

Predictors of resistant hypertension in an unselected sample of an adult male population in Italy

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Abstract Prevalence, incidence and predictors of resistant hypertension (RH), (defined as blood pressure persistently above goal in spite of the concurrent use of three antihypertensive agents of different classes) in the general population remain largely unknown. A complete database including anthropometric and biochemical data was collected in 1994–1995 (baseline examination) in 1,019 participants (mean age 51.8, range: 25–79 years) and again in 2002–2004 in 794 male participants of the Olivetti Heart Study (OHS) in southern Italy. The incidence of RH over the average follow-up time of 7.9 years was 4.8% (38/794) in the whole study population and 10.1% (31/307) among hypertensive participants. Basal blood pressure (systolic, diastolic or pulse pressure), cholesterol and urinary albumin/creatinine ratio (ACR) significantly predicted the risk of developing RH using a logistic regression model that also included age as covariates. If in the same model we added basal pharmacological treatment, the fractional excretion of sodium (FENa) also became a statistically

significant predictor, and this last model explained nearly 25% of the risk of developing RH. In this unselected sample of an adult male population, ACR (an early marker of organ damage), an elevated FENa (a proxy for dietary sodium intake), cholesterol and a higher basal blood pressure level were independent predictors of RH.

Keywords Resistant hypertension · Salt intake · Microalbuminuria · Drug therapy

Introduction

In spite of the efforts of clinicians and public health authorities, and of the increasing availability of effective and safe antihypertensive agents, inadequate control of blood pressure (BP) is still a feature of the majority of hypertensive patients, causing persistently elevated cardiovascular risk [1]. Resistant hypertension (RH), defined as blood pressure that remains above the target goal in spite of the concurrent use of three antihypertensive agents of different classes or reaches the goal with four or more drugs, is part of this phenomenon, and is a reason for serious concern because of its impact on both primary care and specialist centres, as recognised in the recent American Heart Association guidelines on diagnosis, evaluation and treatment of this condition [2]. Patients with RH are more likely to have developed target-organ damage, and to have a particularly elevated long-term cardiovascular risk compared with patients with satisfactorily controlled BP [3].

Cross-sectional and hypertension outcome studies suggest that RH is relatively common among hypertensive patients referred to Hypertension Clinics [2, 3], and, in particular, a few older studies—mostly carried out in tertiary care centres—estimate a prevalence of RH in the

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range of 5–18% [4–9] within the hypertensive population. Information about the overall prevalence and incidence of RH in the general population is scanty and inconclusive. Furthermore, although a number of factors have been involved in the development of RH in hypertensive patients, e.g. alcohol consumption, illicit use of drugs, poor compliance with therapy, volume overload, obesity and sleep apnoea, the independent precursors of RH in the general population are substantially undetermined because of the lack of epidemiological data [2].

The Olivetti Heart Study (OHS) is an occupation-based investigation of the genetic, nutritional and metabolic precursors of cardiovascular disease in an unselected sample of an adult male population in southern Italy. We thus analysed the OHS database to evaluate the prevalence and incidence of RH among OHS participants and to identify demographic, anthropometric and metabolic determinants of RH in this population.

Methods

Study population and procedures

The OHS population is drawn from the male workforce of the Olivetti factories of Pozzuoli (Naples) and Marcianise (Caserta). One thousand seventy nine subjects were seen at baseline examination between May 1994 and December 1995; however, a complete database for the evaluation of RH was available for 1,019 participants. Of these, after the exclusion of participants with RH at baseline ($n = 7$), and of those with inadequate information about BP, antihypertensive Rx or metabolic and anthropometric variables ($n = 135$), 794 subjects (78%) were seen again between November 2002 and May 2004, after an average of 7.94 years (range: 5.7–7.9 years), and are the object of the present report (Fig. 1). Subjects lost to follow-up were 143, and apart from a borderline difference in blood pressure, they did not differ from participants revisited at follow-up (Appendix 1). In both visits, the participants were seen in the morning, in a quiet and comfortable environment, while fasting for at least 13 h. We obtained anthropometric measurements, performed a blood test, and administered a fixed-sequence questionnaire about the subject's medical history. The study was approved by the local Ethics Committee, and participants gave their informed consent to participate. The methodology of the study has been described in detail elsewhere [10, 11].

Blood pressure, anthropometrics and cardiometabolic markers

After the subject had been sitting upright for at least 10 min, systolic and diastolic (phase V) BP were taken

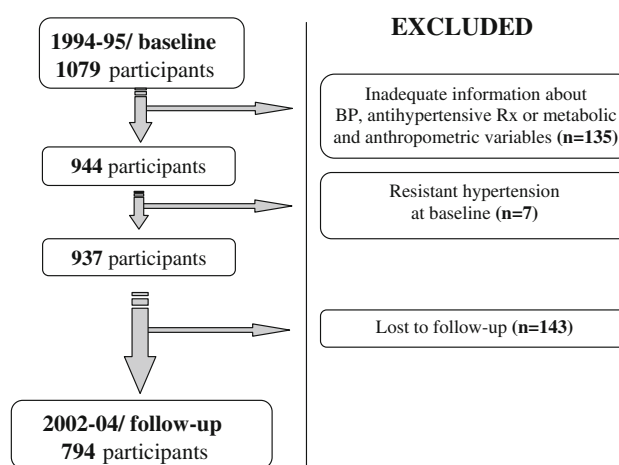


Fig. 1 Selection of the study population

three times, 2 min apart, with a random zero sphygmomanometer (GelmanHawksley Ltd, Sussex, UK). The first reading was discarded, and the average of the second and third reading was used for systolic and diastolic BP.

Body weight and height were measured as described [12]. The body mass index was calculated as weight (kg) divided by the height squared (m^2). The waist circumference was measured at the umbilicus level with the subject standing erect, with the abdomen relaxed, arms at each side, and feet together. The measurements were performed with a flexible, non-extendable plastic tape to the nearest 0.1 cm. Both anthropometric and BP measurements were performed by professional operators who had attended training sessions for standardization of the procedures.

A fasting venous blood sample was obtained for determination of serum glucose, total and HDL cholesterol (LDL cholesterol being calculated by Friedwald equation), triglyceride, uric acid, insulin concentration. The blood specimens were immediately centrifuged and stored at -70°C until analysed. Serum cholesterol, triglyceride, glucose and uric acid levels were measured by automated methods (Cobas-Mira, Roche, Milan, Italy). Serum insulin concentration was measured by radioimmunoassay (InsulinaLisophase, Technogenetics, Milan, Italy). Insulin sensitivity was estimated by the homeostasis model assessment (HOMA) index, which is the product of fasting plasma insulin ($\mu\text{U}/\text{mL}$) and fasting serum glucose (mmol/L)/22.5, as described by Matthews et al. [13]. Although this method does not give a direct measure of insulin-dependent glucose utilization, it has been validated against the euglycemic hyperinsulinemic clamp as a reasonably accurate way to estimate insulin resistance [14].

ECG and left ventricular hypertrophy

A 12-lead surface ECG was obtained from each subject in the supine position. The ECG was measured at a paper

speed of 25 mm/s, at a gain of 10 mm/mV, using a standard ECG device. Analyses of ECG parameters were performed by two independent observers. Cornell voltage was calculated as $RaVL + SV_3$, Cornell product as the product of Cornell voltage times QRS duration.

Protocol for the study of renal parameters (fractional sodium excretion and albuminuria)

The day before the examination, participants consumed their evening meal at no later than 19:00 h. On the morning of the study, after having first voided, discarded overnight urine and consuming 400 ml of water, they produced a fasting timed urine collection. The collection time and volume were recorded, and a specimen was used for the analysis. At the mid-point of the urine collection, a blood sample was obtained by venipuncture with the subject in the seated position and without stasis. Creatinine and sodium in serum and urine samples were measured by the picric acid colorimetric method and by atomic absorption spectrophotometry, respectively, and were used to estimate the renal clearance of each substance, as described previously [15]. The fractional excretion of sodium (FENa) was calculated as the ratio of sodium clearance and creatinine clearance ($\times 100$). While creatinine clearance was taken as an estimate of glomerular filtration rate (GFR), the use of fractional excretion of sodium permitted the neutralization of the confounding effects of age, body mass and incomplete urine collection on the evaluation of sodium handling. We used FENa as a proxy for dietary sodium intake; the higher the FENa, the higher the sodium intake [16].

Urinary albumin concentration was measured by an immunoturbidimetric assay (Horiba ABX Diagnostics, Rome, Italy) using a Cobas-Mira analyser (RocheInstrumentCenter, Rotkreuz, Switzerland) according to the manufacturer's instructions. The gold standard to assess urine albumin excretion is a 24-h urine collection, according to the American Diabetes Association (ADA) [17]. However, a more feasible method to detect albuminuria is the albumin (mg)/creatinine (g) ratio (ACR) measured in a timed urine specimen [18]. ACR is also less prone to errors due to inappropriate urine collection, and to variation in 24-h protein excretion [18]. According to ADA [17], we defined micro and macro-albuminuria as an ACR between 30–300 mg/g and greater than 300 mg/g, respectively.

Evaluation of cardiometabolic risk

Participants were defined overweight if the BMI was equal or higher than 25 kg/m^2 , and less than 30 kg/m^2 , obese if equal or higher than 30 kg/m^2 . A diagnosis of abdominal obesity was made if the waist circumference was higher

than 102 cm [19]. Diabetes was diagnosed if a fasting serum glucose was higher than 126 mg/dL, or participants reported current consumption of antidiabetic medications.

Hypertension was diagnosed if the participants had a BP of 140 over 90 mmHg or higher, or they reported being under regular antihypertensive treatment. A fixed-sequence questionnaire was administered to participants in order to define the number, type and dose of the antihypertensive drugs they were currently taking.

Participants were defined to be affected with RH if the BP remained above the target goal in spite of the concurrent use of three antihypertensive agents of different classes [2]. The goal, according to the JNC 7 [20], guideline was defined as an office BP below 140 over 90 mmHg for subjects who were non diabetic and had normal renal function. In patients with hypertension and diabetes or renal disease (defined as reduced excretory function with an estimated glomerular filtration rate $<60 \text{ mL/min/1.73 m}^2$ or the presence of proteinuria ($>300 \text{ mg/die}$ or 200 mg/g creatinine)) the BP goal was below 130/80 mmHg. Moreover, participants with BP controlled but requiring four or more medications were also considered RH.

Insulin resistance was defined as a HOMA index higher than 2.77, previously identified as the 80th percentile for a population of non-obese subjects with no metabolic disorder [14]. Hyperlipidemia was defined as a serum triglyceride concentration greater than 2.3 mmol/L or a serum total cholesterol greater than 5.2 mmol/L [19] or concomitant use of hypolipidemic agents.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-PC version 11; SPSS Inc., Chicago, Illinois, USA). As the distributions of most of the variables under study deviated significantly from normality, they were normalized by log transformation and log-transformed values were used in the analysis. The Mann–Whitney *U* test was used to evaluate statistical differences between groups. The results were expressed as means and range or 95% confidence intervals (C.I.) unless otherwise indicated. Two-sided *p* values < 0.05 were considered statistically significant. Analysis of variance (ANOVA) was used to assess differences between group means when variables were normally distributed. Differences in the prevalence of categorical cardiometabolic risk factors between participants with and without RH were tested by Chi-square. Logistic regression analysis, using resistant hypertension (yes/no) at follow-up as dependent variable and selected anthropometric and biochemical variables at baseline as independent factors, was made to identify the potential predictors of RH at follow-up. To allow a comparative evaluation of the effects of the

different factors on the risk to develop RH, Z scores were calculated for each factor and used for the analysis. Nagelkerke *R* square was used to estimate the percent of variance in the dependent variable explained by the independent factors. The goodness-of-fit of the final model was evaluated by the Hosmer–Lemeshow test.

Results

Baseline prevalence of obesity, hypertension and diabetes were, respectively, 15.0% ($n = 120$), 38.7% ($n = 307$) and 6.7% ($n = 53$), and increased, respectively, to 19.9% ($n = 158$), 67.0% ($n = 532$) and 12.5% ($n = 99$) after 8 years. One hundred and eight subjects (13.6%) were on current antihypertensive treatment at baseline and 275 (34.6%) at follow-up examination.

RH incidence in 8 years was 4.8% (38/794) in the whole study population, and 10.1% (31/307) among participants who were already hypertensive at baseline. According to ESH/ESC guidelines [20, 21], at baseline, of the 38 participants who developed RH during the follow-up period, 1 was in the optimal, 1 in the normal, 5 in the high normal, and 31 were in the hypertensive range.

The main baseline differences between participants who developed resistant hypertension at follow-up and, respectively, those with controlled (CH) or not controlled

hypertension (NCH), and those with normal BP (NT) are reported in Table 1: compared with RH, systolic, diastolic and pulse pressure, serum cholesterol and prevalence of micro- and macroalbuminuria were significantly lower in all other BP groups. The BMI, serum glucose, triglyceride and uric acid were significantly lower in the CH and the NT groups, whereas age, central obesity, HOMA index and Cornell product were lower only in the normotensive group (NT). The FENa was higher in participants who developed RH, although this did not reach statistical significance. At the 2002–2004 follow-up examination, (Table 2), compared with the RH group, the prevalence of micro- and macroalbuminuria and FENa was significantly lower in all other BP groups. Systolic, diastolic and pulse blood pressure and serum glucose were lower in the CH and the NT groups, while diastolic pressure was higher in the NCH group. Age, BMI, central obesity, serum creatinine, triglyceride and uric acid, HOMA index and Cornell product were significantly lower among NT subjects.

Of the 38 participants who developed RH, 19 (50.0%) were not taking any medication, 7 (18.4%) were not affected by hypertension and 11 (28.9%) and 8 (21.1%) were taking, respectively, 1 or 2 antihypertensive drugs at baseline (Appendix 2). For the 38 participants who developed RH, Table 3 reports the antihypertensive pharmaceuticals class and the most common associations prescribed by the patient's general practitioner. Thirty-two

Table 1 Baseline differences in selected variables between participants who developed resistant hypertension (RH) at follow-up and, respectively, those with normal BP (NT) and those with controlled (CH) or not controlled (NCH) hypertension

Variable (1994–1995 examination)	RH ($n = 38$)	NCH ($n = 424$)	CH ($n = 70$)	NT ($n = 262$)
Age (years) ^a	53.7 (44.2–65.4)	52.0 (29.4–73.0)	52.6 (36.3–71.1)	49.8* (25.6–74.0)
BMI (Kg/m ²)	27.9 (22.5–36.7)	27.4 (19.2–37.0)	26.6 * (19.3–32.5)	25.9** (19.0–34.6)
Waist circumference (cm) ^a	97.2 (80.0–118.0)	95.6 (42.0–122.0)	94.5 (73.0–112.0)	91.9** (72.0–121.0)
Systolic BP (mmHg) ^a	144.6 (102.0–185.0)	132.8** (96.0–185.0)	132.3 ** (101.0–181.0)	119.0** (90.0–165.0)
Diastolic BP (mmHg) ^a	90.3 (72.0–110.0)	86.2* (64.0–111.0)	85.6 * (59.0–115.0)	78.1** (58.0–99.0)
Pulse Pressure (mm Hg) ^a	54.3 (30.0–92.0)	46.6** (21.0–90.0)	46.7 * (28.5–75.0)	40.8** (16.0–68.0)
Creatinine (mg/dL) ^a	1.05 (0.90–1.24)	1.06 (0.48–4.43)	0.99 (0.48–1.24)	1.04 (0.48–2.00)
Serum glucose (mg/dL) ^a	106.4 (74.0–233.0)	104.1 (74.0–300.0)	96.5* (77.0–198.0)	97.4* (71.0–296.0)
HOMA index ^a	3.02 (0.86–11.54)	2.67 (0.24–22.90)	1.94 (0.63–3.80)	1.96* (0.44–10.21)
Creatinine clearance (mL/min) ^a	88.7 (62.3–115.1)	90.7 (20.7–201.3)	92.1 (54.5–211.9)	88.8 (33.0–160.8)
Serum cholesterol (mg/dL)	244.6 (184.0–351.0)	220.0** (67.0–375.0)	221.2* (145.0–385.0)	220.5** (115.0–329.0)
Serum triglyceride (mg/dL) ^a	195.7 (42.0–670.0)	155.8 (28.0–978.0)	144.6* (43.0–499.0)	143.4* (21.0–928.0)
Serum uric acid (mg/dL) ^a	6.1 (4.0–9.6)	5.9 (2.0–9.6)	5.5* (3.6–8.8)	5.5* (1.6–9.7)
Fractional excretion of Na ⁺ (%) ^a	1.33 (0.41–8.10)	1.19 (0.04–8.18)	1.11 (0.21–2.07)	1.28 (0.25–2.81)
Abnormal ACR (%)	26.3	6.1**	4.3**	4.6**
Cornell product (mm × ms) ^a	1497.9 (339.8–3216.4)	1361.1 (190.3–3913.2)	1419.9 (342.0–3074.5)	1184.8* (67.0–3375.0)

* $p < 0.05$; ** $p < 0.001$; Mean (range); p from ANOVA for normal distributed variables and from ^aMann–Whitney *U* for not normal distributed variables; for Cornell product, $n = 714$

Table 2 Differences at follow-up in selected variables between participants with resistant hypertension (RH) and, respectively, those with normal BP (NT) and those with controlled (CH) or not controlled (NCH) hypertension

Variable (2002–2004 examination)	RH (<i>n</i> = 38)	NCH (<i>n</i> = 424)	CH (<i>n</i> = 70)	NT (<i>n</i> = 262)
Age (years) ^a	61.9 (53.7–72.3)	60.0* (37.3–80.3)	60.4 (44.3–78.2)	57.7** (32.9–81.6)
BMI (kg/m ²)	28.5 (21.9–37.1)	28.0 (18.3–39.0)	27.0 (20.1–35.8)	26.1** (17.9–37.0)
Waist circumference (cm) ^a	99.9 (84.0–118.0)	99.3 (65.0–126.0)	97.7 (65.0–122.0)	94.9* (74.0–122.0)
Systolic BP (mmHg) ^a	147.5 (118.0–192.0)	146.2 (111.0–205.0)	128.6** (113.0–139.0)	125.5** (99.0–139.0)
Diastolic BP (mmHg) ^a	92.6 (78.0–120.0)	94.6* (70.0–131.0)	82.1** (62.0–89.0)	82.1** (69.0–89.0)
Pulse Pressure (mm Hg) ^a	54.9 (20.0–105.0)	51.6 (21.0–91.0)	46.5* (33.0–65.0)	43.4** (24.0–62.0)
Serum creatinine (mg/dL) ^a	1.2 (1.0–3.3)	1.2 (0.8–3.7)	1.1 (0.9–1.5)	1.1* (0.9–2.0)
Serum glucose (mg/dL) ^a	107.7 (78.0–175.0)	107.1 (48.0–282.0)	94.5* (71.0–236.0)	97.3* (64.0–227.0)
HOMA index ^a	2.8 (0.6–15.4)	2.7 (0.1–19.4)	2.1 (0.6–8.1)	2.0* (0.4–10.1)
Creatinine clearance (mL/min) ^a	72.3 (24.6–98.1)	75.5 (21.1–123.9)	73.0 (40.2–102.5)	74.7 (30.4–141.8)
Serum cholesterol (mg/dL)	215.6 (124.0–291.0)	214.3 (104.0–417.0)	210.3 (119.0–325.0)	219.1 (120.0–391.0)
Serum triglyceride (mg/dL) ^a	141.3 (39.0–331)	133.3 (26.0–682.0)	128.7 (42.0–588.0)	123.0* (36.0–460.0)
Serum uric acid (mg/dL) ^a	5.3 (2.5–7.3)	5.2 (2.4–9.0)	5.2 (3.2–8.3)	4.8* (2.0–7.7)
Fractional excretion of Na ⁺ (%) ^a	1.30 (0.59–2.26)	1.15* (0.15–7.50)	1.04* (0.15–1.79)	1.13* (0.16–3.24)
Urinary Na excretion (mmol/24 h)	218.9 (68.6–441.7)	203.0 (30.8–449.3)	183.1* (28.6–390.2)	208.9 (40.9–557.7)
Abnormal ACR (%)	27.8	13.5*	6.1*	4.1**
Cornell product (mm × ms) ^a	1600.8 (406.8–3757.7)	1408.4 (232.3–3933.6)	1363.0 (412.5–3245.0)	1222.6** (147.2–3716.6)

* $p < 0.05$; ** $p < 0.001$; Mean (range); p from ANOVA for normal distributed variables and from ^aMann–Whitney U for not normal distributed variables; for Cornell product, $n = 732$

Table 3 Antihypertensive pharmaceutical classes and drug associations currently used by participants with resistant hypertension at follow-up ($n = 38$)

Pharmaceuticals class	<i>n</i> (%) of patients
Diuretics (DIUR)	32 (84.2)
Calcium channel blockers (CCB)	26 (68.4)
Angiotensin-converting enzyme inhibitors (ACE-I)	18 (47.4)
Angiotensin receptor blockers (ARB)	20 (52.6)
Anti-adrenergic drugs	20 (52.6)
Antihypertensive associations	
ACE-I/ARB + CCB + DIUR	13 (34.2)
ACE-I/ARB + DIUR + Anti-adrenergic	10 (26.3)
ACE-I/ARB + CCB + Anti-adrenergic	4 (10.5)
ACE-I + ARB + DIUR + Anti-adrenergic	5 (13.2)
Others	6 (15.8)

RH patients were taking diuretics (DIUR) (84.2%), the second most frequently prescribed pharmaceutical class being calcium channel blockers (CCB) (68.4%), followed by angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-receptor blockers (ARB) and anti-adrenergic drugs (respectively, used in 47.4, 52.6 and 52.6% of participants affected by RH). Among the drug associations, the one most frequently prescribed was (ACE-I or ARB) + CCB + DIUR (34.2%), followed by (ACE-I or ARB) + DIUR + anti-adrenergic drug (26.3%).

To evaluate the relative impact of anthropometric and cardiometabolic factors measured in 1994–1995 on the risk to develop RH, logistic regression models were set up, including age, pulse pressure (or alternatively systolic or diastolic), waist circumference or BMI, serum cholesterol, triglyceride, uric acid, FENa, serum glucose (or HOMA index), ACR or Cornell product as fixed covariates. To allow a comparative evaluation of the effects of the different factors on the risk to develop RH, Z scores were calculated for each factor and used for the analysis.

Logistic regression analysis produced a model that is shown in Table 4: pulse pressure (PP), ACR and cholesterol were the factors that appeared to influence the risk of development of RH to a significant extent. This model explained about 19% ($R^2 = 0.190$) of the overall risk of development of RH over the follow-up period. For one standard deviation increase, respectively, in basal PP and cholesterol, the risk of development of RH at follow-up increased by 2.1 (95% C.I. = 1.5–3.0) and 1.5 (1.1–2.2) times, respectively. If participants had an ACR greater than 30 mg/g at baseline, the risk of development of RH increased by 3.0 (1.2–7.4) fold. Adding to the same model basal antihypertensive therapy (yes or no) (Appendix 3), we found a similar relation for PP, ACR and cholesterol. The risk of development of RH at follow-up was 5.6 (2.5 to 12.5) times higher in participants under antihypertensive treatment at baseline. In this model also the FENa was a significant predictor, a 1 standard deviation increase in

Table 4 Binary logistic regression analysis using resistant hypertension (yes/no) at follow-up as dependent variable and baseline age, pulse pressure, BMI, FENa, serum cholesterol, triglyceride, uric acid and ACR (yes/no) as covariates ($n = 794$)

Variables entered						
Variables	Odds ratio	95% confidence interval		<i>p</i>	Adjusted <i>R</i> Square	Hosmer–Lemeshow Test
		Lower bound	Upper bound			<i>p</i>
Age	0.864	0.583	1.280	0.465	0.190	0.846
BMI	1.320	0.929	1.877	0.122		
Pulse pressure	2.087	1.467	2.969	<0.001		
Serum cholesterol	1.518	1.057	2.180	0.024		
Serum glucose	0.975	0.679	1.398	0.889		
Serum triglyceride	1.103	0.833	1.461	0.495		
Serum uric acid	1.202	0.843	1.712	0.309		
FENa	1.200	0.943	1.528	0.138		
Abnormal ACR* (y/n)	3.048	1.250	7.432	0.014		

To allow a comparative evaluation of the effects of the different factors on the risk to develop RH Z scores were calculated for each variable (except for albumin/creatinine ratio * (>30 mg/g))

FENa raising the risk of RH by 1.3 (1.0–1.6) times. This second model explained 25% ($R^2 = 0.251$) of the overall risk of the development of RH.

As according to the AHA definition of RH, one of the drugs being taken by the patient should “ideally” be a diuretic, and given that 6 of our 38 RH patients were not actually on diuretics, we repeated our analysis in the 32 RH patients who were on diuretics to check whether similar results were obtained as for the whole RH patients’ group. Using a logistic regression model similar to the one shown in Appendix 3, baseline BP, serum cholesterol, ACR and FENa remained significantly independent predictors of the risk of the development of RH (data not shown).

Discussion

In this sample of an unselected Italian adult male population, the prevalence of RH at baseline was 0.7% (1.3% among hypertensive participants). The incidence over 8 years of follow-up was 4.8% in the whole study population and 10.1% among hypertensive participants. To our knowledge, these are the first estimates of the prevalence and incidence rates of RH in a sample of general population, following the definition proposed by the American Heart Association [2].

The prevalence of RH in our population was lower at baseline but similar at follow-up to that found in other studies conducted largely in tertiary care centres (with RH ranging between 5 and 18%) [4–9]. Possible explanations of our low rate of RH at baseline are twofold: (1) the relatively young mean age of the OHS participants (52 years) and (2) the rather high proportion of hypertensive individuals, who were unaware of their condition and

as a consequence untreated, thus making a potential diagnosis of RH impossible by definition. This second feature also accounts for the low rate of current antihypertensive drug treatment among hypertensive subjects overall, only 35%, i.e. lower than that reported for other samples of Italian population [22, 23].

On the other hand, the prevalence of RH at follow-up among hypertensive participants was higher than that found by Alderman et al. in a large cohort study 20 years ago: however, in that study, the authors used a different cut-off for the diagnosis of hypertension (i.e. BP > 160/95 mmHg) and different criteria for definition of RH, i.e. uncontrolled hypertension with at least two antihypertensive agents prescribed simultaneously [24]. Finally, it must be noted that the prevalence of RH appears to change according to the study setting, as described by Kaplan who highlights how the diagnosis of RH ranges from 5% in the general medical practice to over 50% in nephrology clinics [25].

Although basal systolic, diastolic and pulse pressure were each a strong independent predictor of the risk of future RH in our study, as expected, it is noteworthy that even individuals in the optimal to high normal BP range as defined using the ESH/ESC 2007 Guidelines definition [21], at baseline, were among those who developed RH after 8 years (nearly 20% of the total): this observation should alert physicians to continue to frequently measure BP in their “normotensive” patients in order to attain a timely identification of new hypertensive and potentially severely hypertensive individuals.

In our population, abnormal urinary albumin excretion, an early indicator of renal damage, also proved superior to an electrocardiographic index of left ventricular mass (the Cornell product) as a predictor of RH.

Baseline cholesterol levels were also independently associated with the development of RH: among the possible explanations of this relation is the impaired bioavailability of nitric oxide leading to endothelial dysfunction and possibly decreased arterial wall expansibility [26]. Impaired endothelial function, well recognised stigmata of arterial hypertension, has been commonly demonstrated in populations with difficult-to-treat hypertension, such as elderly patients [27] and African-American patients [28]. Moreover, experimental studies in rats demonstrate that a high-cholesterol diet acutely induces a BP increase, secondary to excess lipid oxidation induced by hypercholesterolemia [29].

Besides these factors, fractional sodium excretion (a surrogate measure of dietary salt intake) was a further independent predictor of RH, when the analysis was adjusted for basal antihypertensive treatment. This result was strengthened by two additional findings: (1) the difference in FENa observed at baseline between those who did and those who did not develop RH, was reinforced at follow-up examination, and (2) the significant difference in 24-h urinary sodium excretion, a highly reliable estimate of sodium intake observed at follow-up examination between RH and controlled hypertensive (CH) participants. This result confirms and supports previous reports of high or very high habitual salt intake among patients with RH as compared with the general population [30]. Several experimental and clinical studies in animal models and humans support the contention that high dietary salt intake exerts adverse effects on target-organs for BP (heart, brain, kidney) [31–33]. High dietary salt intake may contribute to the occurrence of RH by inducing volume overload [34], found in almost 90% of patients with RH [35]. These results add to the vast literature supporting the evidence that a reduction in habitual sodium intake lowers blood pressure [36–38] and can help prevent organ damage [39].

Study limitations

This study has some limitations, largely due to its nature of epidemiological investigation. The diagnosis of RH was based on a single-occasion BP measurement: thus, the possible white-coat effect was not ruled out, and we were unable to exclude all causes of secondary hypertension. Moreover, we were unable to evaluate the hypertensive patients' compliance with medical prescriptions, so pseudo-resistant hypertension could not be ruled out. We also did not know whether RH patients assumed an optimal dose of their antihypertensive drugs, although Nuesch et al., in a relative small series of patients taking at least two antihypertensive drugs, show that non-compliance with treatment is not more prevalent in patients with RH than in responsive hypertensive patients [40].

A further limitation of our study was the fact that 6 out of the 38 patients diagnosed as having RH were not taking a diuretic, at variance with the recommendation of the AHA guidelines. Nevertheless, when we restricted our analysis to the 32 RH patients who were on diuretics, we obtained similar results as for the whole RH patients' group.

Finally, our results are generalizable only to a comparable white adult male population.

Conclusions

In this prospective evaluation of an unselected sample of adult white male population in Southern Italy, the risk of the development of resistant hypertension in 8 years was directly and independently associated with baseline BP, with current pharmacological treatment for high BP at baseline, with the urinary albumin-to-creatinine ratio, and with a surrogate measure of dietary sodium intake. Given the high incidence of target organ damage associated with uncontrolled hypertension and its high mortality rate, every effort should be made to identify the subjects at greater risk to develop this condition. Based on our results, reduction of habitual salt intake is expected to be an effective preventive measure.

Conflict of interest None.

Appendix 1

Differences in selected variables between participants who were or were not lost to the follow-up

Follow-up (2002–2004 examination)	Lost (<i>n</i> = 143)	Re-visited (<i>n</i> = 794)	<i>p</i>
Age (years)*	53.2 (28.5–79.4)	51.4 (25.6–74.0)	0.085
BMI (kg/m ²)	27.1 (18.8–34.9)	26.8 (19.0–37.0)	0.417
Waist circumference (cm)	94.9 (70.0–125.0)	94.3 (42.0–122.0)	0.393
Systolic BP (mmHg)*	133.2 (89.0–225.0)	128.7 (90.0–185.0)	0.010
Diastolic BP (mmHg)*	84.3 (44.0–130.0)	83.7 (58.0–115.0)	0.452
Serum creatinine (mg/dL)*	1.06 (0.82–3.59)	1.05 (0.48–4.43)	0.775
Serum cholesterol (mg/dL)	220.6 (111.0–344.0)	221.6 (66.0–385.0)	0.795
Serum trygliceride (mg/dL)	151.0 (42.0–498.0)	152.6 (21–978)	0.847
Serum uric acid (mg/dL)	5.64 (2.10–9.70)	5.71 (1.60–9.70)	0.533
Fractional excretion of Na+ (%)*	1.25 (0.31–3.47)	1.22 (0.04–8.18)	0.548
Cornell product (mm × ms) [§]	1,293.2 (376.0–3,477.0)	1,315.7 (67.0–3,913.2)	0.842

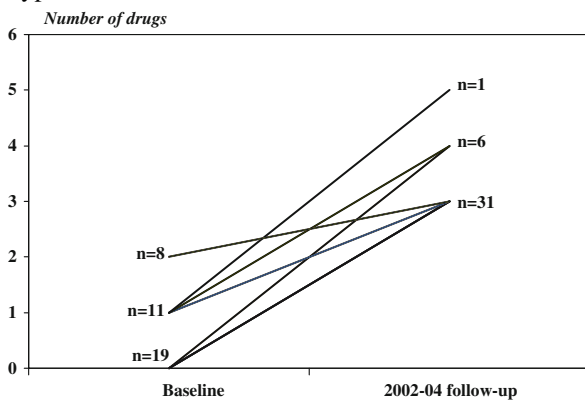
Appendix continued

Follow-up (2002–2004 examination)	Lost (<i>n</i> = 143)	Re-visited (<i>n</i> = 794)	<i>p</i>
Hypertension (%)	50	38.7	0.010
Diabetes (%)	5.5	6.7	0.583
Abnormal ACR (%)	11.5	6.4	0.029

Mean (range); *p* from ANOVA for normal distributed variables and from *Mann–Whitney *U* for not normal distributed variables; [§]*n* = 732

Appendix 2

Changes in anti-hypertensive drug consumption over 8 years among participants with resistant hypertension at the 2002–2004 visit



Appendix 3

Binary logistic regression analysis using resistant hypertension (yes/no) at follow-up as dependent variable and baseline age, pulse pressure, BMI, FENa, serum cholesterol, triglyceride, uric acid, ACR (yes/no) and antiHPT Rx (yes/no) as covariates (*n* = 794)

Variables entered						
Variables	Odds ratio	95% confidence interval		<i>p</i>	Adjusted R square	Hosmer–Lemeshow test
		Lower bound	Upper bound			<i>p</i>
Age	0.773	0.508	1.177	0.230	0.251	0.717
BMI	1.207	0.840	1.736	0.310		
Pulse pressure	2.087	1.467	2.969	<0.001		
Serum cholesterol	1.532	1.055	2.222	0.025		
Serum glucose	0.863	0.563	1.322	0.497		
Serum triglyceride	1.083	0.801	1.464	0.604		
Serum uric acid	1.061	0.734	1.534	0.753		
FENa	1.281	1.018	1.611	0.035		
Abnormal ACR* (yes/no)	2.812	1.089	7.263	0.033		
AntiHPT Rx (yes/no)	5.558	2.478	12.463	<0.001		

To allow a comparative evaluation of the effects of the different factors on the risk to develop RH

Z scores were calculated for each variable (except for AntiHPT Rx and albumin/creatinine ratio *(>30 mg/g))

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