg than in those with normal blood pressure, and the risk of developing heart failure is two times higher in persons after the age of forty [3, 4].

Etiopathogenesis of AH

Etiology of these undiagnosed diseases remains to be a major problem in the fight against AH. Today it is well known that many factors play a role in the development of hypertension and therefore we can say that the development of this disease is caused by multiple factors. The ones that may play a role

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in the genesis of essential hypertension can be divided into genetic (predisposition), exogenous-behavioral (obesity, excessive salt intake, physical inactivity, chronic stress, increased alcohol consumption, inadequate nutrition) and endogenous physiological factors (renin-reactivity, cell membrane dysfunction, endothelial dysfunction, prostaglandins function disorder, baroreceptor activity, etc.). There is no direct evidence that AH is a hereditary disease. Previous studies have indicated that 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 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 Tsioufis 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/m^2), 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, nondipping 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 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 drug class [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 cra-

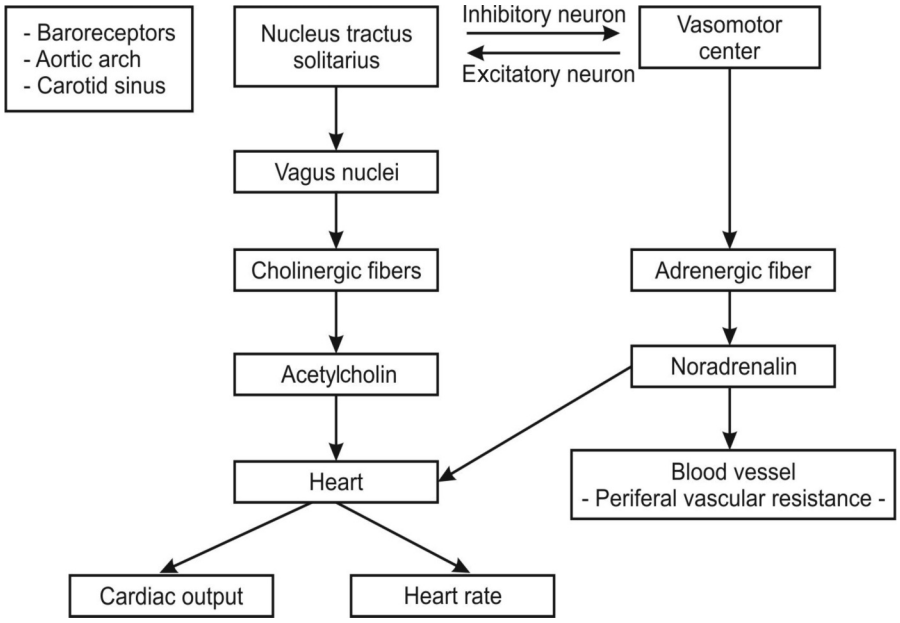

Figure 1. Physiological aspect of the baroreceptors function.

nial 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 antidiuretic hormone, which reduce the intravascular volume and tone [27]. The stimulation of carotid baroreceptors reduces kidney sympathetic tone and thus express their effects [31]. However, on the basis of his experimental work, Lohmeier has suggested that the levels of natriuretic atrial peptide (AMP) are increased under chronic baroreflex activation, which causes enlarged excretion through the kidneys, which in turn reduces the blood pressure [32].

It is thought that disruption of proper functioning of this system is one of the most important factors in essential hypertension. It is assumed that a reduced sensitivity of the mentioned system to normal stimulation, or operatona at a higher sensitivity level, may lead to the increase and maintenance of high blood pressure [1].

Some animal experiments support this hypothesis by showing that when continuously stimulated in arterial hypertension, baroreceptors may fail to lower the blood pressure, which becomes physiological blood pressure but at a higher level [30].

However, some recent studies suggest that the dysfunction of baroreceptors plays a small role in the etiology of hypertension, but can influence the severity of the disease instead [1, 2].

History of baroreceptor investigation

Early studies of the baroreceptor's role in blood pressure modulation date back in 1950's. A study by McCubbin in 1956 investigating the baroreceptor of both normotensive and hypertensive dogs provided early evidence of the firing threshold and showed that a higher pressure was required to elicit baroreceptor function in the hypertensive dogs [33].

Studies in later decades with electrically stimulated canine carotid sinus reported an arterial blood pressure variation that was frequency-dependent and maintained even over a 90 min period of continuous stimulation [34].

In a study published in 1958 Carlsten et al. examined humans undergoing neck/head surgery and confirmed that carotid stimulation did reduce blood pressure in a frequency-dependent manner [35].

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 may be a realistic and necessary alternative. In 2004 Lohmeier examined nor-

motensive 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-adreneric therapy. This theory is supported by experiments conducted by Irwin et al. on anesthetized dogs [40].

Schimidlli 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].

Data from previous studies confirmed efficacy of interventional approach. Blood pressure reduction was noted by using Rheos device [31]. In designed clinical studies in a patients with resistant hypertension was noted the clinical utility and long-lasting reductions in blood pressure with carotid baroreceptor stimulation [43–45]. The relevant and significant reduction in blood pressure was shown in a study with device-based therapy of hypertension (DEBuT-HT) trail, with resistant hypertension [46]. Data suggest that in a period of 3–year's efficacy was recently presented verifying the long-lasting effect of carotid baropacing. However, some preliminary information's from studies suggest that some patient may not respond to the carotid baroreceptor stimulation. It may be considered and the process of selection of patients should be improvement.

Data from an early US trail, the Rheos feasibility trail, 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 barorecteptors 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

The risk of cardiovascular events in patients with resistant hypertension is a high. Nevertheless, as a relatively novel therapy for blood pressure control deserves our attention. In some patients despite therapeutic lifestyle modification and intensive drug therapy blood pressure is a high and in those persons risk from the cardiovascular complications associated with uncontrolled hypertension is a high.

Data suggest that the carotid baroreflex represents an essential component of blood pressure regulation in uncontrolled hypertension. Treatment of severe hypertension with carotid nerve activation has been used in the past decade. 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.

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