Etiopathogenesis of AH

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].

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 pathophysiological basis of carotid baroreceptor stimulation as well as the current data available from ongoing trials.

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 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].

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 become 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 Tsoufis 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 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 anti-diuretic 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].

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 Mc. Cubbin 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 in resistant hypertension has been advocated. The rationale is that persistent baroreceptor stimuli is key to resetting the baroreflex gain. Three clinical approaches are available for the stimulation of baroreceptors: medical, surgical and interventional.

Medical approach in the form of medication and dietary intervention is often used in the early stages of treatment to bring blood pressure under control. Surgery and interventional approaches may be necessary in patients who do not adequately respond to medical or dietary intervention.

Medical approach

Several medications may be used to normalize blood pressure. The choice of medication depends on the patient’s profile and medical condition. In general, antihypertensive drugs work by decreasing the cardiac output, dilating peripheral resistance and increasing the cardiac filling pressure. Baroreceptors play a central role in the modulation of autonomic tone and regulation of blood pressure. When blood pressure is increased, the baroreflex is activated to reduce sympathetic activity and increase parasympathetic activity. This leads to a decrease in heart rate and cardiac output, and an increase in systemic vascular resistance. The ultimate goal of antihypertensive therapy is to normalize blood pressure without causing adverse effects.
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-adreneric therapy. This theory is supported by experiments conducted by Irwin et al. on anesthetized dogs [40].

Schmidli 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 patients 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.

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