Journal of Human Hypertension (2013), 1–6

www.nature.com/jhh

REVIEW

Resistant hypertension: a practical clinical approach

ES Muxfeldt, F de Souza and GF Salles

Resistant hypertension (RH) is defined as an uncontrolled office blood pressure (BP) despite the use of at least three antihypertensive drugs. With an increasing prevalence, RH implies in a very high cardiovascular risk and needs a careful clinical approach, aiming to control BP and to reduce its morbidity and mortality. The initial diagnostic approach involves drug adherence checking and the evaluation of antihypertensive scheme, emphasizing the use of diuretics and adequate combination and dosages of the two other drugs, which preferentially reduces cardiovascular risk and promotes prevention/regression of target organ damages. Because of an exaggerated white-coat effect, ambulatory BP monitoring (ABPM) at baseline is mandatory to classify patients into true RH (uncontrolled ambulatory BPs) and white-coat RH (controlled ambulatory BPs), and define initial therapeutic approach. Ideally, the objective is ambulatory BP control, so the treatment follow-up shall be based on ABPM measurements. The treatment involves lifestyle changes and use of adequate combinations of antihypertensive agents from different classes. In this way, patients with true RH need to intensify antihypertensive treatment by adding aldosterone antagonists as the fourth drug and also changing antihypertensive treatment to bedtime. Otherwise, in patients with controlled ambulatory BP, the therapeutic scheme should be maintained and ABPM or home BP monitoring repeated serially. Despite pharmacological interventions, ambulatory BP control in RH patients remains challenging and new interventional procedures have been recently proposed, as renal denervation and baroreflex activation therapy. Currently, these procedures shall be reserved to true RH patients in whom other alternatives have failed.

Journal of Human Hypertension advance online publication, 2 May 2013; doi:10.1038/jhh.2013.34

Keywords: resistant hypertension; ambulatory blood pressure monitoring; diagnostic approach; therapeutic approach

INTRODUCTION

Hypertension is associated to an elevated morbidity and mortality, contributing directly to higher risk of stroke, heart failure, myocardial infarction and renal disease.[1,2] It is well established that anti hypertensive treatment effectively reduces high blood pressure (BP) and consequently reduces cardiovascular risk, hence the greatest challenge worldwide is to achieve sustained BP control of hypertensive patients.[1,2]

Resistant hypertension (RH) is diagnosed when there is failure to reach office BP control ($<$140/90 mm Hg or $<$130/80 mm Hg in diabetes and chronic kidney disease) despite using at least three antihypertensive medications in adequate dosages, ideally including one diuretic.[3] Hypertensive patients under treatment with four or more antihypertensive drugs, independent of BP control, can also be diagnosed as RH.[3] This is a group extremely relevant, once about 10–30% of all hypertensives have been described as resistant[3], and recent data have demonstrated that its prevalence seems to be increasing in the last years.[4] In previous studies, those patients were identified as having several characteristics that imply a high cardiovascular risk profile, including older age and obesity,[3,5,6] two of the factors that might be related to current increase of RH rates.[4] Moreover, RH is more frequent in patients with diabetes, dyslipidemia, physical inactivity, chronic kidney disease, and left ventricular hypertrophy (LVH),[3,5,6] and these patients often developed major cardiovascular events such as coronary artery disease, stroke and heart failure.

Despite its high prevalence and increased cardiovascular morbidity, RH is a clinical condition of difficult appropriate approach. After diagnosis, it is advisable to rule out secondary causes related to resistance.[3,7] Equally, the treatment and follow-up of RH patients deserve special considerations, including obligatory ambulatory BP monitoring (ABPM) performance[3,8] or, although less well established, home BP monitoring (HBPM) as an alternative. Notwithstanding, the most important aim is to target BP control continuously. The objective of this review is to provide a practical clinical approach to RH management, from diagnosis to treatment, discussing some controversial points and emphasizing recommendations heretofore established.

DIAGNOSTIC APPROACH

Step 1: first diagnostic approach

Before the diagnosis of RH, it is recommendable to evaluate common causes of pseudo resistance, namely: inaccurate measurement of BP, especially the cuff size, as obesity is one of the important risk factors for RH (large and extra large cuffs for arm circumferences higher than 35 cm),[9] poor drug adherence and inadequate antihypertensive therapeutic scheme (Figure 1).[3]

Drug choice is very important, specially to verify the prescription of diuretics in adequate dosages,[10] as well as the use of at least two other synergic drugs that reduce cardiovascular morbidity and mortality.[1–3]

Moreover, therapeutic adherence is a very complex challenge in the RH management. The use of a great number of drugs, not only for hypertension but also for other comorbidities (diabetes, dyslipidemia), hinders adherence. Checking adherence may include different methods as self-reported adherence, simple tests (Morisky Green test), pill count and, when available, the electronic compliance monitoring.[1–3] Low adherence is not

Arterial Hypertension Program, University Hospital Clementino Fraga Filho, Faculty of Medicine, Internal Medicine Department, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. Correspondence: Professor ES Muxfeldt, Arterial Hypertension Program, University Hospital Clementino Fraga Filho, Faculty of Medicine, Universidade Federal do Rio de Janeiro, Av. Professor Rodolpho Paulo Rocco, 255, 3rd floor, Ilha do Fundão, Rio de Janeiro 20510-180, Brazil.
E-mail: bethmux@hucff.ufrj.br
Received 2 January 2013; revised 17 March 2013; accepted 26 March 2013

attributable to simply forgetting to take medication, but also to high cost, drug side effects, complicated proposal scheme and low schooling. In a recent study, female sex, physical inactivity, depressive symptoms and a history of coronary artery disease were the principle factors associated with low adherence in RH patients.[11] Reducing the number of daily drug intake, better education about side effects and raising awareness about the importance of continuous use of antihypertensive drugs to sustain their benefits, are all important steps to strengthen adherence. A multidisciplinary team approach generally facilitates these actions and improves drug adherence. After all these adjustments, if office BP remains uncontrolled, patients can be diagnosed as resistant hypertensives.

Step 2: the diagnosis—how to do it?

Although the RH definition is based on office BP measurements, 24-h ABPM is crucial to a best evaluation and correct follow-up of these patients,[3,8,12,13] because of an exaggerated white-coat effect[8,12,13] and also the need for nocturnal BP evaluation (Figure 1).[8,14–16]

In this way, baseline ABPM distinguishes between true RH (office BP $\geqslant$140/90 mm Hg and either daytime BP $\geqslant$135/85 mm Hg or night time BP $\geqslant$120/70 mm Hg) and white-coat RH (office BP $\geqslant$140/90 mm Hg and both daytime BP $<$135/85 mm Hg and night time BP $<$120/70 mm Hg),[8] and this classification is important both to define therapeutic approach[3,16] and prognosis.[14]

Approximately one third of patients with initial diagnosis of RH indeed have white-coat RH[8,12,13] and do not need treatment intensification, avoiding overtreatment and drug side effects. On the other hand, patients who confirm resistance in ABPM, properly called true RH, need review of their therapeutic scheme[16] and frequently treatment intensification with the addition of a new drug.[3]

Moreover, the baseline ABPM provides important information in relation to prognosis in RH. True RH is associated with higher prevalences of diabetes,[12,13] physical inactivity,[12] current smoking,[13] subclinical organ damage such as LVH,[8,12,13] and microalbuminuria,[12,13] and previous cardiovascular diseases;[8,12,13] and its diagnosis doubles the risk of fatal and non-fatal cardiovascular events, and of all-cause mortality in relation to those with a baseline diagnosis of white-coat RH.[14] Furthermore, all ambulatory BPs, in special the night time systolic BP, are powerful predictors of cardiovascular events, while office BPs seem to have no prognostic value in RH patients.[14] A blunted nocturnal BP reduction and the non-dipping pattern are also important risk predictors in this group of patients.[15]

Regarding identification of the white-coat effect, HBPM can be an alternative to ABPM,[17] although it seems to still overestimate BP and cannot detect night time resistance. Considering ABPM as the gold standard, sensitivity, specificity, positive and negative predictive values of HBPM in detecting true RH were 90%, 55%, 71% and 82%, respectively. ABPM may be more suitable for the initial diagnostic assessment of RH, for the evaluation of treatment effects on 24-h BP variability and for follow-up of true RH patients, whereas HBPM may be more suitable for the long-term follow-up of white-coat RH.

Complementary exams. At first approach, all RH patients shall have laboratory examination evaluating the metabolic profile, as they present high prevalences of diabetes and dyslipidemia,[3,5,6] and renal function (serum creatinine, microalbuminuria and proteinuria), because of a high association with chronic kidney disease[3,5,6,18] and its prognostic importance.[19,20] Impaired renal function represented by parenchymal disease is related to resistance due to excessive activation of the renin–angiotensin–aldosterone system and fluid retention.[18] The presence of microalbuminuria and reduction of glomerular filtration rate combined identifies patients with a very high cardiovascular risk,[20] and reduction of albuminuria may be a therapeutic goal in RH patients.[19]

Furthermore, electrocardiogram should be performed to identify LVH and also because this exam provides important prognostic markers in RH, such as prolonged ventricular repolarization and serial changes in strain pattern, and in LVH voltage criteria.[21]

Step 3: investigating secondary causes—what is really important to know?

Secondary causes of hypertension can be surprisingly common in RH patients.[7] Hyperaldosteronism has been described as one

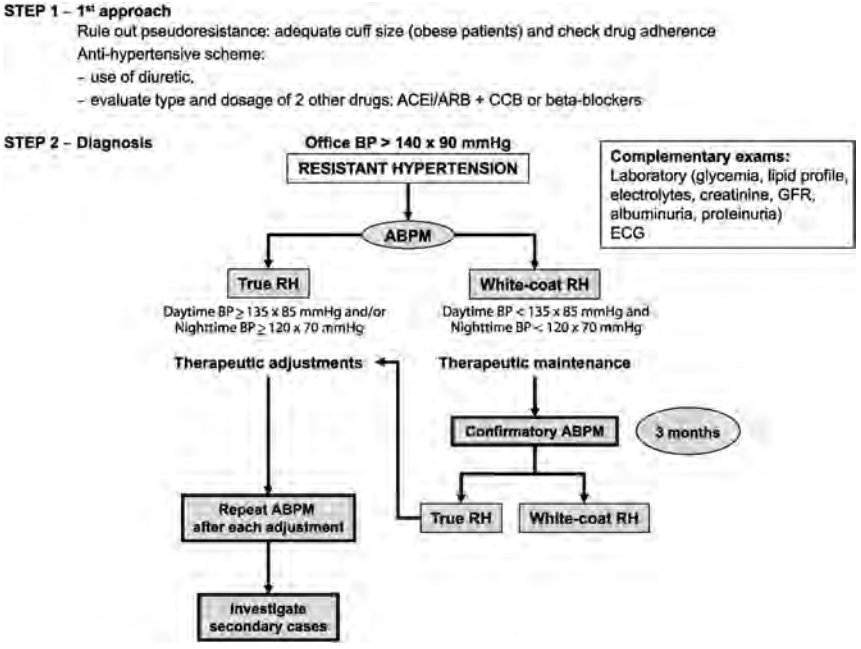

Figure 1. Diagnostic approach in resistant hypertension.

of the most frequent, achieving ~20% of these patients.[22] In the last years, many authors have reported an increasing association between hyperaldosteronism and uncontrolled hypertension. Commonly defined as primary aldosteronism, the term hyperaldosteronism seems to be more adequate, as the majority of cases are not represented by the classical adrenal adenoma.[23] Otherwise, unilateral hyperplasia can be treated surgically, but it is also treatable by mineralocorticoid receptor (MR) blockage.[22,23] Actually, despite the robust evidence regarding the central role of aldosterone excess on treatment resistance, and although we do not discourage a correct evaluation when the necessary tools are available, often the treatment will be the same, independent of establishing or not the diagnosis of hyperaldosteronism (Figure 2).[22,23]

Obstructive sleep apnea (OSA) and hypertension are also closely related.[23] OSA syndrome is represented by daytime somnolence and fatigue, associated with obstructive breathing disorders during sleep (apneas or hypopneas events), and has been described with a very high prevalence in RH, reaching 65–80% in different series.[7,24] Obesity and a blunted nocturnal BP reduction increase the chances of coexisting OSA.[24] Many mechanisms are proposed to explain how OSA causes treatment resistance, including fluid retention around the neck, sympathetic over activation, oxidative stress, inflammation and endothelial dysfunction.[23] Despite all the above arguments, it still remains unanswered whether patients with RH will obtain any benefit from routine investigation and treatment of OSA, with substantial BP reduction, as continuous positive airway pressure (CPAP) effect in this way is controversial.[24] The best results were found in individuals with more severe OSA, higher baseline BPs and in those with optimal adherence to CPAP,[24,25] although most of the studies are uncontrolled trials, enrolled few patients with a short follow-up, or assessed office BPs instead of ambulatory BPs. In fact, the question about the extent of CPAP usefulness to RH treatment remains unanswered.

Renovascular disease, represented by unilateral or bilateral stenosis of renal artery, is a cause of RH in about 2.5% of cases.[7] Its prevalence increases with age, mainly when associated to declining kidney function. Although the problem is not uncommon, the interventional treatment remains controversial due to the lack of positive evidences related to BP control.[26]

Because of a low prevalence, the investigation of other secondary causes, such as Cushing, pheochromocytoma and thyroid disorders, are recommended only in patients with typical symptoms.[7]

THERAPEUTIC APPROACH

Step 4: treatment

In spite of many therapeutic options with several drugs, we know that BP control is not easily reached in RH, and one of the most important barrier is the adherence to lifelong treatment, where patients will take pills twice or more times a day. It is necessary to take awareness about how much important and effective are the established options as changes in lifestyle and intensive pharmacological treatment (Figure 3).

Changes in lifestyle. The first step in treatment of any hypertensive patient is to reduce salt intake, increase physical activity and keep optimal weight. Salt reduction has unquestionable effectiveness in general hypertensives,[2,3] and recently it was demonstrated also in a randomized cross-over study of RH patients.[27] Low-salt diet reduced systolic and diastolic 24-h BP by 20 and 10 mm Hg, respectively. These results suggest that patients with RH may be especially salt sensitive.[3,27] Moreover, obesity is closely related with RH,[3,5,6] and all efforts shall be done aiming weight loss. Although it has not been particularly evaluated in RH, weight loss and physical activity are clearly related to decrease in BP levels.[1,2]

The first three drugs. After considering modifications in lifestyle, it is time to check the therapeutic scheme. Patients with RH frequently have subclinical volume retention, and effective diuretic therapy is essential for BP control.[10] Thiazide diuretics are effective in the majority of RH patients, and chlorthalidone, because of its longer action, is preferred by some authors, when compared with hydrochlorothiazide.[3,22] It is very important to

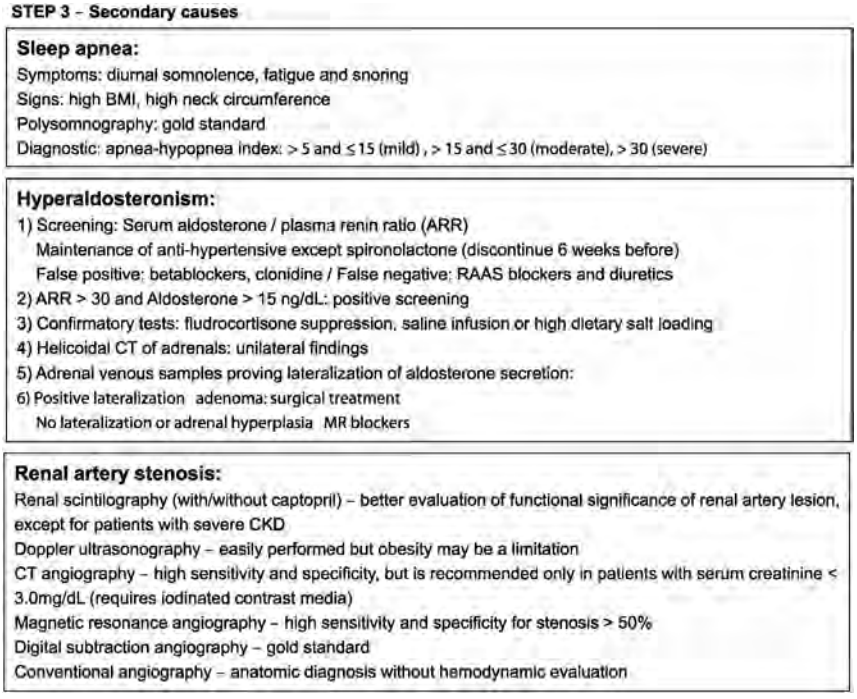

Figure 2. Investigation of secondary causes.

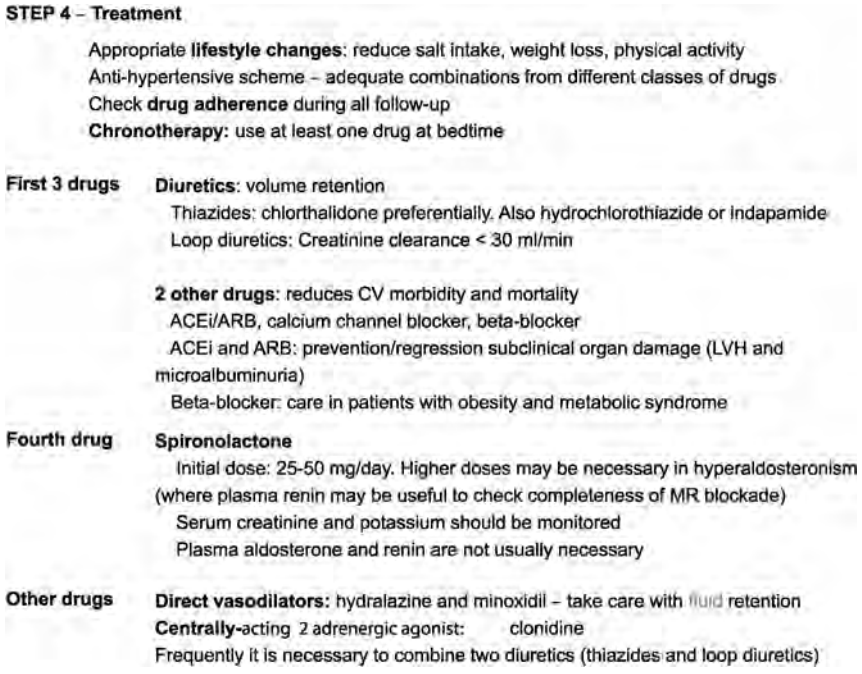

Figure 3. Therapeutic approach in resistant hypertension.

notice that loop diuretics are preferable in patients with chronic kidney disease if glomerular filtration is $<30\,ml\,min^{-1}$ per $1.73\,m^2$. In this case, furosemide must be prescribed ideally with the second dose after 6–8 h due to its short-acting.[1,2]

The other two drugs should be capable of reducing cardiovascular morbidity and mortality.[1,2] Full doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, calcium channel blocker and beta-blockers are generally effective and well tolerated, and they shall be prescribed according to current guidelines.[1,2] Previous studies pointed to the importance of using drugs (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker) that could prevent/reduce microalbuminuria and LVH.[19,21] Furthermore, as obesity and metabolic syndrome are very common in RH patients, the use of beta-blockers should be cautious, because they can worsen the metabolic profile.[2]

The fourth drug. There is substantial evidence supporting MR blockers as the fourth-drug of choice. Independent of aldosterone and renin levels, low-dose spironolactone is effective in reducing BP in patients with RH.[28,29] In a prospective open trial conducted in a large Brazilian cohort of true RH patients, we showed a mean 24-h BP systolic and diastolic BP reduction of 14 mm Hg and 7 mm Hg, respectively, after the addition of spironolactone.[29] Moreover, spironolactone in low doses is safe and well-tolerated.[28,29] On the basis of current knowledge, it is reasonable to conclude that even when hyperaldosteronism is highly suspicious, the majority of cases will be clinically treated with MR blockers (spironolactone or eplerenone).[3,23,28,29]

After the four-drug scheme, if ambulatory BP control is not achieved, other drugs largely used in our experience are beta-blockers (preferentially the new vasodilating ones), centrally acting alpha agonists (clonidine), particularly in patients with high nocturnal BP and direct vasodilators (hydralazine and more rarely minoxidil).[1–3] None of them are preferable to others due to higher side effects incidence.

Another important point is the use of at least one drug at bedtime, as the importance of nocturnal BP control is well-established.[14,15] The adjustment of therapeutic scheme by chronotherapy based on ABPM findings helps to reach 24-h BP control and reduce the prevalence of the non-dipping pattern.[16] In our experience, the chronotherapy really increases the BP control rate, although more evidence in literature is necessary to support this recommendation.

Step 5: follow-up

During follow-up, the treatment should be ideally based on ambulatory BPs and not on office BPs, because of a high magnitude of the white-coat effect, even in true RH patients.[12,13] If ABPM is not available, HBPM can replace it or at least, self-measurement of BP at home should be encouraged.[2,17] ABPM classify these patients with controlled or uncontrolled office BP in four well-defined groups. Patients with controlled office BP using four or more antihypertensive drugs are diagnosed as controlled RH (office BP $<140/90$ mm Hg, and both daytime BP $<135/85$ mm Hg and night time BP $<120/70$ mm Hg) or masked RH (office BP $<140/90$ mm Hg and either daytime BP $\geqslant 135/85$ mm Hg or night time BP $\geqslant 120/70$ mm Hg). Otherwise, patients with persistently uncontrolled office BP are diagnosed as true RH (office BP $\geqslant 140/90$ mm Hg and either daytime BP $\geqslant 135/85$ mm Hg or night time BP $\geqslant 120/70$ mm Hg) or white-coat RH (office BP $\geqslant 140/90$ mm Hg and both daytime BP $<135/85$ mm Hg and night time BP $<120/70$ mm Hg) (Figure 4).[3,8,12,13]

In our experience, evaluating 473 RH patients of our cohort, after a follow-up of 5 years, 20% of the patients (94 patients) reached office BP control. Subsequent ABPM showed that 62% of them (58 patients) had controlled RH and 38% (36 patients) had masked RH. Otherwise, persistently uncontrolled office BP was found in 379 patients (80%), in whom ABPM showed that 40% (153 patients) achieved ambulatory BP control (white-coat RH), while 60% (226 patients) had true RH (uncontrolled ambulatory BP) (unpublished data).

In this way, patients with uncontrolled ambulatory BP (true and masked RH) needs therapeutic scheme adjustment (higher doses of current medications or addition of a new drug) and ABPM or HBPM shall be repeated after each adjustment. Otherwise, when BP goal is finally achieved, the challenge becomes the maintenance of control. How long the results obtained in ABPM are reliable and can be useful to guide treatment is not clear. In the course of the time, patients frequently change their categories

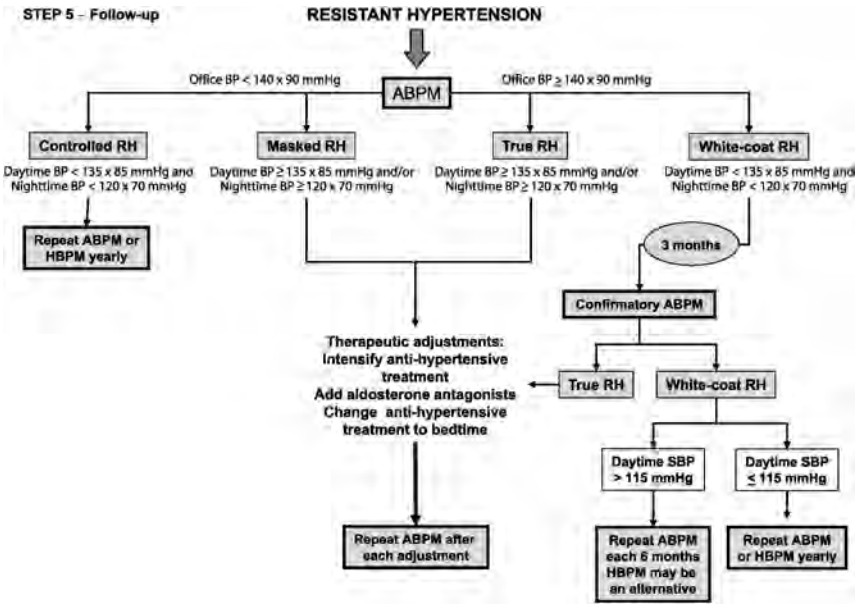

Figure 4. Follow-up in RH (Adapted from Muxfeldt ES, Salles GF. How to use ambulatory BPmonitoring in resistant hypertension. *Hypertens Res* 2013, in press).

between controlled/uncontrolled ambulatory BPs without significant changes in their office BPs. In this direction, we conducted a study that aimed to evaluate the most appropriate time interval to repeat ABPM to assure sustained ambulatory BP control in patients with white-coat RH.[30] Patients were submitted to a second confirmatory examination 3 months later and repeated twice at 6-month intervals. On the basis of this study, we concluded that a confirmatory ABPM is necessary after 3 months of the first white-coat RH diagnosis, and the procedure should be repeated at 6-month intervals, except in patients with daytime systolic BP $\leqslant$115 mm Hg, in whom it may be repeated annually. As discussed before, HBPM may be easier than ABPM for the long-term follow-up,[17] but more evidence is necessary for recommending its use in RH patients.

After the diagnosis and while BP reduction is aimed, it is recommended to refine cardiovascular risk stratification of these patients, because of the expected high cardiovascular mortality and morbidity.[21] More prospective studies in RH patients are needed to define whether tight ambulatory BP control and regression of subclinical organ damage will really translate into better cardiovascular outcomes.

PERSPECTIVES

New drugs in development

Among the new drugs are the inhibitors of neprilysin (degradative enzyme for natriuretic peptides) and endothelin-converting enzyme (endothelin system). Together with the well-known angiotensin-converting enzyme inhibitor, they form a group called vasopeptidase inhibitors, which likewise have many theoretical benefits, but none is yet available in clinical practice.[31] Darusentan, a endothelin antagonist receptor, was also tested in RH, but the results are still conflicting and with a high incidence of side effects.[32] Other molecules under development include aldosterone synthase inhibitors, other endothelin antagonists, nitric oxide donors and many other molecules in a preclinical stage. Indeed, none of them have any practical application until now.[31]

Baroreflex activation therapy (BAT)

New strategies directed to reducing peripheral sympathetic drive are under intensive research, for instance, the BAT. It is a surgically implantable device that, by stimulating carotids sinus baroreceptors, causes a reduction in sympathetic response and consequently BP reduction. The Rheos Pivotal Trial,[33] was a double-blind, randomized, placebo-controlled device trial conducted in RH patients. There was a mean reduction in office systolic BP of up to 35 mm Hg after 12 months, and over 50% of subjects achieved systolic BP control. This effect was sustained over longer follow-up of 22–53 months. It is important to note that this trial did not evaluate ambulatory BPs, just office BP reduction. A similar trial conducted in Europe (DEBuT—Device Based Therapy) evaluated ambulatory BP.[34] After 12 months, office systolic BP was reduced in $\sim$30 mm Hg, whereas ambulatory systolic BP showed a mean reduction of 13 mm Hg.

Therefore, the future of this procedure is uncertain. We believe that some doubts are not completely clarified yet. More investigations about the long-term safety and to evaluate whether the reduction in ambulatory BPs compared with the addition of a new drug, for example, will be sufficient to justify such a high-cost invasive procedure. Maybe it would be reserved to patients in whom other alternatives failed or in a group with increased cardiovascular risk.

Renal sympathetic denervation (RSD)

The ablation of the renal sympathetic nerves with a radio-frequency catheter has been evaluated with great enthusiasm in the last years. By now, the results seem promising in BP lowering. Although the early results appear more attractive than BAT, it is also an invasive procedure, and for this reason deserves greatest considerations before it can be widely indicated.

Renal sympathetic outflow is activated in essential hypertension, and basically the aim of the treatment is, by endovascular technique, to interrupt this activation causing BP reduction. A randomized study (Symplicity HTN-2 trial) enrolled 106 patients and demonstrated a mean reduction of 32/12 mm Hg at 6 months in office systolic and diastolic BP, respectively,[35] and this effect was maintained after 2 years of follow-up. Nevertheless, the results were based on office BPs, whereas ABPM data were available only in a small subgroup, showing a less impressive BP reduction (11/7 mm Hg in 24-h BP) after 6 months.[35] Moreover, it is not clear if BP reduction was sustained over long-term follow-up.[36]

The disparity between reductions in office and ambulatory BPs might be explained by the sympathetic overactivity involved in the white-coat effect, which is reduced by these two procedures. In this way, it has been proposed that these procedures, BAT and RSD, may induce downregulation of the white-coat effect, explaining the greater responses in office than in ambulatory BPs.[37]

In agreement with some experts, we believe that RSD shall be reserved to more severe RH patients, in whom ambulatory BPs remain uncontrolled despite using four or more antihypertensive drugs, including MR blockers. Elevated office BPs need to be obligatory confirmed by ABPM, otherwise the indication does not seem reasonable.[37]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was partially supported by research grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and from the Fundação Carlos Chagas Filho de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ).

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