REVIEW ARTICLE

Treatment Resistant Hypertension—Investigation and Conservative Management

Franz Weber, Manfred Anlauf

SUMMARY

Background: The introduction of invasive treatments, some of which are irreversible, for the entity called treatment-resistant hypertension (TRH) creates the need for a comprehensive discussion of the diagnostic evaluation that TRH requires and the available options for its conservative treatment.

Method: The pertinent literature is selectively reviewed in the light of the authors' longstanding clinical experience.

Results: Our review of the literature suggests that the high prevalence of TRH in Germany (ca. 20%) can be nearly halved with the aid of more thorough diagnostic evaluation. Such an evaluation should include a review of the patient's antihypertensive drugs (adherence, daily dosing, concomitant medication), investigation for other vascular changes that might affect blood pressure measurement, and exclusion of white-coat hypertension, sleep apnea syndrome, and secondary rather than essential hypertension. As there have been no randomized trials of treatment for TRH, the physician confronted with such cases must devise treatments on the basis of observational data and pathophysiological reasoning (volume status considering renin levels, sympathetic blockade, vasodilatation). Such measures can presumably lower the number of truly treatment-resistant cases still further.

Conclusion: To save patients from preventable harm, patients should undergo a thorough diagnostic evaluation and—under close monitoring for side effects—conservative pharmacological and nonpharmacological treatments should be deployed before any invasive treatment is performed.

► Cite this as:
Weber F, Anlauf M: Treatment resistant hypertension— investigation and conservative management. Dtsch Arztebl Int 2014; 111: 425–31. DOI: 10.3238/arztebl.2014.0425

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The advent of renal sympathetic denervation (1, 2) and baroreflex activation therapy (3, 4) triggered an increased interest in treatment-resistant hypertension (TRH). These interventions are not risk-free and, while they improve the condition, they cannot normalize the blood pressure and the need for antihypertensive medications remains high (1–4). Thus, in the absence of established guidelines, we will highlight here the diagnostic steps and conservative treatment options which we believe are indicated prior to the use of interventional treatment techniques. Strong evidence of the high success rate of consistent antihypertensive pharmacotherapy among patients with treatment-resistant hypertension was already available in 1982, although under different conditions (e1).

Definition of treatment-resistant hypertension

Most commonly, TRH is defined in the literature as failure to achieve target blood pressure in spite of use of at least three antihypertensive agents of different classes, including a diuretic, at optimal dose (5, e2).

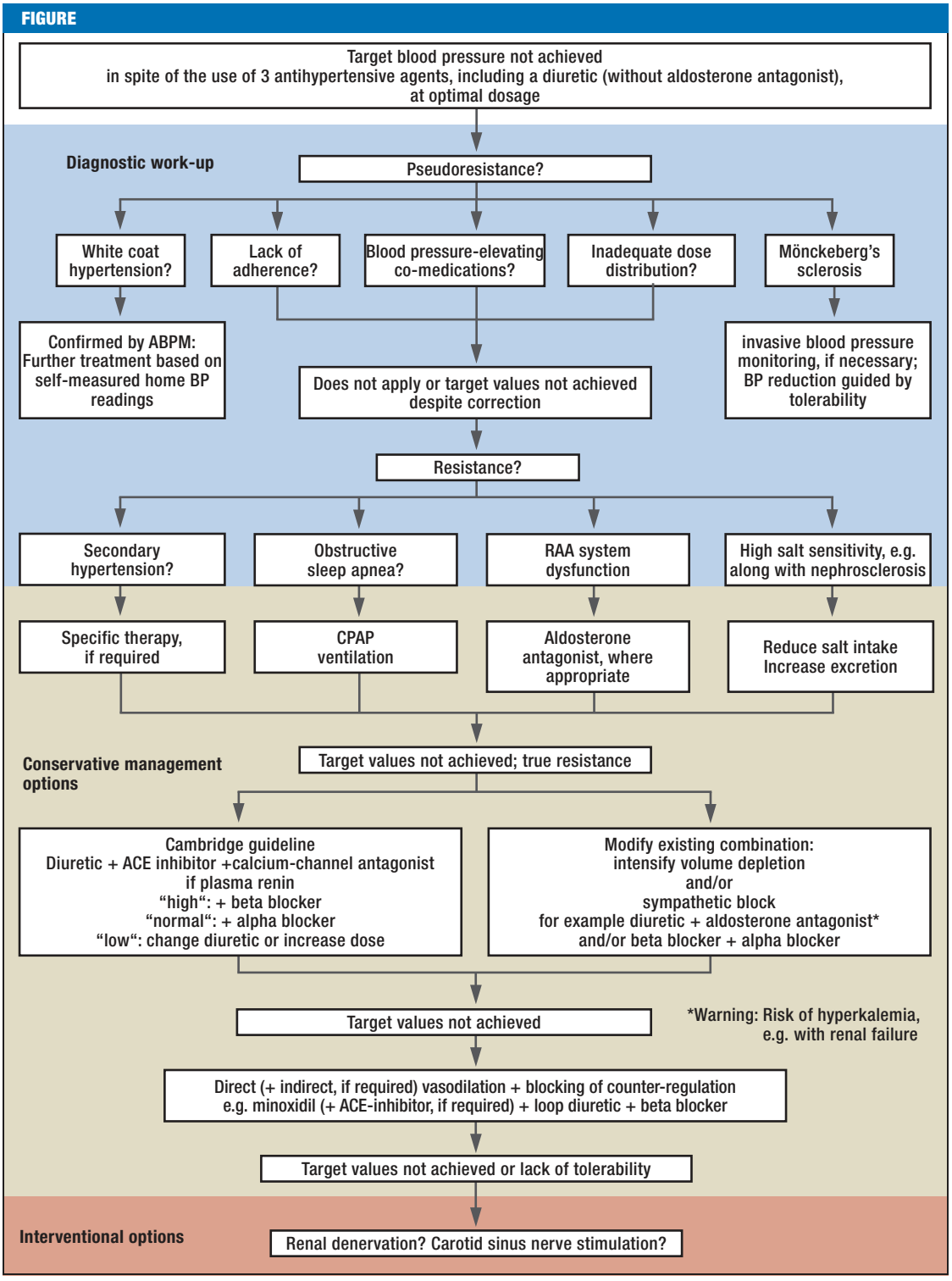
The target blood pressure typically lies for office measurements below 140/90 mm Hg; for fit elderly patients >80 years systolic at 140–150 mm Hg; for patients with diabetic nephropathy and proteinuria below 130 mm Hg, if tolerated; for diabetics diastolic at 80–85 mm Hg (6). As an additional criterion for treatment resistance, some authors (7) include the lack of nocturnal decrease of blood pressure ("non-dipper") in 24-hour ambulatory blood pressure monitoring (ABPM).

Prevalence, incidence, and prognosis of treatment-resistant hypertension

As a result of inconsistencies in the definition of treatment resistance and differences between the populations studied, reported prevalence rates range between 5% and 50% (8), with 22% for Germany according to a cross-sectional study (9). The incidence is reported at 1.3% per year after start of treatment (10). Risk factors include older age, male sex and diabetes mellitus.

Patients with resistant hypertension have a 3-fold poorer prognosis than those with controlled hypertension (11, e3). This is particularly true for non-dippers, who in many cases present with end organ damage and further risk factors, such as diabetes, chronic renal disease (12, e4) or obstructive sleep apnea (e5). Organ

FIGURE



Investigation and management of suspected or confirmed treatment-resistant hypertension.
ABPM, 24-hour ambulatory blood pressure monitoring; BP, blood pressure; RAA, renin angiotensin aldosterone; CPAP, continuous positive airway pressure

damage which has already developed may promote treatment resistance (13). For treatment resistance and chronic renal disease or primary aldosteronism a poor prognosis has also already been shown (odds ratio: 4.61) (e6).

Work-up preceding further treatment

In patients with increased blood pressure readings despite treatment it has to be established whether pseudoresistance or true resistance to treatment is present (5, e5, e7) *(Figure)*.

Pseudoresistance

White coat hypertension

According to various studies, almost 40% of "treatment-resistant" patients have white coat hypertension; without 24-hour ambulatory blood pressure monitoring (ABPM) these patients may be misclassified as "treatment-resistant" (12, 16).

Lack of adherence

By measuring serum drug levels, a medication adherence study showed that two thirds of the patients did not take their drugs as prescribed (e8). The potentialities (14) and positive effects (15) of improved adherence have only recently been reported und shall not be repeated here.

Blood pressure–elevating co-medications

Selected co-medications which may increase blood pressure are listed in the *Box*.

Inadequate distribution of the medication dose over the day

The use of at least one antihypertensive drug at bedtime significantly reduced the incidence of treatment resistance from 54% to 39% in ambulatory monitoring (17).

Most severe vascular changes (Mönckeberg's sclerosis)

Circular atherosclerosis reduces arterial compressibility and therefore results in falsely high blood pressure measurements. Indicative here is an ankle-brachial index (Doppler examination) of clearly above 1.3 and discrepancies between blood pressure level and the absence of organ damage; moreover evidence may emerge from spontaneous angiograms performed along with radiological examinations (e9).

Possible resistance

In many patients with difficult-to-control blood pressure, the underlying pathophysiological factors can be identified and specifically treated.

Other types of secondary hypertension

TRH should always be reason to definitely rule out secondary hypertension (22), in particular renal artery stenosis (e16), but also pheochromocytoma (e17).

Obstructive sleep apnea syndrome

CPAP (continuous positive airway pressure) treatment of obstructive sleep apnea, a condition not uncommonly associated with resistant hypertension, did not only significantly lower blood pressure by 10/7 mm Hg in a randomized controlled trial (RCT), but also allowed in 71% of the patients a reduction in medications (e15).

These data show that it is vital to specifically address sleep apnea (daytime sleepiness?) when taking the patient's history (snoring, apnea episodes?), including information from the spouse. Treatment resistance should always prompt apnea screening or investigation in a sleep laboratory.

Disorders of the renin angiotensin aldosterone system (RAAS)

Primary aldosteronism is suspected in 10–20% of patients with treatment resistant hypertension (5, 18). Positive experiences with low-dose spironolactone treatment further support the important role of the RAAS (19, e11). Similarly, positive experiences with eplerenone have been reported (e12). In case of intolerance, amiloride can also be used to further lower blood pressure markedly (e13). Of the three agents mentioned, spironolactone is said to have the strongest effect (e14).

Not in all of the patients successfully treated with an aldosterone antagonist an adrenocortical adenoma, adrenocortical hyperplasia or one of the rare genetic disorders can be found. A study involving 157 patients with a high aldosterone-to-renin ratio and elevated plasma aldosterone levels showed that aldosterone may contribute to treatment resistance even in patients without adenoma or hyperplasia (20).

BOX

Blood pressure–increasing substances*

- Alcohol
- NSAR, steroids, estrogens
- Cyclosporine A, tacrolimus
- Erythropoietin
- Neuroleptics, monoamine oxidase inhibitors, tricyclic antidepressants
- Licorice
- Cocaine, amphetamine, methylphenidate
- Sympathomimetics, nasal drops
- Plant-derived substances, e.g. ephedra (contains ephedrine and norephedrine; "Mormon tea", "Ma Huang") or bitter orange (contains synephrine)
- VEGF/VEGFR inhibitors, tyrosine kinase inhibitors

*Compiled from the literature (5, 6, 39, 40, e47) and the authors' experiences. Depending on necessity these medications may be continued under antihypertensive therapy

TABLE

Information to differentiate volume overload and/or increased sympathetic activity in treatment-resistant hypertension*

Volume overload:	Increased sympathetic activity (vasoconstriction)
High salt intake	Sinus tachycardia
Edema	Status post stroke
Low plasma renin activity	Sleep apnea
Absence of increase in blood urea nitrogen, creatinine, and uric acid levels under diuretic treatment	Alcoholism
Chronic renal disease	Paroxysmal or labile hypertension

*adapted from (24)

Measuring plasma renin activity (or plasma renin levels) and plasma aldosterone should be regarded as an essential part of the work-up for resistant hypertension.

High salt sensitivity

High salt intake can increase blood pressure and reduce or neutralize the blood pressure–lowering effect of antihypertensive agents, resulting in treatment resistance (e10). By repeatedly measuring 24-h urinary sodium excretion, patients with high salt intake (>5–6 g/day corresponding to a sodium excretion of 80–100 mmol/24 h) can be identified, allowing for targeted treatment based on thorough advice and special drug selection.

Options for the pharmacotherapy of resistant hypertension

The following information only applies to patients with true treatment resistance. The therapeutic regimen for the majority of these patients includes

- an ACE inhibitor or angiotensin receptor blocker (A)
- a beta blocker (B)
- a calcium channel blocker (C)
- and, by definition, a diuretic (D).

The earlier AB/CD rule (e18) from the British Hypertension Society's guidelines was revised regarding the use of beta blockers (B) by the National Institute for Health and Clinical Excellence in 2006 after a meta-analysis (e19) revealed a 16% higher stroke rate for beta blockers compared with other antihypertensive agents. Since no RCTs evaluating the following treatment strategies are available, it is not possible to provide any evidence levels; however, the strategies presented here are based on well-founded pathophysiological considerations.

Drug regimen strategies for treatment-resistant hypertension

The goal of the following recommendations is to put special emphasis on certain drugs within the triple combination or to help with the targeted selection of a fourth antihypertensive agent.

Volume depletion and treatment guided by plasma renin activity (Cambridge αβΔ-guideline)

For difficult-to-treat hypertensive patients, the British Hypertension Society (BHS) suggested triple-combination therapy with A+C+D drugs as early as 2003 (e18).

This regimen was developed further to the Cambridge αβΔ guideline for hypertensive patients without concomitant diseases, taking into consideration the results of plasma renin testing (23, e20). The basic pathophysiological concept is the well-known idea that hypertension is maintained by volume overload (=sodium retention) and/or vasoconstriction. Plasma renin levels are measured to determine where a specific patient is located on the continuum between the two pathophysiological extremes. As a result, inadequately controlled patients will receive in addition to the A+C+D regimen a beta-blocker (β) in case of high renin levels, an alpha-blocker (α) in case of normal renin levels, while in case of low renin levels the diuretic drug is changed or its dose increased (Δ). Here it must be considered that normal renin levels under A+C+D therapy may indicate non-compliance or aldosteronism as all three classes of antihypertensive agents (at optimum dose, with the exception of verapamil) stimulate renin.

The classification based on renin status has proven its value as shown in several TRH studies of recent years (e21, e22). However, it is expected that the evaluation of the sensitivity and the specificity of renin testing as well as the success rate of this treatment strategy will only be possible on the basis of the BHF/BHS PATHWAY 2 study in 2015 (http://cvrisk.mvm.ed.ac.uk/ research/pathway2.htm).

Volume depletion and sympathetic block

Based on the same pathophysiological considerations but without obligatory renin testing, Mann (24) suggests a similar differentiation. His approach is mainly based on clinical symptoms *(Table)*. In suspected volume retention, an aldosterone antagonist (spironolactone, eplerenone, each 25–50 mg/day) as an additional diuretic and/ or another potassium-sparing diuretic (amiloride 5–10 mg/day) is recommended; in the presence of assumed increased sympathetic activity a combined α/β blockade should be used, preferably with doxazosin, plus a beta blocker without or with only minor hepatic first pass effect because this offers a more balanced bioavailability (for example atenolol, bisoprolol and others). With this approach, Mann and Parikh achieved their therapeutic goal in 24 of 27 treatment-resistant patients (89%) (25).

Direct vasodilation and blocking of counter regulation

In our experience, this strategy is often successful as a last resort in cases of treatment resistance, even though it is no longer listed in the current guidelines due to a

lack of supporting evidence (6). As direct vasodilator drugs, minoxidil and dihydralazine are available.

As early as 1976, the strong vasodilating effect and the outstanding role of minoxidil in otherwise uncontrollable hypertension was discovered (e23), among others in advanced renal failure (e24). In 1979 it was approved for the treatment of TRH by the U.S. Food and Drug Administration (FDA) (e25). Due to its adverse effects it had since been nearly forgotten; however it has seen a revival in recent years (26). It is crucial to prevent the regularly occurring adverse effects of reflex tachycardia and salt-water retention by prescribing a β-blocker as co-medication (as an alternative clonidine) and a diuretic (typically a loop diuretic) (e26). According to the product information, pericardial effusions are found in one out of 10 to 100 patients, or more rarely according to other sources in the literature (e27); thus, regular ultrasound monitoring is recommended. Among the other possible adverse effects, the reversible hirsutism should be mentioned, because it may limit the use of this drug in women.

There are no hard data available to support the use of the weaker direct vasodilator dihydralazine in patients with treatment-resistant hypertension. However, it was, as an add-on medication, part of numerous hypertension intervention studies in patients not adequately responding to older study medications. In cases of contraindications/intolerance of minoxidil, a treatment attempt can be made in patients with suspected vasoconstriction. Due to its short duration of action, dihydralazine is to be given in three to four doses throughout the day, while a single dose is required with minoxidil. Heart rate–reducing and diuretic concomitant therapy is identical with the procedure described for minoxidil.

Comments on the various groups of antihypertensive agents

Diuretics

The particular importance of volume retention as a cause of treatment resistance was confirmed in a study where volume status was assessed by measuring thoracic impedance, the diuretic treatment was adjusted accordingly, and consequently a higher success rate was achieved compared with specialist care (e28). An important requirement for the effectiveness of diuretics is keeping a low-salt diet.

The most prescribed diuretic agent in Germany, hydrochlorothiazide (HCT), was criticized because of a lack of evidence of its efficacy, insufficient blood pressure reduction and poor adherence rates (27, e11). It is therefore recommended that treatment-resistant patients should receive chlorthalidone (CTD) (e29) which is well researched and effectively reduces morbidity and mortality. Compared with HCT, it provides better blood pressure reduction (28), is superior in the prevention of cardiovascular complications (29), and has proven to be effective in TRH (30). However, this antihypertensive agent is prescribed only occasionally in patients with treatment resistance (31). Indapamide is ranked at the same level as CTD (e30).

If the therapeutic goal is not achievable under this medication, a sequential nephron block (e31) (thiazide + loop diuretics) along with weight and electrolyte monitoring may resolve the volume retention.

With all hypokalemia-causing diuretics, it is important to maintain serum potassium levels within the normal range. The positive effect of blood pressure lowering is partly undone by arrhythmias triggered by hypokalemia (e32).

In contrast, under potassium-sparing diuretics and aldosterone antagonists, hyperkalemia may occur, in particular in cases of renal failure if combined with an ACE inhibitor/AT1 inhibitor, an NSAR or beta blocker. Potassium levels and kidney function are to be checked before and under every diuretic therapy, subject to the overall clinical condition. With serum creatinine levels above 2 mg/dL, a loop diuretic should be preferred. Aldosterone antagonists, amiloride and triamterene should not be used in the presence of serum potassium levels above 4.5 mmol/L or renal failure and only with monitoring of potassium levels.

Drugs of last resort

Again for the following antihypertensive drugs (not included in the *Figure*), there are no convincing data from large interventional studies available which provide good reason for their use in patients with TRH. However, they have been used as a co-medication or as last-resort treatment in many large interventional studies to achieve target blood pressure. Essentially, these drugs should only be used once all previous treatments have failed.

Centrally-acting antihypertensive agents (antisympathotonics)

Clonidine has been used early in cases with severe uncontrollable hypertension because of its strong blood pressure–lowering potency (e33, e34). In particular patients with multiple-agent therapy, including diuretics, respond well to this medication (32). For differential therapy, clonidine is well suited in patients with high heart rates and in combination with the sympathetic tone–stimulating agent minoxidil or dihydralazine as it reduces the sympathetic tone (e35).

Moxonidine, although frequently prescribed, is not recommended because it leads to increased morbidity and mortality in heart failure patients (32). Data from a small study may justify the use of urapidil, a drug with proven benefits in emergency care, for the management of patients with treatment-resistant hypertension and advanced renal failure (e36).

Comment on recently introduced invasive methods

Renal sympathetic denervation, where a catheter introduced via the femoral artery delivers radiofrequency energy to ablate the sympathetic nerve fibers in both renal artery walls, may represent a new therapeutic option for the treatment of resistant hypertension (33). However, this technique is still experimental and numerous questions have yet to be answered (e37).

Following the initial hype (33) and the uncritical use of the method in Germany (34), the Symplicity HTN-3 study (e38), initiated by the U.S. Food and Drug Administration, was terminated in February 2014 by Medronic, the manufacturer of the catheter used, because the primary endpoint—lowering of the systolic occasional blood pressure by ≥ 5 mm Hg—was not achieved after 6 months compared with a sham control arm. The study, published online in March 2014, showed only a group difference of 2 mm Hg for office and 24h ambulatory systolic blood pressure (35). The European Society of Hypertension and national expert teams have so far remained rather reserved regarding the indication for this interventional method (6, 36, 37, e40). Before their statements have not been released one should refrain from referring further patients for treatment with this method. Given the apparent absence of safety concerns (35, e39), the method may be useful for the altogether rather small patient population with true treatment resistance, provided all contraindications are observed and only after rigorous investigations and treatment, as described in this paper (38).

Another invasive method is baroreflex stimulation (electrical stimulation of the carotid sinus nerve) which underwent a revival based on two studies (3, 4). Although the method proved very effective in lowering blood pressure (e41), no negative effect on renal function was found (e42) and even a positive effect on structural and functional cardiac parameters was demonstrated (e43).

In contrast to renal sympathetic denervation, baroreflex stimulation is an essentially reversible method; the system can be switched off in the event of hypotension or shock and be adapted to the requirements of a circadian blood pressure rhythm by external programming via radiofrequency telemetry (e44, e45). In Europe, baroreflex stimulation has been approved for the treatment of patients with resistant hypertension and a high cardiovascular risk (e46); however, it should be reserved to selected centers with great expertise in the treatment of hypertension and undertaken in close collaboration with vascular surgeons.

KEY MESSAGES

- In Germany, approx. 20% of all hypertensive patients are considered treatment-resistant.
- Controlled intervention studies on the pharmacotherapy of this high-risk group are not available.
- In-depth investigations can reduce the number of patients with treatment-resistant hypertension.
- Pharmacotherapy based on pathophysiological considerations further cuts the number of patients with treatment-resistant hypertension.
- Baroreceptor stimulation or renal denervation may be considered, as still experimental treatment options in the context of registers/treatment studies, as a last resort after all other pharmacotherapy options have been exhausted.

Acknowledgment
Dedicated to our teacher Prof. Dr. med. Klaus Dietrich Bock.

Conflict of interest statement
The authors declare that no conflict of interest exists.

Manuscript received on: 27 December 2013; revised version accepted on 7 April 2014

Translated from the original German by Ralf Thoene, MD.

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