REVIEW ARTICLE

Treatment Strategies for Resistant Arterial Hypertension

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SUMMARY

Background: Resistant hypertension is defined as blood pressure above the target range set by current guidelines despite the concurrent use of three or more antihypertensive drugs of different classes, including a diuretic, at their maximum or highest tolerated doses. This problem affects 5% to 15% of all hypertensive patients and is thus commonly seen by both primary care physicians and specialists.

Methods: Review of current guidelines and pertinent literature revealed by a selective Medline search.

Results: The treatment of resistant hypertension is multimodal, involving systematic identification of secondary causes of hypertension as well as the exclusion of pseudoresistance (inadequate treatment). Non-pharmacological treatment includes weight loss, dietary salt restriction, exercise, and abstinence from alcohol. Drug treatment consists of an individualized combination of antihypertensive agents with different mechanisms of action. Activation of the sympathetic nervous system is considered to be a major element in the pathogenesis of resistant hypertension; a new interventional treatment, selective denervation of the renal sympathetic nerves, results in clinically relevant and sustained blood pressure reduction in ca. 84% of the patients undergoing the procedure (a mean decrease of office systolic blood pressure by 32 mm Hg and by 12 mm Hg at six months, $p < 0.001$). Among the 206 patients who underwent this procedure in the setting of published studies, 5 had complications; these included pseudoaneurysm of the femoral artery and dissection of the renal artery during the introduction of the ablation catheter.

Conclusion: The treatment of resistant hypertension is interdisciplinary and multimodal. The new and promising option of interventional renal sympathetic denervation can be considered for patients whose high blood pressure is inadequately controlled with medication.

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Arterial hypertension is one of the most frequent chronic diseases in the industrialized nations of the West and represents a major risk factor for cardiovascular morbidity and mortality.

In Germany, only 5% to 17% of patients treated for hypertension achieve lasting control of their blood pressure (1, 2). Around 5% to 15% of all patients with high blood pressure have resistant arterial hypertension (3). Care must be exercised to distinguish between true resistance to treatment and so-called pseudoresistance, which may result from poor compliance with treatment, situationally evoked blood pressure elevation (isolated office hypertension, also known as “white-coat hypertension”), or incorrect choice of medications.

In many patients with resistant hypertension there is a secondary, potentially reversible cause of high blood pressure. Thus, systematic evaluation of organic causes of hypertension is an essential part of the treatment program. The goal of this article is to review the treatment of resistant hypertension as reflected in current guidelines and in pertinent literature revealed by a selective Medline search, with particular emphasis on interventional renal sympathetic denervation.

Definition

Resistant arterial hypertension is defined as high blood pressure that cannot be adequately controlled according to the current guidelines (i.e., pressure of $>140/90$ mm Hg in general; $>130/85$ mm Hg in patients with diabetes mellitus, $>130/80$ mm Hg in chronic renal disease) despite concurrent use of three or more antihypertensive drugs of different classes, including a diuretic, at their maximum or highest tolerated doses (3, 4). Cases of pseudoresistance, which may result from poor compliance with treatment, inadequate antihypertensive medication, incorrect means of measurement, or white-coat hypertension, must be identified. White-coat hypertension is present if the patient’s blood pressure is $140/90$ mm Hg or lower when measured at home but $>140/90$ mm Hg in the doctor’s office or the hospital.

Epidemiology

The prevalence of arterial hypertension in Germany is 10% to 35% in the age group 30 to 59 years, rising to 65% in those over 60 years of age (1). The exact prevalence of resistant hypertension is unknown (3). In the Study of

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BOX 1

Medications and other substances that may increase blood pressure and/or reduce the effect of antihypertensive medication

- Non-steroidal anti-inflammatory drugs
- Corticosteroids
- Sympathomimetics
- Amphetamines
- Oral contraceptives
- Cyclosporine
- Tacrolimus
- Erythropoietin
- Tricyclic antidepressants
- Alcohol
- Licorice

BOX 2

Causes of secondary arterial hypertension (3)

- **Frequent**
 - Obstructive sleep apnea syndrome
 - Chronic renal disease
 - Primary hyperaldosteronism
 - Renal artery stenosis
- **Rare**
 - Pheochromocytoma
 - Cushing syndrome
 - Hyperparathyroidism
 - Coarctation of the aorta

Health in Pomerania (SHIP study) and in three surveys carried out in the Augsburg area of Germany (MONICA S2, MONICA S3, and MONICA S4), the prevalence of resistant arterial hypertension was 18% in men and 22% among women (1). A large study in the USA, with over 260 000 patients, found a 16% rate of resistant hypertension.

Etiology

The etiology of resistant arterial hypertension is multifactorial: Numerous risk factors and comorbidities are associated with therapy resistance. These include advanced age, high systolic blood pressure, obesity, high salt consumption, chronic renal disease, diabetes mellitus, left ventricular hypertrophy, and female sex (3). Suboptimal combination of antihypertensive medications can also be a reason for failure to bring blood pressure back to normal (5). One study showed that 18% to 27% of patients with inadequately controlled blood pressure were being treated with fewer than three antihypertensive agents (6). Other medications may also have the effect of increasing blood pressure or reducing the effect of the antihypertensive agent (*Box 1*). Particular attention must be paid to the frequently employed non-steroidal anti-inflammatory drugs (NSAIDs), which may lead to increased sodium retention and thus result in hypervolemia with a consequent increase in total blood volume (6, 7). Other important groups of drugs that can cause an increase in blood pressure are the sympathomimetics (diet pills, amphetamines), the glucocorticoids, the estrogens in contraceptives, the antidepressants, and erythropoietin (8). Immoderate alcohol and salt consumption and a lack of exercise can also contribute to hypertension.

Secondary hypertension

Secondary hypertension is not the focus of this article but will be reviewed in brief (*Box 2*). The principal causes of secondary hypertension are obstructive sleep apnea syndrome, chronic renal diseases, primary hyperaldosteronism, and renal artery stenosis (3). There is a high prevalence of obstructive sleep apnea syndrome among patients with resistant arterial hypertension. The pathomechanisms discussed in the literature include elevated sympathetic activity, primary hyperaldosteronism, and obesity (9). In two studies the prevalence of obstructive sleep apnea syndrome (apnea-hypopnea index $\geq 10/h$ in one study, $\geq 5/h$ in the other) was 71% and 85% respectively in patients with resistant hypertension, against only 38% in patients with controlled arterial hypertension (9, 10). The guidelines recommend consideration of sleep apnea screening in patients with resistant hypertension and commensurate history or risk factors (4). Chronic renal failure frequently causes not only resistant hypertension but is also a frequent complication of hypertension in the sense of hypertensive end-organ damage. The bidirectional pathomechanism between renal failure and hypertension means that fewer than 15% of patients with chronic renal disease achieve the target value of $<130/80$ mm Hg despite taking a combination of three or more medications

(3). Around 10% to 20% of patients with resistant arterial hypertension have primary hyperaldosteronism (11). The tell-tale symptom is often hypokalemia, although up to 50% of patients with confirmed primary hyperaldosteronism display normokalemia (12). Hemodynamically relevant renal artery stenosis (>70%) is found in about 10% of patients with resistant arterial hypertension over 65 years of age (3). Renovascular imaging carried out in association with coronary angiography shows a higher prevalence of renal artery stenosis—up to 20% although not every detectable stenosis can be seen as a causative factor (3). Fibromuscular dysplasia should be considered, particularly in women under 50. The rarer causes of resistant arterial hypertension include pheochromocytoma, Cushing syndrome, thyrotoxic crisis, vasculitis, and coarctation of the aorta.

Diagnosis of resistant arterial hypertension

Before concluding that a patient has essential resistant hypertension, reversible or organic causes must be systematically excluded (*Figure 1*). Pseudoresistance (white-coat hypertension) and pseudohypertension (non-invasive measurement owing to Mönckeberg sclerosis may indicate high blood pressure in the presence of arterial normotension) must also be ruled out. Potentially reversible causes include life-style factors (obesity, lack of exercise, excessive intake of alcohol and/or salt), suboptimal antihypertensive treatment, and side effects of other medications. In addition to detailed history-taking (including medications), physical examination, and ambulatory blood pressure measurement, patients with resistant arterial hypertension should undergo blood testing (serum electrolytes, glucose, and creatinine) and urinary diagnosis (protein determination and salt excretion). Screening for primary hyperaldosteronism comprises determination of the aldosterone-renin ratio, with careful attention to possible interactions with antihypertensive substances. If any signs of primary hyperaldosteronism are found, the next steps are diagnostic imaging and separate analysis of blood samples from the left and right adrenal glands. Patients with episodic hypertensive crises should be investigated for pheochromocytoma. Diagnostic ultrasonography of the renal arteries is particularly advisable in young patients with suspected fibromuscular dysplasia and patients at increased risk of atherogenesis to exclude atherosclerotic renal artery stenosis.

Treatment

The goal of treatment for high blood pressure is prevention of hypertensive end-organ damage and reduction of cardiovascular morbidity and mortality. In addition to the tried and tested treatments, two new, partially still experimental therapy options are available.

Pharmacological treatment

By definition, the pharmacological treatment of resistant arterial hypertension consists of administration of at least three antihypertensive substances, including a

FIGURE 1

Proposed algorithm for diagnosis and treatment of arterial hypertension that cannot be brought under control by medicinal means

diuretic. The selection and combination of these medications depends, among other factors, on comorbidities and on the presence or absence of hypertensive end-organ damage. The use of fixed combinations is a sensible measure that has been demonstrated to improve compliance (13). Few randomized controlled trials of pharmacological treatment have been conducted in patients with resistant hypertension (3). *Table 1* lists the active substances that lend themselves to treatment of resistant arterial hypertension.

Percutaneous renal denervation

Background

A prominent part in both the pathophysiology of hypertension that cannot be controlled by drugs and the development of end-organ damage and comorbidities is played by marked activation of the sympathetic nervous system (14). Afferent and efferent sympathetic nerve fibers form a connection between the kidneys and the central nervous system.

Method

The activity of the sympathetic nervous system is modulated by selective interruption of this neural connection by means of interventional intravascular (both renal arteries) radiofrequency ablation (15, 16). A

TABLE

Drug treatment of resistant hypertension

Initial treatment	If blood pressure does not decrease
ACE inhibitors/ angiotensin receptor blockers	Renin inhibitor (aliskiren)
Diuretics (especially aldosterone antagonists)	Direct vasodilators (minoxidil, dihydralazine)
Calcium channel blockers	Central alpha-2-receptor agonists (moxonidine, clonidine)
Beta receptor blockers	Alpha-1-receptor antagonists (urapidil) Alpha receptor blockers Endothelin antagonists (darusentan, atrasentan)

FIGURE 2

The decrease in
systolic and di-
astolic blood pres-
sure up to 24
months after renal
denervation (modi-
fied from [18]);
M, month(s)

special ablation catheter (Symplicity™ Catheter System, Ardian/Medtronic Inc., California, USA) is introduced percutaneously via the femoral artery and advanced to the distal segment of the renal artery under image guidance. The vessel wall is focally heated to 50 to 70 degrees Celsius by means of high-frequency energy (maximum: 8 W for 2 min), meanwhile the vessel is cooled intraluminally by the high blood flow. The heating of the wall ablates the sympathetic nerve fibers in the adventitia. The catheter is then withdrawn from distal to proximal in steps of at least 5 mm, with ablation at each new site. This results in four to six areas of ablation distributed spirally along the renal artery. Bilateral percutaneous renal denervation can be accomplished in ca. 40 to 60 min.

Recent studies

Interventional renal denervation for treatment of resistant arterial hypertension was successfully employed and clinically evaluated in the multicenter proof-of-

concept study Symplicity HTN-1 (15) and the randomized controlled trial Symplicity HTN-2 (17). Before renal denervation, the patients in the Symplicity HTN-1 study (n = 45) were taking an average of 4.7 antihypertensive substances but had a mean blood pressure of 177/101 mm Hg. The primary endpoints of the study were the blood pressure-lowering effect and the periprocedural and long-term safety of the intervention. Postprocedural renal function and norepinephrine spillover rate were defined as secondary endpoints. After only a month systolic and diastolic blood pressure had both decreased significantly, by 14 mm Hg and 10 mm Hg respectively, and by 12-month follow-up the decreases were 27 mm Hg and 17 mm Hg (p = 0.026). No subsequent increase in blood pressure was observed, either in the original study period or in the recently published extended follow-up (n = 153) over a period of 24 months (Figure 2) (18). Functional regeneration or reinnervation is therefore unlikely, so a long-term effect on blood pressure can be assumed. The reduction in sympathetic activity due to the renal artery denervation was confirmed by a significant decrease of 47% (n = 10) in the renal norepinephrine spillover rate (secondary endpoint) and correlated with a blood pressure reduction (–22/–12 mm Hg) after 6 months (15). In the recently published randomized controlled Symplicity HTN-2 trial (17), 106 patients with resistant hypertension (systolic blood pressure ≥ 160 mm Hg; for patients with diabetes mellitus type 2, ≥ 150 mm Hg) were enrolled between June 2009 and January 2010. An initial 2-week observation period was followed by randomization (1:1) into a treatment group and a control group (continuation of drug treatment). The patients' mean blood pressure at the beginning of the study was 178/96 mm Hg despite their intake of a mean 5.3 antihypertensive substances. Six months after renal denervation, the mean blood pressure in the treatment group had decreased significantly by 32/12 mm Hg (p<0.0001), while the blood pressure in the control group remained unchanged. The blood pressure as measured by the patients themselves at home also decreased by 20/12 mm Hg (p<0.0001, n = 32), compared with a slight increase of 2/0 mm Hg (n = 40) in the control group. In 20% of patients the reduction in blood pressure permitted a decrease in the number or dosage of antihypertensive medications. Long-term blood pressure recordings were available for 20 patients in the denervation group. The reduction in blood pressure after 6 months was 11/7 mm Hg (p = 0.007/0.014). In contrast, there was no significant change in the control group.

As expected, given the common pathways of sympathetic nerves and C pain fibers, the delivery of high-frequency current caused pain. This necessitated the administration of analgetics and sedatives. Pain ceased immediately on termination of radiofrequency ablation. Seven patients (13%) who experienced transient bradycardia during the intervention were successfully treated with atropine. The frequency of the combined cardiovascular endpoint did not differ significantly between the treatment group and the control group (three

versus two cases). In approximately one quarter of patients renal denervation was followed by an increase (>20%) in glomerular filtration rate (GFR), while one patient displayed a GFR decrease (>20%), possibly due to pronounced lowering of blood pressure. Renal denervation led to a reduction of at least 10 mm Hg in systolic blood pressure in 84% of patients. High systolic blood pressure at the time of measurement ($p < 0.001$) and consumption of centrally acting sympatholytics ($p = 0.018$) were independent predictors of a marked reduction in blood pressure (18). Because of the low non-response rate (currently ca. 12%), no factors predicting lack of response have been identified.

Safety

The procedure was carried out without complications in 201 (98%) of the 206 patients systematically recorded in studies. Four patients (1.9%) experienced pseudoaneurysms of the femoral artery (prevalence in other interventions: 0.8% to 2.2% [19]); all could be treated conservatively. In one patient advancement of the catheter into the renal artery led to renal artery dissection. This complication was unconnected with radiofrequency ablation and was treated unproblematically with a stent. Another patient showed worsening of a pre-existing renal artery stenosis after 6 months; this was also managed by stenting. No ablation had been performed in the vicinity of this stenosis, making it unlikely that the progression was due to the administration of high-frequency current. The remaining 205 patients showed no detectable changes of the treated renal vessels on duplex sonography, magnetic resonance imaging, or computed tomography; in particular, there was no evidence of renal artery aneurysms or significant stenoses. The minor complications after renal denervation, each found in one patient, comprised short-term back pain, a post-procedural decrease in blood pressure, urinary tract infection, and prolongation of hospital stay due to paresthesias. Repeated spiroergometry, carried out in 46 patients, showed that renal denervation was followed by a significant reduction in blood pressure at rest and during exercise and by preservation of blood pressure adaptation (20) with no signs of chronotropic incompetence or a negative influence on ventilatory parameters.

Contraindications

The current contraindications to renal denervation are anatomical unsuitability of the renal artery (diameter <4 mm; length <20 mm; fibromuscular dysplasia; significant renal artery stenosis) and $\text{GFR} < 45 \text{ mL/min/1.73m}^2$ as measured by the Modification of Diet in Renal Disease (MDRD) formula (Box 3). The advisability of the procedure may also need to be considered with care in the presence of normal anatomical variants such as multiple or accessory renal arteries.

Effect on glucose metabolism and insulin sensitivity

Early results indicate that the glucose metabolism can be favorably influenced by renal denervation (21). In a

BOX 3

Criteria to be met before a patient can be considered for interventional renal denervation (15, 17)

- Office systolic blood pressure $\geq 160 \text{ mm Hg}$ ($\geq 150 \text{ mm Hg}$ for patients with diabetes mellitus type 2)
- Intake of ≥ 3 antihypertensive substances (true resistance in patients with good compliance)
- Exclusion of secondary causes of hypertension
- Normal or only slightly reduced renal function (estimated glomerular filtration rate $\geq 45 \text{ mL/min/1.73 m}^2$)
- Suitable renal artery anatomy: no previous renal artery interventions, no significant stenosis or other abnormalities of the renal arteries

All of these criteria should be fulfilled

study of 50 patients, renal denervation achieved significant reductions in glucose and insulin concentration and a distinct improvement in insulin sensitivity by interruption of the bidirectional pathomechanisms between sympathetic overactivity and insulin resistance (21).

Baroreflex stimulation of the carotid sinus

Stimulation of the baroreceptor afferents leads, via a negative feedback system, to stimulation of parasympathetic fibers of the vagus nerve (22). This, in turn, lowers the blood pressure and reduces the heart rate (23). The Rheos stimulator (CVRx, Minneapolis, USA) is a fully implantable device for baroreflex stimulation. Electrodes are implanted bilaterally on the carotid artery and connected by leads to a device placed subcutaneously near the clavicle. The Device Based Therapy in Hypertension Trial (DEBuT-HT) investigated the use of this system in patients with resistant hypertension and showed reductions of $33 \pm 8 \text{ mm Hg}$ in systolic and $22 \pm 6 \text{ mm Hg}$ in diastolic blood pressure after 2 years ($p = 0.001/0.002$; $n = 17$) (24). However, 8 (19%) of 42 implantations were followed by severe complications (e.g., stroke, glossoplegia, infection, or device displacement). The recently published randomized, placebo-controlled Rheos study of 265 patients with resistant hypertension showed a significant reduction in blood pressure in the group with baroreflex stimulation; however, the endpoints for acute response and procedural safety were not attained (25). Baroreflex stimulation seems to achieve effective, lasting reduction of blood pressure. Nevertheless, its clinical application is limited by the necessity for vascular surgery involving the carotid artery with the patient under general anesthesia, the need for frequent replacement of the subcutaneously implanted device, and the risk of infection entailed by device implantation. A new system requiring implantation on only one side is currently undergoing clinical testing. Baroreflex stimulation of the

carotid sinus represents an experimental treatment option in selected patients with severe resistant hypertension.

Summary

The treatment of resistant hypertension requires a multimodal interdisciplinary strategy. Apart from individualized pharmacological therapy and the treatment of potentially reversible causes, secondary forms of hypertension must be systematically identified and treated appropriately. Two new alternative treatment options, minimally invasive renal denervation and baroreceptor stimulation, are available for selected patients with resistant hypertension. Renal sympathetic denervation is an interventional procedure with a low complication rate that can yield a significant and lasting reduction in blood pressure. To what extent this technique can be used to treat other diseases with raised sympathetic activity (e.g., chronic or terminal kidney failure, chronic heart failure) remains to be investigated. Continuous prolonged monitoring is necessary before the long-term effects and the safety of the new procedure can be properly evaluated. To this end, the German Renal Denervation (GREAT) registry has been established to enable systematic follow-up of patients treated with renal denervation.

Conflict of interest statement

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KEY MESSAGES

- Optimization of body weight, restriction of salt intake, physical exercise, and abstinence from alcohol are important non-medical treatment measures.
- Besides optimal individualized pharmacological therapy (especially administration of diuretics), reversible and secondary causes of hypertension must be systematically identified and treated appropriately.
- Clinically evaluated procedures such as minimally invasive renal denervation should be considered in selected patients with resistant arterial hypertension.
- Renal denervation is an interventional procedure with a low complication rate that can yield a significant and lasting reduction in blood pressure.
- Clinical trials and registries with long-term (>2 years) follow-up are needed to enable proper assessment of the value of this new procedure.

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