Cardiac and Vascular Remodeling in Older Adults With Borderline Isolated Systolic Hypertension

The ICARe Dicomano Study

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Abstract—Although borderline isolated systolic hypertension (ISH), defined as a blood pressure of 140 to 159/<90 mm Hg, is a proven cardiovascular risk factor, the major clinical trials on treatment of ISH have used a cutoff of 160 mm Hg. Moreover, no data exist on the cardiovascular modifications associated with borderline ISH. Therefore, we compared subjects with borderline ISH to subjects with diastolic hypertension (diastolic blood pressure ≥90 mm Hg) or ISH. Community-dwelling residents (age ≥65 years) of a small town in Italy (Dicomano) underwent extensive clinical examination, echocardiography, carotid ultrasonography, and applanation tonometry. Only untreated subjects were included in this analysis: 95 with diastolic hypertension, 87 with borderline ISH, and 43 with ISH. Despite lower systolic and mean pressures in borderline ISH, left ventricular mass was similar to that in diastolic hypertension. In univariate and multivariate analysis, pulse pressure but not systolic pressure was related to left ventricular mass. Borderline ISH subjects had a tendency to greater carotid cross-sectional area and stiffness index than did diastolic hypertensive subjects despite lower mean carotid pressure, whereas the number of atherosclerotic plaques was similar in the 2 groups. Pulse pressure but not systolic pressure was independently related to carotid remodeling. In our community-based, older population, individuals with borderline ISH had a similar prevalence of left ventricular hypertrophy and carotid atherosclerosis as that of subjects with diastolic hypertension, despite lower systolic and mean pressures. Among blood pressure values, pulse pressure was the single or strongest independent predictor of cardiovascular remodeling. **(*Hypertension*. 2001;38:1372-1376.)**

Key Words: age ■ carotid arteries ■ atherosclerosis ■ arterial compliance ■ hypertrophy

The prevalence of isolated systolic hypertension (ISH), defined as a systolic blood pressure (SBP) of ≥160 mm Hg with a diastolic blood pressure (DBP) <90 mm Hg, increases with age and becomes particularly high among subjects >60 years of age.[1] In 1993, the Fifth Joint National Committee on High Blood Pressure changed the definition of ISH by reducing the SBP threshold from 160 to 140 mm Hg.[2] This change was based on the observation that subjects with borderline ISH, defined as a SBP of 140 to 159 mm Hg with a DBP <90 mm Hg, suffered a higher incidence of cardiovascular death than did normotensive subjects.[3] However, despite this evidence, the major clinical trials on the effects of antihypertensive treatment of ISH have used a cutoff of 160 mm Hg.[4,5] Moreover, no data are available regarding the cardiac and vascular modifications associated with borderline ISH. Therefore, the present study was undertaken to analyze the cardiac and vascular characteristics of subjects with borderline ISH compared with subjects with diastolic (essential) hypertension (HTN) or ISH.

Methods

Study Population

All community-dwelling residents aged ≥65 years of a small town in Italy (Dicomano) underwent an extensive assessment consisting of home interview, laboratory testing, and clinical examination. Further clinical information was gathered from primary care physicians of the participants with a structured questionnaire regarding the history and treatment of clinical conditions, including hypertension. The general design of this survey (ICARe Dicomano Study) has been previously published in detail.[6]

Blood pressure was measured by the first and fifth Korotkoff phases using a cuff sized for arm circumference. Three measures were obtained 1 to 2 minutes apart; the second and the third blood pressure measurements were averaged, and mean values were considered as the reference SBP and DBP. Mean blood pressure was calculated as DBP+[0.33×pulse pressure].

Subjects receiving antihypertensive medication were excluded from the present study. Enrolled subjects were grouped according to the following criteria: HTN is DBP ≥90 mm Hg; borderline ISH is SBP 140 to 159 mm Hg and DBP<90 mm Hg, and ISH is SBP ≥160 mm Hg and DBP <90 mm Hg. Subjects with blood pressure

Received March 14, 2001; first decision April 6, 2001; revision accepted July 10, 2001.

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<140/90 mm Hg were considered normotensive; their data were previously published.[7]

One hundred seventy-three subjects were normotensive, and 438 were hypertensive[8]: 265 subjects had HTN, 106 had borderline ISH, and 67 had ISH. There were 95 unmedicated subjects in the HTN group, 87 in the borderline ISH group, and 43 in the ISH group. Previously treated hypertensive subjects were off medications for at least 1 month.

Echocardiography

2D-targeted M-mode echocardiograms were recorded using previously described procedures.[9] Left ventricular (LV) walls and chamber dimensions were measured according to the American Society of Echocardiography convention.[10,11] LV diastolic filling parameters were derived from the pulsed-wave Doppler mitral inflow pattern.[12] Echocardiographic measurements were averaged from up to 6 cardiac cycles.

Subjects were considered to have normal LV mass if LV mass/body surface area was ≤116 g/m^2 in men and ≤104 g/m^2 in women.[13] Subjects were classified as having significant valvular disease if moderate-severe stenosis and/or insufficiency was detected by Doppler echocardiography. Of the 225 untreated subjects included in the present study, 98.7% underwent echocardiographic examination.

Carotid Ultrasonography

As previously described,[14,15] 2D-guided M-mode tracings of the distal left common carotid artery were obtained with simultaneous contralateral carotid pressure waveform tracings (see below). Measurements included the intimal-medial thickness of the far wall at end diastole,[16] as well as end-diastolic and peak-systolic internal dimensions. All measurements were performed on several cycles and averaged. Carotid ultrasound examination and carotid pulse recording were obtained in 224 subjects. Relative wall thickness of the common carotid artery and carotid intimal-medial cross-sectional area were also calculated.[17,18]

Both carotid arteries were scanned using 2D imaging to identify the presence and size of atherosclerotic plaques; standard wall thickness measurements were never obtained at the level of a discrete plaque. Plaque number was defined as the number of discrete plaques within both right and left carotid arteries. Plaque thickness was measured in the projection that showed maximal encroachment into the vessel lumen.

Carotid Artery Stiffness

As previously described,[19] simultaneous carotid pressure waveforms were obtained[20,21] using a high-fidelity tonometer. To obtain carotid blood pressure values, the waveforms were externally calibrated with the brachial mean blood pressure and DBP. Carotid artery stiffness was calculated by the pressure-independent Beta stiffness index.[22,23]

The contribution of reflected pressure waves to the central pulse pressure (PP) was measured by the augmentation index.[24,25] In view of the fact that the contribution of the reflected wave might be somewhat attenuated by the larger PP found in the ISH patients, a modified augmentation index was calculated by dividing the amplitude of the reflected wave by the mean blood pressure. Measurements were averaged from several cycles.

Statistical Analysis

Data are expressed as mean±SD. Differences between the 3 groups were tested by 1-way ANOVA and Scheffé post-hoc test for continuous variables. ANCOVA with Sidak post-hoc test was performed to compare groups after controlling for age, PP, and SPB. Differences between groups were tested by χ^2 statistics for proportions and Bonferroni correction for multiple comparisons. Relations between continuous variables were evaluated by linear regression analysis. Variables that were found to be significant in univariate analyses were considered as potentially independent variables in

TABLE 1. Characteristics of Patients With HTN, Borderline ISH, and ISH

Variable	HTN (n=95)	*P* (1 vs 2)	Borderline ISH (n=87)	*P* (2 vs 3)	ISH (n=43)	*P* (1 vs 3)	*P*
Age, y	73±7	NS	75±7	NS	77±7	0.013	0.020
Female, %	48 (51%)		57 (66%)		22 (51%)		NS
Height, cm	158±10		156±9		158±9		NS
Weight, kg	69±12	0.012	64±12	NS	64±11	NS	0.006
Body surface area, m^2	1.70±0.18	0.022	1.63±0.18	NS	1.65±0.17	NS	0.019
Body mass index, kg/m^2	27.69±4.10	NS	26.31±3.66	NS	25.77±3.54	0.026	0.009
Heart rate, bpm	70±12		68±13		66±16		NS
SBP, mm Hg	159±16	<0.0001	148±6		170±9	<0.0001	<0.0001
DBP, mm Hg	94±5		80±5	NS	83±5		<0.0001
MBP, mm Hg	116±8	<0.0001	103±4	<0.0001	112±5	<0.0001	<0.0001
PP, mm Hg	65±14	NS	67±8	<0.0001	87±9	<0.0001	<0.0001
Glucose, mmol/L	5.8±1.6		5.7±1.4		6.3±2.2		NS
Total cholesterol, mmol/L	5.82±1.16		5.95±1.34		5.56±1.09		NS
HDL cholesterol, mmol/L	1.47±0.47		1.47±0.47		1.50±0.41		NS
LDL cholesterol, mmol/L	3.54±1.06		3.75±1.19		3.44±1.14		NS
Triglycerides, mmol/L	1.70±0.96		1.55±1.17		1.34±0.51		NS
Dyslipidemia	45 (54%)		40 (46%)		16 (44%)		NS
Stroke, TIA	5 (5%)		2 (2%)		3 (7%)		NS
Coronary artery disease	6 (7%)		6 (7%)		3 (7%)		NS
Peripheral vascular disease	10 (11%)		11 (13%)		6 (14%)		NS
Diabetes	7 (7%)	NS	7 (8%)	NS	9 (21%)	NS	0.032
Former or current smoker	44 (46%)		37 (43%)		18 (42%)		NS

Values are mean±SD or n (%). MBP indicates mean blood pressure; TIA, transient ischemic attack.

TABLE 2. Echocardiographic Characteristics of Hypertensive Subjects

Variable	HTN (n=94)	*P* (1 vs 2)	Borderline ISH (n=85)	*P* (2 vs 3)	ISH (n=43)	*P* (1 vs 3)	*P*
IVS_d, mm	8.4±1.7		8.5±1.9		9.0±2.2		NS
PWT_d, mm	8.1±1.4		7.8±1.3		8.4±1.4		NS
$LVID_{diastole}$, mm	51.6±6.9		52.3±6.0		53.0±4.9		NS
$LVID_{systolic}$, mm	32.4±7.0		32.2±6.4		32.6±6.4		NS
LV mass, g	153±49		153±47		170±53		NS
LV mass index, g/m^2	89±26	NS	94±27	NS	102±26	0.048	0.047
LV relative WT	0.32±0.09		0.30±0.06		0.32±0.05		NS
LV hypertrophy (LVMI)	13 (14%)	NS	19 (22%)	NS	13 (30%)	NS	0.049
Fractional shortening, %	38±8		39±7		39±9		NS
E wave, m/sec	0.58±0.16		0.62±0.17		0.61±0.19		NS
A wave, m/sec	0.78±0.16	NS	0.77±0.17	0.016	0.87±0.19	0.042	0.012
E wave/A wave	0.74±0.18	0.031	0.84±0.33	0.010	0.69±0.18	NS	0.003
Relaxation time, msec	96±19		98±16		95±21		NS
Deceleration time, msec	242±61	NS	221±54	NS	248±71	NS	0.021
Significant valvular disease	13 (14%)		15 (18%)		7 (16%)		NS

IVS_d indicates inter-ventricular septum thickness in diastole; PWT_d, left ventricular posterior wall thickness in diastole; LVID, left ventricular internal diameter; WT, wall thickness; and LVMI, left ventricular mass index.

multiple linear regression analysis. Two-tailed $P<0.05$ was considered significant.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results

Clinical Features of Hypertensive Patients

Demographic features, laboratory data, and pertinent cardiovascular history of the 3 groups are compared in Table 1. Subjects with ISH were older and had lower body mass index than patients with HTN, but no differences were found in gender distribution, height, or body surface area. Compared with HTN subjects, borderline ISH subjects had lower weight and body surface area. By definition, borderline ISH subjects had lower blood pressure values than did ISH patients; however, when compared with HTN patients, borderline ISH patients had lower SBPs, DBPs, and mean blood pressures with similar PP. Lipid profile tended to be most favorable in the ISH, but differences did not reach statistical significance; no differences were found between the 3 groups regarding previous history of stroke, transient ischemic attack, and coronary artery or peripheral vascular diseases. Diabetes tended to be more prevalent in the older ISH subjects than in borderline ISH or HTN patients. The percentage of current or former smokers was similar in the 3 groups.

Echocardiographic Findings in the HTN Group and ISH Groups

Echocardiographic findings in the 3 groups are compared in Table 2. LV mass and LV mass indexed for body surface area in borderline ISH were similar to those in HTN subjects despite lower systolic and mean pressures. ISH subjects tended to have higher LV mass than HTN subjects, and this difference became significant when indexing for body surface area. Borderline ISH patients had increased LV mass index compared with that of previously reported normotensive subjects (83±23 g/m^2, $P=0.023$), whereas HTN patients did not.[7] When this index was used to identify patients with LV hypertrophy, borderline ISH and ISH patients exhibited a 1.5- to 2-fold increase in the prevalence of LV hypertrophy (22% and 30%, respectively) compared with that of HTN patients (14%), whereas normotensive subjects had a lower prevalence (9%). LV mass exhibited a positive correlation with PP ($r=0.182$, $P=0.010$), whereas LV mass index correlated positively with PP ($r=0.230$, $P=0.001$) and negatively with DBP ($r=-0.169$, $P=0.016$). When all blood pressure measures (SBP, DBP, mean blood pressure, and PP) were included in a multivariate analysis, both LV mass and LV mass index were independently related only to PP ($\beta=0.182$, $P=0.010$ and $\beta=0.230$, $P=0.001$, respectively). LV fractional shortening, an index of systolic function, was similar in the 3 groups. Borderline ISH patients had a significantly greater E/A velocity ratio and a tendency to a shorter deceleration time than did the other 3 groups.

Comparison of Carotid Artery Structure and Stiffness in Hypertensive Groups

In the borderline ISH group, the carotid intimal-medial thickness and internal diameters were intermediate between the values observed in the HTN and ISH groups, despite having lower DBPs and mean blood pressures than those of the HTN patients (Table 3), but the differences between the 3 groups did not reach statistical significance. The carotid cross-sectional area, an index of vascular remodeling similar to LV mass, tended to increase from HTN to borderline ISH to ISH patients. A similar trend was present when carotid cross-sectional area was indexed for body surface area. When carotid SBP, DBP, mean blood pressure, and PP were included in a multivariate analysis model, only PP was independently related to carotid cross-sectional area, both absolute ($\beta=0.270$, $P<0.0001$) and indexed ($\beta=0.289$,

TABLE 3. Carotid Artery Pressure, Structure, and Stiffness in Hypertensive Subjects

Variable	HTN (n=95)	*P* (1 vs 2)	Borderline ISH (n=87)	*P* (2 vs 3)	ISH (n=42)	*P* (1 vs 3)	*P*
SBP, mm Hg	142±19	NS	137±17	<0.0001	154±23	0.009	<0.0001
DBP, mm Hg	83±11	<0.0001	75±9	NS	73±9	<0.0001	<0.0001
MBP, mm Hg	103±13	0.001	95±10	NS	100±11	NS	0.001
PP, mm Hg	59±14	NS	62±15	<0.0001	81±21	<0.0001	<0.0001
IMT, mm	0.83±0.16		0.84±0.19		0.89±0.17		NS
Diastolic diameter, mm	6.09±0.96		6.16±1.04		6.44±1.07		NS
Systolic diameter, mm	6.85±0.96		7.01±1.09		7.35±1.17		NS
Systolic expansion, %	13±4		14±5		14±5		NS
RWT	0.28±0.07		0.28±0.07		0.28±0.07		NS
Cross-sectional area, mm^2	17.98±4.19	NS	18.68±5.72	NS	20.60±5.48	0.040	0.043
CSA index, mm^2/m^2	10.60±2.55	NS	11.46±3.41	NS	12.46±3.51	0.013	0.012
Subjects with plaques, %	72 (76%)		68 (78%)		36 (86%)		NS
Plaque number	2±2	NS	2±2	0.007	3±2	0.001	0.001
Plaque maximum thickness, mm	2.14±0.62	NS	2.33±0.66	NS	2.47±0.66	0.048	0.041
Beta stiffness index	4.99±2.33	NS	5.19±2.95	NS	6.42±3.03	NS	0.030
Reflected wave, mm Hg	18±10	NS	21±11	NS	25±14	0.014	0.009
AI (corrected for PP)	0.30±0.12		0.32±0.13		0.30±0.15		NS
AI (corrected for MBP)	0.17±0.08	0.035	0.22±0.11	NS	0.25±0.13	0.002	0.001

IMT indicates intimal-medial thickness; RWT, carotid relative wall thickness; CSA index, cross-sectional area/body surface area; and AI, augmentation index.

$P<0.0001$). Number and thickness of carotid plaques and carotid artery Beta stiffness index exhibited an increase from HTN to borderline ISH to ISH group; however, these values were not statistically different between borderline ISH and HTN subjects. In univariate analysis, the number of carotid plaques was independently related to PP ($r=0.273$, $P<0.01$) but not to SBP. Both borderline ISH and HTN patients had stiffer carotid arteries than did normal subjects (Beta stiffness index=3.97±1.93, $P=0.006$ and $P=0.041$, respectively). In multivariate analysis, only carotid PP ($\beta=0.590$, $P<0.0001$) and SBP ($\beta=-0.448$, $P<0.0001$) were related to the stiffness index. The negative correlation coefficient of SBP is an indication of a strong collinearity between PP and SBP; in fact, when PP was removed from the model, SBP exhibited a positive coefficient ($\beta=0.228$, $P=0.016$). Despite similar carotid SBP, borderline ISH patients had higher augmentation index, adjusted for mean blood pressure, than did HTN or normotensive subjects (0.15±0.09, $P<0.0001$).

Discussion

In our population aged ≥65 years, subjects with borderline ISH demonstrated the same cardiac and vascular abnormalities as those of patients with HTN, despite lower values of systolic and mean blood pressure. Moreover, borderline ISH patients exhibited comparable prevalences of ischemic heart disease and cerebrovascular events as those of patients with HTN or ISH.

Recently, several observational studies have yielded evidence to suggest that in older subjects, PP compared with SBP may be a better predictor of cardiovascular events.[26–30] Despite these data, the classification of hypertension is still based on SBP and DBP without special consideration of PP.[31] The present study supports previous observations[32] that PP is a stronger predictor of cardiovascular disease than SBP. In fact, when comparing borderline ISH to HTN subjects, the 2 groups exhibited a similar prevalence of established cardiac and cerebrovascular diseases despite the lower values of SBP and mean blood pressure that were found in the borderline ISH group. Moreover, this study indicates possible underlying mechanisms to explain the strong association of PP with cardiac and cerebrovascular events. In fact, borderline ISH patients exhibited cardiac and carotid remodeling that was similar to ISH patients, an observation that has never previously been documented in a geriatric population. Thus, based on our observations and previous studies, older patients with borderline ISH may be especially likely to benefit from antihypertensive treatment.

Potential Study Limitations

Our data were collected from a population of older white subjects living in a small town in Italy; therefore, the conclusions derived from the results presented in this study may not be directly applicable to subjects in other geographical areas or with a different racial composition. However, the prevalence of borderline ISH found in our population (17%) is similar to that of previous studies (20 to 26%).[3,33]

In this study, subjects were classified as borderline ISH based on the study blood pressure measurements and may include individuals with white-coat hypertension. Recently, Fagard et al[30] found that 24% of ≈700 ISH patients had SBP <140 mm Hg on ambulatory blood pressure monitoring. However, because white-coat hypertensive patients have less cardiac and vascular remodeling than do sustained hypertensive patients,[34] the exclusion of these patients might increase the association of PP with cardiovascular remodeling and its importance when compared with SBP.

Acknowledgments

Sponsored in part by the Italian Ministry of Scientific and Technological Research (National Special Project on Heart Failure), by the Regional Government of Tuscany, and by the Azienda Ospedaliera Careggi-Firenze, Italy.

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