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Review

Electrical carotid sinus stimulation in treatment resistant arterial hypertension

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ABSTRACT

Treatment resistant arterial hypertension is commonly defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. The sympathetic nervous system promotes arterial hypertension and cardiovascular as well as renal damage, thus, providing a logical treatment target in these patients. Recent physiological studies suggest that baroreflex mechanisms contribute to long-term control of sympathetic activity and blood pressure providing an impetus for the development of electrical carotid sinus stimulators. The concept behind electrical stimulation of baroreceptors or baroreflex afferent nerves is that the stimulus is sensed by the brain as blood pressure increase. Then, baroreflex efferent structures are adjusted to counteract the perceived blood pressure increase. Electrical stimulators directly activating afferent baroreflex nerves were developed years earlier but failed for technical reasons. Recently, a novel implantable device was developed that produces an electrical field stimulation of the carotid sinus wall. Carefully conducted experiments in dogs provided important insight in mechanisms mediating the depressor response to electrical carotid sinus stimulation. Moreover, these studies showed that the treatment success may depend on the underlying pathophysiology of the hypertension. Clinical studies suggest that electrical carotid sinus stimulation attenuates sympathetic activation of vasculature, heart, and kidney while augmenting cardiac vagal regulation, thus lowering blood pressure. Yet, not all patients respond to treatment. Additional clinical trials are required. Patients equipped with an electrical carotid sinus stimulator provide a unique opportunity gaining insight in human baroreflex physiology.

Contents

1. Treatment resistant arterial hypertension

Arterial hypertension has a high prevalence in many countries and remains among the most important treatable cardiovascular risk factors. Yet, blood pressure control is achieved in an unacceptably small proportion of hypertensive patients (Wolf-Maier et al., 2004). Even in well conducted clinical trials with rigorous dose escalation and addition of antihypertensive drugs, such as the ALLHAT study, approximately one third of the patients did not achieve the blood pressure target of <140/90 mm Hg (Annon., 2002). Commonly, treatment resistant arterial hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal doses (Calhoun et al., 2008). Treatment resistant arterial hypertension is associated with excessive target organ damage including left ventricular hypertrophy, increased carotid intima media thickness, retinopathy, and nephropathy among others (Cuspidi et al., 2001). The mechanisms driving treatment resistant arterial hypertension and

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mediating cardiovascular and renal organ damage are not completely understood. Excessive sympathetic activity and impaired baroreflex regulation are prime candidates.

2. Sympathetic activity and cardio-renal organ damage

Sympathetic activation heralds a poor prognosis in various conditions including heart failure, myocardial infarction, and chronic kidney failure. In patients with different levels of kidney disease severity, the level of sympathetic activation parallels the degree of renal dysfunction (Hausberg et al., 1997; Zilch et al., 2007). Moreover, patients with severe arterial hypertension show the highest sympathetic activity (Grassi et al., 1998). Finally, patients with arterial hypertension show a greater increase in muscle sympathetic nerve activity after myocardial infarction compared with normotensive patients (Hogarth et al., 2006). Sympathetic activation appears to be more than a prognostic "biomarker" in cardiovascular and renal disease. Indeed, attenuation of cardiac sympathetic stimulation through pharmacological beta-adrenoreceptor blockade has been remarkably effective in improving cardiovascular morbidity and mortality in myocardial infarction and in heart failure patients. Similarly, sympatholytic drug treatment attenuates albumin excretion in animals and in patients with diabetic nephropathy (Amann et al., 2000; Strojek et al., 2001). Sympatholytic treatment also prevents glomerulosclerosis in experimental hypertension (Irzyniec et al., 1992). Selective renal sympathetic denervation improves renal failure progression (Hamar et al., 2007), thus, suggesting a direct effect of the sympathetic nervous system on renal failure progression. Indeed, the kidney is densely innervated by autonomic, predominantly adrenergic, efferent neurons (Dibona, 1994). Conversely, electrical renal nerve stimulation in animals increases renin–angiotensin system activity, sodium reabsorption, and renal vascular resistance in a graded fashion. Catheter-based renal sympathetic nerve ablation has recently been introduced as treatment of human treatment resistant arterial hypertension (Schlaich et al., 2009; Esler et al., 2010). Thus, interventions attenuating sympathetic activity are promising in terms of blood pressure reduction as well as organ protection.

3. Baroreflex mechanism in the tonic control of sympathetic activity

Blood pressure increases activate stretch-sensitive baroreceptors in the carotid artery and aortic wall. Counter-regulatory adjustments in sympathetic and parasympathetic activities lead to blood pressure stabilization. Several non-invasive and invasive procedures have been developed to assess baroreflex function in man. Among other methodologies, baroreflex heart rate regulation can be assessed by plotting changes in RR interval over spontaneous or drug induced changes in blood pressure. The relationship provides an estimate of baroreflex sensitivity in the regulation of heart rate. Baroreflex regulation of sympathetic vasomotor tone can be assessed in a similar fashion.

The importance of baroreflex mechanisms in short-term blood pressure control is undisputed. Patients with damage to baroreflex afferents or efferents present with baroreflex failure and autonomic failure, respectively (Ketch et al., 2002; Heusser et al., 2005). The idea that baroreflex mechanisms are also involved in long-term control of sympathetic activity and blood pressure is more controversial. Based on observations in sinoaortic denervated dogs, some investigators suggested that the baroreflex is not involved in long-term arterial blood pressure control (Cowley et al., 1973). Indeed, the baroreflex was thought to reset almost completely to the prevailing arterial blood pressure level, which would exclude a chronic effect on sympathetic activity and blood pressure. However, these animals were housed under somewhat artificial conditions with minimal sensory input. In another study, sinoaortic denervation produced sustained arterial hypertension in approximately 75% of the operated rats (Krieger, 1964). Another possible explanation for the discrepant results is that carotid chemoreceptor afferents may be spared in some but not all studies, which strongly affects the hemodynamic response to baroreceptor denervation (Van Vliet et al., 1999). In a more recent study in dogs, baroreceptors in the aortic arch and one carotid sinus were denervated. Baroreceptor unloading was induced by ligation of the common carotid artery proximal to the innervated sinus. The procedure elicited a chronic increase in blood pressure (Thrasher, 2002). Together, these observations suggest that baroreflex mechanisms contribute to long-term blood pressure regulation and, possibly, affect cardiovascular and renal structure and function.

4. Electrical carotid baroreceptor stimulation

The concept behind electrical stimulation of baroreceptors or baroreflex afferent nerves is that the stimulus is sensed by the brain as blood pressure increase. Then, baroreflex efferent structures are adjusted to counteract the perceived blood pressure increase. Sympathetic activity and blood pressure are reduced. Electrical stimulators directly activating afferent baroreflex nerves were developed years earlier but failed for technical reasons (Parsonnet et al., 1969; Rothfeld et al., 1969; Peters et al., 1980). In particular, the electrode design and the electrical stimulation mode led to side effects, such as muscle spasms and local pain. Moreover, there have been concerns regarding possible impairments in renal function associated with electrical baroreflex stimulation in dogs (Neistadt and Schwartz, 1967).

Recently, a novel implantable device was developed that may overcome some of these problems (Mohaupt et al., 2007; Tordoir et al., 2007; Scheffers et al., 2010). The device produces an electrical field stimulation of the carotid sinus wall. During surgical implantation, both carotid arteries are exposed. Then, the electrodes are placed around the adventitia to putative carotid baroreceptor areas. Electrode position is adjusted to obtain optimal blood pressure reduction during intraoperative stimulation. Intraoperative testing is complicated by the fact that anesthetics may modulate sympathetic activity, thus, interfering with electrical stimulation. An experienced interdisciplinary team including surgeons and anesthetists is tantamount. In patients responding to intraoperative stimulation, the electrodes are sutured in place. Then, the pacemaker wires are tunneled subcutaneously to the right chest wall where the pacemaker device is placed in a subcutaneous pocket (Tordoir et al., 2007). Following implantation, patients recover for one month before the stimulator is switched on. First, patients undergo dose–response testing as indicated above such that an optimal blood pressure reduction is achieved without side effects, such as cough, local pain, or muscle contractions. Then, the stimulation is continued in this mode (typically 100 Hz continuous bilateral stimulation, <7 V). In some patients, the stimulator settings are changed later on (e.g., burst mode or unilateral stimulation).

As described above, the first generation carotid sinus stimulators apply electrical impulses bilaterally using an electrode that is wrapped around the carotid sinus. Electrical impulses are transmitted by means of a tripole consisting of one central cathode and two lateral anodes. The distance of the anodes approximates the size of the carotid sinus. Second-generation devices are under clinical development (www.cvrx.com). To simplify surgery, these devices rely on unilateral carotid sinus stimulation. The carotid-sinus electrode is 6 mm in diameter and serves as the cathode. The pulse generator functions as the anode. Because of the small electrode size and its direct application to the carotid sinus wall without vessel mobilization the surgical procedure is further simplified. However, published data in animal models and clinical studies have mainly been conducted with the first generation carotid sinus stimulator.

5. Preclinical experience in animal models

Carefully conducted experiments in dogs provided important insight in mechanisms mediating the depressor response to electrical carotid sinus stimulation. Moreover, these studies showed that the