European Heart Journal Supplements (2022) **24** (Supplement I), I197–I200
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suac094

ESC
European Society
of Cardiology

The enigma of resistant hypertension: from lifestyle changes and pharmacological treatment to renal denervation

Massimo Volpe* and Giovanna Gallo

Department of Clinical and Molecular Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome

KEYWORDS
Resistant arterial hypertension;
Denervation of the renal arteries;
Lifestyle interventions

Resistant hypertension consists in the failure to achieve effective control of blood pressure despite the use of at least three drugs, including a diuretic, at the maximum tolerated dosage. Despite the progress made in terms of improving awareness and effectiveness of the available therapeutic strategies, the percentage of patients with resistant hypertension represents up to 18% of the entire hypertensive population. The management of resistant hypertension includes the combination of different strategies from lifestyle changes to complex interventional procedures. Lifestyle interventions include reducing salt intake, weight loss, quitting smoking and alcohol consumption, and performing aerobic physical activity. With regard to drug therapy, international guidelines recommend the introduction of a mineralocorticoid receptor antagonist or, if not tolerated, of a loop diuretic, or of the beta-blocker bisoprolol, or of the alpha-blocker doxazosin. In the last few years, promising results have been obtained from studies that have evaluated the efficacy and safety of the denervation of the renal arteries by ablation. This procedure may constitute an increasingly widespread option for those patients suffering from resistant hypertension despite the use of different drug classes, or who are intolerant or poorly adherent to medical therapy.

Epidemiology and cardiovascular risk related to resistant hypertension

Arterial hypertension is one of the main cardiovascular (CV) risk factors being independently responsible for a significant increase in the risk of myocardial infarction (MI), ischaemic and haemorrhagic stroke, heart failure (HF), and mortality.[1]

Despite progresses made in improving awareness, percentages of treated patients, and achievement of therapeutic goals, it has been estimated that 9–18% of hypertensive subjects are affected by a resistant form. Resistant hypertension consists in the failure to achieve an effective blood pressure (BP) control despite the use of at least three drugs, including a diuretic, at the maximum tolerated dose.[1]

The diagnosis of resistant hypertension must be confirmed through ambulatory and home BP measurements and after excluding secondary forms (including hyperaldosteronism, renovascular hypertension, and chronic kidney disease) and 'pseudoresistant' hypertension, including the inadequacy of the method of BP measuring, insufficient adherence to the prescribed therapy (accounting for 13–45% of cases), and 'white coat' hypertension.

Epidemiology and cardiovascular risk related to resistant hypertension

Once the diagnosis is validated, the management of resistant hypertension must be started quickly and must include several combined strategies.[2]

*Corresponding author. Email: massimo.volpe@uniroma1.it

Indeed, it has been shown that patients who suffer from resistant hypertension have an increased risk of organ damage and CV events. An observational study conducted in a population of >200 000 patients showed that the risk of death and CV disease (non-fatal MI, HF, stroke, and nephropathy) was 47% higher among subjects with resistant hypertension during a 4-year follow-up.[3] In another study that collected data from about 400 000 subjects, resistant hypertension increased the risk of chronic kidney disease by 32%, of stroke by 14%, and of death by 6%.[4] Other prospective studies, in which the diagnosis of resistant hypertension was confirmed by out-of-office BP monitoring, showed a two-fold higher risk of CV events compared with patients with an adequate BP control.[5] On the other hand, the achievement of BP targets in patients who previously suffered from resistant hypertension has been associated with a significant reduction in the incidence of coronary artery disease, stroke, and HF (−13%).[6]

Lifestyle interventions

Different comorbidities and CV risk factors, including obesity, the presence of hypertension-mediated organ damage (such as left ventricular hypertrophy and albuminuria), and obstructive sleep apnoea, are associated with an increased incidence of resistant hypertension. This condition is also related to metabolic alterations including hyperuricaemia and increased plasma levels of aldosterone.[2] Several studies have shown that a consistent proportion of subjects with resistant hypertension have a high salt-sensitivity and how the reduction of sodium intake may contribute to achieve an adequate BP control. However, it must be emphasized that there is a great inter-individual variability in response to low-sodium intake, with different and complex mechanisms being involved, such as water retention, activation of the sympathetic and renin-angiotensin-aldosterone system, vascular stiffness, and modulation of the immune system.[2]

An excess in body fat, with particular regard to visceral fat, has also been associated with an increased risk of resistant hypertension as a result of vascular and neurohormonal dysfunction. In a recent meta-analysis, body weight loss was associated with a significant reduction in both systolic (−4.5 mmHg) and diastolic (−3.2 mmHg) BP levels.[7] However, there is no evidence with regard to the benefits of specific dietary regimens in patients with resistant hypertension. In addition to the reduction of salt intake and weight loss, the reduction of alcohol intake (<10 g for women and <20 g for men), quitting smoking, and performing regular aerobic physical activity may play an important role. For these reasons, international guidelines recommend to perform at least 150 min per week of moderate or intense physical activity (in three to five sessions of 30–40 min).[1]

Pharmacological treatment

With regard to the pharmacological treatment of resistant hypertension, in addition to a combination therapy with inhibitors of the renin-angiotensin system (angiotensin converting enzyme inhibitors or angiotensin receptor blockers), calcium channel blockers, and thiazide diuretics, international guidelines recommend the introduction of a mineralocorticoid receptor antagonist, in particular spironolactone. In those patients who do not tolerate spironolactone, the choice may fall on eplerenone or amiloride or, alternatively, on a loop diuretic, on the beta-blocker bisoprolol or on the alpha-blocker doxazosin[1] (*Table 1*).

The rationale for the enhancement of diuretic therapy is based on the fact that volume overload represents one of the main pathophysiological mechanisms involved in the development of resistant hypertension. Although >70% of patients with resistant hypertension are optimal candidates for treatment with spironolactone, in clinical practice only a small percentage receive this therapeutic strategy due to the fear of some known adverse effects such as hyperkalaemia, gynaecomastia, and erectile dysfunction. In these cases, eplerenone may represent a valid alternative.[2]

Role of renal denervation

In the last few years, the development of interventional procedures for BP control in patients with resistant hypertension has gained increasing interest.

Several studies have investigated the efficacy and safety of renal denervation (RDN) performing catheter-directed radiofrequency or ultrasound ablation techniques. Indeed, the activation of the sympathetic system produces an increase in renal vascular resistances, resulting in blood flow reduction, stimulation of renin secretion, and reabsorption of sodium and water, which finally lead to hypertension development and maintenance.[8]

Initially, the studies that investigated the effectiveness of RDN showed encouraging results. In the SYMPLICITY HTN-1 (Renal Denervation in Patients With Refractory Hypertension HTN-1) study, conducted on 45 patients with resistant hypertension who received an average of 4.7 drugs, a reduction of 14 mmHg in systolic BP and of 10 mmHg in diastolic BP was achieved after 4 weeks from RDN, with additional benefits at 12 (−27/17 mmHg) and 36 (−33/19 mmHg) months.[9] In the SYMPLICITY HTN-2 (Renal Denervation in Patients With Refractory Hypertension HTN-2) study, 106 patients were randomized to either RDN or standard treatment.

Table 1 Recommendations for the treatment of resistant hypertension

Lifestyle modifications (sodium intake restriction, physical activity)
Addition of low dose spironolactone to ongoing pharmacological treatment
In case of intolerance to spironolactone, use of another diuretic such as eplerenone, amiloride, a higher-dose thiazide diuretic, or a loop diuretic
In case of intolerance to spironolactone, use bisoprolol or doxazosin as an alternative to other diuretics

A 31/12 mmHg BP reduction was achieved in the active group.[10]

The initial enthusiasm deriving from these promising results waned after the publication of SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension HTN-3), the first study in which patients were blinded to the allocation in the active RDN group or in the control group with a sham procedure. In a population of 535 patients with resistant hypertension, the RDN procedure did not cause a significant BP reduction in compared with the control group (−2.4 mmHg, $P=0.26$).[11] However, it should be emphasized that the study did not assess and verify the adherence to the pharmacological treatment prescribed before the randomization and whether lifestyle changes and an increase in drug intake might have contributed to BP reduction also in the control group. Other explanations for the study failure were identified in inadequate patient selection, frequent medication changes, limited training and experience of the proceduralists, and likely incomplete circumferential ablation in most patients due to the use of poorly performing first-generation monopolar catheters.[8]

Following the publication of the SYMPLICITY HTN-3, new randomized trials [including the best known SPYRAL HTN-OFF MED (Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications),[12] SPYRAL HTN-ON MED (Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy)[13] and RADIANCE-HTN SOLO (A Study of the ReCor Medical Paradise System in Clinical Hypertension)[14]] have shown a significant reduction in short-term (2–3 months) and medium-term (6 months) clinical and ambulatory BP levels following ultrasound or radiofrequency ablation. The BP reduction was maintained over 24 h and independently from the drug classes and dosages used in the various therapeutic schemes. In all these studies, adherence to pharmacological treatment before and after the procedure was assessed by measuring drug metabolites in blood and urine samples with mass spectrometry and chromatography analyses. Furthermore, the 3-year follow-up of some of these studies (Global Symplicity Registry, SPYRAL HTN-ON MED[13] and RADIANCE-HTN SOLO[14]) indicates persistence of the long-term efficacy of the RDN procedure, with a continuous trend in the reduction of BP over time.

In evaluating the risk/benefit ratio of a possible RDN procedure, patients' preferences, especially in the case of poor tolerance to the proposed long-term pharmacological treatments, and overall CV risk, based on the presence of HMOD, comorbidities, and previous CV events, must be taken into account. Indeed, some patients refuse to increase the number of pills taken each day, especially when they are affected by several comorbidities that require complex therapeutic schemes.

Further randomized prospective studies are needed to definitively confirm the benefits of RDN. In the coming years, the main clinical challenge will be represented by the adequate identification of those subjects who can benefit the most from this procedure. Based on these considerations, it has been suggested to propose RDN to patients with resistant hypertension and a glomerular filtration rate $\geq$40 mL/min/1.73 m^2, after the exclusion of secondary hypertension.[8,15,16]

Even though renal sympathetic reinnervation is a theoretical concern, it has been shown that regrown nerves do not achieve normal function.

The stimulation of carotid baroreceptors and the creation of a central arteriovenous anastomosis between the iliac vein and artery have been also investigated as interventional procedures for the treatment of resistant hypertension.[2] However, it should be underlined that available studies have produced contrasting results and are burdened by high complication rates, failing to achieve safety and short-term efficacy endpoints, even in the presence of benefits in terms of BP reduction at 6-month follow-up.[2]

Conclusions

In the next future, the use of devices may represent a valid and promising approach to improve the management of resistant hypertension. In this context, RDN will probably represent an important tool for patients with resistant hypertension or who are intolerant or poorly adherent to pharmacological treatment, with a shared-decision process. Beyond the reduction of BP levels, an improvement in CV outcomes still remains to be demonstrated and further efforts are necessary to identify which patients may be candidates for the different procedures with a favourable risk/benefit ratio.

Conflict of interest: None declared.

References

1. Williams B, Mancia G, Spiering W *et al.*; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
2. Carey RM, Calhoun DA, Bakris GL *et al.*; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018;**72**:e53–e90.
3. Daugherty SL, Powers JD, Magid DJ *et al.* Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; **125**:1635–1642.
4. Sim JJ, Bhandari SK, Shi J *et al.* Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int* 2015;**88**:622–632.
5. Tsioufis C, Kasiakogias A, Kordalis A *et al.* Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. *J Hypertens* 2014;**32**:415–422.
6. Egan BM, Kai B, Wagner CS, Henderson JH, Chandler AH, Sinopoli A. Blood pressure control provides less cardiovascular protection in adults with than without apparent treatment-resistant hypertension. *J Clin Hypertens* 2016;**18**:817–824.

7. Semlitsch T, Jeitler K, Berghold A *et al*. Long-term effects of weight-reducing diets in people with hypertension. *Cochrane Database Syst Rev* 2016;**3**:CD008274.
8. Mahfoud F, Azizi M, Ewen S *et al*. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. *Eur Heart J* 2020;**41**:1588–1599.
9. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011;**57**:911–917.
10. Symplicity HTN-2 Investigators; Esler MD, Krum H *et al*. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–1909.
11. Bhatt DL, Kandzari DE, O'Neill WW *et al*.; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–1401.
12. Böhm M, Mahfoud F, Townsend RR *et al*. Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial. *Eur Heart J* 2019;**40**:743–751.
13. Kandzari DE, Böhm M, Mahfoud F *et al*.; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;**391**:2346–2355.
14. Azizi M, Schmieder RE, Mahfoud F *et al*.; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCEHTN SOLO): a multicentre, international, single-blind, randomised, sham controlled trial. *Lancet* 2018;**391**:2335–2345.
15. Bruno RM, Taddei S, Borghi C *et al*. Italian Society of Arterial Hypertension (SIIA) position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient. *High Blood Press Cardiovasc Prev* 2020;**27**:109–117.
16. Mahfoud F, Böhm M, Schmieder R *et al*. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 2019;**40**:3474–3482.