The prevalence of resistant arterial hypertension and secondary causes in a cohort of hypertensive patients: a single center experience

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ABSTRACT

The prevalence of resistant hypertension (RHT) still remains unknown. Aim of the study was to investigate in a large cohort of hypertensive patients the prevalence of RHT, and to identify in these patients the secondary forms of arterial hypertension (SH). We enrolled a series of 3685 consecutive hypertensive patients. All patients underwent complete physical examination, laboratory tests, screening for SH. Ambulatory blood pressure monitoring (ABPM) was performed to exclude white-coat hypertension. Further, we investigated for any obstructive sleep apnea syndrome (OSA). Only 232 (5.8%) hypertensive patients fulfilled criteria for RHT. 91 (39%) had a SH; 56 (61%) hypertensive patients had a primary aldosteronism, 22 (24%) had OSA, 7 (7.7%) had a hypercortisolism, and 5 (5.5%) had a renovascular hypertension (RVH). Only one patient had adrenal pheochromocytoma. An accurate definition and investigation into RHT is needed. We recommend ABPM to all patients at diagnosis. Finally, all patients must be screened for SH, such as adrenal hypertension, OSA and RVH, especially those who are apparently resistant to polypharmacological treatment.

Introduction

Arterial hypertension is responsible for worldwide burden due to high cardiovascular morbidity and mortality. In Westernized countries about 40% of adults are affected by hypertension, responsible for a higher risk of stroke, acute coronary syndromes, heart failure and chronic renal disease.[1]

Although several appropriate and integrated pharmacological strategies are available, blood pressure (BP) control still remains largely unsatisfactory. Considering that uncontrolled hypertension leads to excess target organ damage and complications,[2] the patients with resistant hypertension (RHT) are still exposed to an excess risk of cardiovascular disease events.[3]

RHT is arbitrarily defined when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs, belonging to different classes at adequate doses, fails to lower systolic BP (SBP) and diastolic BP (DBP) values to 140 and 90 mmHg, respectively.[4,5]

Despite the growing number of clinical studies of RHT in the past decade, the RHT prevalence has not been properly examined. Some retrospective studies have examined the prevalence of RHT in various settings and overall small studies suggesting a prevalence ranging from around 5% in general practice (with poor selection of patients) to 50% in high specialized centers, including patients with chronic kidney disease.[6] Among studies performed in larger cohorts examining the epidemiologic characteristics of RHT, two of these have included patients firstly evaluated in tertiary hypertension facilities, showing the prevalence from 11% to 21%.[7]

However, in more than 50% of these patients, one or more of the various subtypes of refractory hyperten-

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sion are present, including white-coat hypertension (isolated clinic or office hypertension: office BP readings usually greater than 140/90 mmHg and reliable out-of-office readings that are routinely less than 140/90 mmHg), pseudo-resistance (lack of adherence and/or BP poor measurement technique) or secondary hypertension (SH).[8]

In the present study we sought to systematically investigate in a large cohort of newly diagnosed hypertensive patients the prevalence of RHT, and evaluate the presence of some secondary forms of arterial hypertension.

Materials and Methods

Participants

From January 2011 to September 2016, we have evaluated 3685 consecutive hypertensive patients who were studied at Departmental Unit of Secondary Hypertension, Department of Internal Medicine and Medical Specialties, La Sapienza University (Rome, Italy), referred by specialist health care. Informed consent was obtained from all subjects after the explanation of the purpose and potential risk of the study. All patients underwent a complete physical examination and laboratory exams. Laboratory tests were reported in Table 1. We performed a screening for SH with the hormones analysis such as plasma aldosterone (PAC), plasma renin activity (PRA), serum cortisol (PC), and 24-h urine excretion for metanephrines, free cortisol (UFC), aldosterone serum electrolytes and creatinine. Any antihypertensive drug was withdrawn at least 3 weeks (up to 2 months for spironolactone) before hemodynamic, biochemical and hormonal evaluation. In patients in whom treatment could not be withdrawn for ethical reasons, calcium-channel blockers (verapamil) or α-receptor blockers (doxazosin) were allowed at the minimal doses required to achieve BP control. All patients were encouraged to adopt lifestyles changes to decrease BP, for example salt restriction, diet low on saturated fat/cholesterol, weight reduction, aerobic physical exercise, limitation of alcohol consumption and smoking cessation. To exclude white coat hypertension, ambulatory blood pressure monitoring (ABPM) and home BP measurement were performed in addition to the office BP at the hospital. The physicians instructed patients to remain adherent to their prescribed antihypertensive therapy. After an optimization of their anti-hypertensive therapy, patients were consecutively reevaluated by a second ABPM. Those patients who had a normalization of their BP were excluded by the definition of RHT and defined as *pseudoresistant*. Moreover, in all patients we evaluated clinical signs of sleep disorders with the use of specific questionnaire (Epworth sleepiness scale).[9] Briefly, the patient can suggest the probability of falling asleep (0-3) in 8 different situations, and a score >10 points represents the probability of excessive daytime sleepness.[9]

Ambulatory blood pressure monitoring

ABPM for 24-h was performed by means of oscillometric device Space-Labs 90207 (Space-Labs Medical, Richmond, WA, USA) which was set to measure BP every 15 min during the day (from 06:00 a.m. to 22:00 p.m.) and every 30 min during the night (from 22.00 p.m. to 06.00 a.m.). The definition of *dipper* and *non-dipper* was established when night time SBP and DBP measure was >10% and <10% respectively. Subjects without complete 24-h BP measurements (14 diurnal and 7 nocturnal) repeated the ABPM.

Diagnosis of renovascular hypertension

Patients with hyperreninemic aldosteronism underwent a Doppler-renal-ultrasonography. Doppler renal artery ultrasonography measurements were performed using a 3.5 MHZ transducer (Toshiba Aplio XV, Crawley, West Sussex, United Kingdom). The pulsatility index was calculated, and a side-to-side difference of >0.20 was used as a criterion for renal artery stenosis. In addition, evaluation of the blood flow velocity during early systole was measured, and on acceleration of the blood flow >3 mm/s^2 a criterion for renal artery stenosis was used. Patients with a positive screening for renal artery stenosis underwent magnetic resonance imaging (MRI) or arterial renal angiography. Those patients, diagnosed with RVH, and whose renal function was not irreversibly degraded, with a resistant index less than 0.7, were considered potentially suitable for endovascular revascularization.[10]

Diagnosis of obstructive sleep apnea

In patients with a positive Epworth sleepiness scale, a nocturnal polysomnography was performed in our Hospital, and included the recording of several parameters. A 6 h minimum duration was required for diagnosis. Data obtained included sleep efficiency, measure and duration of apnea/hypopnea episodes, apnea/hypopnea index (AHI), the number of desaturation greater than 4% below baseline, and the final diagnosis, obstructive sleep apnea syndrome (OSA), was defined as AHI greater than 5 as all subjects undergoing polysomnography were symptomatic.[11]

Diagnosis of primary aldosteronism

Diagnosis of primary aldosteronism (PA) was made as previously described.[12] A cut-off upright PAC/PRA ratio (ARR) of more than 30 in the presence of PAC greater than 15 ng/dL and suppressed PRA (<0.5 ng/mL/h), was used as screening test for PA. In the case

of ARR greater than 30, patient underwent a saline infusion (0.9% NaCl at 500 mL/h) as confirmatory test and only those with PAC that failed to decreased to less than 7 ng/dL after the saline infusion were diagnosed as having PA. In this patient, a computed tomography (CT) scan or MRI of the adrenal glands or adrenal venous sampling (AVS) was performed to differentiate between aldosterone-producing adenoma (APA) from idiopathic hyperaldosteronism (IHA). The diagnosis of APA was confirmed by surgery and histological examination.[12]

Diagnosis of Cushing's syndrome

The Cushing's syndrome (CS) was based on the clinical signs or symptoms, hormonal data and imaging tests (pituitary MRI, adrenal CT, adrenal scintigraphy).

Endocrine test for CS showed lack of diurnal rhythm PC levels (>5 ng/dL), no suppression of PC (>1.8 ng/dL) levels after a low dose (1 mg dexamethasone suppression test) and increased 24 h UFC (>100 µg/24 h). Measurement of plasma adrenocorticotropic hormone (ACTH) differentiated ACTH-dependent CS (ACTH >10 pg/mL) from ACTH-independent CS (<10 pg/mL).[13]

Diagnosis of ACTH-dependent or ACTH-independent CS was further confirmed by hypophysis MRI and abdominal CT or MRI and iodine-norcholesterol scintigraphy. The final diagnosis of hypophysis or adrenal adenoma was confirmed by surgery and histological examination.

Diagnosis of pheochromocytoma

The diagnosis of pheochromocytoma (PHEO) was established on the basis of: i) clinical symptoms; ii) elevated value of 24-h urinary metanephrines. Diagnosis of PHEO was further confirmed by abdominal CT or MRI scans and 123-iodio-benzilguanidin scintigraphy and the diagnosis was finally proven by histopathological findings of the resected adrenomedullary tumor.[14]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences, version 22.0, statistical software (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as frequency distribution. Possible explanatory variables used as independent variable included demographic, clinical, and ABPM values. Between-group differences in continuous variables were calculated using Student's *t*-test. Fisher's exact test or χ^2 was used in comparison of categorical variables. A P value <0.05 was considered significant.

Results

The study population comprised 3685 consecutive hypertensive patients (2175 males and 1059 females; mean age 60.8±14.5 years). In Figure 1, we reported

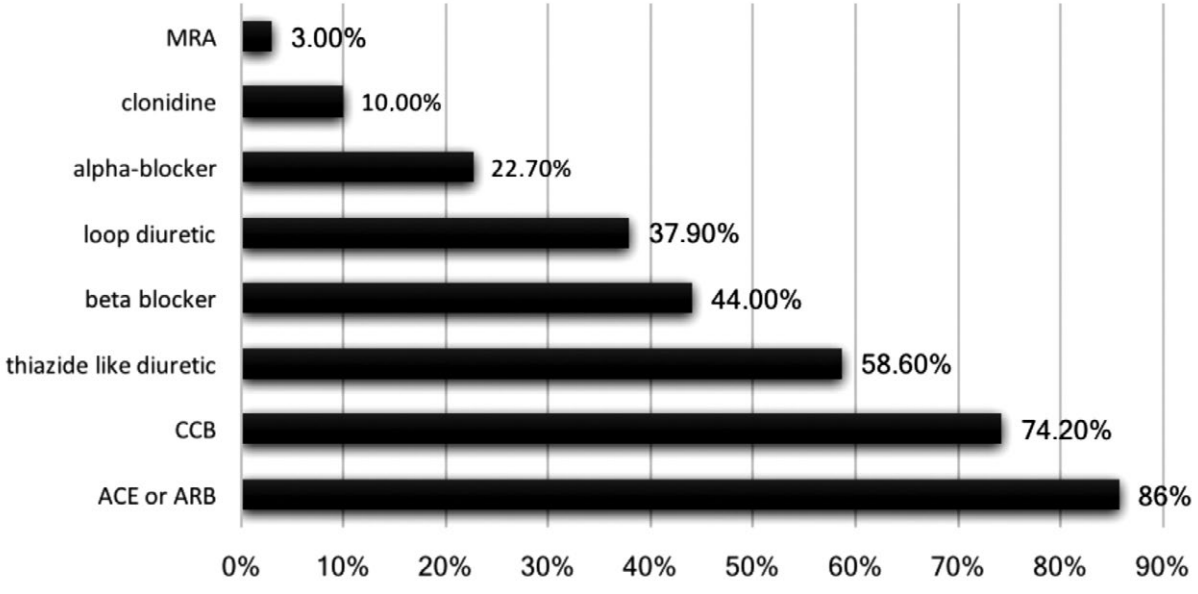


Figure 1. Baseline anti-hypertensive drugs in the study population of 3685 patients (2175 males and 1059 females; mean age 60.8±14.5 years; mean drugs taken: 2.2±1.8). MRA, mineralocorticoid receptor antagonist (spironolactone or eplerenone); CCB, calcium channel blocker; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

the mean of anti-hypertensive drugs that our hypertensive patients took before the study. In Table 1, we reported the demographic, hemodynamic and biohumoral parameters of overall 3250 hypertensive patients with a final diagnosis.

Of these patients, 232 (5.8%) fulfilled standard criteria of RHT (lifestyle, SBP≥140 mmHg and DBP≥90 mmHg, and use of 3 antihypertensive drugs, one of them being a diuretic, and comprised the ABPM),[5,6] had a RHT (Figure 2). Ninety-four (40.5%) of these 232 RHT patients were females (mean age 57.38±12.68 years) and 138 (59.5%) were males (mean age 53.457±12.59 years). Ninety-one (39%) patients had SH (31 females and 61 males; mean age 53.8±12.4 years). Fifty-six (61%) of these patients had PA (16 females and 40 males; mean age 54.2±12 years). Forty (71%) of these 56 PA patients (27 males and 13 females; mean age 55.8±12.4 years) were clinically diagnosed as IHA based on bilateral aldosterone hypersecretion revealed by AVS. Sixteen (29%) PA patients (13 males and 3 females; mean age 55.8±10.7 years) affected by unilateral hypersecretion of aldosterone underwent unilateral laparoscopic adrenalectomy, by expertise surgeons. Histopathological examinations of the resected adrenal gland confirmed a diagnosis of APA.

Twenty-two (24.2%) patients had OSA (7 females and 15 males; mean age 60±10 years). In particular, 8 patients (33%) (5 males and 3 females; mean age 57.6±8.63 years) had severe OSA (apnea-hypopnea index ≥30), while 16 patients (67%) (12 males and 4 females, mean 61±7 years) had mild OSA (apnea-hypopnea index 15-30).

Seven (7.7%) patients had CS (5 females and 2 males; mean age 53.6±11 years). Among these 7 patients, 5 patients (3 males and 2 females; mean age 52.5±3.5 years) had ACTH-independent CS and underwent unilateral laparoscopic adrenalectomy; 2 patients had ACTH-dependent CS and underwent transsphenoidal pituitary adenomectomy. The final diagnosis for adenomas were confirmed by histopathological examinations of the resected specimens.

Five (5.5%) patients had RVH (3 females and 2 males; mean age 43±9.3 years). In these patients, renal arteriography revealed renal artery stenosis, that was determined by fibromuscular degeneration in 3 female patients (mean age 36.7±4 years), and by atherosclerotic changes in other 2 male patients (mean age 52±3.5 years).

One patient (1.1%), a 70-year-old man had adrenal PHEO, underwent unilateral adrenalectomy and histopathological exam confirmed the diagnosis of adrenal PHEO.

In Table 2, we reported the demographic, hemodynamic and biohumoral parameters in patients with some secondary forms of hypertension revealed in RHT pa-

Table 1. Demographic, hemodynamic, biochemical and biohumoral parameters in overall hypertensive 3250 patients enrolled.

	Age (years)	BMI (kg/m^2)	WC (cm)	NC (cm)	Office-SBP (mmHg)	Office-DBP (mmHg)	HR (sec)	Glyc (mg/dL)	Creat (mg/dL)	Na (mmol/L)	K (mmol/L)	Ca (mEq/L)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TGL (mg/dL)	UA (mg/dL)
EH N: 3250 (1397 M; 1853 F)	56.8±14.2	27.4±4.6	97.9±13.4	36.5±4.1	141.7±18.99	85.1±11.4	66.6±9.84	94.9±20.6	0.9±0.29	142.8±2.6	4.3±0.4	9.5±0.7	197.1±34.2	117.5±30.6	54.5±15.4	118.4±53.4	5.2±1.4
		M-SBP (mmHg)	M-DBP (mmHg)	G-HR (bpm)	D-SBP (mmHg)	D-DBP (mmHg)	D-HR (bpm)	N-SBP (mmHg)	N-DBP (mmHg)	N-HR (bpm)	*Non-dipper* pattern						
EH N: 3250 (1397 M; 1853 F)		132.4±13.7	79.9±10.1	73.5±8.3	135.1±13.6	82.7±10.6	75.6±8.5	123.8±19.4	71.4±11.7	67.7±9.6	46.6%						

WC, waist circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; Glyc, glycemia; Creat, creatininemia; Na, serum sodium; K, serum potassium; Ca, serum calcium; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TGL, triglycerides; UA, uric acid; hypercortisolism M-SBP, mean average systolic blood pressure; M-DBP, mean average diastolic blood pressure; G-HR, global average heart rate; D-SBP, daytime average systolic blood pressure; D-DBP, daytime average diastolic blood pressure; D-HR, daytime average heart rate; N-SBP, nighttime average systolic blood pressure; N-DBP, nighttime average diastolic blood pressure; N-HR, nighttime average heart rate.

Table 2. Demographic, hemodynamic, biochemical and biohumoral parameters in patients with secondary forms of hypertension.

	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	WC (cm)	NC (cm)	Office-SBP (mmHg)	Office-DBP (mmHg)	HR (sec)	Glyc (mg/dL)	Creat (mg/dL)	Na (mmol/L)	K (mmol/L)	Ca (mEq/L)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TGL (mg/dL)	UA (mg/dL)
PA N: 56 (40 M; 16 F)	54.2±12.1	95.5±29.9*	166.7±23.2	29.1±6.6	94.9±12.4	40.1±4.2	152.2±19.6	90.5±15.5	67.8±14.2	100.5±22.8	0.9±0.2*	143.4±1.6*	3.5±0.5*	9.3±0.9	196.5±37.5	121.4±35.3	47.9±14.6	152.9±82.8*	7.4±12.9
OSA N: 22 (15 M; 7 F)	60±10.1*	99.8±28.5*	158.2±38.3	31.4±6	107.5±14.7*	45.1±4.9*	154.1±15.1	92.5±17.6	68.9± 10.7	108.3±40.6	1±0.2*	142.50±1.7*	4.3±0.5*	9.4±0.6	206.4±48.4	126.1±46.4	48.4±14.2	159.7±114.1	7.7±9.9
RVH N: 5 (2 M; 3 F)	43±9.3	70.7±26.7	166±12.2	27.2±6.7	98.8±16.7	37±4.6	141±24.6	92±24.9	74.8± 5.1	91.2±8.2	0.7±0.1*	140.2±1.8*	3.8±0.5	9.3±0.5	228.2±50.8	121.4±22.8	57±23.9	196.4±187.5*	6.7±1°
SC N: 7 (2 M; 5 F)	53.5±11	76±22.7	160.8±12.5	28.5±7.9	99±11.4	39.1±3.3	151.4±29.1	93.8±22.1	64.8± 6.8	87.7±14	0.9±0.1*	142±1.3	3.9±0.5	9.4±0.3	228.7±30.1	150.7±29*	55.7±10.7	110.1±48	4.7±0. 8°
P	*P<0.05 OSA *vs* RVH	*P<0.05 OSA *vs* SC and RVH; PA *vs* RV	ns	ns	*P<0.05 OSA *vs* other groups	*P<0.05 OSA *vs* other groups	ns	ns	ns	ns	P<0.05 RVH *vs* SC; PA *vs* OSA	P<0.05 PA *vs* other groups	P<0.05 PA *vs* other groups	ns	ns	P<0.05 SC *vs* other groups	ns	*P<0.05 RVH *vs* other drugs	°P<0.05 RVH *vs* SC

PA, primary aldosteronism; OSA, obstructive sleep apnea; RVH, renovascular disease; SC, hypercortisolism; WC, waist circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; Glyc, glycemia; Creat, creatininemia; Na, serum sodium; K, serum potassium; Ca, serum calcium; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGL, triglycerides; UA, uric acid; ns, not significant. *EXPLAIN THE ASTERISKS AND °.

Table 3. Ambulatory monitoring of blood pressure in patients with resistant arterial hypertension.

	M-SBP (mmHg)	M-DBP (mmHg)	G-HR (bpm)	D-SBP (mmHg)	D-DBP (mmHg)	D-HR (bpm)	N-SBP (mmHg)	N-DBP (mmHg)	N-HR (bpm)	Non-dipper pattern (%)
PA N: 56 (40 M; 16 F)	145.7±21.5	88.3±13	71± 8.2	147.8±21.8	90.2±13.6	72.9±8.6	139.1±22.1	81.2±13.2	65.9±7.7	26.8%
OSA N: 22 (15 M; 7 F)	139.9±18.2	86.5±14.5	75.1± 6.9*	141.9±17.8	88.7±14.6	74.3±7.6	134.2±23.1	81.3±17.9	66.3±6.5	77.3%*
RVH N: 5 (2 M; 3 F)	144.6±13.3	91.2±18.8	72.4± 8.8	147.2±14.9	94.2±19.8	74.2±9.9	133±11.1	80.8±16.7	66±6.8	40%
SC N: 7 (2 M; 5 F)	145.5±21.4	90.5±14.9	70.1±6.7	147.5±21.6	93.1±15.1	76.3±9.9	137.3±22.2	82.4±16	66.8±5.6	28.6%
P	ns	ns	*P<0.05 OSA *vs* other groups	ns	ns	ns	ns	ns	ns	*P<0.05 *vs* other groups

PA, primary aldosteronism; OSA, obstructive sleep apnea; RVH, renovascular disease; SC, hypercortisolism; M-SBP, mean average systolic blood pressure; M-DBP, mean average diastolic blood pressure; G-HR, global average heart rate; D-SBP, daytime average systolic blood pressure; D-DBP, daytime average diastolic blood pressure; D-HR, daytime average heart rate; N-SBP, nighttime average systolic blood pressure; N-DBP, nighttime average diastolic blood pressure; N-HR, nighttime average heart rate; ns, not significant. *EXPLAIN THE ASTERISKS.

tients. In particular, we found that the patients with OSA had major age respect to other patients, associated with high weight and waist circumference compared to other groups (P<0.05, respectively). In particular, in Table 3 we reported the ABPM measurements, and we found that patients with OSA are high global-heart rate values compared to other groups (P<0.05), and a major percentage of *non-dipper* patterns (P<0.05, respectively).

Discussion

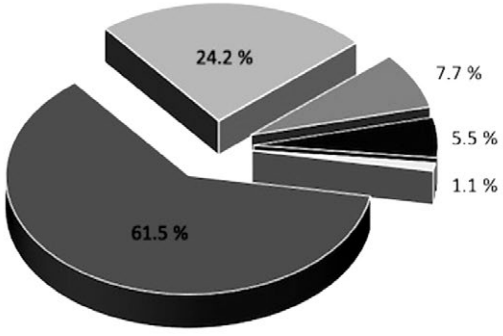
In this study, we aimed to investigate the prevalence of RHT in a cohort of consecutive hypertensive patients who were consecutively referred to our Departmental Unit and we screened for RHT and secondary arterial hypertension. Our results revealed that in all 3685 consecutive hypertensive patients studied, only 232 (5.8%) patients had a RHT diagnosis. The RHT prevalence can be considered real because we have used an accurate enrollment methodology in order to limit and exclude bias selection. In recent years, is estimated that as many as 10-15% of the hypertensive population have RHT.[4,5] In our study we defined RHT patients only those, other 3 drugs treatment (comprised a diuretic) [sentence not clear and not linked to the others, please rephrase], and adherence to life-style changes, with an ABPM that excluded white coat hypertension,[15] still had uncontrolled BP. In fact, ABPM can be useful to rule out white coat hypertension if suspected.[15]

Sometimes, pharmacological BP normalization could be impossible, due to an inappropriate pharmacotherapy or a sub-optimal patient-doctor cooperation. Poor medication adherence results from the side effects of antihypertensive drugs, an incomprehensible dosing regimen, the absence of a subjective feeling of illness or excessive cost to treatment. Tomaszewski *et al.*[16] suggest to test patient's non-adherence by a routinely detecting by high-performance liquid chromatography-tandem mass spectrometry urine analysis of antihypertensive medications. We did not perform this test because it was too expensive, thus physician's role in patient education still remains of primary importance.

Excessive consumption of sodium, licorice, or alcohol is known to increase BP. Many drugs affect BP, and a trial period of potentially offending medications may be all that is needed to reduce BP. If these potential contributors to RHT have been excluded, and concern for SH still remains, the physician can investigate for potential pathophysiologic causes. SH represent a very important contributor to drug-resistance, and may result in resistance to pharmacologic therapy of hypertension.[17] In fact, 10-20% of these patients may have SH, in which an underlying, potentially correctable etiology can be identified.[2] Moreover, SH may be a reason for BP elevation despite comprehensive drug therapy.[2] Today, PA, OSA and intrinsic renal disease represent the most common causes of SH in hypertensive population.[17] The incidence of SH is unknown, but may be as high as 10% in newly diagnosed hypertensive patients. Some authors estimate to be 12.8%, among those treated with antihypertensive drugs. Furthermore, inadequate treatment or poor BP control non-adherence with both pharmacologic and non-pharmacologic therapy may lead to overdiagnosis of RHT.[17] The systematic search for secondary causes of hypertension is mandatory among patients with RHT, because it includes reversible conditions that may help to control BP. However, the prevalence of SH in RHT patients derived from studies with several limitations including the systematic evaluation of secondary forms. In particular, etiology of SH largely depends on studied population, screening tests applied, confirmatory tests and concomitant anti-hypertensive treatment interfering with adrenal hormones.

In this study we showed that in 232 RHT patients, 91 (39%) had SH. In particular, 56 (61%) patients had a PA, 22 (24%) had an OSA, 7 (7.7%) had a CS, and 5 (5.5%) had a RVH. Only one patient had adrenal PHEO.

These results are consistent with other studies, that



Secondary forms of Hypertension	
Primary Aldosteronism (PA)	61.5 %
Obstructive Sleep Apnea (OSA)	24.2 %
Hypercortisolism (SC)	7.7 %
Renovascular Hypertension (RHV)	5.5 %
Pheocromocytoma (PHEO)	1.1 %

Figure 2. Prevalence of secondary forms of hypertension in 91 patients with truly resistant hypertension.

also discover large proportions of patients, often referred from specialist health care, with uncontrolled and undiscovered SH. Besides, in a tertiary work-up of patients with apparent RHT (referred for renal denervation) Heimark and coworkers[17] reported that 30 (36%) patients out of 83, fulfilled the criteria for RHT, and 16 (30%) patients had SH (7 PA, 3 RVH, 3 OSA and 3 with proteinuria as sign of chronic kidney disease). The present study identified in out RHT patients the high prevalence of adrenal hypertension (such as PA, CS and PHEO) followed by OSA and RVH.

PA was considered a rare cause of identifiable or SH until recently. At today, PA represents the most frequent form of SH, with a prevalence of more than 11% in new-onset hypertensive patients.[18] The main causes of PA are bilateral adrenal cortical hyperplasia (IHA) (almost 60% of overall cases), and APA (almost 35% of cases). Rare causes of PA are unilateral adrenal hyperplasia (UAH) (2% of cases), and familial hyperaldosteronism.[12] APA, UAH and aldosterone-producing adenocarcinoma are treated by surgical approach, IHA and familial hyperaldosteronism are treated with medications.[12]

Several studies showed that cardiovascular complications, such as ischemic heart disease, cerebrovascular events, arrhythmias (as well as atrial fibrillation) are more prevalent in PA patients than in essential hypertensive patients, and a specific treatment of aldosterone excess is associated with long-term benefits.[19] Therefore, several investigators have recommended the search of PA in all hypertensive patients and in particular in RHT patients.[19]

SH is common in CS patients. In fact, large series comprising a total of more than some hypertensive patients who have been checked for secondary causes of hypertension, CS was diagnosed in 1% of them, and may persist up to 50% patients even several years after the clinical and humoral remission of their hypercortisolism. Besides, the diagnosis of CS-related hypertension in RHT patients is mandatory.

OSA is a notable cause of SH, particularly in 40-to-59 years old.[20] The standard diagnostic test is polysomnography, but clinical assessment (*e.g.*, Epworth sleepiness scale, sleep apnea clinical score) with night-time pulse oximetry may be sufficient for the diagnosis of moderate to severe OSA.[21] In our study we showed that the prevalence of OSA in RHT patients was 22%, and represents in these patients (in percentage) the second cause of arterial hypertension, after the adrenal hypertension. In particular, we showed that OSA patients had major high weight and waist circumference, and a major percentage of *non-dipper* profile at the ABPM compared to other patients with secondary causes of hypertension.

In patients with OSA the usual variation in BP over 24 h is impaired and it may be beneficial to perform ABPM on these patients to fully evaluate their circadian rhythm.

In the literature, there is growing body of evidence suggesting that *non-dipping* BP pattern is associated with a greater risk of target damage among hypertensive patients.[22] The physiopathological cause of this phenomenon resides in the hypoxia and hypercapnia induced by recurrent episodes of airway obstructions leading to an increased sympathetic neural tone, which causes vasoconstriction.[23] This results in marked increases in BP. Other factors implied in the *non-dipper* pattern of hypertension in OSA patients include impaired endothelium-dependent vasodilation,[23] suffered NO production,[24] oxidative stress,[25] and an activation of the renin-angiotensin-aldosterone system (RAAS).[26] In particular, some studies have associated OSA with excess aldosterone.[27] Excess aldosterone leads to edema of the nasopharyngeal tissues, including tissues in the upper airway. The mineralocorticoid receptor antagonist spironolactone, often used add-on anti-hypertensive therapy, can reduce OSA severity in patients with RHT.[27] Besides, continuous positive airway pressure therapy to treat OSA down-regulates RAAS components and reduces BP.[28]

Approximately 3-5% of patients with hypertension have renovascular etiologies. In these patients, renal artery stenosis results in decreased blood flow to the kidneys and activation of the RAAS which in turn increases systemic BP.[29] Atherosclerotic renal artery stenosis accounts for >90% of cases of renal artery stenosis. This is most commonly seen in older patients (>65 years) and is usually associated with atheromatous disease in other vascular beds. The incidence and prevalence are hard to estimate given the asymptomatic nature of the major cases. Less commonly, renal artery stenosis occurs secondary to fibromuscular dysplasia, which represents a range of pathologic diagnoses differentiated by the layer of the arterial wall that they affect medial fibroplasia is the most prevalent subset of fibromuscular dysplasia, constituting 75%-80% of all fibrous lesions of the renal artery [sentence not clear, please rephrase]. Less common entities include intimal fibroplasia, perimedial fibroplasia, media hyperplasia, and adventitial hyperplasia.

Renal artery stenosis is a progressive problem than can lead to RHT,[30] and gradual loss of functional renal mass resulting in chronic kidney disease. In RHT patients we found that 5.5% patients have RVH supported by renal artery stenosis.

In conclusion, to date an exact estimation of RHT prevalence is not easy, partly due to an inaccurate definition of the problem in scientific research. The use of ABPM is very important in the identification of white coat hypertension and *non-dipper* hypertension. Patients with RHT may often have identifiable underlying secondary cause. Adrenal hypertension, OSA and RVH

are considered to be the most common causes for SH in RHT patients.

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