Optimization of Antihypertensive Drug Treatment in Resistant Hypertension

8

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Abbreviations

ACE	Angiotensin-converting enzyme
BP	Blood pressure
DBP	Diastolic blood pressure
dRHTN	Drug-resistant hypertension
RAS	Renin-angiotensin system
SBP	Systolic blood pressure

8.1 Introduction

When a truly drug-resistant hypertension (dRHTN) has been identified [1], physicians have to decide which therapeutic option might offer the best chance to effectively lower the elevated blood pressure (BP) values, hopefully leading the patient's status to BP control (<140/90 mmHg) [1, 2]. Although invasive procedures such as renal denervation and carotid baroreflex stimulation can achieve this goal in a number of patients [3, 4], there is no question that the first treatment approach to consider is the (1) removal of lifestyle factors that may oppose the BP lowering effect of the administered drugs, such as a high intake of salt, abuse of alcohol, obesity [5, 6] or co-treatments that have direct or indirect pressor effects [7] and (2) modification of the existing treatment regimen by an increase of the dose or the extension of the

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medicaments already prescribed. This chapter will discuss how to make the best use of the medicament option.

8.2 Rationalization of the Three Drug Treatment Regimen

Hypertension guidelines emphasize the need for combination treatment to be based on drugs with different and complementary mechanisms of the BP lowering effect. They recommend a three drug combination to make use of a diuretic, a blocker of the renin-angiotensin system (RAS), be it an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor antagonist and a calcium channel blocker because this fulfils the above requirement and has been shown to markedly reduce BP (up to 30–40 mmHg reduction of systolic values) in hypertensive patients with a variety of clinical characteristics [8–10]. In resistant hypertensive patients under treatment with three drugs, a therapeutic option is thus to ensure that a diuretic/RAS blocker/calcium channel blocker combination is used, provided that (1) no contraindication to one or another of these drugs exists or (2) the clinical condition of the patient requires other drugs to be part of the combination, such as a beta-blocker in patients with a history of coronary disease or heart failure. Of special importance is the inclusion of a diuretic in the three drug treatment regimen because diuretics enhance the antihypertensive effect of most antihypertensive agents, and difficult-to-treat hypertension may not rarely be associated with sodium and fluid retention as well as hypervolemia [11].

8.3 Increasing the Dose of the Prescribed Three Drugs

Drug underdosing is frequent in treated hypertensive patients; its high prevalence is one of the factors responsible for the low rate of BP control exhibited by the hypertensive population worldwide [12]. Careful checking of the drug doses prescribed (or assumed) is thus mandatory when dealing with a BP that remains uncontrolled under a three drug therapeutic regimen, an adequate dose of each of them being indeed a prerequisite for patient inclusion in the dRHTN category. Once this is established, however, a further increase in the dose of the prescribed drugs does not appear to be particularly helpful because (1) the shape of the dose/effect relationship can make the additional BP lowering effect far from substantial and (2) there may be with a number of drug classes (e.g., calcium channel blockers) a more prominent increase in the drug-related side effects [13]. It should nevertheless be emphasized that this may not be entirely true for diuretics because, as shown in Fig. 8.1, increasing the dose of hydrochlorothiazide beyond the usual 25 mg daily has been associated with a clear-cut further BP reduction; that is also the case for an increase of the thiazide-like diuretic chlorthalidone beyond the usual 12.5 mg, daily [14]. Along this line, several studies have shown an increase in the usual dose of diuretics to be accompanied by an increase in the number of resistant hypertensive patients reaching BP control. For

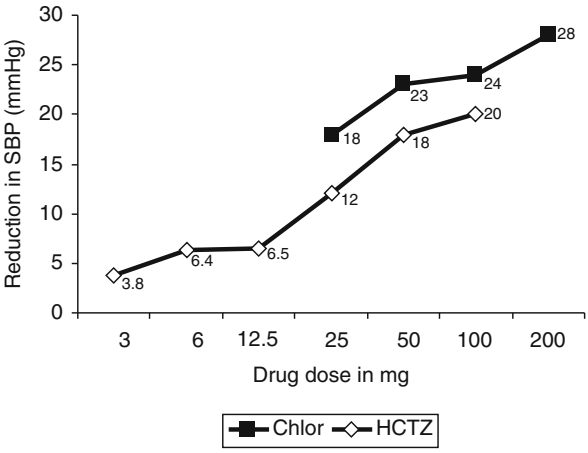

Fig. 8.1 Effect of hydrochlorothiazide (*HCTZ*) and chlorthalidone (*chlor*) on systolic blood pressure (*SBP*) as a function of the daily dose (mg) (From Carter et al. [14], by permission)

example, in an American study on a cohort of about 150 resistant hypertensive patients, optimization of the existing treatment regimen that included an increase of the dose of diuretic was followed by BP control (<140/90 mmHg) in more than 50 % of the cases [15].

8.4 Addition of a Fourth Drug

The drugs that are available as fourth step treatment of dRHTN have mechanisms of action that are only partly different from those of the drugs included in the background of three drug treatment regimen. Beta-blockers, alpha-I blockers and central agents, for example, share their sympatho-moderating influence with RAS blockers [16]. Beta-blockers and mineralocorticoid receptor antagonists share their opposition to the pressor and sodium retaining the effect of angiotensin II with RAS blockers. Direct vasodilators share their ability to reduce vasomotor tone with calcium channel blockers. Despite this potential mechanistic overlapping, however, addition of any fourth drug to the existing drug regimen stands a chance to lower BP and achieve control in a number of resistant hypertensive patients, which makes this approach the preferable one in this clinical condition.

Which drug to select among the available options is difficult to decide on an evidence basis because very few studies have addressed this issue by a randomized double-blind design, making the present fourth drug choice largely empiric. In this context, however, mineralocorticoid receptor antagonists and alpha-I blockers should probably be regarded as the preferred choice for pathophysiological considerations as well as for the extent of therapeutic data. Pathophysiological evidence leaves no doubt that hypertension is accompanied by (1) a sympathetic activation that is increased with the degree of BP elevation [17] and is particularly pronounced in patients whose BP is resistant to treatment (Fig. 8.2) [18] and (2) a

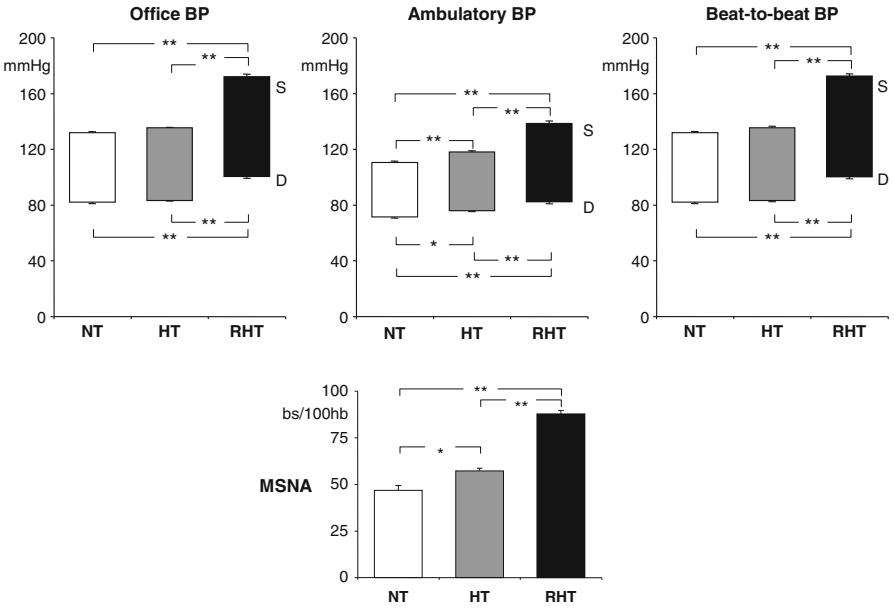

Fig. 8.2 Office, ambulatory and beat-to-beat (finger) blood pressure (*BP*) in normotensives (*NT*), non-resistant hypertensives (*HT*) and resistant hypertensives (*RHT*). Muscle sympathetic nerve traffic (MSNA) measured by microneurography in the three groups is also shown. $*P<0.05$; $**P<0.01$ (From Grassi et al. [18], by permission)

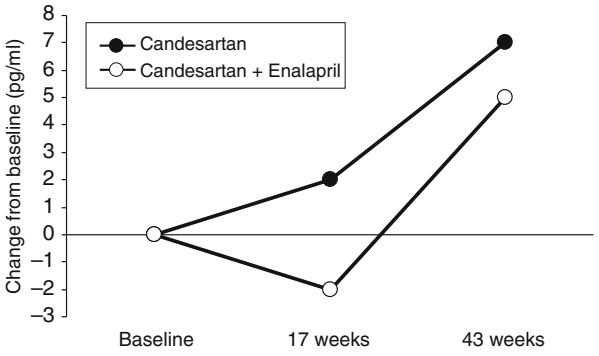

Fig. 8.3 Escape of aldosterone (serum concentration) in patients under treatment with an angiotensin receptor antagonist or an angiotensin receptor antagonist/ACE inhibitor combination (From McKelvie et al. [19], by permission)

plasma and tissue elevation of aldosterone whose secretion by the adrenal glands escapes, for a variety of reasons, the inhibitory effect of RAS blockers even when combined to oppose the production or influence of angiotensin II more effectively [19] (Fig. 8.3). Therapeutic evidence shows that these two drug classes lower BP in patients in whom multidrug treatment did not achieve control. This is exemplified by the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in which the addition of the alpha-I blocker doxazosin in a large

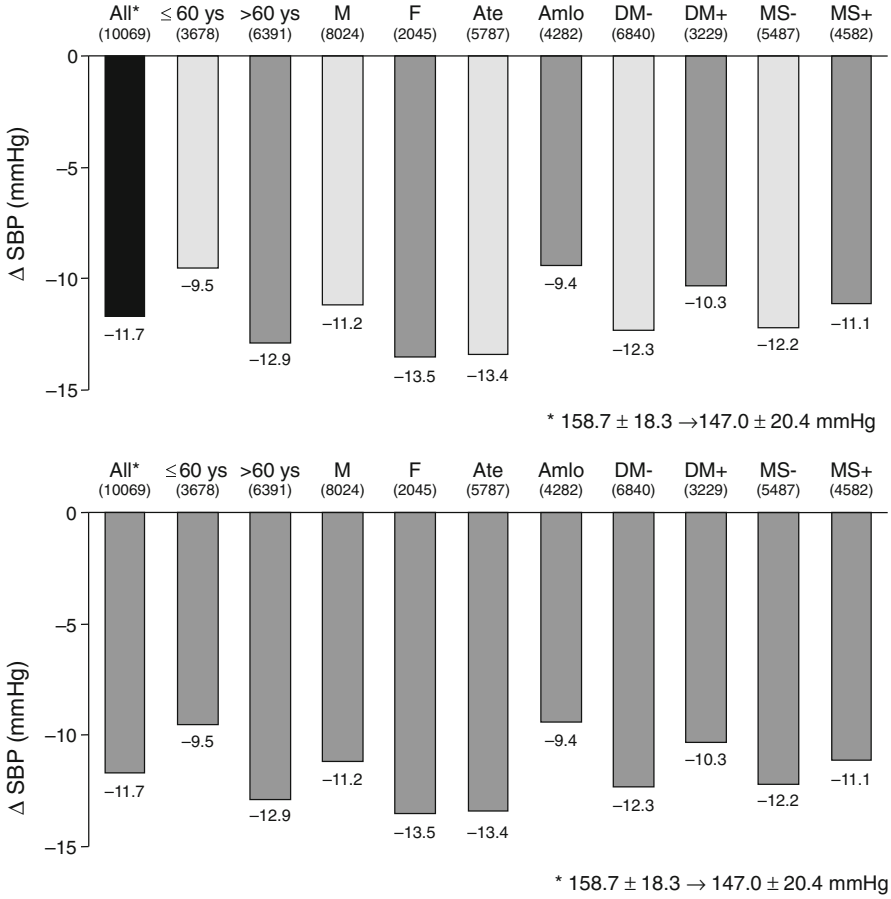

Fig. 8.4 Systolic blood pressure (*SBP*) reduction induced by doxazosin administration in patients in whom SBP was not controlled by multiple drug treatment. Data from different patient subgroups. *Ys* years, *M* males, *F* females, *Ate* group initially treated with atenolol, *Amlo* group initially treated with amlodipine, *DM* diabetes mellitus, *MS* metabolic syndrome (From Chapman et al. [20], by permission)

number of hypertensives uncontrolled by combination of various drugs lowered systolic BP by about 13–14 mm Hg, this being the case in a variety of clinical or demographic conditions (Fig. 8.4) [20]. Interestingly, the BP lowering effect was associated with no major side effect and no increased risk of heart failure, at variance from what has been reported in the doxazosin-treated hypertensive patients of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [21]. It is further exemplified by the BP reduction observed in the same trial when a similarly large number of patients in whom multidrug treatment had failed to achieve BP control were given spironolactone (Fig. 8.5) [22].

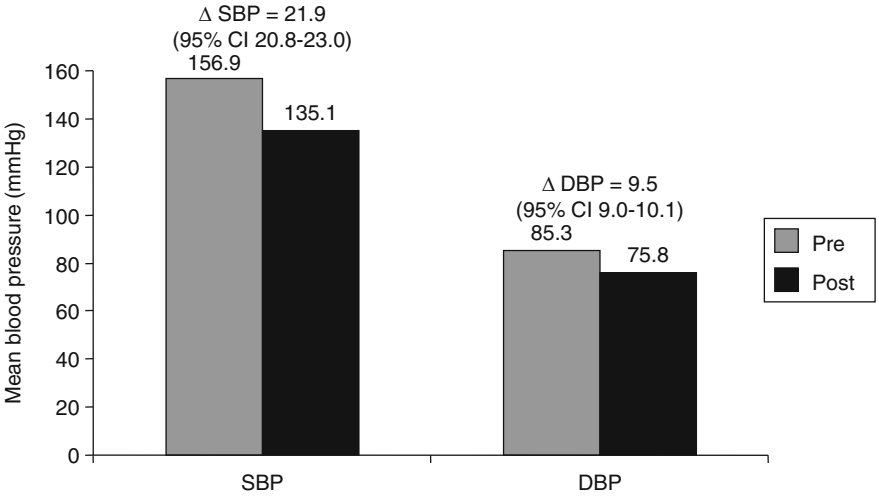

Fig. 8.5 Systolic blood pressure (*SBP*) and diastolic blood pressure (*DBP*) before (pre) and after (post) administration of spironolactone in patients in whom BP was not controlled by multiple drug treatment. Treatment-induced changes are shown at the top of the histograms. *CI* confidence intervals (From Davis et al. [21], by permission)

8.5 Mineralocorticoid Receptor Antagonists: Further Evidence

Support to use of mineralocorticoid receptor antagonists as the fourth drug to be administered in dRHTN can be found in several other studies that have shown, in some instances via a randomized, placebo-controlled design, the BP lowering ability of this class to include not only spironolactone but also eplerenone at adequate doses [23–30]. The most important documentation of the effectiveness of these drugs, however, comes from the recently published The Prevention and Treatment of Hypertension with Algorithm-based therapy (PATHWAY-2) study in which several hundred patients with a BP uncontrolled by the recommended three drug treatment regimen were randomized to the addition of spironolactone, bisoprolol, doxazosin or placebo. Following a few months of treatment, patients taking spironolactone showed a significantly greater BP reduction than patients taking doxazosin or bisoprolol, whose effect was modestly, albeit significantly, more evident than placebo. This was the case not only for office but also for home BP whose treatment-induced modification was the primary end point of the study (Fig. 8.6) [31]. This will probably lead future guidelines to privilege mineralocorticoid receptor antagonists over other drug options as the preferred fourth choice in dRHTN and perhaps also to define hypertension as resistant to treatment only after administration of a drug of this class has proven ineffective.

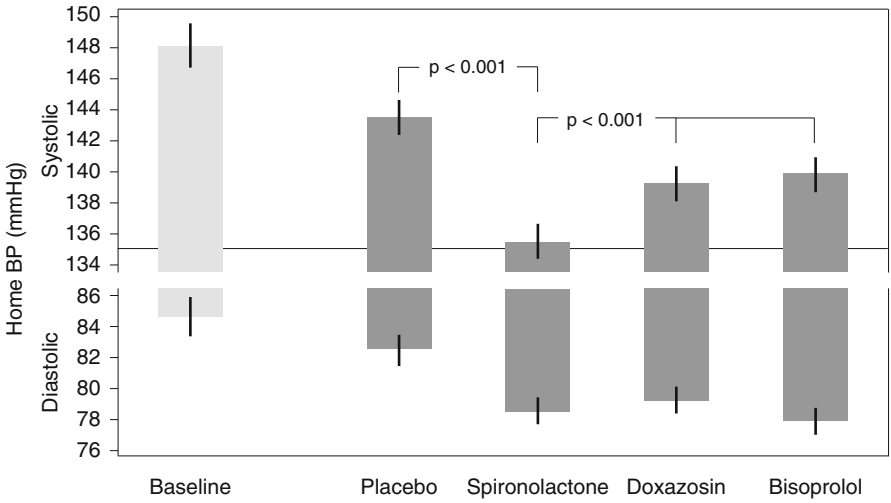

Fig. 8.6 Home blood pressure (*BP*) values at baseline and during treatment with placebo, spironolactone, doxazosin and bisoprolol (From Williams et al. [31], by permission)

8.6 Unmet Needs

Although more effective than any other added drug currently available, mineralocorticoid receptor antagonists by no means take care of all the problems posed by treatment of dRHTN. First, these drugs are associated with a number of serious side effects such as hyperkalemia and reduction of renal function [22, 32]. Second, both hyperkalemia and reduction of renal function are more frequent and severe in patients with a seriously impaired glomerular filtration, a condition that was excluded in the patients enrolled for the PATHWAY-2 study but that is not at all uncommon in dRHTN [33]. Third, despite the greater BP lowering effect in the PATHWAY-2 study, spironolactone failed to effectively lower BP in about 40 % of the study population, i.e. those with a high renin level, and perhaps a concomitant sympathetic hyperactivity (Fig. 8.7) [31]. Thus, more than a single drug class appears to be needed as fourth choice in order to extend effective treatment to the vast majority of resistant hypertensive individuals.

Future studies will have to address this issue by comparing the addition of a fourth drug with the combination of two or more additional agents, hopefully clarifying which combinations have the greatest potential to extend BP control. They may also, however, elect to address alternative possibilities, namely, whether (1) BP can be reduced in a larger number of resistant hypertensive patients by the use of drugs belonging to the same class but having a different site of action [34], an approach that sequential administration of a thiazide diuretic, a loop diuretic and amiloride has proven effective [35], or (2) a more precise assessment of the resistant hypertension phenotype. The latter approach will mean to (1) identify as precisely as possible the nature and extent

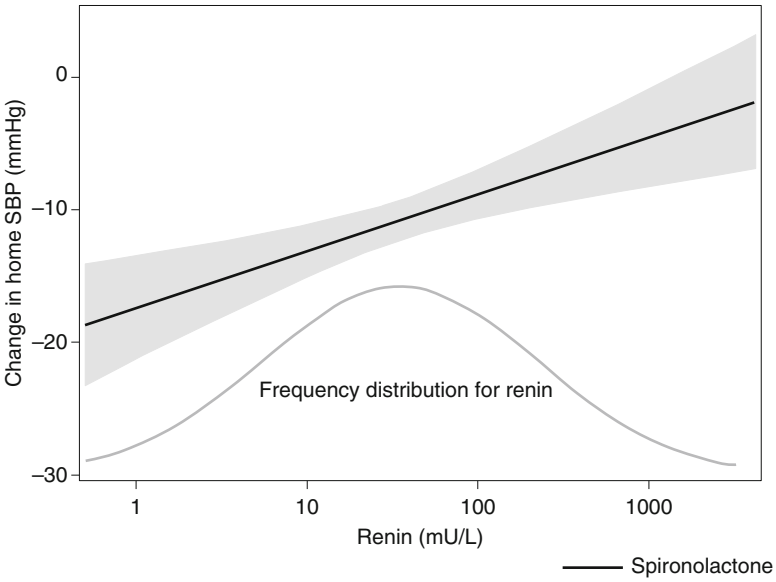

Fig. 8.7 Relationship between the home systolic blood pressure (*SBP*) change induced by spironolactone and plasma renin activity in the PATHWAY-2 study (From Williams et al. [31], by permission)

of the alterations of the structure and function of the organs (the heart, brain, kidney and vessels) targeted by the uncontrolled BP status and (2) determine which among the multiple neural and humoral mechanisms controlling circulation is more severely deranged, in order to try to individualize treatment and increase its success rate.

Finally, drug treatment of dRHTN may in the future count on new effective BP lowering agents. In the past, the use of endothelin antagonists has been disappointing because their BP lowering effect turned out to be questionable and accompanied by an unfavourable side effect profile [36]. Drugs targeting arterial stiffening (a structural alteration majorly responsible for the difficulty of lowering systolic values) have also met with difficulties that have prevented their extensive testing in humans. However, new dual-acting molecules as well as new powerful and better tolerated vasodilators are promising medicaments that may allow to more successfully face therapeutic control of a condition that may have a prevalence greater than 5 % of the overall hypertensive population [1], thereby involving in Europe several hundred thousand individuals.

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