Current Management Strategies for Neurogenic Hypertension

Subjects: Cardiac & Cardiovascular Systems

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Hypertension is a significant risk factor for renal impairment, other cardiovascular diseases, diabetes mellitus, and multiple end-organ damages. Nevertheless, a large pool of recent studies affirms a relatively higher incidence of sympathetic nerve activity (SNA) (as indicated by high levels of norepinephrine and plasma catecholamines) in hypertension unresponsive to conventional treatment, which is also referred to as resistance hypertension or neurogenic hypertension (NH). This strong association between an increase in SNA and elevated blood pressure (BP) forms the basis of NH: a form of hypertension mainly driven by a sympathetic mechanism. The complex nature of NH makes curative treatment difficult. Therefore, the current therapeutic approach to tackling NH aims at bringing BP under control to prevent any cardiovascular events and associated end-organ damage. In addition, surgical procedures that have been explored for NH management interfere with the sympathetic influence on cardiac function. Although several surgical approaches were adopted, only a few progresses toward preclinical stages and still lead to inconclusive outcomes. Both therapeutic and surgical approaches that have been implemented for the management of NH will be briefly discussed.

Keywords: nanotherapeutics ; neurogenic hypertension ; polymer-based nanoparticles

1. Clinical Management—A Cocktail of Antihypertensive Combination Therapy

The primary consideration for managing NH is to prevent end-organ damage [1][2]. Before drug therapy is initiated, non-pharmacological measures are recommended to reduce BP. Lifestyle modifications such as exercising, reducing alcohol and sodium consumption, and ceasing cigarette smoking improve BP control [3][4]. In addition, some dietary components, such as bamboo shoot extract, have shown significant inhibition of ACE and could have a beneficial effect in lowering BP [5][6]. Monotherapy is the recommended therapeutic approach for managing early-stage hypertension. Yet, the lack of sufficient guidance to clinicians on options for individualizing therapies makes drug choice a significant concern, especially in managing NH. In addition, current knowledge cannot confirm if the available therapeutics for hypertension management can impact central sympathetic outflow associated with NH.

Despite the abovementioned fact, combination therapies have become the primary practice for controlling elevated BP in NH patients [7][8]. Usually, a combination of three drug classes (and a stepwise addition of a fourth antihypertensive if BP remains elevated) is often prescribed, which include at least a diuretic, an angiotensin receptor blocker (ARB), and/or ACE inhibitor [7]. However, studies of ARBs show they do not reduce sympathetic nervous outflow in NH when administered alone. Even in some cases, they may augment central neural vasoconstrictor outflow with increased plasma norepinephrine levels [9][10]. On the contrary, a study found that adding valsartan (an ARB) to an ACE inhibitor improves cardiac SNA [11]. However, the current treatment guideline does not recommend combining an ARB with an ACE for hypertension management due to the likelihood of causing renal failure [12]. The American heart association makes several recommendations for managing hypertension resistant to monotherapy, including dose augmentation with the addition of beta blockers, hydralazine, and minoxidil. However, most NH patients are elderly and often have associated cardiovascular (e.g., heart failure, cardiac arrhythmia) and non-cardiovascular comorbidities (e.g., diabetes) that can interfere with current treatment choices. Therefore, NH patients should be treated case by case instead of through a generalized treatment regimen [13].

Table 1 provides a list of current antihypertensive drugs that can be used in combination to manage NH.

Table 1. Current antihypertensive medications in clinical use.

Drug Class	Mechanism	Examples	Special Notes
ACE inhibitors	Block the action of ACE to prevent the conversion of Ang I to Ang II	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	Used in combination with other therapeutic agents [14].
ARBs	Reduce the action of Ang II at its receptor by blocking it, causing vasodilation.	Azilsartan, eprosartan, losartan, irbesartan, olmesartan, valsartan, telmisartan, candesartan	Eprosartan possesses sympathoinhibitory [15].
Calcium channel blockers	Prevents calcium influx into heart and arterial cells by blocking the calcium channels.	Nifedipine, amlodipine, felodipine, nicardipine, isradipine, nisoldipine, diltiazem, verapamil	
Diuretics	Induce excretion of body salt and water by aiding in the movement of sodium into the urine.	Chlorothiazide,# indapamide,# metolazone,# chlorthalidone,# hydrochlorothiazide,# bumetanide,* ethacrynic acid,* furosemide,* torsemide,* spironolactone,& amiloride,& eplerenone,& triamterene&	They can be used as monotherapy or in combination. Three types of diuretics are in clinical use: thiazide,# loop,* and potassium sparing&
Aldosterone antagonist	Block the action of aldosterone resulting in salt and water loss.	Spironolactone, eplerenone, finerenone	
α-blockers	Partially block alpha-adrenergic receptor activity.	Doxazosin, prazosin, terazosin	They are used in combination therapies. Improves urine flow in older men with prostate problems.
Vasodilators	Improve blood flow by relaxing blood vessels.	Hydralazine, minoxidil	
β-blockers	Block beta receptors	Atenolol, pindolol, metoprolol, propranolol, bisoprolol, timolol, labetalol, carvedilol, acebutolol	Not generally recommended as first-line drugs
Renin-inhibitors	Inhibit the enzyme renin from triggering a process that helps regulate BP.	Aliskiren	Have an additive effect when used with diuretics
Centrally acting antihypertensives (α-2 agonist)	Stimulate presynaptic alpha2-adrenergic receptors in the brain stem, which reduces SNA	Methyldopa, clonidine, guanfacine	

Symbols present on examples of diuretic represent their class, ("#","*" and "&" represent Thiazide Loop and Potassium sparing diuretics respectively.)

2. Centrally Acting Agents

Most of the clinically used BP-reducing drugs function outside the CNS. However, a few antihypertensive agents are known to have central activity, reducing overall vasomotor tone by activating receptors within the ventrolateral medulla. Centrally acting drugs either stimulate imidazoline receptors (rilmenidine, moxonidine) or α-2 (Clonidine) within the central nervous system [16]. Although the central actions of these drugs could be useful in NH, their benefits are marred with several adverse effects that limit their suitability for clinical use. Therefore, dose adjustment is proposed as a strategy to circumvent the harsh side effects of these chemotherapeutics; regardless, this approach has not seen much success. A more promising approach has been the development of second-generation imidazoline binding agents. An example of such an agent is rilmenidine, whose beneficial sympatholytic and BP-lowering effects are augmented by its ability to protect from postural hypotension [17]. In addition to its protective effects, rilmenidine is well tolerated and effective in reducing left ventricular hypertrophy associated with essential hypertension [18][19].

3. Renal Denervation

In the early 19th century, “Serious hypertension” was treated by surgically removing the splanchnic nerves [20][21]. The successful surgical interventions developed by Keith Grimson and Reginald Smithwick facilitated the development of chemical sympathectomy agents. However, the major backlashes of earlier surgical approaches were that it was invasive, time-consuming, and unsafe [22][23]. Over the past few decades, a return to surgical procedures has received much attention with the development of a brief (typically performed in 40 minutes) and less deleterious catheter-based renal denervation technique. The procedure only requires the insertion of a catheter into the femoral artery at the groin and advancing it to the renal artery. Radio frequencies are applied at the renal artery to ablate afferent and efferent sympathetic nerves connected to the kidneys [19][24].

In a proof-of-concept study, the SYMPLICITY HTN-1 study, Krum et. al [25] found that catheter-based renal denervation causes substantial and sustained BP reduction. However, they did not deem their findings decisive for managing resistant hypertension and called for more trials [26]. In a follow-up trial, SYMPLICITY HTN-2, similar outcomes were observed. Although both SYMPLICITY HTN-1 and HTN-2 trials had positive outcomes, they lacked sham controls, making the observations inconclusive [26][27][28]. To correctly affirm the suitability of renal denervation, well-designed randomized clinical trials are essential. In the third study with sham control (SYMPLICITY HTN-3), no significant difference was observed between the sham and treated groups. However, procedural insufficiencies such as fewer desirable ablations in the SYMPLICITY HTN-3 trial might be responsible for the unsuccessful findings. The failed attempt of the SYMPLICITY HTN-3 trial has left the fate of what appeared to be a promising treatment with unanswered questions.

Regardless, the idea of this technique being relatively safer has caused it to receive much attention with a significant number of clinical trials been performed. **Table 2** provides a list of some of the registered clinical trials involving renal denervation, their status, and the measured outcomes of their study.

Table 2. Clinical trials involving surgical treatments for drug resistant hypertension.

Study Title	Status	Interventions	Primary Measured Outcome	Clinicaltrials.gov Identifier
Efficacy and safety of renal sympathetic denervation from the adventitia on resistant hypertension	Unknown	Renal denervation via radiofrequency ablation instruments	Change in 24-hour average systolic BP	NCT03758196
A pragmatic randomized clinical evaluation of renal denervation for treatment resistant hypertension	Terminated	Renal denervation	Average systolic 24-hour ambulatory BP	NCT01895140
Renablate feasibility study cs156 (EC12-02) study of catheter based renal denervation to treat resistant hypertension	Completed	Renal denervation using celsius® thermocool®	Incidence of major cardiovascular and/or renal adverse events related to the renal denervation procedure that occurred within 30 days post-procedure.	NCT01756300
The effect of baton bp and sympathetic function in resistant hypertension (the Nordic BAT study) (BAT)	Active	Baroreflex activation therapy	Change in systolic ambulatory BP in response to bat therapy	NCT02572024
Renal denervation in treatment resistant hypertension (ReSET-2)	Terminated	Ablation of the renal arteries	Change from baseline in daytime systolic BP (24-hour ambulatory bp measurement	NCT01762488
Treatment of resistant hypertension using renal denervation in china (REDUCE-HTN-CN)	Terminated	Percutaneous renal denervation with the vessix™ renal denervation system	The mean reduction of systolic bp measured using office-based BP assessment	NCT02027012
Treatment of resistant hypertension using a radiofrequency percutaneous transluminal angioplasty catheter (REDUCE-HTN)	Completed	Renal denervation	Change in systolic and diastolic bp at six (6) months as measured using office-based BP assessment	NCT01541865

Study Title	Status	Interventions	Primary Measured Outcome	Clinicaltrials.gov Identifier
Rapid renal sympathetic denervation for resistant hypertension ii (RAPID II)	Withdrawn	Renal denervation using one-shot™ renal denervation system)	Major adverse event (MAE) rate through 30 days post-randomization	NCT01939392
Renal sympathetic denervation in patients with drug-resistant hypertension and symptomatic atrial fibrillation	Unknown	Renal sympathetic denervation	Change in atrial fibrillation burden	NCT01713270
Feasibility study of renal denervation for the treatment of resistant hypertension	Unknown	Ultrasound-based renal denervation	Major adverse events	NCT01865591
Renal denervation for management of drug-resistant hypertension (INSPiRED)	Completed	Renal denervation	Change in systolic BP from baseline to 6 months on 24-h ambulatory measurement	NCT01505010
Randomized controlled trial of renal denervation for resistant hypertension	Unknown	Renal denervation using radiofrequency ablation catheter with drug treatment: amlodipine, losartan potassium and hydrochlorothiazide	Change in average 24-hour systolic BP using ambulatory bp monitoring from baseline	NCT02900729
Renal denervation in treatment resistant hypertension	Completed	Renal denervation using symplicity catheter system	Change in office BP from baseline to 6 months post-renal denervation	NCT01687725
Effects of renal sympathetic denervation on the cardiac and renal functions in patients with drug-resistant hypertension through mri evaluation (RDN)	Unknown	Renal denervation (enligHTN™) with the enligHTN™ renal denervation system.	Cardiac function (evaluated using MRI)	NCT02164435

4. Baroreceptor Reflex Activation

In 2019, the US Food and Drugs Administration approved the Barostim Neo® System to improve symptoms in patients with heart failure [29]. The Barostim Neo system comprises an implantable pulse generator connected to a lead generator that is attached to the carotid artery in the neck. The device is programmed to deliver electrical impulses called baroreceptors which sense blood flow rate and relay them to the brain. The brain relying on this input transmits signals that regulate the heart and blood vessels to ensure optimum BP [29][30]. Although approved for managing heart failure, the technique employed in the device has previously been proposed for managing resistant hypertension since its first description over half a century ago [31][32]. Despite this promising feature, baroreceptor reflex activation has its pitfalls. Firstly, baroreceptor denervation significantly increases the short-term lability of arterial pressure but does not reduce arterial hypertension chronically. Also, in a phase III trial, the prototype device was associated with questionable efficacy and induced facial nerve palsy [19]. Fortunately, the production of a miniaturized second-generation pacing electrode allows the possibility of avoiding the significant side effect of facial nerve palsy [31].

5. Other Unconventional Strategies- Drugs Proposed and Drugs under Investigation

Recent studies show nitric oxide biosynthesis is impaired in hypertension, and its acute inhibition further exaggerates hypertension. Incidentally, nitric oxide levels are known to influence SNA (sympathoexcitation at a low level and inhibition at a high level). Although the mechanism behind this pathophysiology is not fully understood, stimulating nitric oxide synthesis has been proposed as a possible target for the treatment of NH. [19][33][34][35][36]. Although a conclusion of this potential therapy is not yet presented, a study confirmed that inhaled nitric oxide treatment could improve systemic oxygenation in infants with persistent pulmonary hypertension [37], further strengthening this claim.

Another unconventional therapy proposed is statins, a class of drugs more frequently prescribed for their potent cholesterol-lowering properties. Additionally, statins are known to stimulate nitric oxide production and possess anti-

inflammatory and antioxidant properties [38][39][40][41]. In animal models of heart failure, statins were identified to lower renal SNA and cause marked improvements in heart rate variability indices of cardiac autonomic balance [19][38][42][43]. Although there is not enough data to claim statins' suitability for hypertension, their potential to impact SNA requires further investigation.

Inflammatory molecules generated by vascular endothelial cells and leukocytes can infiltrate the brain parenchyma via disrupting the BBB. When these inflammatory chemicals interact with microglia, they release more ROS and chemokines/cytokines, which can have an immediate impact on neuronal function. As a result, the role of inflammation and oxidative stress in NH pathophysiology is another area of active research. Further, substantial evidence suggests that diets rich in antioxidants cause significant reductions in blood pressure [44]. Thus, food components such as oatmeal which are rich in antioxidants and can regulate metabolic syndrome, hold potential as a dietary approach to managing NH [45][46][47][48].

Also, neurosteroid allopregnanolone is identified as a potential treatment for NH. Allopregnanolone facilitates high-affinity extra-synaptic γ-aminobutyric acid A receptors through allosteric modulation and transcriptional upregulation.

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