Cardiac and Vascular Alterations in Resistant Hypertension

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4.1 Introduction

Resistant hypertension is defined as systolic and diastolic blood pressure that remains above goal (i.e., >140/90 mmHg in the general population of hypertensive patients and >130/80 mmHg in high-risk individuals such as patients with diabetes or chronic kidney disease), despite adherence to lifestyle measures and to pharmacological treatment with full doses of at least three antihypertensive medications, including a diuretic [1]. RH is recognized as a clinical phenotype carrying a high cardiovascular risk [1].

The risk of clinical complications including stroke, acute aortic dissection, myocardial infarction, congestive heart failure, and renal failure is higher in patients with resistant hypertension, when compared with other groups of hypertensive patients, including not only well-controlled subjects, but also false resistant and masked hypertension [2–4].

In fact, Redon et al. [5] followed 86 patients with RH, for an average period of 49 months, and was able to show that the overall incidence rate of cardiovascular events was 24.6 %; the incidence of events was related to BP values (assessed by 24-h BP monitoring) increasing progressively from 2.2 per 100 patient-years in the lowest tertile of diastolic BP, to 9.5 in the intermediate tertile, and to 13.6 in the highest tertile.

More recently Daugherty et al. [6] confirmed the high rate of incident cardiovascular events in patients with RH. In that study, among 205,750 patients with hypertension, 1.9 % developed resistant hypertension, and these resistant hypertensive patients were more often men, older, and diabetics than non-resistant

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patients. The rate of cardiovascular events was significantly higher in those with RH, as compared with those without (18.0 % versus 13.5 %, $P < 0.001$), and the hazard ratio was 1.47 [confidence interval (CI) 1.33–1.62] after adjustment for patient and clinical characteristics.

Resistant or refractory hypertension (RH) represents a subset of uncontrolled BP strongly associated with organ damage, in particular at the cardiac, renal, and vascular levels [7]. The relationship between RH and cardiovascular disease/target organ damage may be bidirectional: RH may directly cause the development and worsening of target organ damage, through the persistent elevation of blood pressure. On the other hand, the presence of cardiovascular damage may contribute to worsen the resistance to treatment, making hypertension more difficult to control [8, 9].

In patients with renal disease, microvascular disease, left ventricular hypertrophy, aortic stiffness, cerebrovascular disease, or secondary hypertension, the prevalence and incidence of RH may be clearly increased.

A number of studies have analyzed the association between RH and some aspects of target organ damage, but only few of them have focused on the presence of more than one [10].

The present review is aimed to update the currently available data on the relationship between RH and subclinical damage in the heart, microcirculation, and macrocirculation.

4.2 Cardiac Damage

Among the different features of hypertensive heart disease, left ventricular hypertrophy, left ventricular dysfunction, and left atrial enlargement have been reported in RH patients.

The most frequent abnormality described in RH is LVH, assessed by both electrocardiography and echocardiography.

Cuspidi et al. [11] have identified a total of 11 cross-sectional and longitudinal studies, including 3,325 patients attending outpatient hypertension clinics and have observed that prevalence rates of echocardiographic LVH, as assessed by updated criteria, ranged from 55 to 75 % of patients with RH, peaking to 91 % in the subgroup with concomitant electrocardiographic (ECG) LV strain (Fig. 4.1). Reduction in ECG-LVH induced by treatment showed a relevant beneficial impact on cardiovascular prognosis.

A large amount of evidence on ECG and echocardiographic findings related to RH has been provided by a number of studies conducted in Brazil by Salles et al. [12–17].

In these studies, true RH patients were identified by ambulatory BP monitoring, ruling out the presence of white-coat hypertension. In 471 RH patients, the prevalence rates of ECG (Cornell's product >240 mV*ms) and echocardiographic

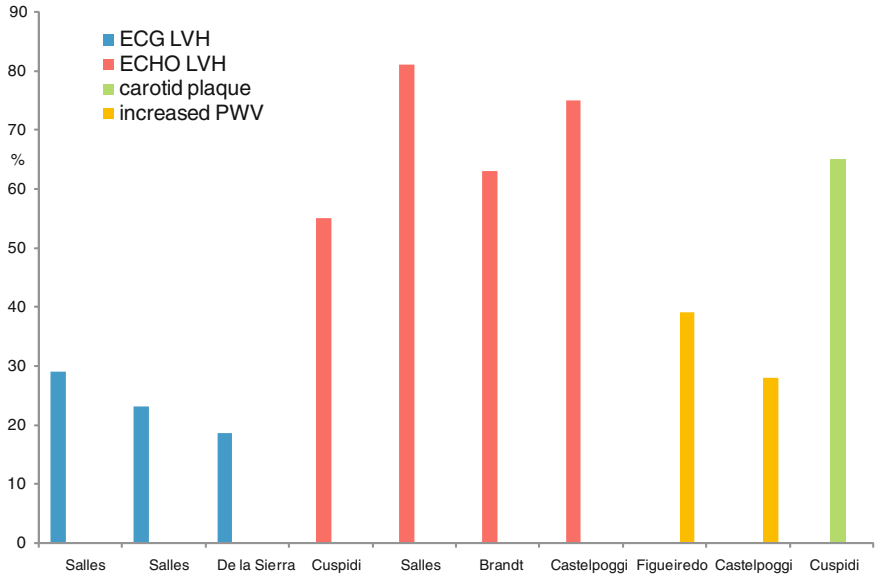

Fig. 4.1 Prevalence (%) of ECG or echocardiographic left ventricular hypertrophy (LVH), of increased aortic stiffness, and of carotid alterations in patients with RH

LVH were 29 and 81 %, respectively. Authors have initially assessed the relationship between QT interval-derived parameters and echocardiographic LVH and observed that values of QTc interval >440 ms and Cornell's product >240 mV*ms were associated respectively, with a 2.0-fold and 2.6-fold greater chance of having an increased left ventricular mass at the echocardiographic examination [12]. When the presence of a prolonged QT interval and an increased Cornell's product was combined, the relative risk of having echocardiographic LVH increased by 5.3- to 9.3-fold, compared with a normal QT interval and Cornell's product.

Salles et al. [13] have thereafter investigated the clinical significance of ECG strain pattern that was identified in 101 patients (23 %); in these patients, the prevalence rate of echocardiographic LVH was 91 %. Patients with strain were more frequently men with lower body mass index and had more target organ damage, higher 24-h blood pressure, higher serum creatinine and 24-h microalbuminuria, and more prolonged QT interval duration than those without strain. In a multivariate analysis, the presence of ECG strain was associated with increased LVM ($P < 0.001$), higher 24-h systolic blood pressure ($P < 0.001$), prolonged maximum QTc-interval duration ($P < 0.001$), lower waist circumference ($P = 0.009$), male gender ($P = 0.011$), physical inactivity ($P = 0.020$), higher serum creatinine ($P = 0.031$) and fasting glycemia ($P = 0.027$), and the presence of coronary heart disease ($P = 0.001$) and peripheral arterial disease ($P = 0.045$).

Cuspidi et al. [10] have investigated the prevalence of organ damage in the heart, carotid arteries, and kidney in 54 true RH (mean age 57 ± 10 years) and compared the findings with age- and sex-matched hypertensive patients with a good control of blood pressure using a combination of 2 or 3 drugs. LVH prevalence was higher in RH patients ranging from 40 to 55 %, in relation to the different criteria for LVH. Concentric LVH was the more common type of geometric pattern in these patients.

Castelpoggi et al. [14] have collected the largest number of RH patients with echocardiographic examination at the Rio de Janeiro University. They studied 600 patients at high or very high CV risk (23 % coronary heart disease and 15 % previous cerebrovascular events) and observed that LVH was present in 75 % of patients.

The same group of authors was able to assess the prognostic value of alterations in ECG repolarization and voltage parameters in a large group of 538 RH patients (75 % with echo LVH), prospectively followed for an average period of 4.8 years [15]. Authors have shown that among all repolarization parameters, only the QTc interval duration resulted an independent predictor of cardiovascular mortality and all-cause mortality.

In a subsequent analysis of the same database [16], the prognostic significance of serial changes on LV strain pattern (present at baseline in 21 % of RH patients) was evaluated. Persistence or development of strain during the follow-up was associated with an increased risk of stroke (hazard ratio 3.09, 95 % CI 1.40–6.81) and of death for all causes (hazard ratio 1.99, 95 % CI 1.10–3.61).

Finally, the prognostic significance of serial changes on LVH voltage criteria was analyzed in a slightly larger group of 552 patients [17]. The presence of Cornell's voltage and product criteria at baseline, but not of Sokolow-Lyon voltage, was independently associated with an increased incidence of cardiovascular morbidity and mortality and with all-cause mortality during the follow-up. In addition, the regression or the absence of ECG-LVH from baseline to follow-up was associated with a lower incidence of major cardiovascular events.

The data strongly suggest the importance of evaluating cardiac target organ damage in patients with RH, both at the initial evaluation and also during treatment [18].

Despite the fact that the evidence of the prognostic significance of LVH regression was confirmed in several studies [19, 20], only few studies have addressed the effect of antihypertensive treatment on LVH and LV mass changes in the setting of RH patients [21, 22].

De Faire et al. have compared the effects of captopril therapy (with a large dose range, from 75 to 450 mg per day) to a combination of three drugs (i.e., diuretic, beta-blocker, calcium antagonist, or direct vasodilator) in a small group of 10 patients with RH. In this study, a decrease in LV wall thickness was observed after 12 months of treatment, despite no significant changes in LV mass were shown [21].

More recently, Gaddam et al. have assessed the effects of spironolactone (25–50 mg per day) on LV mass, right ventricular, and LV volumes, measured by magnetic resonance imaging, in 34 RH patients. After 3 months of treatment with

the aldosterone antagonist, a significant decrease in LV mass, in LV wall thickness and volume, and in left atrial size was observed, and the effect was greater in the group of 19 patients with RH due to primary aldosteronism [23].

The effect of renal denervation on echocardiographic LV mass has been demonstrated by Brandt et al. in 46 RH patients, compared with 18 controls receiving only medical treatment (mean number of drugs 4.7) [24]. At echocardiographic controls performed 1 and 6 months from baseline, LVM and the E/E′ ratio (index of increased LV filling pressure) were significantly reduced after the renal denervation procedure, while these did not change during medical treatment. In the whole group of patients, the improvement in LV mass index and E/E′ ratio was related to the decrease in BP induced by treatment, although it was observed also in those patients defined as "non-responders" on the basis of clinic BP values, suggesting some additional effect of sympathetic renal denervation of cardiac target organ damage, independent of pressure load.

4.3 Large Arteries

A relation exists between vascular calcification, arterial stiffness, and difficult to control hypertension. In patients with RH, the presence of structural alterations in large caliber vessels, such as carotid arteries and aorta, may have a great impact of blood pressure control [25].

In some studies, an increased prevalence of carotid wall thickness, atherosclerotic plaques, and aortic stiffness has been demonstrated.

Cuspidi et al. [10] for the first time documented the increased prevalence of intima-media thickening or of plaques in the carotid arteries of RH patients as compared with a group of patients treated with a combination of antihypertensive drugs, but with controlled BP values in the clinic and during 24-h BP monitoring (prevalence 58 and 65 % versus 29 and 32 %, respectively).

It was also suggested that among patients with carotid arteries stenosis, the prevalence of RH was fairly high. Spence et al. analyzed 170 patients with carotid arteries stenosis who participated in the North American Symptomatic Carotid Endarterectomy Trial or the Asymptomatic Carotid Artery Study and observed that RH was present in 79 (47 %) related to renovascular hypertension in 20 and to adrenocortical hyperplasia in 7 [26].

More recently, Schmieder et al. analyzed the presence of vascular target organ damage in 42 RH patients, who were investigated by brain magnetic resonance imaging. Twenty-three patients had cerebral microangiopathy that was associated with higher systolic blood pressure during nighttime. In addition, RH patients with cerebral microangiopathy had similar carotid intima-media thickness but higher pulse wave velocity, central pulse pressure, and aortic augmentation pressure [27].

Some other studies have evaluated the increase in aortic stiffness in patients with RH. Figueiredo et al. have measured carotid femoral pulse wave velocity in 44 patients with RH, 35 patients with controlled blood pressure values, and 25

normotensive subjects, showing a significant increase in PWV in patients with RH as compared with the other 2 groups [28]. Since endothelial function may contribute to the regulation of large artery elasticity, authors have also evaluated flow-mediated changes in the vessel diameter and observed that a greater decrease in brachial artery flow-mediated vasodilation was more evident in RH when compared with well-controlled hypertensive patients.

In the largest cross-sectional study including 600 resistant hypertensive patients without peripheral arterial disease, Castelpoggi et al. [14] assessed arterial stiffness by aortic pulse wave velocity (PWV) measurements and found that 168 patients (28 %) had aortic PWV >12 m/s. Patients with increased PWV were older and had a higher prevalence of cardiovascular risk factors than did those patients with normal PWV. A blunted nocturnal decrease in BP was independently associated with increased aortic stiffness in RH patients, together with older age, diabetes, microalbuminuria, low HDL cholesterol, and a widened 24-h BP.

4.4 Microcirculation

In hypertension, small artery remodeling is the most prevalent form and one of the first manifestations of target organ damage. The magnitude of remodeling of small resistance arteries in hypertension has been demonstrated to have prognostic significance with worse prognosis for subjects with greater structural alterations, as evaluated by the media thickness/lumen diameter ratio [29].

The available evidence shows that in patients with secondary hypertension (and a greater prevalence of RH), the increase in the media-to-lumen ratio is particularly pronounced in comparison with essential hypertensive patients [30]. Most interestingly in patients with renovascular hypertension and to a lesser extent in those with primary aldosteronism, a more evident contribution of cell growth, leading to the development of hypertrophic remodeling, (indicating smooth muscle cell growth), has been observed. In addition, a more pronounced fibrosis in the tunica media, in terms of total collagen content, with a more evident increase in collagen type III, has been demonstrated in patients with primary aldosteronism [31] (Fig. 4.2). In the development of hypertrophic remodeling, a relevant role is played by growth factors, especially endothelin-1 and angiotensin II, while the mechanisms leading to eutrophic remodeling (increased media-to-lumen ratio without muscle cell growth) are less clear. Endothelin-1 is a powerful vasoconstrictor and mitogen, contributing to the elevation of blood pressure and related target organ damage. Vascular effects of aldosterone may be mediated, as suggested by Schiffrin et al., by the stimulation of endothelin production. In patients with RH, the content of endothelin -1 was significantly greater than in mild hypertensive patients or normotensive controls [32].

The evaluation of retinal vessels may represent a method for the evaluation of microcirculation. Cuspidi et al. [10] observed that patients with RH, undergoing a traditional fundoscopic examination, had a very high rate of retinal vascular

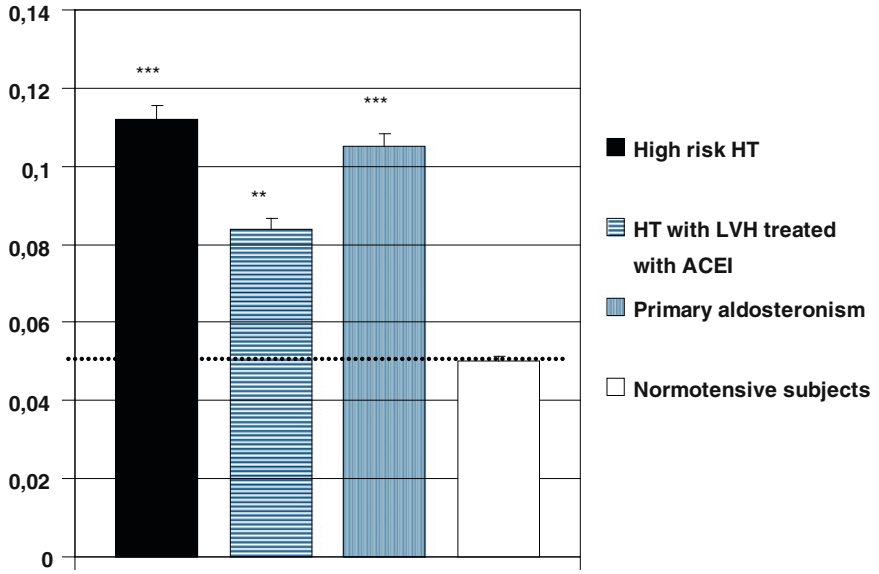

Fig. 4.2 Media thickness/lumen diameter ratio (M/L) in patients at high cardiovascular risk, in patents with primary aldosteronism, in patients with essential hypertension, and in normotensive subjects

changes (narrowings and arteriovenous crossings) and a greater prevalence of grade 2 and 3 retinopathy (73 and 5 %), according to the Keith–Wagener classification, as compared with a control group (38 and 0 %).

Another study examined the fundus oculi in 497 patients, of whom 63 % with true RH and 37 % with white-coat hypertension, and the results confirmed a higher prevalence of retinopathy in true resistant patients (55.2 vs. 40 %, $P = 0.002$) [33].

More recently, measurements of retinal arterioles have been taken in vivo with scanning laser doppler flowmetry in 40 patients with resistant hypertension. All the parameters indicating the presence of microvascular abnormalities, that is, the wall-to-lumen ratio, the wall thickness, and the wall cross section area, were strongly associated with urinary sodium excretion and less consistently with 24-h blood pressure. In this group of patients, urinary sodium excretion represented the only independent determinant of wall thickness and of wall cross section area of retinal arterioles. Since retinal arteriolar alterations are related to cerebral vascular structure, these results might prove to have important implications on risk stratification in patients with resistant hypertension [34].

We have investigated the possible predictive effect of vascular structural alterations in relation to the time course of blood pressure after surgical correction of primary aldosteronism [35]. We calculated receiver-operating characteristic

curves for identification of patients with aldosterone-producing adenoma, who achieved normotension post-adrenalectomy, compared with those who did not [35]. For both the media-to-lumen ratio of subcutaneous small arteries, evaluated before surgical correction, and known duration of hypertension, the area under the curve differed significantly from the area under the curve under the identity line, thus indicating the usefulness of either variable for predicting the outcome on blood pressure in these patients [35]. Therefore, the extent of alterations of microcirculation predicts the pressor outcome after adrenalectomy, both in terms of absolute blood pressure values and/or in terms of number or doses of drugs needed.

4.5 Concomitant Cardiac and Vascular Damage

Few studies have evaluated the association between RH and the presence of more than one target organ damage [10, 14, 27] and have found a correlation between cardiac, vascular, and renal damage in patients with resistant hypertension.

In the Vobarno Study, the prevalence of resistant hypertension and the presence and degree of associated cardiac, vascular, and renal target organ damage were assessed in a general population sample, participating in a prospective epidemiological study, originally aimed to measure the association between cardiovascular risk factors and target organ damage (Vobarno Study) [36, 37]. Resistant hypertension prevalence was 9,5 % according to the definition proposed by Calhoun et al. [1], and in RH individuals, a higher LV mass index, PWV, and carotid intima-media thickness are shown (Figs. 4.3, 4.4 and 4.5) [38], confirming and extending previous results.

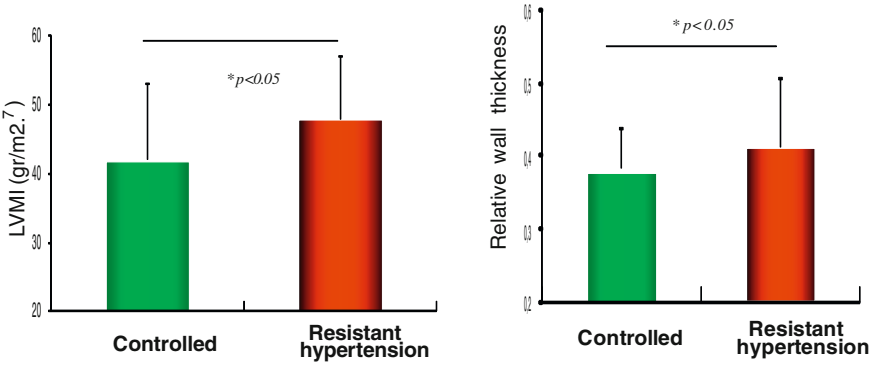

Fig. 4.3 Left ventricular mass index in resistant and controlled hypertensives

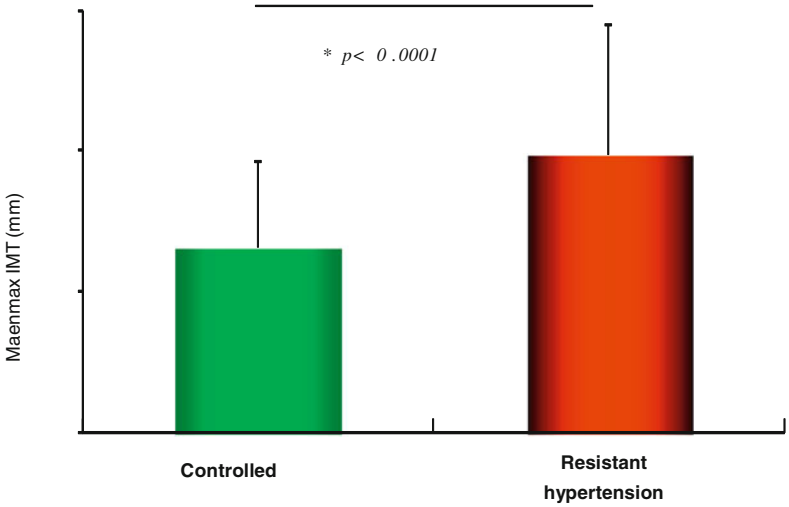

Fig. 4.4 Intima-media thickness in resistant and controlled hypertensives

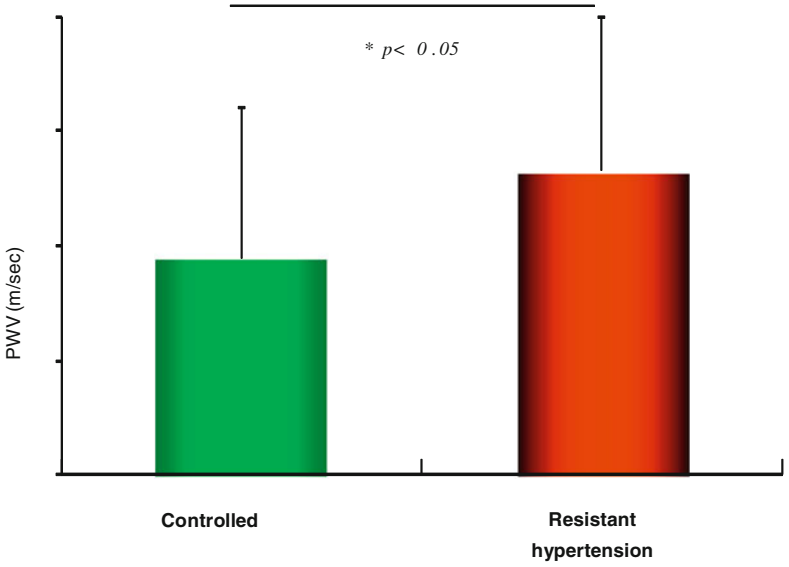

Fig. 4.5 Pulse wave velocity in resistant and controlled hypertensives

4.6 Conclusions

- Resistant hypertension is associated with multiple cardiovascular risk factors and organ damage.
- The proportion of patients with clinical target organ damage is greater in subjects with true resistant hypertension than in those with white-coat resistant hypertension.
- In patients with resistant hypertension, subclinical organ damage itself may be responsible for high blood pressure values, but it is also the result of detrimental effects of hypertension on large arteries as well as on the microvascular network. The early correction of such vascular abnormalities is vital for medium- and long-term blood pressure control.

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