Treatment Strategies for Resistant Arterial Hypertension
Felix Mahfoud*, Frank Himmel*, Christian Ukena, Heribert Schunkert, Michael Böhm, Joachim Weil

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.

► Cite this as:
In 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 disease, 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 ≥ 10/h in one study, ≥ 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 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 intravasal (both renal arteries) radiofrequency ablation (15, 16).
Drugs used in the treatment of resistant hypertension

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Initial treatment</th>
<th>If blood pressure does not decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>renin inhibitor (aliskiren)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (especially</td>
<td>Direct vasodilators</td>
<td></td>
</tr>
<tr>
<td>aldosterone antagonists)</td>
<td>(minoxidil,</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>dihydralazine)</td>
<td></td>
</tr>
<tr>
<td>Beta receptor blockers</td>
<td>Alpha-1-receptor antagonists (urapidil)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha receptor blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endothelin antagonists (darusentan)</td>
<td></td>
</tr>
</tbody>
</table>

The decrease in systolic and diastolic blood pressure up to 24 months after renal denervation (modified from [18]; M, month(s))

As expected, given the common pathways of sympathetic nerves and pain fibers, the delivery of high-frequency current caused pain. This necessitated the administration of analgesics 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

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 pain fibers, the delivery of high-frequency current caused pain. This necessitated the administration of analgesics 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 frequency 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 paresthesia. 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 GFR < 45 mL/min/1.73m² 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 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).

**Box 3**

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

- Office systolic blood pressure ≥ 160 mm Hg (≥ 150 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 ≥ 45 mL/min/1.73 m²)
- 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.
carotid sinuses 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
The authors received research funding from Ardian/Medtronic Inc., Palo Alto, USA to finance the conduct of clinical trials.
Dr. Mahfoud, Dr. Ukena, and Prof. Böhm are supported by the Ministry for Economics and Science of the Saarland and by the German Research Foundation (DFG; Clinical Research Group KFO 196).
Dr. Mahfoud is supported by the German Hypertension League (Deutsche Hochdruckliga) and has received fees for lectures and consultancy from Berlin-Chemie, Boehringer Ingelheim, Medtronic, Novartis, and Takeda Pharm.
Dr. Himmel is supported by Medtronic within the scope of the AF grant program and has received fees for lectures and consultancy from Medtronic and St. Jude Medical.
Dr. Ukena has received fees for lectures and consultancy from Boehringer Ingelheim and Medtronic.
Prof. Schunkert has received fees for lectures and consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, Pfizer, Sanofi-Aventis, Berlin-Chemie, MSD, Takeda, and Servier.
Prof. Böhm has received fees for lectures and consultancy from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi-Aventis, Servier, Medtronic, and Pfizer.
Prof. Weil has received fees for lectures and consultancy from Actelion, AstraZeneca, Bayer, Daiichi-Sankyo, Novartis, Medtronic, and Pfizer.

REFERENCES

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.


Corresponding author
Dr. med. Felix Mahfoud
Klinik für Innere Medizin III
Kardiologie, Angiologie und Internistische Intensivmedizin
Universitätsklinikum des Saarlandes
Kirberger Str., Gebäude 40
66421 Homburg/Saar, Germany
felix.mahfoud@uks.eu