RESISTANT HYPERTENSION: THE ROLE OF INTERVENTIONAL THERAPY

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RESISTANT HYPERTENSION: THE ROLE OF INTERVENTIONAL THERAPY (Abstract): Resistant hypertension still represents a major health problem, incompletely resolved by the current therapeutic interventions. Based on the interference of sympathetic overactivity in resistant hypertension, novel invasive strategies such as sympathetic renal denervation and carotid baroreceptor stimulation have recently emerged. Despite the promising results and their good tolerability profile, the optimal role of these non-pharmacologic therapies relative to conventional medical regimens, remains unknown. Further investigation is also necessary to establish their real long-term efficacy and safety in clinical practice. Keywords: RESISTANT HYPERTENSION, INTERVENTIONAL THERAPY, SYMPATHETIC OVERACTIVITY, RENAL DENERVATION, BARO-REFLEX STIMULATION.

Arterial hypertension is one of the most common worldwide diseases of this century, characterized by an alarming percentage of patients with uncontrolled blood pressure (BP) values. It was estimated that 25% of adult population had arterial hypertension in 2005, and this figure is predicted to rise to 1,5 billion by 2025 (1). There is a linear relationship between BP and cardiovascular risk, accounting for 13.5% premature deaths, 54% of all cases of stroke and 47% of ischemic coronary events in worldwide statistics (2, 3). Despite the availability of various effective antihypertensive agents, target BP is not achieved in a large number of subjects.

In current guidelines, arterial hypertension is defined as resistant to treatment when the concurrent use of at least three antihypertensive drugs (mandatory a diuretic) in appropriate schemes and at maximum doses fails to optimally lower BP (4). The target values are different according to the type of hypertensive patient: < 140/90 mm Hg in general or < 130/80 mm Hg in high risk hypertension (diabetics, patients with chronic renal or ischemic coronary disease etc). The importance of the phenomena is highlighted by the prevalence of 15-20% reported in literature (5). In fact the prevalence of resistant hypertension ranges from 5% to 50% depending on the studied population or hypertension centre. For this reason the exact prevalence is difficult to determine (6-9). The direct consequences of raised BP values, respectively the significant percentage of target organ damage and particular metabolic profile, set patients at high risk for major cardiovascular events, thus making resistant hypertension a clini-
In clinical practice, the workup of suspected resistant hypertension involves the following steps (11):

1. to prove failure in controlling BP values irrespective of the type of measurement used: office BP, home BP or 24-hour ambulatory monitoring;

2. to differentiate true resistant hypertension from pseudoresistance caused by BP measurement artifact, white-coat effect, physician inertia, pseudohypertension, poor patient adherence to prescribed therapy because of lack of education/information or treatment regimen (inappropriate/unaffordable combinations, frequent changes in therapeutic scheme, adverse effects, high cost of medication);

3. to establish the potential causes of resistance related to:
   a. medication: inadequate diuretic therapy, drug interaction (non-steroidal anti-inflammatory, corticosteroids, anabolic drugs, erythropoietin, oral contraceptives, cyclosporin, tricyclic antidepressants sympathimetics, cocaine, amphetamines etc), inappropriate combinations/dosing, rebound effect (e.g. for clonidine), adverse effects (reflex vasoconstriction, hydro-saline retention);
   b. comorbid conditions: excessive salt intake > 10 g/day, alcohol abuse, smoking>20 cigarettes/day, chronic renal disease, obesity, diabetes mellitus, sleep apnea, elderly, panic attacks, chronic disease causing pain) or ignored secondary causes of hypertension, most common renal parenchymal/renovascular disease, primary aldosteronism.

Along these lines, hypertension can be considered as true resistant and treated according this judgment only after completing the previous analysis. The complex therapeutic schemes and the new classes of antihypertensive drugs are the common option for treatment. However, it is believed that about 10% of patients will continue to be resistant although on 6-7 antihypertensive drugs (12). According to the current recommendations, if arterial hypertension was labeled as true resistant to treatment and subsequent therapy was correctly and completely applied (first and second steps), interventional therapy, which represents the third step, can be considered (13).

PHYSIOPATHOLOGICAL BASIS FOR INTERVENTIONAL THERAPY

The interference of sympathetic overactivity, which is shown to be present in most cases of resistant hypertension with no secondary cause, is fundamental for developing the interventional concept (14). Based on the demographic data of Framingham and ALLHAT studies, a particular "phenotype" in resistant hypertension is suggested, in which older age, obesity, aldosterone excess and obstructive sleep apnea are covering most part of patients characteristics. It is well documented that sympathetic nervous system (SNS) activity increases with aging, especially in skeletal muscles (15). Second-ly, aldosterone excess, obesity, and obstructive sleep apnea are not only common comorbid conditions in resistant hypertension, but also mechanisms which actively interact. Although not fully elucidated, SNS activation may be a major contributing factor to these interactions.

By using sophisticated techniques for the measurement of sympathetic nerve fibers activity or excess plasma norepinephrine, it was clearly documented that in normotensive obese patients efferent sympathetic fibers to the kidneys and skeletal muscle vasculature are overactive, normal to the skin and hepatomesenteric circulation, and
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reduced to the heart. In obese hypertensive patient this kind of heterogeneity is depressed, while the suppression of cardiac efferent sympathetic fibers disappears. It is the visceral adipose tissue distribution that seems to be crucial for SNS activation (16). The discussed mechanisms are extremely complex, including high plasma leptin concentration, hyper-insulinemia, decreased arterial baroreflex sensitivity, but also bidirectional interaction with renin-angiotensin-aldosterone system (RRAS) which promotes inflammation, endothelial dysfunction, arterial stiffness (16-18). The increased variability of BP is the consequence of arterial stiffness, but is also a clinical marker for intensive sympathetic traffic, with negative impact on prognosis (19).

Obstructive sleep apnea, common in obesity, is also independently related to the occurrence of resistant hypertension. Although the mechanisms are elusive, the causal relationship between sleep apnea and SNS overactivation in skeletal muscle is postulated. Sympathetic stimulation during sleep and transient hypoxemia would provide the causal connection. The data are pertinent for hypoxemia, which is clearly involved in tonic chemoreflex activation of sympathetic inflows. The up regulation of endothelin A and angiotensin II receptors in the carotid body by hypoxia supports the role of these molecules as peripheral chemoreceptors and central neuromodulators (20-22).

Aldosterone excess has a reported prevalence of 17-22% in resistant hypertension (23), and the mechanism of SNS activation is becoming increasingly clear. It is experimentally documented that mineralcorticoid receptors in the paraventricular nuclei are closely linked to central sympathetic overactivity (24, 25).

![Fig. 1. Effect of SNS on BP regulation (adapted from 12). RBF – renal blood flow, GFR – glomerular filtration rate, NE – norepinephrine, Aldo – aldosterone, Ang II – angiotensin II](image-url)
The role of renal sympathetic nerves lying in the adventitia of renal arteries is crucial for SNS activation. Efferent sympathetic fibers from the central nervous system activate the RRAS in juxtaglomerular apparatus of the kidneys via $\beta_1$-adrenergic receptors, resulting in renin release. There is a concomitant direct stimulation of sodium and fluid reabsorption via $\alpha_2$-adrenergic receptors, followed by renal vasoconstriction and a consecutive reduction in renal blood flow. Efferent sympathetic activation is linked to the development of insulin resistance, responsible for hyperinsulinemia and metabolic syndrome in over 50% of cases with resistant hypertension. At the same time, afferent sympathetic fibers maintain the central nervous system stimulation with subsequent vasoconstriction, direct structural and functional cardiac effects, hepatic gluconeogenesis (12) (fig. 1).

**SYMPATHETIC RENAL DENERVATION**

The sympathetic innervations of the kidneys are achieved through a dense network of postganglionic neurons which arise from the dorsal root T10-L1. The postganglionic nerves run alongside the renal arteries and penetrate the cortical and juxta medullary areas. The activation of these nerves is responsible for deleterious effects on renal hemodynamics. Renal afferent sensory nerves derive from renal pelvis and contain mechanoreceptors which respond to stretch and chemoreceptors which detect renal ischemia, hypoxia and other chemical injuries. From kidneys, the signal travels to the dorsal root ganglia T6-L4 and hypothalamus, area responsible for vasopressin and oxytocin release with subsequent modulation of BP level and vascular resistance (26). Electrical stimulation followed by BP elevation, mesenteric ischemia and muscle vasoconstriction is a model for afferent sympathetic fibers action. Conversely, renal afferent sympathetic denervation attenuates the effects, delays or prevents arterial hypertension in several experimental models (13).

In 1930, the overcoming of renal sympathetic stimulation consequences is first reported.

Supradiaphragmatic splanchnicectomy or radical surgical sympathectomy was applied as the last therapeutic options for malignant hypertension, resulting in over 70 mm Hg decrease of BP (12). Despite the spectacular results observed in more than 1000 hypertensive patients, including a parallel improvement of target organ damage, the surgical technique was driven to total obscurity due to severe postoperative complications (27). However, the concept was then developed in experimental studies.

The current therapeutic option is interventional renal denervation, a minimally invasive percutaneous procedure characterized by a fast effect on BP level and absence of significant systemic adverse effects (13, 26, 27). The technique requires renal angiography to assess anatomic eligibility for the procedure and to exclude renal artery stenosis. Denervation is performed using a special flexible catheter (Simplicity TM Catheter System, Ardian/Medtronic Inc.) placed into the distal segment of renal artery, and connected through its proximal end to a radiofrequency generator for ablation (27, 28). Bilateral percutaneous denervation can be accomplished in about 40-60 minutes, after at least six ablations for each renal artery (fig. 2).
The clinical efficacy of the procedure has been proven in Symplicity Hypertension trials (HTN-1 and HTN-2) (29-31). In HTN-1 trial which included 45 patients with resistant hypertension on 5-6 antihypertensive drugs, percutaneous renal denervation induced a progressive and sustained BP decrease. After two years, mean BP was reduced by 32/14 mm Hg. The procedure was considered safe, with no complications in 97% of patients, and stable renal function. HTN-2 trial assessed 106 patients and demonstrated similar rates for BP reduction (by 32/12 mm Hg) at 6 months, with no apparent change in renal function or other significant complications.

For several reasons, the open question remains estimation of long-term procedural efficacy. First of all, renal reinnervation phenomena have been observed in experimental models, and this may attenuate procedural effect (12, 32). Secondly, ambulatory BP monitoring was performed in a limited number of patients in HTN-2 trial, and showed no significant reductions compared to office or home measurements (13). Cardio-circulatory adaptation to exercise is another problem to be evaluated, taking into account the unclear response of these patients and because SNS functional integrity is required. Finally, estimation of the benefit on cardiovascular risk may be necessary, assessing target organ damage outcome, metabolic profile, major cardiovascular events and mortality.

A successful method is subject to compliance with the eligibility criteria. The main criteria for an appropriate application of the method are an accurate practice of the first two steps for analysis and treatment of resistant hypertension, pre-procedural renal artery imaging for assessment of anatomic contraindications (e.g. CT or magnetic resonance renal angi-
A complete sympathetic denervation is also necessary for the procedural success. From this point of view, any preprocedural efficient marker is currently missing and this could be the answer for some patients which are "nonresponders" or experience an unsatisfactory response. (33). Recently, Steigerwald and coworkers have conducted a morphological assessment of renal arteries after denervation in a porcine model. The authors have proposed optical coherence tomography imaging as a useful method for assessment of postprocedural success and immunostaining technique for neurofilament proteins detection as a relevant surrogate marker for postprocedural nervous viability (34). Finally, it is recommended the method to be performed only in very experienced centers.

A current requirement of experts is comparison of the classic method with different promising experimental procedures. It is about sympathetic denervation performed by local delivery of neurotoxic drugs, cryoablaction, ultrasound-induced denervation or using different catheters (Ablation Induced Renal Sympathetic Denervation Trial study) (35). Furthermore, it is currently experimented the effect of local circumferential drugs delivery (guanetidine is the ideal agent) in adventitia of renal artery by using a special balloon catheter (Cricket™ and Bullfrog® Micro-Infusion Catheter), in order to precisely reduce renal sympathetic overactivity without harming SNS in other territories. The authors consider the multiple advantages of this method: removal of adverse drug effects, increase of therapeutic effectiveness, and improvement of patient outcomes and prognosis with concomitant decrease of medical costs (36). The method provides the perspective for treating other different hypertensive patients, including young hypertensive or patient with heart failure and chronic kidney disease (26).

**BAROREFLEX STIMULATION**

There are many neurohumoral reflexes which regulate the neural feedback mechanism of circulation. The arterial baroreflexes from aortic arch and carotid sinus adventitia play a key role in the short-term control of mean BP level, heart rate and contractility, vasomotor tone. Signals to the nucleus tractus solitarius and parasympathetic stimulation are the mechanisms involved. However, the long-term mode of action is less clear. First experimental studies have observed that baroreceptor response gradually diminishes (over minutes to days) in the face of a sustained increase in BP by "blunting" the reflex response. Although a minimal interference in chronic BP modulation has been postulated, it has been recently suggested that baroreceptors may have a substantial role by modulating renal salt excretion and, consequently, systemic fluid balance. Therefore, prolonged baroreflex activation may be responsible for BP sustained fall (36-38). Preliminary experimental studies conducted to reveal how baroreceptors function is restored, showed that carotid sinus stimulation (interpreted by the brain as a rise in BP) leads to BP decrease and reduces plasma NE level (39).

This principle has been applied in clinical practice by using a system that works in a similar fashion to a pacemaker (The Rheos CVRx Baroreflex Hypertension Therapy System). The device consists of a pulse generator which delivers activating energy of 1-7.5 V, connected to two electrodes, one for each carotid sinus, and a program-
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The pulse generator is surgically implanted below the right clavicle (40). Recently, in Europe, a second generation miniaturized implantable system has been approved (Barosim neo™ CVRx) (fig. 3).

![Image of implantable baroreflex stimulators for resistant hypertension](adapted from 40)

The first clinical results have been reported by two prospective, phase II studies conducted in Europe (DE-BuT-HT) and USA (US Rheos Feasibility Trial), which documented a mean five-year decrease of BP by 53/30 mm Hg, left ventricular hypertrophy regression, and one-year renal function preservation (41-43). The beneficial results are confirmed by the recent Rheos Pivotal trial report (2011), a double-blind, randomized, prospective, multicenter, phase III clinical study of 265 patients with resistant hypertension. The trial shows a sustained drop in BP after 12 months (88% responders), the safety of method and used device. It appears that at least 6 months are necessary for achieving a sustained effect, and some procedural adverse events can occur. Simultaneously, a multicenter European study conducted by Scheffers and coworkers also demonstrates a more consistent decrease of BP measured by ambulatory monitoring, by 24/13 mm Hg after two-years of treatment, compared to renal
denervation (44).

RESPeRATE® system is another type of device approved by FDA as an adjunctive therapy in resistant hypertension. The principle is based on slow and deep breathing ("paced breathing") as a trigger for baroreflex/cardiopulmonary receptors stimulation, increase of central inhibiting rhythms or decrease of chemoreceptors sensitivity (36). The direct consequence is modulation of sympathetic traffic and BP level. The system can be used in daily sessions (45 minutes per week) in order to achieve a decrease in breaths number to < 10/min. The beneficial effect has been documented in seven prospective studies, eight weeks of treatment being necessary for achieving this goal. A larger reduction in BP was observed in older patients and those with higher baseline BPs. This therapy can be combined with other pharmacologic or non-pharmacologic interventions (36).

A growing number of studies also support the significant antihypertensive effect of isometric exercises (e.g. isometric hand-grip). The medical literature confirms the benefit on BP decrease after 4-8 weeks, the modulation of muscle sympathetic nerve and autonomic nervous system activity and stimulation of reactive oxygen species being involved (36). Zona PlusTM device has been designed to guide this kind of exercises, recommended to be performed in 12-minute sessions, at least three times weekly. Three randomized studies assessed the effect after at least 4 weeks of treatment and showed a mean BP decrease by 13.6/6.1 mm Hg. It appears that the effect acts in a linear fashion, with no side events (36).

In conclusion, in resistant hypertension, interventional therapy decreases sympathetic stimulation by specific mechanisms depending on each method and involves
direct, beneficial and sustained consequences on BP level, with no notable complications. Current results should be judged with caution taking account of multiple open questions in this early phase. However, the perspective for interventional methods to be used as an effective and well tolerated alternative, and also less long-term expensive for medical system, exists. Systematic and long-term follow-up of a large number of patients with resistant hypertension are the targets for new trials in progress such as Simplicity HTN-3, Global Symplicity Patient Registry or GREAT (German Renal Denervation) in order to settle the current dilemmas (26).

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A PROTEIN IS LINK TO SEXUALLY TRANSMITTED INFECTIONS SUSCEPTIBILITY

The sexually transmitted infections (STI) caused especially by chlamydia and herpes simplex virus that affects the young population, predominantly female, are a global health problem. Into a study on mice, Prof. Hertzog and his team have revealed a protein called interferon epsilon (IFN-ε) with a protective effect against the viral and bacterial STI. IFN-ε is an unusual type I IFN because it is not induced by immune cells after contact with a virus or bacteria, by known pattern-recognition receptors pathways. The IFN-ε is a constitutively cytokine produced by epithelial cells of the female reproductive tract and is hormonally regulated, with the variables levels during menstrual cycle but in pregnancy and menopause with his absence. The authors of study finding that the deficit of IFN-ε is associated with increased susceptibility to STI. “Because IFN-ε follows different rules of normal immunomodulatory proteins, it might be an important link to new therapeutic opportunities for STI”, noted authors of the study (Fung KY, Mangan NE, Cumming HJ et al. Interferon- Protects the Female Reproductive Tract from Viral and Bacterial Infection. Science, 2013; 339: 1088-1092).

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