Phenotypic Characteristics of Resistant Hypertension in the Brazilian Population

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Abstract

Resistant hypertension (RH) is defined as blood pressure that remains above target in spite of the concurrent use of three or more classes of antihypertensive drugs at optimized doses (UCRH), with one of them being a diuretic. Moreover, patients whose blood pressure is controlled while using four or more antihypertensive medications are also considered controlled resistant hypertensive (CRH) subjects. Although this definition may be useful in terms of categorizing a larger group of resistant hypertensive individuals, as these two subgroups share high cardiovascular risk, some important clinical and pathophysiologic particularities need to be better evaluated, before considering resistant controlled and uncontrolled patients as part of the same group. We compared cardiovascular characteristics of these two subgroups with resistant hypertension. In spite of some similar features, the UCRH subgroup has cardiovascular phenotypes with worse prognosis, such as increased vascular stiffness and left ventricular hypertrophy, as well as more impaired endothelial function and lower nocturnal blood pressure dipping, among others. Considering these differences, the UCRH subgroup is associated with greater cardiovascular risk and may be considered as more resistant to antihypertensive treatment. In addition to the importance of better prevention and treatment of resistant hypertension by identifying early risk factors and optimizing drug therapy, some clinical implications must be considered when managing controlled and uncontrolled patients as similar to the resistant hypertension group.

Introduction

Resistant hypertension (RH) is characterized by patients whose blood pressure (BP) remains above target in spite of the concurrent use of three or more antihypertensive drugs of different classes. Ideally, one of the agents should be a diuretic and all agents should be prescribed at optimal doses[1,2]. The revised definition includes a subgroup of resistant hypertensive patients whose BP is controlled using four or more antihypertensive medications[1,2]. Although this new definition may be useful to categorize a broader group of patients with treatment-resistant hypertension, we demonstrated that some important clinical findings differ between controlled (CRH) and uncontrolled resistant hypertensive (UCRH) subjects[3,4]. Indeed, recent data suggest that arterial stiffness, cardiac hypertrophy, high plasma aldosterone levels, autonomic dysfunction, endothelial dysfunction, obesity and plasma adipokine alterations may interact to have an important association with RH[3,5-7].

As hypertension is a multifactorial and polygenic disease, it is also possible that there are differences regarding the cardiovascular phenotypes related to CRH and UCRH subgroups in the Brazilian population. These subgroup differences point out to necessity to better assess subjects when considered as belonging to the same antihypertensive resistant group.

Keywords

Resistant hypertension; refractory hypertension; population; Brazil.

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General aspects

In general, blood pressure (BP) remains high in patients with resistant hypertension (RH) due to persistent elevation of systolic BP (SBP)[1,2]. The disparity in the control of SBP increases with age, peaking in individuals over 75 years old when compared with diastolic BP (DBP)[3]. Thus, advanced age is a major factor related to the difficulty in obtaining adequate or "normal" BP values. Parallel to this observation, the Framingham study found a correlation between the difficulty in controlling BP and the presence of elevated basal SBP levels[4]. Moreover, two additional strong predictors of failure to control hypertension are the presence of left ventricular hypertrophy (LVH) and obesity, with the latter being more related to difficulties in controlling DBP[1,2]. Clearly, high levels of sodium intake[5], chronic kidney disease (serum creatinine > 1.5 mg/dL), diabetes, Black ethnicity and female gender add to the picture of clinical features associated with the difficulty in attaining “normalized” BP levels[1,2].

More recently, other conditions have been associated with this syndrome, such as the presence of early silent lesions[6] in hypertensive target organ disease, such as microalbuminuria[7], LVH[8,9], obstructive sleep apnea syndrome[10-13] and metabolic syndrome[14]. Although some studies have indicated common mechanisms between obesity, metabolic syndrome, diabetes, sleep disorders and inflammatory activity in hypertensive subjects, the cause-and-effect relationship with RH has yet to be fully established[15,16].

Recently, an association was observed between a positive screening test for hypercortisolism with diabetes, older age and non-dipper pattern in the resistant hypertensive population[17]. Furthermore, resistant hypertensive patients with diabetes mellitus type 2 (DM2) have a high degree of autonomic dysfunction associated with elevated body mass index (BMI) and low plasma adiponectin levels[18]. Finally, elevated plasma aldosterone levels have been identified as relevant in BP control failure[19], which seem to be associated with sympathetic activity in RH patients with and without DM2[20], justifying the reintroduction of spironolactone, an aldosterone-receptor antagonist, into the antihypertensive therapy[21]. However, a recent retrospective study comparing larger populations of controlled (CRH) and uncontrolled (UCRH) resistant hypertensive individuals has not confirmed the differences regarding plasma and urinary aldosterone levels[22]. According to the authors, these data suggest that UCRH subjects do not show the characteristic aldosterone excess or greater fluid retention when compared with CRH subjects. Conversely, these findings emphasize cardiovascular phenotypic differences as responsible for the failure to attain optimal BP levels in this condition.

Taken together, all aforementioned clinical and laboratory characteristics play a crucial role in maintaining high blood pressure levels in some portion of the general population of hypertensive patients. This difficulty to obtain adequate BP levels, even using three antihypertensive drugs and including a diuretic, has been called "refractory hypertension" or "resistant hypertension" for over four decades. But, as recently reported in an editorial comment[23], the terms "resistant" and "refractory" are not synonymous.

The introduction of controlled RH concept in the literature

In 2008, the AHA Guidelines defined resistant hypertension (RH) as the condition in which blood pressure (BP) remains above target levels in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of these three agents should be a diuretic and all agents should be prescribed at optimal doses. According to this important scientific statement by the AHA, patients adhering to pharmacological and nonpharmacological treatments are also included[1,2], as well as all patients whose blood pressure is controlled, but who require four or more classes of antihypertensive drugs. The inclusion of this "controlled RH" (CRH) group may be justified by the fact that, before receiving four or more medications, these patients probably had previously taken three classes of drugs with no BP control, thus demonstrating the difficulty to manage them and considering their high cardiovascular risk.

Although understanding this conceptual explanation, there are some caveats to be discussed before considering these two subsets of RH patients as one. Frequently, RH subjects share several clinical characteristics such as age, obesity, renal dysfunction, high plasma aldosterone levels, sleep disorders and silent target organ damage[6]. For instance, it was unknown whether these characteristics were similar between CRH and UCRH patients. Furthermore, it was unknown whether other vascular and hemodynamic "phenotypes" such as endothelial function, arterial thickness, arterial stiffness and pulse pressure would be similar or different between these groups. Recently, considering the abovementioned questions, the clinical and cardiovascular characteristics for these two groups with resistant hypertension were compared. The answers to these questions could help us find what causes resistant hypertension (uncontrolled) to be refractory to treatment[24].

Cardiovascular phenotypes in resistant hypertension

Recently, we have studied[24] a group of 90 patients with RH who were identified as controlled (CRH, n = 43) or uncontrolled (UCRH, n = 47), according to the "AHA Statement for Resistant Hypertension – 2008". In addition to office and ambulatory BP measurements (ABPM), all patients underwent echocardiography and were evaluated for pulse wave velocity (PWV), plasma renin activity (PRA), plasma aldosterone concentration (PAC). As expected, high systolic (SBP) and diastolic BP (DBP) levels were found in UCRH subjects, as well as pulse pressure (PP) values, body mass index (BMI), PAC and ARR. Additionally, ARR was elevated in 21% of uncontrolled and only in 4% of controlled RH patients. Lipid profile, fasting glycemia and creatinine clearance were similar in both groups (data not shown). Regarding the cardiovascular "phenotype", UCRH patients had higher values of both carotid intima-media thickness (IMT) and PWV as an expression of thicker and stiffer arteries[25]. Multivariate linear regression analysis showed that PWV was significantly dependent on age in RH patients, but for any studied age strata, stiffer arteries were observed in the UCRH group. Left ventricular mass index (LVMI) was also significantly higher in UCRH subjects. Circadian BP patterns and vascular functions (endothelial-dependent and -independent) were also assessed in these patients[26]. The nocturnal dip in SBP and DBP was less marked in the UCRH than in the CRH group, as well as endothelial flow-mediated dilation (FMD) was significantly more impaired (5.9±2.3% vs. 7.1±1.5%; $P<0.0001$) in uncontrolled patients. We also observed a cluster correlation between a reduction in dipping status and impaired endothelial dysfunction in both RH groups, mainly in the uncontrolled group. When assessing adipose tissue hormones, UCRH patients had higher plasma leptin levels associated with increased plasma aldosterone, as well as SBP and DBP levels when compared with CRH and well-controlled subjects[27] (Table 1).

Implications

These observations may have some implications for daily clinical practice. First, at least in part, the supposedly increasing prevalence of RH in Western countries may not be as high as previously thought. The inclusion of "controlled patients" as RH in the recent AHA statement overestimates its prevalence. Probably, many of these CRH subjects taking "four or more antihypertensive drugs" were not "uncontrolled with three medications" and were put on this multiple regime because their physicians chose the reasonable option to combine many antihypertensive drugs at lower doses, instead of the previously considered

Table 1 - General characteristics of UCRH and CRH subgroups

	UCRH (n = 47)	CRH (n = 43)
Female gender (%) (n)	61.7 (29)	65.1 (28)
Age (years)	59 ± 7.8	56 ± 6.8
Body Mass Index (kg/m^2)	32 ± 2.1*	28 ± 1.5
Number of antihypertensive drugs	4.9*	4.3
Systolic BP (mmHg)	171 ± 10.2*	134 ± 5.8
Diastolic BP(mmHg)	105 ± 14*	81 ± 8.1
Pulse Pressure (mmHg)	68 ± 9.7*	56 ± 6.7
Left Ventricular Mass Index (g/m2)	179 ± 49.2*	140 ± 30.1
Carotid Intima-Media Thickness (mm)	1.2 ± 0.3*	1.1 ± 0.5
CF-Pulse Wave Velocity (m/s)	12.8 ± 0.8*	11.9 ± 1.0
Flow-mediated dilation (%)	5.9 ± 2.3* (n = 26)	7.1 ± 1.5 (n = 40)
Systolic BP dip (%)	1.9 ± 1.6* (n = 26)	4.9 ± 1.7 (n = 40)
Diastolic BP dip (%)	7.5 ± 1.8* (n = 26)	10.9 ± 1.8 (n = 40)
Plasma Aldosterone level (ng dL^{-1})	24.4 ± 3.2*	19.7 ± 2.6
Plasma Renin Activity (ng mL^{-1} per h)	2.3 ± 1.1*	5.5 ± 1.1
Aldosterone–renin Ratio (ng dL^{-1} per ng mL^{-1} per h)	22.9 ± 8.6*	4.3 ± 3.9
Leptin (ng.mL^{-1})	38.2 ± 21.4* (n = 41)	19.6 ± 8.7 (n = 39)

*UCRH: uncontrolled resistant hypertension; CRH: controlled resistant hypertension; BP: blood pressure; CF: carotid- femoral; *p< 0.05 vs. CRHTN.*

optimal ones. In fact, according to Acelajado et al[22], of the 304 patients referred for RH, 29 (9.5%) remained refractory to treatment[22].

Second, the fact that all the abovementioned clinical alterations were more prominent in uncontrolled patients may contribute to explain the increased treatment refractoriness of patients in the UCRH group, then constituting the physiopathological substrate for the development of higher BP levels. These data suggest that specific clinical differences between CRH and UCRH can identify the latter group as being exposed to increased cardiovascular risk.

The differences exhibited by our patients may reflect a worse cardiovascular prognosis for UCRH subjects, although this hypothesis should be tested using prospective studies designed specifically for primary clinical outcomes.

Finally, the importance of early identification of these characteristics in the hypertensive population along with changes in lifestyle and early pharmacological therapy is crucial to prevent the increasing prevalence of RH. Conversely, researchers should be careful when including CRH individuals in their studies, especially those of which aim is to analyze the association between "resistant hypertension" and gene polymorphisms related to hypertension. Negative findings may be due to a "mix of CRH and UCRH individuals", which decreases the chance of obtaining clear associations between some polymorphisms and resistant hypertension.

Author contributions

Conception and design of the research and Acquisition of data: de Faria APC, Moreno H; Analysis and interpretation of the data: de Faria APC, Sabbatini AR, Coca A, Moreno H; Statistical analysis: de Faria APC, Sabbatini AR, Moreno H; Writing of the manuscript and Critical revision of the manuscript for intellectual content: de Faria APC, Coca A, Moreno H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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