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ORIGINAL ARTICLE

Identification of phenotypes at risk of transition from diastolic hypertension to isolated systolic hypertension

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Little is known about the potential progression of hypertensive patients towards isolated systolic hypertension (ISH) and about the phenotypes associated with the development of this condition. Aim of this study was to detect predictors of evolution towards ISH in patients with initial systolic–diastolic hypertension. We selected 7801 hypertensive patients free of prevalent cardiovascular (CV) diseases or severe chronic kidney disease and with at least 6-month follow-up from the Campania Salute Network. During 55 ± 44 months of follow-up, incidence of ISH was 21%. Patients with ISH at the follow-up were significantly older ($P < 0.0001$), had longer duration of hypertension, higher prevalence of diabetes and were more likely to be women (all $P < 0.0001$). They exhibited higher baseline left ventricular mass index (LVMi), arterial stiffness (pulse pressure/stroke index), relative wall thickness (RWT) and carotid intima-media thickness (IMT; all $P < 0.001$). Independent predictors of incident ISH were older age (odds ratio (OR) = 1.14/5 years), female gender (OR = 1.30), higher baseline systolic blood pressure (OR = 1.03/5 mm Hg), lower diastolic blood pressure (OR = 0.89/5 mm Hg), longer duration of hypertension (OR = 1.08/5 months), higher LVMi (OR = 1.02/5 g $m^{-2.7}$), arterial stiffness (OR = 2.01), RWT (OR = 1.02), IMT (OR = 1.19 mm^{-1}; all $P < 0.0001$), independently of antihypertensive treatment, obesity, diabetes and fasting glucose ($P > 0.05$). Our findings suggest that ISH is a sign of aggravation of the atherosclerotic disease already evident by the target organ damage. Great efforts should be paid to prevent this evolution and prompt aggressive therapy for arterial hypertension should be issued before the onset of target organ damage, to reduce global CV risk.

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INTRODUCTION

Systolic blood pressure (SBP) increases with ageing,[1,2] in relation to environmental stimuli.[3] The age-related increase in SBP is also associated with decline of diastolic BP (DBP), mainly owing to loss of elasticity and consequent stiffening of conduit arteries,[1–4] often producing isolated systolic hypertension (ISH).[4]

In the past, ISH has been considered almost as a physiological condition, but in more recent decades, several studies have provided evidence that elevated SBP is an independent predictors of adverse cardiovascular (CV) outcomes, even more potent than elevated DBP, and that aggressive treatment of ISH might reduce hospitalisation and mortality for CV causes.[5–7] It has been calculated that for every 10 mm Hg increase in SBP there is a 26% increase in overall mortality.[7]

Although some information is available on characteristics of subjects from a general population who develop ISH,[8] little is known on the possible evolution towards ISH in treated hypertensive patients initially presenting with diastolic or systolic–diastolic hypertension.

Accordingly, the present study was designed to assess whether and in which circumstances systolic–diastolic or isolated diastolic hypertension (IDH) progresses into ISH. We focussed on the identification of potential predictors of this progression in a large outpatient hypertensive population sample from our tertiary care center.

METHODS

Patients

The Campania Salute Network (CSN) is an open registry collecting information from a network of 60 general practitioners and 23 community hospitals networked with the Hypertension Research Center of the Federico II University Hospital (Naples, Italy). The database generation of the CSN was approved by the Federico II University Hospital Ethic Committee. Signed informed consent was obtained from all the participants to use data for scientific purposes. Detailed characteristics of this population have been previously reported.[9–11] The database included $>12\,000$ patients, of whom 10 254 had confirmed arterial hypertension.

For the present study, we selected 7801 patients with systolic–diastolic or IDH and with at least 6-month follow-up. The presence of ISH at baseline was an exclusion criteria for our selection. Moreover, all patients were free of prevalent CV disease (defined as previous myocardial infarction, angina or procedures of coronary revascularisation and/or history of stroke) and without chronic kidney disease more than stage 3. In the CSN, both prevalent and incident CV disease were adjudicated by an internal Committee for Event Adjudication and was based on patient history, contact with the reference general practitioner and clinical records documenting occurrence of disease.

All hypertensive patients of the network underwent baseline echocardiograms and ultrasound evaluation of carotid arteries.

Protocol and definitions

During baseline and follow-up visits, blood pressure, heart rate, body mass index (BMI), lipid and glucose profile were measured by standard methods. Diabetes was defined according to the American Diabetes Association

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criteria.[12] Obesity was defined by BMI $\geqslant$ 30 kg m^{-2}.[13] Glomerular filtration rate (GFR) was estimated using serum creatinine and simplified Modification of Diet in Renal Disease equation.[14] According to GFR values, we excluded patients with chronic kidney disease over stage II (GFR $<$ 59 ml min^{-1} 1.73 m^{-2} in KDOQI classification)[14] SBP and DBP were measured by standard aneroid sphygmomanometers after 5-min rest in the supine position, according to current guidelines. Three BP measurements were obtained in the sitting position at 2-min intervals. The averages of these measurements were used for the analysis. The sphygmomanometers used in the CSN are recalibrated every 6 months.

Diastolic hypertension was defined as DBP $\geqslant$ 90 mm Hg in at least two consecutive visits combined or not with SBP $\geqslant$ 140 mm Hg (systolic–diastolic hypertension). Diagnosis of follow-up ISH was made at the time of the last available outpatient visit, according to European Guidelines (SBP $\geqslant$ 140 mm Hg with DBP $<$ 90 mm Hg).[15]

Cardiac ultrasounds

Patients underwent M-mode and 2D-echocardiography using a dedicated ultrasound machine (SONOS 5500; Philips, Andrews, MD, USA). Measurements were performed as previously reported,[16,17] according to the American Societies of Echocardiography/European Association of Echocardiography Recommendations.[18]

Left ventricular mass (LVM) was measured at end diastole and normalised for body height in metres to the power of 2.7 (LVM index (LVMi)).[19] Left ventricular hypertrophy was defined as LVMi $\geqslant$ 49.2 g m$^{-2.7}$ in men and $\geqslant$ 46.7 g m$^{-2.7}$ in women.[20] Relative wall thickness (RWT) was calculated as posterior wall thickness/left ventricular end-diastolic radius.[21] Pulse pressure (PP) to stroke volume index (SVi, by *z*-derived, normalised by height$^{2.04}$)[21,22] was used as a crude estimate of arterial stiffness.

Carotid ultrasound

Carotid ultrasound was carried out in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (SONOS 2500/5500, HP, Philips) equipped with a 7.5 MHz high-resolution transducer with an axial resolution of 0.1 mm. Examinations were recorded on S-VHS videotapes and then analysed off-line. The maximal arterial intima-media thickness (IMT) was estimated offline, including the right and the left, near and far distal common carotid (1cm), bifurcation and proximal internal carotid artery, and using an image-processing dedicated workstation (MediMatic, Genova, Italy) as previously reported in detail.[23]

Statistical analysis

Data were analysed using SPSS20 (Chicago, IL, USA) and expressed as means $\pm$ 1 s.d. Descriptive statistics were performed using analysis of variance and χ^2 distribution. To account for antihypertensive therapy, single classes of medications, including anti-renin–angiotensin system (RAS, that is, angiotensin-converting enzyme inhibitors and/or AT1 receptor
antagonists), calcium-channel blockers, β-blockers and thiazide diuretics, were dichotomised according to their overall use during the individual follow-up, based on the frequency of prescription during the control visits. Thus all medications prescribed for $>$50% of control visits were considered as covariates in logistic regression analysis. To isolate independent predictors of incident ISH, we used binary logistic regression using backward stepwise selection of main potential confounders, including age, gender, diabetes, obesity, baseline BP and duration of hypertension. In a second step, the markers of preclinical CV disease (LVMi, RWT, IMT, PP/SVi) were added to the first model. Finally, the classes of antihypertensive medications were forced into the model as a third step in the hierarchical procedure. A two-tailed $P < 0.05$ was considered significant.

RESULTS

The median follow-up was 46 months (IQR = 24–89 months). At the the time of the last outpatient visit, 1339 patients (17%) exibited ISH, 51% of whom were women. Among our hypertensive patients, we could identify 483 cases (or 6%) of IDH, 32% of whom were women; interestingly none of the IDH patients developed ISH.

The initial demographic and clinical characteristics of patients with or without follow-up progression to ISH are listed in Table 1. As shown in this table, patients developing ISH were older, more often women and diabetic (all $P < 0.0001$) and had higher initial SBP and lower DBP, producing a clear difference in PP. Duration of hypertension was also significantly greater in patients progressing to ISH (all $P < 0.0001$). The two groups had not significant differences in heart rate, BMI, average number of antihypertensive medications and prevalence of smokers. Fasting glucose was higher and GFR lower in patients progressing to ISH (both $P < 0.0001$), whereas lipid profile and electrolytes were similar in the two groups.

Patient developing ISH exhibited higher baseline LV internal dimension, LVMi, RWT, arterial stiffness and IMT than those without incident ISH (Table 2, all $P < 0.001$). Accordingly, the prevalence of baseline carotid plaque was also significantly greater in patients with (55%) than in those without (41%) incident ISH (OR = 1.80 (1.57–2.05), $P < 0.0001$)

In multivariable logistic regression, probability of progression to ISH was independently predicted by female gender ($P < 0.001$),

Table 1. Baseline demographic and clinical characteristics dichotomised by evidence of ISH at the end of follow-up

	No ISH (n = *6462)*	*ISH* (n = *1339)*	P-*value*
Age, years	51.2 $\pm$ 10.7	56.8 $\pm$ 11.0	$<$ 0.0001
Women, %	41.8	50.9	$<$ 0.0001
Body mass index, kg m^{-2}	27.8 $\pm$ 4.1	27.8 $\pm$ 4.2	NS
Systolic BP, mm Hg	157.4 $\pm$ 19.4	162.1 $\pm$ 19.5	$<$ 0.0001
Diastolic BP, mm Hg	100.5 $\pm$ 9.3	99.4 $\pm$ 8.1	$<$ 0.0001
Heart rate, b.p.m.	71.8 $\pm$ 11.8	71.9 $\pm$ 11.9	NS
Duration of hypertension, years	10.7 $\pm$ 7.5	13.4 $\pm$ 8.9	$<$ 0.0001
Average no. of antihypertensive medications	1.7 $\pm$ 1.1	1.8 $\pm$ 1.1	NS
Diabetes, %	11.3	18.9	$<$ 0.0001
Smoking habits, %	48.6	45.9	NS
Fasting glucose, mmol l^{-1}	5.44 $\pm$ 1.17	5.61 $\pm$ 1.44	$<$ 0.0001
Total cholesterol, mmol l^{-1}	5.3 $\pm$ 1.0	5.4 $\pm$ 1.0	NS
HDL-cholesterol, mmol l^{-1}	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3	NS
Triglycerides, mmol l^{-1}	1.5 $\pm$ 0.9	1.5 $\pm$ 0.8	NS
GFR, ml min^{-1} 1.73 m^{-2}	79.5 $\pm$ 18.0	77.1 $\pm$ 18.3	$<$ 0.0001
Sodium, mmol l^{-1}	141.0 $\pm$ 3.2	141.2 $\pm$ 3.3	NS
Potassium, mmol l^{-1}	4.4 $\pm$ 0.4	4.4 $\pm$ 0.4	NS

Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; ISH, isolated systolic hypertension; NS, not significant. Values are means $\pm$ s.d. or percentage.

Table 2. Baseline target organ damage by evidence of ISH at the end of follow-up

	No ISH (n = *6462)*	*ISH* (n = *1339)*	P-*value*
LVMi, g $m^{-2.7}$	47.4 ± 9.1	49.6 ± 9.8	< 0.0001
LVIDD/ht, cm m^{-1}	2.96 ± 0.19	3.00 ± 0.20	< 0.0001
Relative wall thickness	0.38 ± 0.03	0.39 ± 0.04	< 0.001
PP/SVi, mm Hg ml^{-1} $beat^{-1}$ $m^{-2.04}$	2.3 ± 0.6	2.6 ± 0.7	< 0.0001
Max IMT, mm	1.5 ± 0.7	1.8 ± 0.8	< 0.0001

Abbreviations: IMT, intima-media thickness; ISH, isolated systolic hypertension; LVMi, left ventricular mass index; LVIDD/ht, left ventricular internal diastolic diameter/height; PP/SVi, pulse pressure/stroke volume index. Values are means ± s.d.

Table 3. Independent predictors of ISH at logistic regression

Predictors	*OR*	*95% CI for OR*	P-*value*
		Lower–upper	
Female sex	1.29	1.12–1.50	< 0.001
Age (×5 years)	1.14	1.10–1.18	< 0.0001
Systolic BP (×5 mm Hg)	1.03	1.01–1.06	< 0.0001
Diastolic BP (×5 mm Hg)	0.89	0.83–0.95	< 0.0001
Duration of hypertension (×5 months)	1.11	1.06–1.16	< 0.0001
LV mass index (×5 g $m^{-2.7}$)	1.08	1.04–1.12	< 0.0001
Relative wall thickness	0.02	0.01–0.15	< 0.0001
PP/SVi	1.99	1.77–2.23	< 0.0001
Carotid intima-media thickness (mm)	1.19	1.07–1.33	< 0.0001
Anti-RAS prescription	0.85	0.73–0.99	< 0.04

Abbreviations: anti-RAS, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; ISH, isolated systolic hypertension; LV, left ventricular; OR, odds ratio; PP/SVi, pulse pressure/stroke volume index. Values are means ± s.d. Diabetes, body mass index and other classes of antihypertensive medications did not enter into the final model ($P > 0.05$).

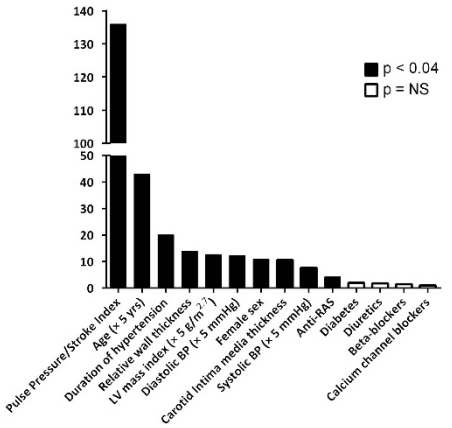

Figure 1. Wald statistics of the logistic regression model reported in Table 3.

older age, higher baseline SBP, lower DBP, longer duration of hypertension, higher values of baseline LVMi, RWT, PP/SVi ans IMT (all $P < 0.0001$) and the lack of anti-RAS (angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers) prescription ($P < 0.04$), with no significant effect for diabetes, BMI and other classes of antihypertensive medications (Table 3). Interestingly the association of incident ISH with diabetes was significant (OR = 1.26, 1.03–1.53, $P < 0.02$) until markers of CV damage were added to the model.

Forcing classes of antihypertensive medications did not change the phenotypic profile at risk of evolution towards ISH. Classes of antihypertensive therapy were not independently related to development of ISH.

Figure 1 displays the relative contribution of all covariates used in the complete logistic model: the initial PP/SVi was by far the most important predictor of ISH followed by age, with the other significant components impacting similarly.

DISCUSSION

This analysis demonstrates that, in the context of arterial hypertension, the evolution towards ISH is actually a progression and can be predicted by a number of characteristics that define a specific phenotype at risk. Hypertensive patients evolving more often to ISH are older women with higher PP, signs of target organ damage, specifically increased LVMi, concentric LV geometry and increased arterial stiffness. Our findings also suggest that transformation of a combined systolic–diastolic hypertension into ISH is related to the progression of arteriosclerotic disease, further reducing distensibility and elastic recoil of conduit arteries.

ISH is the most common hypertension subtype for patients aged between 50 and 59 years, and it is the overwhelmingly dominant hypertensive subtype in the sixth decade of life. [24] ISH is characterised by elevated systolic BP in the presence of normal or decreased DBP and it is associated with substantially increased PP and with an increased risk for adverse CV outcomes. In the Framingham Heart Study, SBP was a better independent predictor of CV risk than DBP, particularly in patients aged > 50 years.[25,26]

Staessen *et al*.[6] reported that, in elderly patients with ISH, risk of death was associated positively with systolic BP and negatively with DBP.

In the Framingham Heart Study population,[8] including subjects free of antihypertensive therapy and CV disease, according to baseline BP values, the group which had highest probability to develop ISH was the one which had normal or high-normal basal BP compared with the group that had basal systolic–diastolic hypertension. The best independent clinical risk factors for new-onset ISH were age, female gender and increased BMI during follow-up. In contrast with the Framingham population,[8] we studied patients with diastolic hypertension with or without high SBP, on antihypertensive treatment, also considering the impact of treatment and of markers of preclinical disease. Similar to the Framingham Heart Study, aging and female sex were two important characteristics for evolution towards ISH.

Another important difference from our study is that in the Framingham Heart Study the condition of preclinical CV disease[27] was not considered. This difference is substantial and explains why we did not find an independent effect of diabetes and obesity, which was reported in the Framingham Heart Study. In our logistic model, we considered not only both risk factors but also the clinically unapparent consequences of exposition to those

risk factors. Our analysis suggests that concentric left ventricular hypertrophy, increased carotid IMT and high arterial stiffness, albeit in the presence of diastolic hypertension, already express CV conditions that will progress to ISH. Our findings indicate that, once the organ damage is established, the direct link between exposition to risk factors and overt CV disease is interrupted. Accordingly, ISH might be considered a further step in the progression from atherogenic risk factor exposition to CV adverse events, proposed by Devereux and Aldermann.[27] This progression seems not only to be the result of the progressive stiffening of conduit arterial system, in part related to age, but also to the greater susceptibility to, and/or to the greater severity of, atherosclerotic disease, documented by the more severe target organ damage. Interestingly, women are more exposed than men to this progression, a finding that needs to be examined in depth. This scenario is consistent with the evidence that ISH is the most severe form of hypertension[6] and also more difficult to control than DBP. Unfortunately, we do not have at this time the possibility to evaluate the trend of progression towards ISH, an information that might add to what we have shown in our present analysis and that needs to be studied in future data mining.

Normalisation of systolic BP in the context of ISH is a difficult challenge.[28] It is possible that a greater effort should be paid to prevent progression to ISH. Our findings support current recommendations by guidelines,[15,29,30] to prompt aggressive therapy for arterial hypertension before the onset of target organ damage, to reduce global CV risk. This strategy might be very important to control incidence of ISH, especially in elderly female patients.

What is known about topic?

- ISH is the most prevalent form of hypertension, especially in elderly populations, and is more difficult to control than diastolic BP.
- The best independent known risk factors for new-onset ISH are age, female gender and increased BMI during follow-up.

What this study adds?

- This is the first study identifying a complete phenotype at risk of progression to ISH from diastolic hypertension with or without high systolic BP, on antihypertensive treatment.
- Our study also included target organ damage (preclinical CV disease) in the phenotype definition.
- Our analysis suggests that baseline concentric LV geometry, increased carotid IMT and high arterial stiffness are critical characteristics of progression to ISH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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