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Review

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Treating arterial hypertension: from guidelines to physiology and back again – the issue of increased sympathetic drive

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Abstract

In the era of evidence-based medicine, the current European Society of Cardiology (ESC) guidelines for the management of arterial hypertension rely on results from randomized clinical trials. The 2018 version aims to simplify the management of hypertensive patients and generally recommends the combined use of a renin-angiotensin-aldosterone system inhibitor and a calcium channel blocker or a thiazide-like diuretic as first-line therapy. Drugs targeting the increased sympathetic drive are only recommended if the combination of all three drug classes fail to provide adequate control of blood pressure values. Although beta-blockers are still prescribed in hypertensive patients who have coronary artery disease and/or heart failure, alpha-blockers are seldom used. However, the sympathetic drive is an important link in the pathophysiology of arterial hypertension, raising the question whether some patients may obtain additional benefit from sympathetic inhibition.

Keywords: Hypertension, sympathetic drive, α-blockers.

Introduction

Over the last three decades, the treatment of arterial hypertension entered the era of evidence-based medicine. Accordingly, all recommendations are based on results from randomized clinical trials, which strived to demonstrate the benefit of various drug classes on morbidity and mortality rates. The current European Society of Cardiology (ESC) guidelines on the management of arterial hypertension provide a synopsis of these trials and recommend the combined use of a renin-angiotensin-aldosterone system inhibitor and a calcium channel blocker or a thiazide-like diuretic as first-line therapy [1]. Each of these drug classes targets a certain pathophysiological mechanism of arterial hypertension, and their combined use increases the probability of an adequate therapeutical response. However, some patients do not even respond to triple-drug therapy (including a diuretic) and are labeled as hav-

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ing resistant hypertension. In this population, further evaluation, as well as the addition of a fourth drug class are warranted, based on the premise that aldosterone inhibition is not sufficient (thus the recommendation to add spironolactone) or sympathetic drive is extremely elevated (and then beta- and alpha-blockers can be added). The purpose of this manuscript is to discuss the contribution of increased sympathetic drive in the pathophysiology of hypertension and the possibility of patient-tailored therapy.

The role of the sympathetic nervous system in the development of arterial hypertension

Sympathetic overactivity has been observed in all stages [2], clinical forms [3], and patterns of essential hypertension. Also, it has been observed in secondary hypertension (HTN), irrespective of the cause [4], and its activity is correlated to the degree of blood pressure (BP) rise, supporting the hypothesis that it precedes the appearance of HTN in a cause-effect relationship. The increase in the sympathetic drive is not only due to changes in peripheral synapses and receptors number and function [5], but it is mainly due to central sympathetic activation.

The increased central sympathetic activity occurs due to disinhibition of reflex centers in the medulla in response to input from arterial baroreceptors, humoral changes (angiotensin II, leptin, insulin), and blood osmolarity.

Although baroreflexes are mainly involved in acute beat-to-beat blood pressure regulation, chronic unloading of arterial baroreceptors (either due to increased salt intake [6] or structural changes in the vessel wall [7]) causes a higher pressure operating set-point, with an increase in sympathetic activity. This information is integrated at the solitary tract nucleus, caudal ventrolateral medulla and rostral ventrolateral medulla. These are also the areas where angiotensin acts to cause sympathoexcitation [8], modulation of baroreflexes being one of the mechanisms. Nevertheless, the sympathetic stimulation of angiotensin II is complex and at multiple sites, one of which is the paraventricular nucleus, where it binds to the AT-1 receptors. Here it increases the glutamatergic input and this mechanism is involved in hypertension pathogenesis [9]. Information from renal mechano- and chemoreceptors such as reduced renal blood flow and hyponatremia is also transferred to the paraventricular nucleus causing an increase in sympathetic activity [10].

Moreover, sympathetic overactivity is not only a cause for cardiovascular and metabolic disorders, but also their consequence, in a vicious circle. For example, sympathetic activation has been observed in obese patients, and one of the proposed mechanisms is hyperleptinemia [11]. Leptin binds to specific OB receptors to finally stimulate the paraventricular nucleus to promote satiety, causing a simultaneous sympathetic outflow, which is one of the links between obesity and hypertension [12]. There is also evidence of an interrelation between hyperinsulinemia and overactivity of the sympathetic nervous system, mediated by increased neuropeptide Y neurons function with an excitatory effect on the paraventricular nucleus through the arcuate nucleus [13].

Finally, sympathetic overactivity causes increased postsynaptic noradrenaline release, mainly in the heart, skeletal muscle blood vessels and kidneys, not only causing arterial hypertension but also setting the ground for a positive feedback loop. Its consequences are left ventricular hypertrophy [14], endothelial dysfunction [15], increased arterial stiffness [16], renal vasoconstriction with salt and water retention [17], renin-angiotensin system activation, further hyperinsulinemia, and insulin resistance. These phenomena overamplify sympathetic nervous activity, leading to hard-to-treat hypertension.

Sympathetic drive targeted therapy

The standard therapy of hypertension, as directed by current guidelines, relies on the one-size-fits-all paradigm. This simplified and pragmatic approach is supported by evidence from multiple clinical trials endorsing the use of angiotensin-converting enzyme (ACE) inhibitors, sartans, diuretics and calcium channel blockers, which not only provide adequate blood pressure control but reduce morbidity and mortality rates in hypertensive patients, while having rare and usually mild, easily tolerated, side effects [1].

By contrast, drugs targeting increased sympathetic drive are underused, mainly due to more unwanted side effects and the apparent lack of benefit for preventing cardiovascular disease [18].

However, in some categories of patients, the standard therapy including a combination of renin-angiotensin-aldosteron inhibitors, calcium channel blockers, and a diuretic (usually thiazide or thiazide-like drug) does not provide adequate blood pressure control. These patients are considered to have resistant hypertension, and this finding warrants further investigation and the addition of a fourth drug class, which may include an antialdosteronic agent, beta- or alpha-blockers [1].

In the PATHWAY-2 trial, which compared spironolactone, bisoprolol, and doxazosin as fourth-line drugs in the treatment of arterial hypertension, spironolactone therapy yielded the best results, suggesting that increased sodium retention was the

main cause of resistance to treatment [19], rather than increased sympathetic tone.

However, some patients do not respond to the addition of spironolactone or eplerenone. Refractory hypertension is defined as the lack of response to the administration of ≥5 drugs belonging to different classes, including a diuretic and a potassium-sparing drug [19]. In the study of Acelajado *et al.*, patients with refractory hypertension and those with resistant hypertension which responded well to treatment with antialdosteronic drugs had similar aldosterone levels and plasma renin activity [20], thus suggesting that treatment failure was due to other mechanisms. Moreover, in the study by Dudenbostel *et al.*, 24-hr urinary normetanephrine levels were significantly higher in patients with refractory hypertension compared to patients with controlled resistant hypertension, while urinary aldosterone and cortisol excretion were not different between the two groups [21]. Consequently, the increased sympathetic drive is a likely cause for the lack of response to treatment in some populations. Also, the main risk factors for refractory hypertension include higher body mass index, reduced estimated glomerular filtration rate, albuminuria, diabetes mellitus, and coronary heart disease [22], all correlated with increased sympathetic drive [11-14, 21, 23, 24].

Accordingly, the rational approach in these patients would be to use sympathetic system-targeted therapy. To that purpose, surgical and interventional procedures, as well as pharmacological therapy, have been developed over the years.

Renal sympathetic denervation

The role of sympathetic signaling between the central nervous system and the kidneys in maintaining increased BP values is well known [17]. Consequently, over the last hundred years, attempts have been made to break this connection.

One of the first attempts to reduce BP by alleviating central sympathetic control over the kidneys was surgical renal denervation, first performed to that purpose in the 1930s on a 25 years old woman with severe hypertension. Although the expected drop in BP did not occur after the procedure, there were no immediate or later complications [25].

Since 1935 and into the 1960s, sympathectomy was further developed and shown to increase survival rates in hypertensive patients with cardiovascular disease but caused invalidating side effects, such as postural hypotension and even syncope [26]. Eventually, it was abandoned in favor of pharmacological therapy.

However, the idea of targeting the nervous sympathetic afferent fibers to the kidney was preserved and later used for developing minimally invasive procedures.

Renal sympathetic denervation is a minimally invasive procedure that aims to decrease the renal afferent and efferent sympathetic activity by radiofrequency ablation of renal nerve fibers located in the renal artery's adventitia [27]. Although a painful procedure that requires analgesia and anesthesia, renal sympathetic denervation initially showed promise [27], but further studies led to conflicting results, and a definite conclusion was impossible to achieve.

The open-label Simplicity HTN-1 and HTN-2 trials demonstrated the safety of radiofrequency ablation of renal sympathetic afferent and efferent fibers, and a significant drop in BP compared with the baseline values has also been documented [28]. Unlike its predecessors, however, Simplicity HTN-3 was a single-blind study – patients in the control group underwent a sham procedure. The largest trial at that point, Simplicity HTN-3, randomized 535 patients with resistant hypertension in a 2:1 ratio - 364 patients being assigned to the renal denervation group and 171 to the sham procedure group. Surprisingly, after 6 months of follow-up, there was no significant BP lowering in the renal denervation group [29]. The similar results reported in another sham-controlled trial (ReSET) seemed to endorse skepticism [30].

Another open-label trial - The Renal Denervation for Hypertension (DENERHTN) trial [31] showed increased efficacy in BP-lowering in the renal denervation group vs. the optimal medical treatment-only group. In contrast, the PRAGUE-15 trial yielded no significant difference in similarly designed groups, but with an increased incidence of side effects in the group treated with optimal medical therapy (including spironolactone) [32].

Consequently, despite extensive efforts, a definite conclusion regarding the use of sympathetic renal denervation has not been reached. Furthermore, a trial that would alleviate all confusion would be difficult to conduct considering that the pathophysiology of hypertension is complex, there is currently no method by which complete renal denervation can be certified, and there are no clinically applicable methods of measuring sympathetic activity [33]. Also, compliance with adequate lifestyle changes that may influence response to treatment is challenging to assess and might be uneven across a study population.

The pharmacological approach to increased sympathetic drive

Medication addressing the increased sympathetic drive is often the last resort in most patients with hypertension due to either limited ability to lower blood pressure or side effects.

Beta-blockers, for instance, are rather poorly tolerated by patients, therefore treatment is often disrupted [34], and these agents are associated with significant side effects, such as poor glycaemic control in patients with abnormal glucose metabolism [35] and abnormal lipid levels [36]. When administered in primary prevention, beta-blockers increase the risk of cardiovascular events, including acute myocardial infarction and stroke [37, 38], particularly in diabetic patients, as documented in a subanalysis of the ACCORD trial [39]. Therefore, although potentially useful for people with increased sympathetic drive, they should be used in patients in which the benefits outweigh the risks, such as patients with confirmed coronary artery disease or heart failure.

Another option is alpha-blockers, which are also seldom used to treat patients, again because of multiple and rather poorly tolerated side effects, as well as modest antihypertensive effects for some agents included in this class [40]. Moreover, prolonged use of alpha-blockers is associated with an increase in sodium and water retention; when used, a diuretic should also be associated [41].

Central acting agents can also be used to suppress sympathetic drive. Clonidine and α-methylnoradrenaline belong to the first generation of central sympathetic nervous system inhibitors. These agents act directly on the α-2A-adrenoreceptor located on the interneuron containing gamma-aminobutyric acid in the rostral ventrolateral medulla [42], as well as on imidazoline receptors, to which they bind with equal affinity [43]. However, in clinical practice, these drugs are seldom used due to their short half-life and serious side effects such as sedation, dry mouth, and rebound when treatment is discontinued [44]. Interestingly, it seems that side effects are mostly due to activation of α2-adrenoreceptors [43]; for instance, sedation occurs as a consequence of α2-adrenoreceptors activation, inhibiting the activity of locus coeruleus neurons involved in arousal [45].

By contrast, the second generation of central sympatholytics, including minoxidil and rilmenidine, have a higher affinity for imidazoline I1 receptors, inhibiting presynaptic norepinephrine release [42]. These receptors are significantly present not only in the rostral ventrolateral medulla but also in the nucleus of the solitary tract [46]. Although less effective in lowering BP compared to clonidine, the lower affinity of rilmenidine for the α2-adrenoreceptors makes it preferable for treatment as it has milder side effects [41, 47], in addition to having a more prolonged half-life.

Conclusion

Although often seen as a last resort, targeting the sympathetic nervous system can be a viable solution for patients with refractory hypertension who have an increased sympathetic drive. Centrally-acting imidazoline receptor blockers may provide satisfactory BP-lowering with few, if any, notable side effects. Further research is needed for demonstrating the utility of renal sympathetic denervation, provided that a valid method for defining procedure success is found.

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Conflict of Interest

The author confirms that there are no conflicts of interest.

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