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REVIEW

Prevention

Resistant hypertension: what the cardiologist needs to know

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Treatment-resistant hypertension (TRH) affects between 3 and 30% of hypertensive patients, and its presence is associated with increased cardiovascular morbidity and mortality. Until recently, the interest on these patients has been limited, because providing care for them is difficult and often frustrating. However, the arrival of new treatment options [i.e. catheter-based renal denervation (RDN) and baroreceptor stimulation] has revitalized the interest in this topic. The very promising results of the initial uncontrolled studies on the blood pressure (BP)-lowering effect of RDN in TRH seemed to suggest that this intervention might represent an easy solution for a complex problem. However, subsequently, data from controlled studies have tempered the enthusiasm of the medical community (and the industry). Conversely, these new studies emphasized some seminal aspects on this topic: (i) the key role of 24 h ambulatory BP and arterial stiffness measurement to identify 'true' resistant patients; (ii) the high prevalence of secondary hypertension among this population; and (iii) the difficulty to identify those patients who may profit from device-based interventions. Accordingly, for those patients with documented TRH, the guidelines suggest to refer them to a hypertension specialist/centre in order to perform adequate work-up and treatment strategies. The aim of this review is to provide guidance for the cardiologist on how to identify patients with TRH and elucidate the prevailing underlying pathophysiological mechanism(s), to define a strategy for the identification of patients with TRH who may benefit from device-based interventions and discuss results and limitations of these interventions, and finally to briefly summarize the different drug-based treatment strategies.

Keywords Arterial hypertension • Arterial stiffness • Isolated systolic hypertension • Secondary hypertension • Renal denervation

Introduction

There is wide variability in the reported prevalence of treatment-resistant hypertension (TRH) with rates from 3 to 30% of hypertensive patients.[1–7]

Medical care for these patients has been proved to be difficult, time-consuming, and often frustrating. Accordingly, for those patients with documented TRH, the guidelines suggest to refer them to a hypertension specialist/centre in order to perform adequate work-up and treatment strategies. Although TRH is a relevant problem associated with significant cardiovascular (CV) morbidity and mortality (*Table 1*),[8,9] until recently, it received little attention from the medical establishment. With the advent of catheter-based renal denervation (RDN), the interest for this high-risk population has increased dramatically.[10] Driven by a medico-industrial complex and sustained by a large echo in the media, the initially very promising blood pressure (BP)-lowering effects of TRH in patients with TRH[11,12] were used to suggest that this novel therapeutic option may represent an easy solution for a complex problem. However, this overoptimistic view has been tempered by recent data from controlled studies that failed to demonstrate efficacy of TRH[13] or showed efficacy only in highly selected patients.[14]

The revitalized scientific interest for this topic has allowed us to identify several important aspects that need to be considered in the evaluation and management of patients with TRH. The aim of this review is to discuss some points that are seminal for the cardiologist, namely (i) the key role of 24 h ambulatory BP measurement (ABPM) for the assessment of patients with suspected TRH to rule out white coat hypertension, confirm the diagnosis, and guide the further evaluation; (ii) the importance of excluding secondary hypertension as underlying cause of TRH by appropriate work-up; (iii) evaluate the presence of vascular remodelling to guide further investigation;

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Table 1 Co-morbidities associated with resistant hypertension

Co-morbidities	Odds ratio (95% CI)
Coronary artery disease	1.3 (1.1–1.5)
Peripheral vascular disease	1.3 (1.1–1.5)
Cerebrovascular disease	1.3 (1.1–1.5)
Congestive heart failure	2.9 (2.4–3.4)
Atrial fibrillation	3.5 (2.0–6.2)
Left ventricular hypertrophy	2.1 (1.2–3.6)
Chronic kidney disease	2.1 (1.8–2.5)
Albuminuria	2.4 (1.7–3.5)

(iv) define a strategy to identify patients with TRH who may benefit from device-based interventions; (v) discuss results and limitations and provide indications for the use of device-based interventions in TRH; and (vi) briefly summarize the medical treatment for TRH.

Definition and prevalence of treatment-resistant hypertension

The reported variation in the prevalence of TRH in a general hypertensive patient population is due to differences in the definition of and in the methods used for the assessment of BP resistance.

According to the most recent European Society of Hypertension/European Society of Cardiology guidelines on hypertension, TRH is defined as office systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg despite appropriate life-style measures and antihypertensive treatment including a diuretic (at full dose) and two other antihypertensive drugs of different classes at adequate doses.[7] A drawback of this definition is based on office BP measurements and, therefore, may result in the inclusion of a significant proportion of patients with white coat hypertension.

Work-up of patients with suspected resistant hypertension

Key role of 24 h ambulatory blood pressure measurement

Rule out white coat hypertension

Given the high prevalence of white coat hypertension in patients with suspected TRH based on office BP measurements, 24 h ABPM should be part of the routine work-up (*Figure 1*). Clinical signs suggestive of white coat hypertension are high office BP values without signs of target organ damage (discussed subsequently) and the presence of symptoms associated with hypotension (i.e. dizziness, fatigue, and blurring) that may be related to antihypertensive over-treatment. The importance of 24 h ABPM to rule out white coat hypertension in the setting of suspected TRH is demonstrated by de la Sierra *et al.*[15] in a large cohort of hypertensive patients. In this study, the prevalence of TRH based on office BP (systolic office BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on three or more antihypertensive drugs, one of them being a diuretic) was 12.2%. Of these patients, roughly one-third had white coat hypertension, suggesting that in unselected patients treated for hypertension, the prevalence of TRH based on 24 h ABPM is <10%. In line with this estimation, in a study using 24 h ABPM to determine the eligibility for catheter-based RDN, the proportion of patients with TRH was <10%,[16] and a recent survey of a very large population (>172 000) of patients with hypertension reported a prevalence of TRH of <5%.[17] Parenthetically, it should be noted here that inaccurate BP measurement techniques are a common cause of pseudo-resistance in patients treated for hypertension. Particular attention should be paid to adequate cuff size, because the use of a cuff size that is too small for the circumference of the arm may result in the overestimation of BP by >15 mmHg.[18]

Based on these observations and in accordance with recent guidelines (i.e. NICE guidelines)[19] and other experts in the field,[20,21] we deem 24 h ABPM to be mandatory for the diagnosis, risk stratification, and work-up in patients with suspected TRH (*Table 2*).

Alteration of the dipping status as a clue for the presence of secondary hypertension

In patients with TRH, the prevalence of secondary hypertension is significantly higher than that in the general hypertensive population.[22] This is illustrated by Azizi *et al.*[14] in a cohort of 1416 patients with TRH who were screened for eligibility of RDN, and of whom >50% had to be excluded because of the presence of secondary hypertension.

Twenty-four-hour ABPM allows the assessment of night-time BP. The absence of a night-time drop (dipping of >10% relative to the daytime BP) or the increase of BP during night time ('reverse nocturnal dipping') is often associated with secondary hypertension.[22] The most common causes of secondary hypertension in the context of treatment resistance and non-dipper status are obstructive sleep apnoea (OSA), renal parenchymal and/or vascular disease, and primary aldosteronism (PA). Screening for these common causes should be performed as follows (for more detailed information, see our recent review[22]).

Rule out secondary hypertension as a cause of treatment-resistant hypertension

Obstructive sleep apnoea

OSA has been identified as one of the most common causes of secondary hypertension. Non-dipping or reverse dipping associated with a history of snoring, daytime sleepiness, and morning headache should prompt to suspect OSA. Screening for OSA can easily be done by assessing daytime sleepiness using a questionnaire (Epworth screening questionnaire) and by home sleep testing using a portable sleep monitor device. If the latter reveals an increased apnoea–hypopnoea index (i.e. >5 apnoeas/hypopnoeas per hour of sleep), the patient should be referred to a specialist for further evaluation and treatment.

Renal parenchymal or renovascular disease

Screening for renal parenchymal disease should be performed by urine analysis (protein, erythrocytes, and leucocytes) and measurement of serum creatinine concentration. In the case of a pathological finding, renal ultrasound should be the next step.

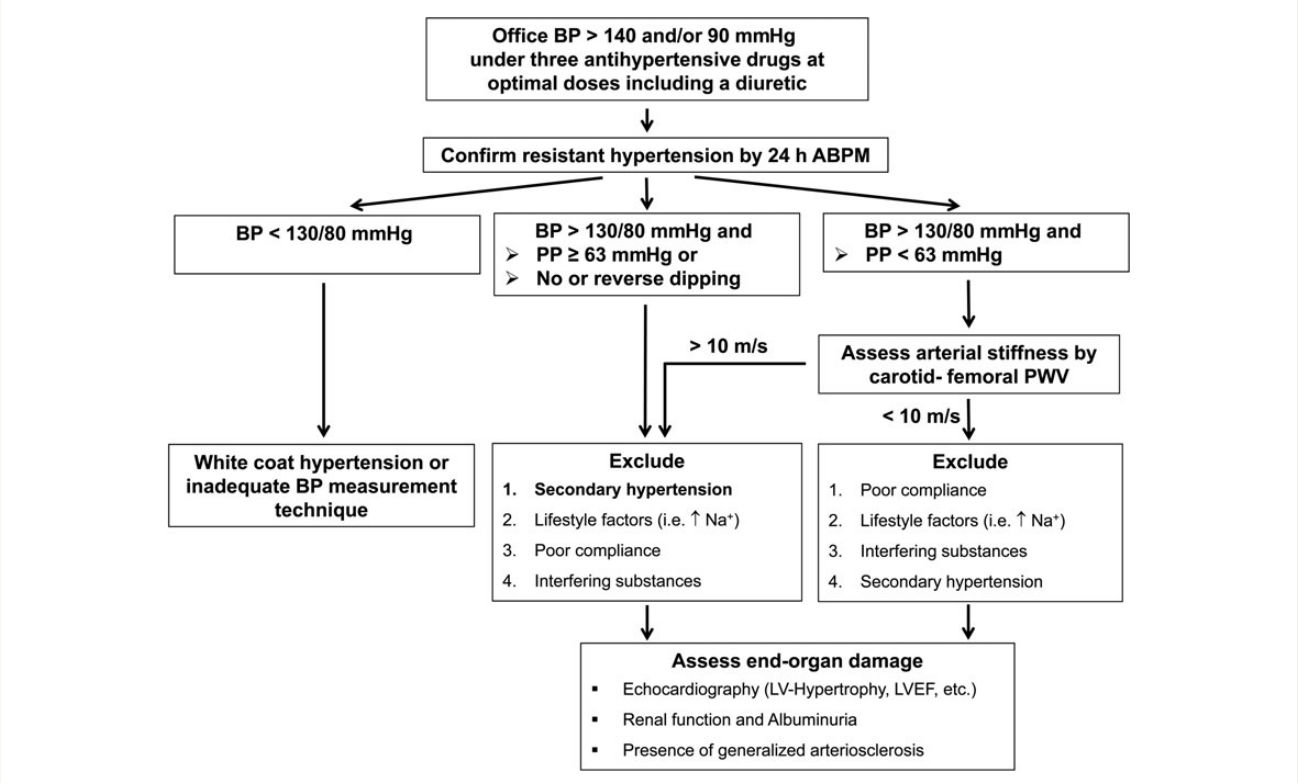

Figure 1 Work-up of patients with suspected treatment-resistant hypertension. The work-up comprises three main steps: (i) confirmation of resistant hypertension by 24 h ABPM; (ii) evaluation of night-time BP dipping; and (iii) assessment of vascular stiffness. After confirmation of TRH by 24 h ABPM and if altered dipping or increased vascular stiffness is present, exclusion of secondary hypertension should be the next step. In those patients with normal dipping status and 24 h PP $<$ 63 mmHg, carotid-femoral PWV should be measured. If normal (i.e. $<$10 m/s), poor compliance, life-style factors, and interfering substances should be excluded, before searching for secondary hypertension. ABPM, ambulatory blood pressure measurement; BP, blood pressure; Na^+, sodium; LVEF, left ventricular ejection fraction; PWV, pulse-wave velocity; PP, pulse pressure.

Table 2 Value of office, home, and 24 h ambulatory blood pressure measurement in resistant hypertensive patients

Significance	Office BP	Home BP	24 h ABPM
Diagnosis of resistant hypertension	+/−	+	+++
Prognostic value	+/−	+	+++
Exclusion of white coat hypertension	−	+/−	++
Assessment of therapy adherence	−	+/−	++
Differentiation primary/secondary hypertension	+/−	+/−	++

Although in the general hypertensive population the presence of atherosclerotic renal artery stenosis (RAS) is low (1–8%),[23,24] its prevalence in patients with TRH is much higher (i.e. 15–40%).[22] Non-dippers with abrupt progression of the severity of hypertension or recent renal function deterioration [particularly after therapy with angiotensin-converting enzyme (ACE)-inhibitors or angiotensin-receptor blockers] or patients presenting with flash pulmonary oedema (i.e. Pickering syndrome)[25,26] should be screened for RAS by duplex ultrasound, computed tomography, or magnetic resonance imagining.

Primary aldosteronism

Primary aldosteronism refers to inappropriately high aldosterone synthesis that is independent of the renin–angiotensin system and cannot be suppressed by sodium loading. Clinical signs of PA are not very specific, and hypokalaemia is present in only ∼40% of the patients with confirmed PA. As a first screening step, the plasma aldosterone–renin ratio (ARR) should be assessed after adequate preparation of the patient.[22] In the case of increased ARR, the patient should be referred to a hypertension specialist/centre for additional work-up and treatment.

Less common causes of secondary hypertension

For an extensive discussion about screening for less common causes of secondary hypertension, we refer to our previous review.[22]

Evaluate the presence of vascular remodelling

In the next step, we propose to evaluate the presence of increased arterial stiffness, because in patients with true TRH vascular remodelling is likely to be present. The gold standard method to non-invasively assess arterial stiffness is the measurement of carotid-femoral pulse-wave velocity (PWV).[27] This is easily done by using appropriate devices,[28] and normal values have been published.[29] Alternatively, it is often forgotten that pulse pressure (PP = systolic BP − diastolic BP) is a valid and widely available proxy of vascular stiffness.[27] PWV > 10 m/s,[29] 24 h PP ≥ 63 mmHg,[30] or central PP > 55 mmHg[31] suggests vascular remodelling. The absence of increased arterial stiffness suggests the presence of pseudo-resistance, and we suggest to search for poor treatment adherence, life-style factors known to increase arterial BP, and drugs interfering with the antihypertensive treatment.

If vascular remodelling is absent, rule out poor treatment adherence, life-style factors that increase arterial BP, and substances interfering with efficacy of antihypertensive treatment

Poor treatment adherence

Non-adherence is one of the most frequent causes of treatment 'resistance',[32] with up to 50% of the patients with apparent resistance not taking their medication as prescribed, when adherence is assessed by urine analysis.[33] Accordingly, when adherence is monitored, roughly one-third of patients with 'apparent' TRH normalize their BP.[34] Several strategies have been proposed to assess and improve therapy adherence, including the measurement of drug concentrations in serum or urine, the use of pillboxes recording every opening event, and specific counselling programmes. This topic has been recently extensively discussed[35] and is beyond the scope of our article, but as an example, electronic pillboxes have been shown to improve and normalize BP in roughly 30% of the 'resistant' hypertensive patients.[34] Performing 24 h ABPM immediately after the patient has taken his/her antihypertensive drugs in the presence of a nurse or physician is an easy way to assess the effect of the prescribed medication.

Rule out life-style factors causing RHT

Life-style modifications reduce BP by 5–10 mmHg in non-selected hypertensive patients.[36] Obesity, excessive salt intake, and alcohol consumption are frequently associated with TRH.

Obesity. Treatment-resistant hypertension and more severe hypertension are often associated with obesity.[37] Underlying mechanisms contributing to this problem are an increased cardiac output related to sodium retention and subsequent volume expansion[38] and increased sympathetic nervous system (SNS) activity, particularly in obese patients suffering from concomitant OSA.[39] It has to be kept in mind, however, that in the general hypertensive population, weight loss is associated with modest BP reduction (i.e. systolic/diastolic BP reduction of 2/1 mmHg per kg of body weight loss),[40] and data on the effect of weight loss on BP in obese patients with TRH are scarce.[37] It appears that interventions targeting simultaneously several life-style modifications (i.e. weight loss, lower salt, and alcohol consumption) are more effective than interventions targeting each of these factors sequentially.[41]

Sodium consumption and water retention. Patients with TRH often are salt-sensitive and are characterized by an increased salt intake and impaired renal function.[42–45] Increased sodium consumption (i.e. >6 g/day) is associated with a gradual rise in BP and CV risk in normotensive and hypertensive subjects.[42] The BP-lowering effect of decreased sodium consumption is particularly marked in 'salt-sensitive' patients with HT (i.e. Africans and East Asians, obese and elderly of all ethnicities),[46] which may be related to the altered responsiveness of the renin–angiotensin–aldosterone system (RAAS).[42] In patients with TRH, excessive salt intake contributes importantly to resistance, as shown by a marked decrease in both office (by 22.7/9.1 mmHg) and 24 h ambulatory BPs (by 20.7/9.6 mmHg) during dietary sodium restriction in a cross-over study by Pimenta *et al.*[44] The magnitude of the sodium restriction-induced decrease of BP is substantially greater in patients with TRH than in normotensive subjects or general hypertensive patients. This observation is consistent with the hypothesis that in TRH, excessive sodium consumption is a major contributor to treatment resistance, particularly when associated with increased arterial stiffness.[44] The relationship among vascular stiffening, ageing, and volume expansion is shown in *Figure 2*:[47] with ageing and consequent stiffening of the vasculature, a small increase in volume is associated with an exaggerated increase in BP. Thus, vascular remodelling and volume expansion are two important mechanisms involved in the pathogenesis of TRH (*Figure 3*).

Alcohol consumption. Acute alcohol intake increases BP by sympathetic activation that appears to be centrally mediated.[48] Moreover, chronic heavy alcohol intake (>60 g/day ethanol) increases BP even in normotensive subjects.[48,49] There is, however, little information on the role of excessive alcohol consumption and the effect of its reduction in patients with TRH.[50]

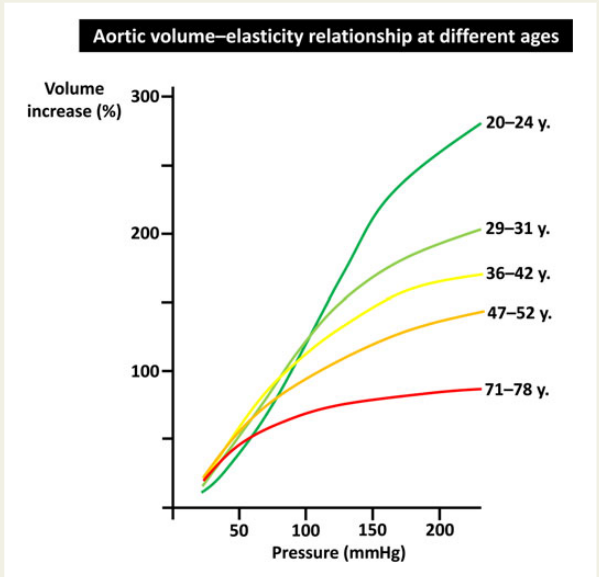

Figure 2 Age dependency of the aortic volume–pressure relationship. With increasing age, volume expansion results in a markedly larger increase of aortic pressure, reflecting the increasing vascular rigidity associated with ageing [modified from (37) with permission].

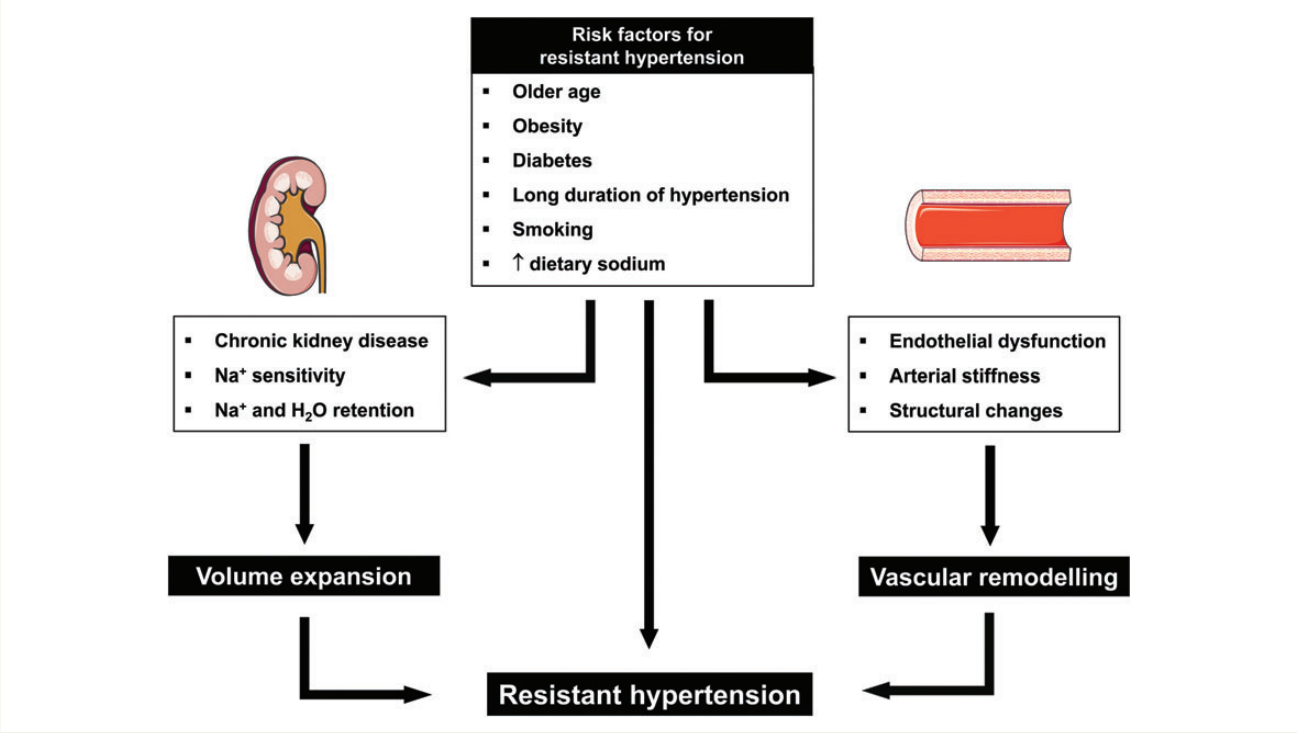

Figure 3 Risk factors and pathogenic mechanisms associated with treatment-resistant hypertension. Risk factors for treatment-resistant hypertension often induce vascular remodelling and volume expansion, two factors known to contribute to resistant hypertension. BP, blood pressure; Na^+, sodium; PWV, pulse-wave velocity; LV, left ventricular; EF, ejection fraction.

Substances or drugs interfering with antihypertensive treatment. Several substances and drugs can induce arterial hypertension or interfere with antihypertensive medications. For an extensive discussion of this topic, we refer to a previous review.[51] In the context of TRH, the potential role of a BP rising effect by non-steroidal anti-inflammatory drugs (NSAIDs) needs to be considered. NSAIDs induce sodium and water retention by inhibition of renal prostaglandin synthesis as well as other mechanisms. In susceptible patients (i.e. elderly, salt-sensitive, and pre-existing renovascular disease), this effect may lead to treatment resistance and/or acute renal failure. Moreover, NSAIDs may interfere with several important antihypertensive drug classes [ACE-inhibitors, angiotensin-receptor blockers (ARBs), and β-blockers].

Identification of patients with treatment-resistant hypertension who may benefit from device-based interventions

Patients who remain hypertensive despite treatment with a combination of 'A' (ACE-inhibitor or ARB) with 'C' [calcium channel blocker (CCB)] plus 'D' (thiazide-like diuretic, i.e. chlortalidone or indapamide) at the maximal tolerated dosage and a fourth-line antihypertensive agent (i.e. aldosterone antagonist, discussed subsequently) may qualify for a device-based intervention.

With the demonstration of the failure of RDN to lower BP in the general population of patients with TRH, identification of patients with TRH who may/may not benefit from device-based intervention becomes of major importance. In the following, we focus on sympathetic activation, isolated systolic hypertension (ISH), and arterial remodelling as potential predictors of the success and/or failure of device-based intervention (*Figure 4*).

Excessive sympathetic activity does not predict the BP response to device-based intervention

Excessive activity of the SNS has been suggested to contribute importantly to the sustained BP increase in hypertensive patients.[52] This notion was confirmed by Grassi *et al.*,[53] showing marked sympathetic activation and baroreflex dysfunction in TRH. It needs, however, to be kept in mind that the pathogenic role of sympathetic activation seems to be most relevant in young (and/or obese) hypertensive patients.[52,54] In line with this hypothesis, surgical sympathectomy has been documented to reduce BP and mortality in young (mean age 42 years) hypertensive patients.[55] In contrast, several recent studies refute the hypothesis of a major role of the SNS in the pathogenesis of TRH in elderly patients,[13,56] and BP changes after RDN were reported to be temporarily, qualitatively, and quantitatively independent of sympathetic and baroreflex effects.[57] Taken together, the current evidence suggests that pre-intervention assessment of sympathetic nerve activity is a poor predictor of BP response to RDN.

Isolated systolic hypertension, a contraindication for device-based intervention?

Twenty-four-hour ABPM should be performed to confirm the presence of therapy resistance (24 h ambulatory pressure >130/80 mmHg) and to check whether marked ISH (24 h ambulatory

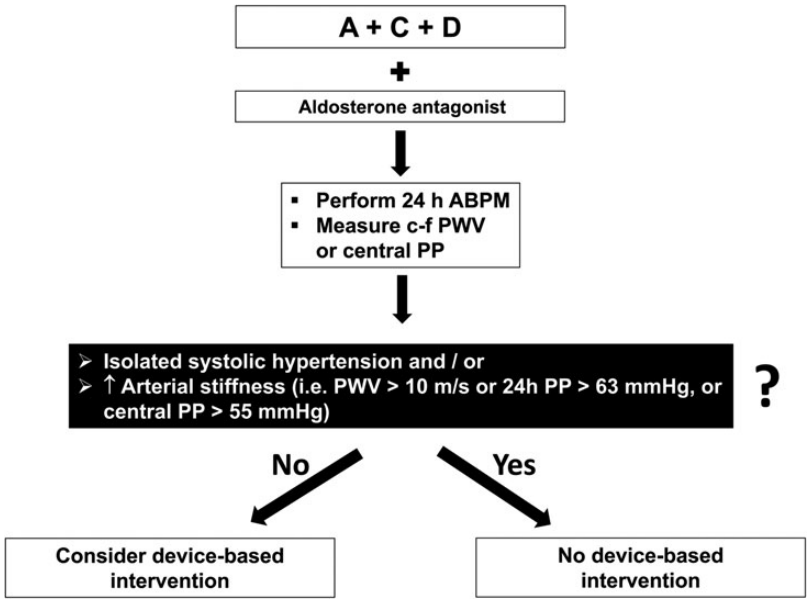

Figure 4 Screening for device-based interventions. Patients remaining hypertensive under therapy with the combination A + C + D plus an aldosterone antagonist should undergo 24 h ABPM and arterial stiffness assessment. If isolated systolic hypertension or increased arterial stiffness (i.e. carotid-femoral PWV > 10 m/s and/or 24 h PP > 63 mmHg and/or central PP > 55 mmHg) is found, device-based interventions should be not performed. A, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; C, calcium channel blocker; D, thiazide(-like) diuretic; ABPM, ambulatory blood pressure measurement; PWV, pulse-wave velocity; PP, pulse pressure.

PP ≥ 63 mmHg)[30] is present. Systolic and diastolic BPs increase until the age of about 50 years. Thereafter, due to age-related progressive stiffening of the vasculature, systolic BP continues to increase whereas diastolic BP decreases. This has three important consequences: (i) the proportion of patients with ISH increases with age, from about 47% in the decade of the 50–59 years old to >75% a decade later;[58] (ii) in people >50 years, systolic BP becomes the most important determinant and predictor of CV risk;[59] and (iii) ISH is a marker for increased arterial stiffness (also discussed subsequently) and has been associated with blunted BP response to RDN.[56] Accordingly, we suggest that the presence of ISH is a contraindication to device-based interventions.

Pronounced arterial stiffness, a contraindication for device-based intervention

Advanced vascular remodelling represents a 'common denominator' for ISH, TRH, and poor systolic BP control (*Table 3*). Most importantly, vascular remodelling is an important factor associated with a blunted BP-lowering effect of device-based interventions. In line with this concept, patients with pronounced arterial stiffening[31,60] and/or ISH[56] show no or a reduced effect of RDN on BP. Indeed, in a recent observation, roughly 30% of the patients with TRH taking six antihypertensive drugs failed to attain target BP values (home BP <135/85 mmHg) after RDN.[14]

Therefore, assessment of arterial stiffness by measuring carotid-femoral PWV or central PP should be part of the work-up of patients with TRH before considering device-based interventions.

Table 3 Patient characteristics associated with increased arterial stiffness, resistant hypertension, and isolated systolic hypertension

Characteristic	↑ Arterial stiffness	Resistant hypertension	Isolated systolic hypertension
Older age	++	++	+++
Poor systolic BP control	++	++	+++
Obesity	+	++	+/−
Diabetes mellitus	+	++	++
Smoking	++	++	++
Vascular atherosclerosis	++	++	++
↑ Carotid IMT	++	++	++
LV hypertrophy	++	+++	+++
Chronic kidney disease	+++	++	++

IMT, intima-media thickness; LV, left ventricle.

The presence of exaggerated arterial stiffness (i.e. carotid-femoral PWV > 10 m/s,[29] or 24 h PP > 63 mmHg,[30] or central PP > 55 mmHg[31]) represents a contraindication for device-based intervention.

Device-based and medical therapy of patients with resistant hypertension

Device-based interventions

Attenuation of exaggerated activity of the SNS represents the aim of device-based interventions (i.e. carotid baroreceptor stimulation and RDN) for the treatment of TRH. Some (patho)physiological differences between these two interventions should, however, be kept in mind. Although carotid baroreceptor stimulation decreases central neural sympathetic outflow through electrical activation of this sympatho-inhibitory reflexogenic area, RDN decreases sympathetic over-activity by ablation of renal sympatho-excitatory afferents. Moreover, carotid baroreceptor stimulation significantly decreases resting heart rate, whereas RDN has no detectable effect on this variable.

In the following, we will briefly review the pathophysiological background and the clinical evidence of these two device-based therapeutic options.

For an extensive overview on this topic, we refer to a previous review.[61]

Carotid baroreceptor stimulation

Electrical stimulation of the carotid baroreceptor(s) causes a sustained reduction of sympathetic outflow and arterial BP in animal models of hypertension and humans.[62–64] Similarly, in animal models of obesity-induced hypertension, baroreceptor activation induces a sustained BP decrease through global- and renal-specific inhibition of SNS activity.[65] In contrast, in animal models of angiotensin II-induced hypertension and aldosterone hypertension,[66] baroreflex-induced reductions in arterial BP are blunted,[62,67] suggesting that this intervention may not be very effective in the presence of high concentrations of angiotensin II or aldosterone. In humans with TRH, baroreceptor stimulation has been found to decrease 24 h ambulatory BP (−10/6 mmHg) by reducing central neural sympathetic outflow and renin release at 4-month follow-up.[68] Interestingly, recent data suggest that unilateral right-sided carotid baroreceptor stimulation may be more effective than left-sided or bilateral stimulation in lowering office BP in patients with TRH.[69]

The main disadvantages of this technique are the need of surgical implantation and the lack of data on its effectiveness on CV events. Therefore, in accordance with recent guidelines, we suggest that baroreceptor stimulation should be considered in patients with TRH only after documented failure of adequate drug treatment, and the implantation of the device should be performed by experienced surgeons in selected hypertension centres (Class IIb, Level C).[7] Moreover, it should be kept in mind that the BP-lowering effect of baroreceptor stimulation may be attenuated in TRH associated with hyperaldosteronism.[66]

Catheter-based renal denervation

The initial enthusiasm for this minimally invasive technique has recently been tempered by the publication of the negative results of the first randomized SHAM-controlled study.[13] As a consequence of these disappointing results, most industry-sponsored studies were stopped, and the scientific community has started an intensive search for possible explanations of this debacle. *Table 4* outlines potential factors and co-morbidities that may result in a blunted BP-lowering effect of RDN in TRH. In the following, we will elaborate a few of them.

Table 4 Potential factors and co-morbidities related to blunted blood pressure lowering effect of renal denervation

Patient-related factors
Vascular remodelling (i.e. exaggerated arterial stiffness)
Older age
Presence of isolated systolic hypertension
Increased pulse-wave velocity and increased pulse pressure
Long duration of hypertension
Generalized arteriosclerosis
Smoking and diabetes
Chronic kidney disease
Pathophysiological factors (i.e. exaggerated sympathetic activation is not a major contributor)
Older age
Ethnicity
Exaggerated salt retention and volume expansion
Anatomical factors
Presence of accessory renal arteries
Secondary renal artery stenosis
Renal sympathetic re-innervation
Medication adherence
Technical factors
Incomplete ablation of the renal nerves
Insufficient number of ablation points
Localization of ablation (should comprise all four quadrants)
Device-related factors
No direct feedback for success of denervation
Insufficient ablation depth
Operator experience

Patient-related factors

Vascular remodelling is often present in TRH and may represent an important factor associated with blunted BP-lowering effect of RDN. In line with this hypothesis, RDN had little or no BP-lowering effect in patients with pronounced arterial stiffening[31,60] and/or ISH.[56]

Another important aspect that needs to be considered is the role of SNS activation in the pathogenesis of TRH. In the elderly, and patients of African and East Asian origin (i.e. salt-sensitive populations) with TRH, increased SNS activity appears to play a minor pathogenic role. In line with this hypothesis, African and East Asian ethnicities have been identified as independent predictors of poor BP response to RDN in the Symplicity HTN-3 trial.[70]

The anatomy of the renal vasculature has been identified as another relevant factor for patient selection and the subsequent BP response to RDN. Roughly 50% of the non-selected patients with

arterial hypertension do not meet the current anatomical eligibility criteria for RDN.[71–73] For example, accessory renal arteries appear to be important for the BP response to RDN, as these arteries, which often are not accessible to denervation, are surrounded by sympathetic nerves.[74] In line with this hypothesis, in patients with accessory renal arteries, the BP reduction achieved by RDN is less pronounced than in patients with bilateral single renal arteries.[75]

Finally, the so-called 'Wilder's principle' (i.e. the pre-treatment value determines the magnitude of the post-treatment response) should be kept in mind, when considering BP responses to an antihypertensive treatment.[76] In the context of RDN, different BP measurement methods (i.e. office BP and 24 h ABPM) have been used to determine the antihypertensive response. In general, office BP values often are significantly higher than ambulatory 24 h BP values. It is not surprising, therefore, that in studies using office BP measurements (higher pre-treatment values→greater post-treatment effect), the BP-lowering effect of RDN is more pronounced than in studies using 24 h ABPMs (lower pre-treatment values→smaller post-treatment effect).[76]

Technical factors

As evidenced by the recent failure of RDN to lower BP in TRH[13] and the ensuing search for anatomical and technical explanations for this failure, effective catheter-based RDN is not as simple as it was initially believed. An extensive discussion on this topic[77,78] is beyond the scope of this review. Nevertheless, we wish to point out a few important aspects: first, incomplete ablation of the renal nerves (i.e. insufficient number of ablation points and/or inadequate localization of ablation) results in a blunted BP-lowering effect.[70,74,79–81] Accordingly, the recent Expert Consensus Guidelines on RDN recommend four-quadrant ablation in order to obtain sufficient ablation of renal sympathetic nerves.[78,81] Of note, in the Symplicity HTN-3 trial, only 6% of the patients underwent bilateral four-quadrant ablation,[81] and a high number of ablations and energy delivery in a four-quadrant pattern were associated with a greater decrease in office and ambulatory systolic BPs in this trial.[70] Secondly, and along the same lines, no ablation device has a useful direct feedback system to detect successful ablation, and, as a consequence, operator experience is essential for successful RDN. The importance of the latter is highlighted by the results of two recent trials. In the Symplicity HTN-3 trial, >30% of the operators performed only one intervention and only 50% performed more than two interventions. In the recently published DENERHTN trial, showing a significant decrease in ambulatory BP in patients treated with standardized stepped-care antihypertensive medications and RDN compared with those without RDN, >80% of the procedures were performed in five centres treating five or more patients.[14,82]

Finally, it has to be noted that even if (and there still remains an 'if') RDN will be documented to consistently decrease BP, we do not know whether or not this decrease in BP will translate into a decrease in stroke, heart attack, and CV death. Interestingly, data in apoprotein E knockout mice suggest that RDN may have favourable CV effects beyond BP lowering as, in this experimental model, RDN attenuated the progression of atherosclerosis.[83]

We recommend considering RDN in patients with TRH under A + C + D plus aldosterone antagonist after exclusion of isolated systolic HT and increased arterial stiffness. Keeping in mind that even when fulfilling the abovementioned criteria, salt-sensitive populations with TRH (i.e. Asians and American Africans) and patients with accessory renal arteries are expected to respond poorly to RDN.

Standard medical treatment approach for treatment-resistant hypertension

The standard medical treatment of TRH has been discussed in detail by others. Briefly, we recommend the following approach (*Figure 5*).

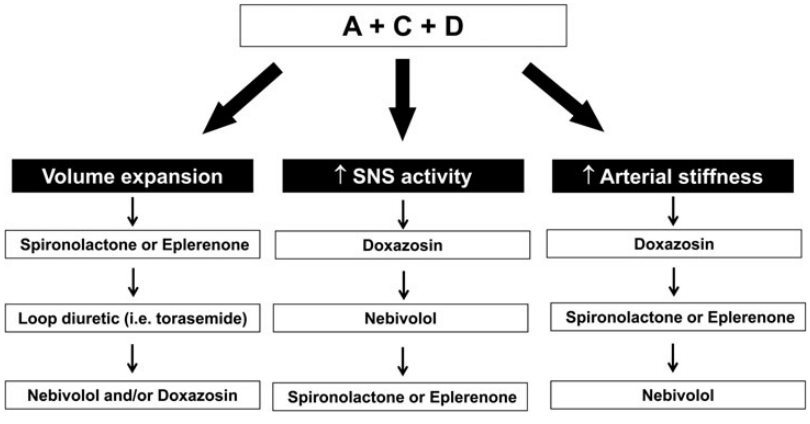

Figure 5 Antihypertensive drug therapy in patients with resistant hypertension. We recommend to start with the combination A + C + D. If the patient remains hypertensive, we recommend a clinical evaluation to determine which one among the three potential pathogenic mechanisms volume expansion, sympathetic over-activity, and increased arterial stiffness prevails over the others, and to add additional drugs in function of this evaluation. A, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; C, calcium channel blocker; D, thiazide(-like) diuretic; SNS, sympathetic nervous system.

First step: A + C + D

RAAS activation plays an important role in the pathophysiology of hypertension. In accordance with several guidelines,[19,84,85] we recommend as first step in the treatment of TRH the combination of A (ACE-inhibitor or ARB) with C (CCB) plus D (thiazide-like diuretic, i.e. chlortalidone or indapamide) at the maximal tolerated dosage. This recommendation is based on a pathophysiological rationale.[86] The 'A + C + D' combination acts on different BP regulatory systems in a way that both activated and counter-regulatory mechanisms are inhibited: although all A + C + D promote natriuresis and vasodilation, A inhibits the RAAS and the SNS activated by 'C + D'.[86] Of note, RAAS activation is often absent in elderly patients and in patients of African origin in whom a low renin status is frequently found.[87] In line with this observation, sequential nephron blockade appeared to be more effective than sequential RAAS blockade for the treatment of TRH,[88] suggesting that these patients may be more sensitive to intensified sodium depletion than to reinforced RAAS blockade.

In patients with a moderate-to-severe impairment of renal function [i.e. glomerular filtration rate (GFR) $\leq$ 45 mL/min/1.73 m^2], a shift from a thiazide(-like) to a loop diuretic should be considered. Although C strategy is often based on dihydropyridine CCBs (i.e. amlodipine, felodipine, lercanidipine, and nifedipine), in some cases (i.e. increased heart rate), non-dihydropyridine CCBs (i.e. verapamil and diltiazem) should be considered.

There is sound evidence that 'A + C',[89–91] 'A + D',[92–94] and 'C + D'[95] are very effective in reducing hard CV endpoints in hypertensive patients. Moreover, recent data show that A + C + D is associated with a significantly greater reduction of all-cause mortality in patients with TRH and diabetes than 'A + Placebo + D'.[96] We recommend, whenever possible, to use single-pill combinations of A + C + D, as these combinations are more effective in lowering BP,[97] have a better adverse effect profile,[98] and improve therapy adherence.[98]

Second step: clinical evaluation to detect whether a pathogenic mechanism prevails over others

If the patient under A + C + D is still hypertensive (i.e. office BP > 140/90 mmHg and/or 24 h ABPM > 130/80 mmHg), we recommend a clinical evaluation to determine whether sodium and water retention [search for peripheral oedema, increased urinary sodium excretion, increased left ventricular (LV) filling pressures, etc.] or sympathetic activation and increased arterial stiffness (increased average heart rate on 24 h ABPM and increased PWV or PP) predominate.

Third step: addition of a fourth-line antihypertensive agent

We recommend different drugs depending on the prevailing pathogenic mechanism detected during step 2. If volume expansion predominates, spironolactone (25–50 mg/day) or eplerenone (50–100 mg/day in the case of gynaecomastia with spironolactone) should be added.[99,100] In the case of increased SNS activity and/or arterial stiffness, an alpha-blocker (i.e. doxazosin) that may have favourable effects on BP and vascular remodelling should be added.[101–103]

Fourth step: addition of a fifth/sixth antihypertensive agent

In the case of persistent volume expansion, we propose to add (in addition to the thiazide, not instead) a long-acting loop diuretic (i.e. torasemide). If persistent sympathetic over-activity is suspected, adding a β-blocker with vasodilator properties (i.e. nebivolol which is also NO donor) or a combined α-/β-blocker (i.e. carvedilol and labetalol) should be considered.[104] In the case of increased arterial stiffness, aldosterone antagonists have been shown to have favourable effects on BP and vascular remodelling.[105] For further steps, see *Figure 5*.

Assessment of target organ damage and co-morbidities in patients with treatment-resistant hypertension

Patients with TRH are at high risk for CV morbidity and mortality and are characterized by an increased prevalence of target organ damages and co-morbidities (*Table 1*).[8,9,106] It is, therefore, important to search for these problems in order to evaluate the overall CV risk and to take appropriate measures.[7]

Cardiac evaluation by echocardiography

Echocardiography allows us to detect morphological alterations that are common in TRH, such as LV hypertrophy ($\geq$115 g/m^2 for men and $\geq$95 g/m^2 for women), left atrial ($\geq$34 mL/m^2), and aortic enlargement,[107] and, in patients with cardiac symptoms, to search for functional alterations such as LV diastolic [septal tissue Doppler early diastolic velocity (e') <8.0 cm/s] and/or systolic dysfunction (LV ejection fraction <55%) and altered LV filling pressures [increased if transmitral E and septal e' (E/e') $\geq$13].[108]

Renal function and (micro)albuminuria

Hypertension-induced renal damage should be searched for by assessment of renal function and by measurement of urinary albumin excretion. The cut-off value for impaired renal function is an estimated GFR (eGFR) <60 mL/min/1.73 m^2, and for microalbuminuria a urinary albumin/creatinine ratio >3.9 mg/g for men and >7.5 mg/g for women. If excessive salt intake is suspected, assessment of 24 h urinary Na^+ excretion is recommended.

Arteriosclerosis

Generalized arteriosclerosis (i.e. coronary, peripheral, and cerebrovascular) is a common finding in patients with TRH[8] and its presence is predictive for future CV events.[2,109] Physical examination should therefore at least include fundoscopy (presence of retinopathy) and the search for carotid, abdominal, and femoral bruits.

If patients with TRH report symptoms evoking generalized arteriosclerosis (i.e. angina pectoris, claudication, and cerebrovascular symptoms) and/or the physical examination reveals suspicious signs, rapid diagnostic work-up (i.e. coronary angiography and duplex of cerebral and peripheral arteries) should be performed, because TRH increases the risk for CV disease,[4] and if associated with coronary artery disease, it markedly increases CV morbidity and mortality.[1]

Follow-up of patients with treatment-resistant hypertension

According to the current European guidelines on hypertension, we recommend 24 h ABPM and assessment of end-organ damage (i.e. search for arteriosclerosis on physical examination, fundoscopy, eGFR, albuminuria, and echocardiography) on a yearly basis.[7]

Conclusions and perspectives

The development of new therapeutic approaches during the last years awakened the 'hibernated' interest on resistant hypertensive patients. Correct diagnosis of 'true' drug resistance through 24 h ABPM, exclusion of a secondary form of hypertension, and assessment of arterial stiffness are indispensable steps in the work-up. The different pathogenic mechanisms involved in therapy resistance are still incompletely understood. Sodium retention and consequent volume expansion and vascular remodelling appear to play a central role; however, specific de-stiffening therapeutic strategies are still under investigation and not available at a large scale.[110] Future studies should elucidate the role of SNS activation in different resistant hypertensive subpopulations and confirm (rule out) its role as an important modifiable determinant of CV morbidity and mortality in these subpopulations. A better understanding of the underpinning pathogenic mechanisms is expected to result in a more personalized therapeutic approach. In particular, there is an urgent need to refine the selection criteria for device-based interventions. Finally, technical advancements of interventional therapy may result in better BP control and, in turn, reduce CV morbidity and mortality in this growing high-risk population.

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