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ORIGINAL ARTICLE

Diagnosis and treatment of resistant hypertension

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Abstract

Hypertension resistant to lifestyle interventions and antihypertensive medications is a common problem encountered by physicians in everyday practice. It is most often defined as a blood pressure remaining ≥ 140/90 mmHg despite the regular intake of at least three drugs lowering blood pressure by different mechanisms, one of them being a diuretic. It now appears justified to include, unless contraindicated or not tolerated, a blocker of the renin–angiotensin system and a calcium channel blocker in this drug regimen, not only to gain antihypertensive efficacy, but also to prevent or regress target organ damage and delay the development of cardiorenal complications. A non-negligible fraction of treatment-resistant hypertension have normal "out of office" blood pressures. Ambulatory blood pressure monitoring and/or home blood pressure recording should therefore be routinely performed to identify patients with true resistant hypertension, i.e. patients who are more likely to benefit from treatment intensification.

Key Words: *Ambulatory blood pressure monitoring, combination therapy (antihypertensive medications), diuretic therapy, hypertension guidelines (hypertension), refractory hypertension, renin–angiotensin–aldosterone system, self-measurement of blood pressure*

Introduction

Current international guidelines recommend to lower clinic blood pressure (BP) levels at least below 140/90 mmHg in hypertensive patients, using both lifestyle and pharmacological interventions (1–3). Achieving such BP targets still represents a difficult task today, even in countries where healthcare is widely accessible. This is reflected by the unsatisfactory BP control observed in treated hypertensive patients across surveys (4–10). This has important implications since treated patients with uncontrolled hypertension exhibit a poorer outcome than those having their BP normalized during antihypertensive therapy (11,12).

Different terms can be used to characterize patients exhibiting abnormally elevated BP despite antihypertensive treatment. "Uncontrolled hypertension" refers to patients having their BP remaining above target, regardless the type and the number of BP lowering drugs they are taken. "Difficult-to-treat hypertension" is another term that is not broadly used. It may be regarded as the persistence of high BP despite treatment with two or three drugs (13). By far the most popular term is "resistant" (or refractory or apparent resistant) hypertension, which, according to recent hypertension guidelines, corresponds to patients with clinic BP levels ≥ 140/90 mmHg in spite of appropriate lifestyle measures and the concurrent use of three antihypertensive agents belonging to different classes, all drugs being prescribed at full does and one of them being a diuretic (2,3,14). Patients whose BP is controlled but require three or more drugs to do so might also be considered resistant to treatment (14). Finally, some patients might be resistant to antihypertensive treatment when BP is measured in a clinical setting, but have normal out-of-office BP values. Such a BP pattern corresponds to a

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"white-coat" treatment-resistant hypertension (or pseudo-resistant hypertension), as opposed to a "true" resistant hypertension, a condition characterized by high clinic as well as out-of-office BP. Patients with treatment-resistant hypertension might therefore have either a "white-coat" or a "true" resistant hypertension.

A number of factors or causes of treatment-resistance in treated hypertensive patients are listed in Table I (15). The characterization of what is regarded as an adequate therapy (number and dosage of BP lowering drugs with complementary mechanisms of action) represents, however, only one aspect to be taken into account. Other factors may contribute to the maintenance of abnormally high BP levels despite an apparent "optimal" therapy, including a poor patient's adherence to the prescribed drug regimen (16,17) or the existence of a secondary form of hypertension among others (14,18). Also to be considered is the fact that a large fraction of patients with treatment-resistant hypertension diagnosed in a medical setting might have normal "out of office" BP values, whether obtained by non-invasive 24-h ambulatory monitoring or self-measurement at home (19,20).

The purpose of our present paper is to discuss the appropriateness to include systematically "out of office" BP measurements in the evaluation of patients considered resistant according to current criteria, and whether it would be rational to recommend the use of a blocker of the renin–angiotensin system and a calcium channel blocker as a component of an optimal three-drug regimen.

Table I. Main factors or causes of treatment-resistance pseudo-resistance in treated hypertensive patients (modified from ref. (15)).

Factors related to physician
- Improper blood pressure measurement
- Use of inappropriate antihypertensive medication
  - Inadequate dosages
  - Inappropriate combinations
- Physician inertia (failure to change or increase dose regimens, when not at goal)
- Poor communication between doctor and patient
- Complicated therapeutic plan (especially in the presence of multiple concomitant medications) or complicated dosing schedules of antihypertensive drugs.

Factors related to patient
- White-coat effect
- Drug-related side effects
- Non-adherence
- Inadequate patient education
- Concomitant use of oral contraceptives
- Concomitant use of anti-inflammatory or sympathomimetic agents
- Memory or psychiatric problems and cognitive disorders (elderly subjects)
- Costs of medication (in some healthcare systems)

Other causes
- Obstructive sleep apnoea syndrome
- Chronic kidney disease
- Primary or secondary hyperaldosteronism
- Severe atherosclerotic disease (calcification) of the arterial wall (elderly subjects)
- Aortic valve sclerosis with haemodynamically significant insufficiency

Is the definition of treatment-resistant hypertension possible without "out of office" blood pressure measurements?

BP values obtained by 24-h ambulatory monitoring and self-measurement at home are better predictors of cardiovascular risk than those determined in a clinical setting according to generally accepted guidelines (21–25). Important differences are frequently found in the individual hypertensive patient between clinic and "out of office" BP. This accounts for the common finding of white-coat hypertension, in which BP is normal when determined during usual activities, but abnormally high in the clinical environment (26–28).

Two studies have evaluated prospectively the prognostic value of "out of office" BP in patients with treatment-resistant hypertension. In the first study, 24-h ambulatory BP recordings were performed in 86 patients referred to specialized hypertension clinics in Spain. These patients, who had their clinic diastolic BP $>$ 100 mmHg while receiving three or more antihypertensive drugs, including a diuretic, were followed for an average of 49 months (29). The event-free survival was significantly longer in patients with daytime diastolic BP $<$ 88 mmHg (2.2 per 100 patient-years) than in those with corresponding BP ranging from 88 to 97 mmHg (9.5 per 100 patient-years) or $>$ 97 mmHg (13.6 per 100 patient-years). The second study included 556 patients with treatment-resistant hypertension, with a median follow-up of 4.8 years (30). In this population, both systolic and diastolic ambulatory BP, but not office BP, were significant predictors of the occurrence of fatal and non-fatal cardiovascular events.

The prevalence in the USA of resistant hypertension based on clinical BP readings has been reported recently (31). Patients were classified as resistant if their blood pressure was $\geq$ 140/90 mmHg while taking three antihypertensive medications from different drug classes, or four BP lowering agents from different classes, regardless of their BP levels. The survey involved 3710 drug-treated hypertensive patients. Among them, 12.8% met the criteria of resistant hypertension, which represents a rather small fraction of patients on antihypertensive therapy. The observations made in a large cohort of treated hypertensive patients in Spain are of particular interest (32). Of 68045 treated patients, 12% had resistant hypertension, as defined by office BP $\geq$ 140/90 mmHg, despite a treatment consisting of at least three drugs, one of them being a diuretic. This percentage is similar to the one reported in USA. The

main interest of the Spanish survey derives from the availability of ambulatory BP recordings, which allowed the classification of patients in two groups, those with 24-h BP values ≥135 and/or 80 mmHg (true resistant hypertension) and those with 24-h BP values <135/80 mmHg (white-coat resistant hypertension). The first group comprised 62.5%, and the second group 37.5% of the total population with office treatment-resistant hypertension. These data obtained in a large number of patients strongly support the view that "out of office" BP measurements should be part of the diagnostic procedures in patients with clinic BP remaining too high despite major efforts to normalize their BP.

Home BP measurements might also serve to detect white-coat resistant hypertension (pseudo-resistant hypertension). This is exemplified by the results of a study in which 528 hypertensive patients taking at least three or more different antihypertensive drugs were asked to measure their BP at home every day for at least 2 weeks, in the morning before breakfast and in the evening before bedtime (33). Of these patients, 16.1% exhibited isolated office resistant hypertension, i.e. showed home BP<135/85 mmHg, but office BP≥140/90 mmHg.

Taken together, there is ample evidence that 24-h ambulatory BP monitoring and home BP recording make it possible to discriminate, among patients with high clinic BP despite the taking of an optimal drug regimen, patients with a white-coat resistant form and those with a true resistant form of hypertension. Notably, the former have a clearly better prognosis than the latter, which urges to include "out of office" BP measurements in the evaluation of all patients considered resistant based on clinic BP readings. The utility of 24-h ambulatory BP monitoring and self-measurements of BP in patients unresponsive to antihypertensive therapy is recognized by all major hypertension guidelines (1–3,14,34,35). A further step appears however desirable, i.e. the inclusion in the definition of resistant hypertension of the confirmation of high BP levels by "out of office" measurements (Figure 1). With regard to 24-h ambulatory BP monitoring, the frequency of measurements should be every 15–30 min during daytime, and not less than every 30 min at night. Day and night-time intervals are best defined on awake and asleep periods retrieved from diary cards filled up by the patients during the recording (35).

"Out of office" BP measurements may also be very helpful for adjusting treatment in patients with true resistant hypertension. 24-h ambulatory BP monitoring should not be repeated at short intervals because of the discomfort associated with this technique and the risk of rendering the patient reluctant to accept it. It appears therefore more appropriate to encourage patients to measure their BP at home starting 2–4 weeks after introduction of a treatment

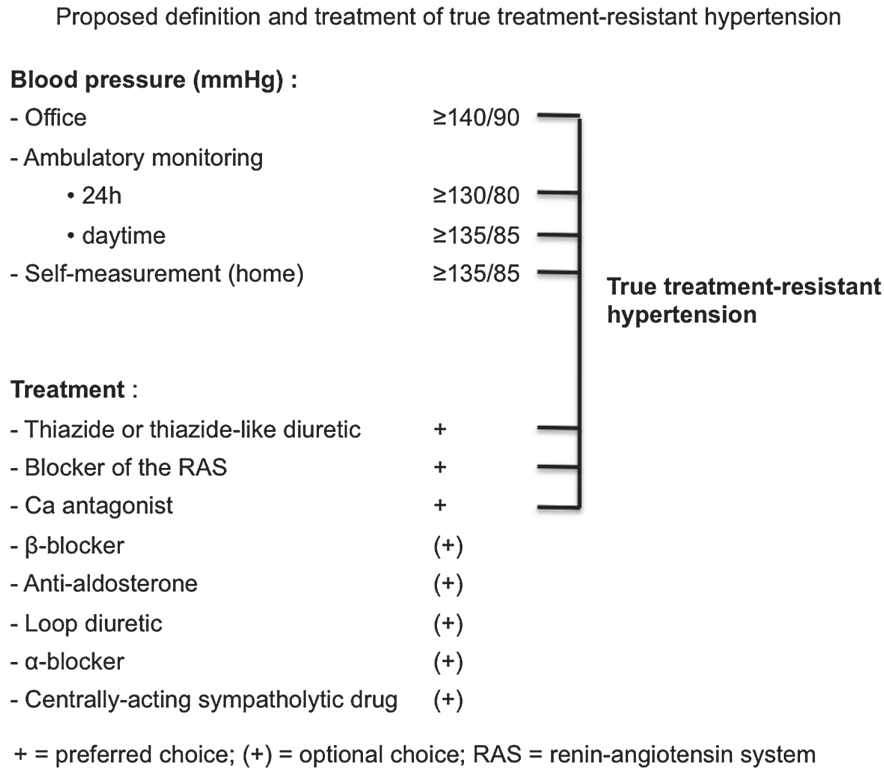

Figure 1. Proposed definition and treatment of true treatment-resistant hypertension. Both office and "out of office" blood pressure (obtained either by 24-h ambulatory monitoring and/or self measurement at home) have to be abnormally high in spite of a treatment consisting preferably of a thiazide or thiazide-like diuretic, a blocker of the renin–angiotensin system and a calcium antagonist. If needed, a beta-blocker, an anti-aldosterone or a loop diuretic, an α-blocker or a centrally acting sympatholytic drug might be added to the three-drug regimen, or replace one of the three first-choice options, if not tolerated.

Table II. Clinical variables showing differences between resistant hypertensive patients and hypertensive patients with blood pressure controlled with three or fewer antihypertensive drugs (from ref. (36)).

Parameters	OR	95% CI	*p*
Duration of hypertension	1.07	1.06–1.08	<0.001
BMI ≥ 30 kg/m^2	1.62	1.32–1.99	<0.001
Abdominal obesity (yes vs no)	1.43	1.16–1.76	0.001
LVH on ECG (yes vs no)	2.32	1.76–3.06	<0.001
UAE >30 mg/g	2.19	1.74–2.76	<0.001
eGFR <60 ml/min per 1.73 m^2	1.40	1.11–1.71	<0.003

OR, multivariate odds ratio; BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion.

change. Twenty-four-hour ambulatory BP monitoring could be repeated 3 months after the first recording if home BP remains abnormally high despite efforts to bring it under control (2). It may be necessary, however, to repeat 24-h ambulatory BP monitoring at a shorter interval in patients with severe hypertension or target organ damage. Regular home BP monitoring is strongly recommended as an approach complementary to 24-h ambulatory BP monitoring during the long-term follow-up of patients with treatment-resistant hypertension. In those patients, it is wise to ensure the maintenance of BP control every 6 months by 24-h ambulatory BP monitoring (2,35).

A simple schedule for home BP monitoring should be proposed, for example two BP readings in the morning and the evening for 7 consecutive days (34). For decision making, all BP values should be averaged, with the exception of those measured on the first day, which should be discarded.

Clinical features of patients with white-coat and true resistant hypertension

Patients with treatment-resistant tend to have an increased cardiovascular risk (14). This is illustrated by the observations made recently in Spain (36). The aim of this study was to compare clinical differences and target organ damage between hypertensive patients having or not having their BP controlled during antihypertensive therapy. The study population consisted of a large cohort of patients having their office BP either $<140/90$ mmHg on three or fewer drugs ($n = 13{,}436$) or $\geq 140/90$ mmHg in spite of the use of at least three drugs, including a diuretic, or the taking of four or more drugs, irrespective of office BP levels ($n = 14{,}461$). All patients underwent a 24-h ambulatory BP monitoring. A large fraction of patients with resistant hypertension (40%) had white-coat hypertension, as defined by a 24-h BP $<130/80$ mmHg in the presence of an office BP $\geq 140/90$ mmHg. Daytime, night-time and 24-h BP was significantly higher in treatment-resistant patients than in patients having normalized their office BP in response to treatment. Table II shows clinical variables that were found significantly different between the two groups of patients. Resistant hypertension was associated with obesity, longer duration of hypertension and enhanced propensity to develop renal and cardiac damage.

One might wonder at that point whether differences in the occurrence of target organ damage also exist between true and white-coat resistant hypertensives. If present, such differences would have important implications in the stratification of cardiovascular risk and, consequently, in the therapeutic approach. Actually, several studies have found a significant difference with regard to the severity of cardiac hypertrophy and albuminuria, the damage being less pronounced in patients with isolated office hypertension (20,32,37,38). Table III summarizes the main differences observed in a large Spanish cohort between true and white-coat resistant hypertensive patients (32). The cardiovascular risk profile was clearly worse in patients with high BP confirmed by 24-h BP monitoring. The true resistance was associated with a propensity to have more cardiovascular risk factors, target organ damages and previous cardiovascular complications.

Table III. Clinical features in patients with true and white-coat resistant hypertension (RH) (from ref. (32)).

Parameters	True RH ($n = 5182$)	White-coat RH ($n = 3113$)	*p*
Age, years	64.0 ± 11.7[a]	65.0 ± 10.9	<0.001
Sex, % men	54.6	46.0	<0.001
Duration of hypertension, years	11.4 ± 8.7	10.5 ± 8.2	<0.001
Smokers, %	14.8	10.3	<0.001
Diabetes, %	35.1	27.8	<0.001
Creatinine, µmol/l	75 (62–89)[b]	72 (61–84)	0.006
UAE, mg/g	11.0 (3.4–44.5)	7.0 (2.7–20.0)	<0.001
LVH by ECG, %	18.5	14.4	<0.001
Previous cardiovascular disease, %	19.1	16.2	0.001

[a]Means $\pm$ SD, [b]median (interquantile range); UAE, urinary albumin excretion; LVH, left ventricular hypertrophy; ECG, electrocardiogram.

Should a blocker of the renin–angiotensin system be included in the drug regimen in patients with resistant hypertension?

Patients with resistant hypertension are taking by definition at least three medications lowering BP by different mechanisms, increasing thereby the risk of poor adherence, which represents a potential cause of pseudo-resistance (17,39). Efforts should therefore be directed to simplify the drug regimen, which facilitates the long-term adherence with the treatment (40). This is possible today using single-pill combinations containing two, or even three different antihypertensive agents such as a thiazide diuretic, an angiotensin receptor antagonist and a calcium antagonist (41,42). Notably, self-measurement of BP at home is not only useful to identify patients with white-coat resistant hypertension, but has also a positive effect on patient's adherence with the prescribed treatment (43).

According to the JNC 7 and ESH/ESC guidelines, patients deemed to have resistant hypertension should receive at least three drugs, one of them being a diuretic (1,2). A blocker of the renin–angiotensin system might be part of this regimen, but this is not specifically advised. NICE guidelines differ in this respect as patients are considered resistant if their office BP remains $\geq 140/90$ mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an angiotensin receptor blocker plus a calcium channel blocker plus a diuretic (3). The NICE experts recommend the use of a thiazide-like diuretic, such as chlortalidone or indapamide, in preference to a conventional thiazide diuretic such as hydrochlorothiazide, which is the most common component of currently available single-pill combinations containing a diuretic. However, it is still debated whether thiazide-like diuretics are superior to thiazide diuretics in preventing the development of cardiovascular complications and metabolic side-effects, in particular diabetes. Notably, the use of spironolactone should also be considered in patients with treatment-resistant hypertension as post patients respond well to this mineralocorticoid antagonist given in addition to a triple-drug combination (44,45).

There are several good reasons to associate systematically a blocker of the renin–angiotensin system with a diuretic in the basic drug regimen of patients with difficult to treat hypertension. The diuretic-induced natriuresis has a stimulatory effect on renin secretion and angiotensin II generation, which limits the blood pressure lowering effect of the decreased total body sodium. Concomitant blockade of the renin–angiotensin renders ineffective the effects of this hyperreninemia (46). Also, blockade of the renin–angiotensin system attenuates the detrimental metabolic effects in particular hypokalemia of diuretics. Finally, a major advantage of blockers of the renin–angiotensin system is their proven beneficial effects in a variety of clinical conditions (Table IV) frequently encountered in patients with resistant hypertension, especially in those with true resistant hypertension (2). These agents can be given to almost all hypertensive patients. The contraindications are very few and comprise, in addition to idiosyncratic reactions, pregnancy and bilateral renal artery stenosis or renal artery stenosis of a single kidney. It now appears that patients with unilateral renal artery stenosis may even improve their outcome, provided renal function is regularly followed and remained stable (47). Angiotensin receptor blockers are further characterized by a placebo-like side effect profile, which is unique among the antihypertensive agents. It is noteworthy that renin–angiotensin system blockers play already today a key role in the management of patients with resistant hypertension. Thus, in a survey carried-out in USA, of 140126 patients taking four or more antihypertensive drugs in USA, 96.2% received an ACE inhibitor or an angiotensin receptor blocker, 93.2% a diuretic, 83.6% a calcium antagonist and 80% a beta-blocker (48). It should be stated here that there are also good reasons to include a calcium channel blocker in the drug regimen of patients with true treatment-resistant hypertension (Figure 1). Such drugs have also been demonstrated to have protective effects in clinical conditions seen frequently in patients with true treatment- resistant hypertension. (Table IV). Moreover, calcium antagonists are potent vasodilators that can be safely combined with diuretics and blockers of the renin–angiotensin system.

Table IV. Clinical conditions in which ACE inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and/or calcium antagonists (CAs) should be preferred (from ref. (2)).

	ACE-Is	ARBs	CAs
Asymptomatic organ damage			
• Left ventricular hypertrophy	+	+	
• Asymptomatic atherosclerosis	+		+
• Microalbuminuria	+	+	
• Renal dysfunction	+	+	
Clinical cardiovascular event			
• Previous stroke	+[a]	+[a]	+[a]
• Angina pectoris			+
• Previous myocardial infarction	+	+	
• Heart failure	+	+	
• Atrial fibrillation, prevention	+	+	
• Atrial fibrillation, ventricular rate control	+	+	+[b]
• Endstage renal disease	+	+	
• Proteiunuria	+	+	
• Peripheral arteriopathy	+		+
Other			
• Isolated systolic hypertension (elderly)			+
• Metabolic syndrome	+	+	
• Diabetes mellitus	+	+	
• Pregnancy			+
• Blocks			+

[a]Any agent effectively lowering blood pressure could be used in this condition. [b]Non-dihydropyridine calcium antagonist.

Conclusion

Resistant hypertension is a frequent problem faced worldwide by practising physicians. Patients with office BP remaining high despite the regular intake of three or more drugs with complementary mechanisms of action might exhibit substantially lower BP levels when pursuing their usual everyday activities out of the clinical setting. This is why "out of office" BP recording, by either 24-h BP monitoring or self-measurement at home, should be part of the routine evaluation of patients with resistant hypertension. This would allow the detection of patients with true resistant hypertension, i.e. patients who are at increased cardiovascular risk and prone to develop target organ damage. The three-drug regimen recommended until now favours the use of a diuretic. It appears today justified to include in this regimen, unless contraindicated, a blocker of the renin–angiotensin system and a calcium channel blocker, which might be beneficial not only to normalize BP, but also to prevent or regress target organ damage and delay cardiorenal complications.

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