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Central But Not Brachial Blood Pressure Predicts Cardiovascular Events in an Unselected Geriatric Population

The ICARe Dicomano Study

Riccardo Pini, MD, FACC,* M. Chiara Cavallini, MD,* Vittorio Palmieri, MD, PHD,† Niccolò Marchionni, MD,* Mauro Di Bari, MD, PHD,* Richard B. Devereux, MD, FACC,† Giulio Masotti, MD,* Mary J. Roman, MD, FACC†

Florence, Italy; and New York, New York

Objectives The present study investigated whether central blood pressure (BP) predicts cardiovascular (CV) events better than brachial BP in a cohort of normotensive and untreated hypertensive elderly individuals.

Background Limited and conflicting data have been reported on the prognostic relevance of central BP compared with brachial BP.

Methods Community-dwelling individuals ≥65 years of age, living in Dicomano, Italy, underwent an extensive clinical assessment in 1995 including echocardiography and carotid ultrasonography and applanation tonometry. In 2003, vital status and CV events were assessed, reviewing the electronic database of the Regional Ministry of Health. Only normotensive (n = 173) and untreated hypertensive subjects (95 diastolic and 130 isolated systolic) were included in the present analysis.

Results During 8 years, 106 deaths, 45 of which were cardiovascular, and 122 CV events occurred. In univariate analyses, both central and brachial systolic blood pressure (SBP) and pulse pressure (PP) predicted CV events (all $p < 0.005$); however, in multivariate analyses, adjusting for age and gender, higher carotid SBP and PP (hazard ratios 1.19/10 and 1.23/10 mm Hg, respectively; both $p < 0.0001$) but neither brachial SBP nor PP independently predicted CV events. Similarly, higher carotid SBP but not brachial pressures independently predicted CV mortality (hazard ratio 1.37/10 mm Hg; $p < 0.0001$).

Conclusions Our prospective study in an unselected geriatric population demonstrates superior prognostic utility of central compared with brachial BP. (J Am Coll Cardiol 2008;51:2432–9) © 2008 by the American College of Cardiology Foundation

As life expectancy has increased in developed countries, cardiovascular (CV) disease has become the most frequent cause of mortality, morbidity, and disability in elderly individuals. However, predictors of CV events in elderly persons have not been evaluated extensively (1). Isolated systolic hypertension (ISH) and associated widened pulse pressure (PP) occur more commonly in older individuals. In an unselected elderly population, we demonstrated that wider PP was associated with higher left ventricular (LV) mass, a greater number of carotid plaques, and increased vascular stiffness (2). In fact, ISH is more strongly associated with cardiac and vascular remodeling than is diastolic hypertension (3–6), which, in turn, might contribute to the greater risk of CV events associated with ISH than with diastolic hypertension (7). However, whether blood pressure (BP) is a predictor in elderly persons of CV events independent of CV target organ damage is unknown.

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Increased arterial stiffness is one of the main determinants of ISH in elderly persons. However, arterial stiffening might be due to atherosclerosis and thereby be an indirect marker of an increased risk of CV events (8), because central BP is more strongly related to atherosclerosis than is brachial BP (2,9,10).

From the *Department of Critical Care Medicine and Surgery—Unit of Geriatric Cardiology, University of Firenze and Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; and the †Department of Medicine, Weill Medical College of Cornell University, New York, New York.

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Thus, the present study investigated associations of central and brachial BP and cardiac and vascular remodeling with CV morbidity and mortality in an unselected elderly population to determine: 1) whether indexes of cardiac and vascular remodeling are more strongly associated with central than brachial BP, and 2) whether central BP predicts CV events better than brachial BP in elderly subjects.

Methods

Participants. The study population was drawn from the ICARe Dicomano (Insufficienza Cardiaca negli Anziani Residenti a Dicomano) study, a longitudinal epidemiologic survey of heart failure in a community-based sample of elderly subjects from the small rural town of Dicomano, near Florence, Italy (11). In 1995, the ICARe Dicomano study recruited the entire community-dwelling elderly (≥65 years) population recorded in the City Registry Office of Dicomano. The only initial exclusion criterion was living in a nursing home. The study was approved by an ad hoc ethics committee. Individual informed consent was obtained, and a letter describing the study design was sent to primary physicians. Informed consent was obtained from the legal caregiver, in the instance of cognitive dysfunction. For the present study, individuals taking antihypertensive drugs were excluded.

Data collection. Participants underwent clinical examination, 12-lead electrocardiogram, echocardiography, carotid ultrasound, and carotid applanation tonometry. During the clinical examination, BP was measured with the participant supine after a 10-min rest. Systolic blood pressure (SBP) was defined as appearance of the first Korotkoff sound, whereas diastolic blood pressure (DBP) was defined as disappearance of the fifth Korotkoff sound. The second and third of 3 consecutive readings were averaged. The PP was calculated as SBP − DBP. Mean BP was computed as DBP + (PP/3). Normotension was defined by clinical SBP <140 mm Hg and DBP <90 mm Hg; diastolic hypertension was defined by DBP ≥90 mm Hg regardless of SBP values; isolated systolic hypertension was defined as SBP ≥140 mm Hg and DBP <90 mm Hg.

Echocardiography. From 2-dimensionally guided M-mode echocardiograms, LV dimensions were measured by American Society of Echocardiography convention; LV mass was calculated by the adjusted American Society of Echocardiography method (12) and indexed for body surface area. Left ventricular mass/body surface area ≤116 g/m^2 in men and ≤104 m/g^2 in women was considered normal (13). Left ventricular fractional shortening (FS) and stress-corrected midwall FS were calculated as described previously (14). Ejection fraction was calculated with bi-dimensional length-area method from apical 4-chamber views.

Carotid ultrasonography. As previously described (15,16), 2-dimensionally guided M-mode tracings of the distal left common carotid artery were obtained with simultaneous contralateral pressure waveform tracings (see following). Measurements included intimal-medial thickness (IMT) of the far wall at end-diastole and end-diastolic and peak-systolic internal carotid diameters; change in diameter was defined as the percent increase between diastolic and systolic internal carotid diameter (17). Relative wall thickness of the common carotid artery and carotid wall cross-sectional area (WCSA) was also calculated (18,19). Both carotid arteries were scanned to identify the presence of atherosclerotic plaques defined as focally increased IMT >50% of the surrounding wall thickness; however, IMT was never measured at the level of a discrete plaque. Plaque score was defined as the number of left and right segments (common carotid, bulb, internal and external carotid arteries, range 0 to 8) with discrete plaques (9).

Abbreviations and Acronyms

- **AI** = augmentation index
- **BP** = blood pressure
- **CI** = confidence interval
- **CV** = cardiovascular
- **DBP** = diastolic blood pressure
- **FS** = fractional shortening
- **HR** = hazard ratio
- **IMT** = intimal-medial thickness
- **ISH** = isolated systolic hypertension
- **LV** = left ventricle/ventricular
- **MBP** = mean blood pressure
- **PP** = pulse pressure
- **SBP** = systolic blood pressure
- **WCSA** = wall cross-sectional area

Carotid artery stiffness. Carotid pressure waveforms were obtained with a high-fidelity external pressure transducer (SPT-301B, Millar Instruments, Inc., Houston, Texas) applied to the skin overlying the common carotid artery (20) and was calibrated with brachial mean and diastolic BP, measured at the end of the vascular ultrasound study with the patient in a supine position. Carotid artery stiffness was calculated by the pressure-independent stiffness index Beta, which takes into account the nonlinear relationship between arterial pressure and diameter (21): Beta = ln(Ps/Pd)/([Ds − Dd]/Dd), where Ps and Pd are the systolic and diastolic carotid pressures and Ds and Dd are the systolic and diastolic carotid diameters, respectively. The amplitude of the reflected waves was expressed as a percentage of the PP, as proposed by Murgo et al. (22), and as a percentage of the MBP; as previously demonstrated (2), this modified calculation of the AI reduces the potential attenuation of the reflected wave contribution to the central pressure in subjects with larger PP, as is commonly found in hypertensive elderly subjects with ISH.

Definitions of events and follow-up. Events and vital status were obtained from the electronic database of the Regional Ministry of Health, updated to December 2003. Follow-up data were obtained for all subjects included in this study. On the basis of nosologic coding, events and cause of death were classified with the use of International Classification of Diseases–9th Revision (ICD-9); ICD-9 codes from 390 to 459 were classified as CV. Nonfatal CV events were counted for all participants either alive or dead at follow-up. If more than 1 CV event was recorded in the

same subject, only the first event was considered in the analysis. When counting for combined fatal and nonfatal CV events, if a subject had a nonfatal CV event and subsequently died of CV disease, only the nonfatal CV event was considered in the analysis (i.e., time to the first nonfatal event was used for time-dependent and survival analyses).

Statistical analysis. Data are expressed as mean ± SD. Differences between 2 groups were tested by Student *t* test for continuous variables and by chi-square statistics for proportions. Bivariate relations were analyzed with Spearman correlation coefficient. Differences in the strengths of association between central and peripheral BP and measures of CV remodeling were compared by calculation of z statistics for comparison of correlations with a single sample. Univariate and multivariate survival analyses were performed with Cox regressions, and hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were derived from these analyses. Analyses were performed separately to explore predictors of CV mortality and combined nonfatal and fatal CV events. All significant univariate predictors were included in the multivariate analysis. With a forward method (likelihood ratio method, with variables in by $p < 0.05$ and out by $p > 0.1$ to avoid biases due to colinearity), separate sets of multivariate analyses were performed on the basis of the aims of the study. To explore whether central pressures predicted events more strongly than brachial pressures, a Cox regression model was constructed for each carotid and brachial SBP and PP adjusting for age and gender. A two-tailed $p < 0.05$ was considered significant. Statistical software SPSS version 14.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analysis.

Results

Study population. Of the 899 residents in Dicomano ≥65 years of age, 864 community-dwelling subjects were eligible for the ICARe Dicomano study and 614 (71%) subjects completed the assessment. Of the initial cohort, 216 subjects were excluded for pharmacologic treatment of hypertension. Of the remaining 398 subjects, 173 were normotensive, 95 had diastolic hypertension, and 130 had ISH.

During an observational period of 2,818 ± 716 days (range 460 to 3,172 days), 106 (27%) deaths were recorded, 45 of which were classified as of CV etiology (32 cardiac and 13 cerebrovascular diseases). One hundred thirteen participants suffered a nonfatal CV event, whereas 9 CV deaths occurred without a prior nonfatal CV event; thus, 122 fatal and nonfatal CV events (31% of the study sample) were considered for subsequent analyses (80 cardiac and 42 cerebrovascular diseases).

Baseline characteristics of the study cohort are shown in Tables 1 to 3. Participants who suffered CV events were older, more frequently male, and had higher SBP, PP, and serum creatinine levels than those who did not suffer CV events; serum glucose levels and lipid profile were comparable between the 2 groups (Table 1). At baseline, comorbidities (previous cerebrovascular accident, peripheral vascular diseases, and coronary artery disease) were more

Table 1 Baseline Characteristics

		Incident Cardiovascular Events		
	Overall	No (n = 276)	p Value	Yes (n = 122)
Age (yrs)	73 ± 6	72 ± 6	<0.0001	76 ± 7
Male gender, n (%)	180 (45%)	112 (41%)	0.005	68 (56%)
BMI (kg/m^2)	26.7 ± 4.3	26.7 ± 4.1	0.938	26.7 ± 4.6
BSA (m^2)	1.67 ± 0.18	1.66 ± 0.18	0.272	1.69 ± 0.19
Heart rate (beats/min)	68 ± 13	69 ± 13	0.058	66 ± 12
Brachial SBP (mm Hg)	145 ± 19	142 ± 19	0.008	147 ± 20
Brachial PP (mm Hg)	61 ± 16	59 ± 15	0.002	65 ± 17
Brachial MBP (mm Hg)	103 ± 11	103 ± 10	0.169	104 ± 11
Glucose (mmol/l)	5.8 ± 1.7	5.8 ± 1.6	0.812	5.8 ± 1.9
Creatinine (μmol/l)	92 ± 15	91 ± 14	0.008	96 ± 18
Total cholesterol (mmol/l)	5.88 ± 1.12	5.93 ± 1.11	0.160	5.76 ± 1.15
HDL cholesterol (mg/dl)	1.48 ± 0.45	1.49 ± 0.44	0.484	1.45 ± 0.47
LDL cholesterol (mg/dl)	3.70 ± 1.06	3.74 ± 1.05	0.194	3.59 ± 1.08
Triglycerides (mmol/l)	0.09 ± 0.05	0.09 ± 0.05	0.684	0.09 ± 0.05
Stroke, TIA, n (%)	20 (5%)	9 (3%)	0.015	11 (9%)
Peripheral vascular disease, n (%)	39 (10%)	21 (8%)	0.026	18 (15%)
Former or current smoker, n (%)	179 (45%)	119 (43%)	0.245	60 (49%)
Alcohol abuse, n (%)	87 (22%)	67 (24%)	0.083	20 (16%)
Coronary artery disease, n (%)	35 (9%)	12 (4%)	<0.0001	23 (19%)
Diabetes, n (%)	37 (9%)	21 (8%)	0.073	16 (13%)

BMI = body mass index; BSA = body surface area; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MBP = mean blood pressure; PP = pulse pressure; SBP = systolic blood pressure; TIA = transient ischemic attack.

Table 2 Baseline Echocardiographic Findings

		Incident Cardiovascular Events		
	Overall	No (n = 276)	p Value	Yes (n = 122)
Left atrium (mm)	38.4 ± 6.9	37.7 ± 6.5	0.003	39.9 ± 7.4
Aorta (mm)	32.7 ± 4.3	32.4 ± 4.4	0.152	33.1 ± 4.2
IVSd (mm)	8.3 ± 1.7	8.2 ± 1.7	0.035	8.6 ± 1.7
PWTd (mm)	7.8 ± 1.3	7.6 ± 1.2	0.002	8.1 ± 1.4
LVIDd (mm)	51.9 ± 6.1	51.2 ± 5.8	0.001	53.6 ± 6.6
LVIDs (mm)	32.3 ± 6.6	31.4 ± 5.9	0.001	34.4 ± 7.6
FS (%)	38 ± 8	39 ± 7	0.008	36 ± 9
Stress-corrected FS (%)	140 ± 23	141 ± 22	0.878	140 ± 26
EF (%)	61 ± 9	62 ± 9	0.005	59 ± 11
LV mass index (g/m^2)	89 ± 25	85 ± 22	<0.0001	98 ± 30
LV relative WT (%)	30 ± 6	30 ± 6	0.428	31 ± 7
LV hypertrophy (LVMI)	60 (15%)	31 (11%)	<0.0001	29 (24%)
E wave (m/s)	0.60 ± 0.17	0.60 ± 0.17	0.872	0.60 ± 0.18
A wave (m/s)	0.77 ± 0.18	0.76 ± 0.18	0.429	0.78 ± 0.19
E/A	0.80 ± 0.25	0.80 ± 0.24	0.786	0.79 ± 0.29
Relaxation time (ms)	98 ± 19	98 ± 18	0.921	98 ± 20
Deceleration time (ms)	232 ± 64	229 ± 58	0.186	239 ± 75

EF = ejection fraction; FS = fractional shortening; IVSd = interventricular septum thickness in diastole; LV = left ventricular; LVIDd = left ventricular internal diameter in diastole; LVIDs = left ventricular internal diameter in systole; LVMI = left ventricular mass index; PWTd = left ventricular posterior wall thickness in diastole; WT = wall thickness.

prevalent in subjects who suffered CV events compared with those who did not; in addition, the former group had larger LV and left atrial diameters, higher LV mass, and lower LV systolic function. However, stress-corrected FS and diastolic function parameters did not differ significantly between the 2 groups (Table 2). At baseline, carotid pressures, IMT, diameters, stiffness, and plaque prevalence were higher in participants who suffered subsequent CV events compared with those who did not (Table 3).

Relation of brachial and carotid pressures to LV mass and carotid artery structure and function. In general, the relation of brachial and central PPs to LV mass and carotid artery structure and function tended to be stronger than corresponding systolic pressures (Table 4). Plaque score exhibited a significantly stronger correlation with PP than with SBP for both brachial and carotid values. All indexes of carotid stiffness (AI corrected by PP or by MBP and stiffness index) exhibited stronger correlations with central PP than with brachial PP; of note, central PP had a stronger correlation with the modified AI corrected for MBP than the AI corrected by PP ($p < 0.0001$). Both AI corrected for MBP and the stiffness index correlated with WCSA ($r = 0.128$, $p = 0.024$ and $r = 0.239$, $p < 0.0001$, respectively) and carotid plaque score ($r = 0.169$, $p = 0.003$ and $r =$

Table 3 Baseline Carotid Artery Pressures, Structure, and Stiffness

		Incident Cardiovascular Events		
	Overall	No (n = 276)	p Value	Yes (n = 122)
Systolic pressure (mm Hg)	134 ± 20	131 ± 18	<0.0001	141 ± 24
PP (mm Hg)	58 ± 18	55 ± 15	<0.0001	65 ± 20
IMT (mm)	0.84 ± 0.16	0.83 ± 0.15	0.046	0.87 ± 0.18
Diastolic diameter (mm)	6.06 ± 0.95	5.92 ± 0.84	<0.0001	6.40 ± 1.13
Systolic diameter (mm)	6.90 ± 0.99	6.76 ± 0.87	<0.0001	7.23 ± 1.17
Strain (%)	14 ± 5	14 ± 5	0.054	13 ± 4
Relative wall thickness	28 ± 6	29 ± 6	0.148	27 ± 6
Wall cross-sectional area (mm^2)	18.3 ± 5.0	17.7 ± 4.4	0.001	19.9 ± 6.0
Plaque score	2 ± 2	2 ± 2	<0.0001	3 ± 2
Plaque, n (%)	284 (71%)	187 (68%)	0.003	97 (80%)
Reflected wave (mm Hg)	17 ± 11	16 ± 10	0.005	20 ± 12
AI (corrected for MBP) (%)	18 ± 11	17 ± 10	0.013	20 ± 12
AI (corrected for PP) (%)	28 ± 14	28 ± 13	0.217	30 ± 14
Peripheral amplification (mm Hg)	11 ± 6	11 ± 5	0.086	10 ± 7
Stiffness index	4.7 ± 2.5	4.5 ± 2.5	0.007	5.3 ± 2.6

AI = augmentation index; BP = blood pressure; IMT = intimal-medial thickness; MBP = mean blood pressure; PP = pulse pressure.

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Table 4 Relations of Brachial and Carotid Pressures to LV and Carotid Remodeling

	Brachial SBP		Brachial PP		Carotid SBP		Carotid PP	
	r	p Value	r	p Value	r	p Value	r	p Value
LV mass/body surface area (g/m^2)	0.241	<0.0001	0.269	<0.0001	0.243	<0.0001	0.276	<0.0001
Wall cross-sectional area (mm^2)	0.190	0.001	0.227	<0.0001	0.221	<0.0001	0.266	<0.0001
Plaque score	0.151	0.008	0.229*	<0.0001	0.192	0.001	0.306†	<0.0001
IMT (mm)	0.086	0.127	0.128	0.023	0.110	0.052	0.161	0.004
AI corrected by PP	0.189	0.001	0.174	0.002	0.355‡	<0.0001	0.301§‖	<0.0001
AI corrected by MBP	0.334	<0.0001	0.402*	<0.0001	0.546¶	<0.0001	0.647†#	<0.0001
Stiffness index	0.335	<0.0001	0.386**	<0.0001	0.348	<0.0001	0.500†‖	<0.0001

Correlations compared by Z statistics: brachial SBP versus brachial PP: *$p < 0.005$; carotid SBP versus carotid PP: §$p < 0.05$; †$p < 0.0001$; brachial SBP versus carotid SBP: ‡$p < 0.001$; ¶$p < 0.0001$; brachial PP versus carotid PP: ‖$p < 0.005$; #$p < 0.0001$; **$p < 0.05$.

LV = left ventricular; SBP = systolic blood pressure; other abbreviations as in Table 3.

0.224, $p < 0.0001$, respectively), whereas the AI corrected for PP did not relate to IMT, WCSA, or plaque score.

Predictors of combined fatal and nonfatal CV events. In univariate analyses, older age, male gender, higher BP, higher creatinine level, comorbidities, LV structure and function, and carotid artery abnormalities were predictors of combined fatal and nonfatal CV events (Table 5). When all significant univariate predictors were included in a multivariate Cox regression model, older age, male gender, history of coronary artery disease, increased carotid SBP, and higher carotid plaque score were independently associated with a higher incidence of CV events at follow-up.

To analyze the relation of brachial and carotid SBP and PP to CV events without adjustment for the presence of coronary and carotid atherosclerosis, separate models were constructed, including age, gender, and each independent pressure (Table 6). Neither brachial pressure entered the models, whereas both carotid SBP and PP were significantly related to outcome. Moreover, when both brachial and carotid SBP or brachial and carotid PP were inserted in a multivariate model with age and gender, only central pressures remained in the models ($p < 0.0001$ for carotid SBP and carotid PP), whereas brachial pressures did not enter the models.

Table 5 Predictors of Cardiovascular Events

	Univariate HR (95% CI)	p Value	Multivariate* HR (95% CI)	p Value
Age (yrs)	1.09 (1.06–1.12)	<0.0001	1.08 (1.03–1.12)	<0.0001
Male gender	1.69 (1.18–2.41)	0.004	1.71 (1.04–2.83)	0.035
Brachial SBP (10 mm Hg)	1.14 (1.04–1.25)	0.004		
Brachial PP (10 mm Hg)	1.23 (1.11–1.38)	<0.0001		
Creatinine (μmol/l)	1.02 (1.01–1.03)	0.001		
Previous stroke/TIA (yes)	2.43 (1.31–4.52)	0.005		
Known PVD (yes)	1.97 (1.19–3.25)	0.008		
CAD (yes)	3.44 (2.18–5.44)	<0.0001	2.99 (1.65–5.40)	<0.0001
Diabetes (yes)	1.76 (1.04–2.98)	0.036		
Left atrium (mm)	1.04 (1.02–1.07)	0.002		
FS (%)	0.96 (0.94–0.99)	0.002		
EF (%)	0.97 (0.96–0.99)	0.001		
LV mass index (g/m^2)	1.02 (1.01–1.02)	<0.0001		
LV hypertrophy (LVMI)	2.33 (1.52–3.59)	<0.0001		
Carotid SBP (10 mm Hg)	1.28 (1.17–1.41)	<0.0001	1.14 (1.02–1.28)	0.026
Carotid PP (10 mm Hg)	1.34 (1.21–1.48)	<0.0001		
IMT (mm)	3.65 (1.17–11.36)	0.025		
Wall cross-sectional area (mm^2)	1.08 (1.04–1.12)	<0.0001		
Plaque score	1.27 (1.17–1.38)	<0.0001	1.14 (1.01–1.28)	0.028
Plaque (Yes)	2.07 (1.28–3.36)	0.003		
Reflected wave (mm Hg)	1.03 (1.01–1.05)	0.001		
AI corrected for MBP (%)	1.03 (1.01–1.05)	0.003		
Peripheral amplification (mm Hg)	0.96 (0.93–0.99)	0.020		
Stiffness index	1.11 (1.04–1.17)	0.001		

*A forward method was used on the basis of likelihood ratio, with variables entered for $p < 0.05$ and excluded for $p > 0.1$.

AI = augmentation index; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; IMT = intimal-medial thickness; LVMI = left ventricular mass/body surface area; MBP = mean blood pressure; PP = pulse pressure; PVD = peripheral vascular disease; SBP = systolic blood pressure; TIA = transient ischemic attack; other abbreviations as in Table 2.

Table 6 Independent Predictors of Cardiovascular Events

	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs)	1.09 (1.07–1.12)	<0.0001	1.09 (1.07–1.12)	<0.0001	1.10 (1.06–1.13)	<0.0001	1.09 (1.06–1.13)	<0.0001
Male gender	1.84 (1.29–1.64)	0.001	1.84 (1.29–1.64)	0.001	1.92 (1.29–2.87)	0.001	1.97 (1.32–2.94)	0.001
Brachial SBP (/10 mm Hg)		0.119						
Brachial PP (/10 mm Hg)				0.063				
Carotid SBP (/10 mm Hg)					1.19 (1.08–1.31)	<0.0001		
Carotid PP (/10 mm Hg)							1.23 (1.10–1.37)	<0.0001

Abbreviations as in Table 5.

Predictors of CV mortality. With the analysis restricted to fatal CV events, age (HR 1.23/year; 95% CI 1.14 to 1.34; $p < 0.001$), male gender (HR 8.21; 95% CI 2.59 to 26.00; $p < 0.001$), history of coronary artery disease (HR 7.41; 95% CI 2.44 to 22.50; $p < 0.001$), and carotid SBP (HR 1.33/10 mm Hg; 95% CI 1.03 to 1.72; $p = 0.029$) were independent predictors of CV mortality. Neither carotid PP nor brachial systolic and PPs were independently related to the small number of fatal CV events.

Discussion

In a cohort of unselected community-dwelling normotensive and untreated hypertensive elderly individuals, those who suffered incident CV events had a significant disease burden at baseline, including LV structural and functional abnormalities, carotid atherosclerosis, and more impaired renal function. However, in a relatively short observational period as in our study, age, male gender, previous coronary artery disease, carotid SBP (but not brachial), and carotid atherosclerosis were strong independent predictors of CV events. Moreover, central pressures were more strongly associated with cardiac and vascular remodeling than were brachial pressures.

Central versus brachial BP and vascular remodeling. Recently, Roman et al. (9) analyzed the relation of brachial and central pressures to carotid hypertrophy and extent of atherosclerosis in a large cohort of American Indians (Strong Heart Study). The correlation coefficients reported by Roman et al. were similar to those in the present study. However, correlation coefficients between IMT and brachial and central PP did not reach statistical significance in the present study, likely owing to the smaller sample size. Moreover, our subjects were older than the subjects enrolled in the Strong Heart Study, and therefore a smaller peripheral amplification of central PP can be expected in our cohort with a consequent reduced difference in the correlation coefficients between IMT and brachial and central PP. In fact, in a group of relatively young adults, Boutouyrie et al. (23) found that brachial over carotid PP ratio was attenuated by aging and that central but not brachial PP was related to carotid internal diameter. The greater impact of central BP compared with brachial BP in arterial remodeling was also reported in 114 men with angiographically documented coronary artery disease; in fact, Waddel et al. (24) demonstrated that the severity of coronary disease was independently related to carotid SBP ($r = 0.47$, $p < 0.001$) and carotid PP ($r = 0.45$, $p < 0.001$) but not to brachial pressures. In our cohort of elderly subjects, the arterial stiffness index and AI exhibited significant correlations with WCSA and plaque score but not with IMT; this difference can be explained by the observations that AI plateaus at the age of 60 years or might even decrease after the age of 60 years (25,26).

Central versus brachial BP and CV events. Our study demonstrated that carotid atherosclerosis and carotid SBP were predictors of CV events independent of age. In the Cardiovascular Health Study, subclinical carotid stenosis (which might underestimate atherosclerotic burden) was an independent predictor of events (27). However, we further demonstrated that incident CV events were more likely in free-living elderly subjects with a higher carotid plaque score, a measure of disease burden. Therefore, therapy targeting central BP and atherosclerosis (or other target organ damage) might impact CV event rates in older populations. In fact, in hypertensive patients from the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study, echocardiographic and electrocardiographic abnormalities identified higher CV risk independent of brachial BP reduction (28,29) and a significant impact of aspirin use on CV combined end point reduction (30) independent of BP. Recently, data from the Strong Heart Study revealed similar strengths of age, male gender, and carotid pressure in predicting CV outcome as in our study (9). In the Strong Heart Study, arterial stiffness was also related to CV outcome but did not emerge as an independent predictor in the present study. This difference can be partially explained by differences in age (ranging from 18 to 88 years in the Strong Heart Study and from 65 to 94 years in the present analysis), because studies have reported that carotid stiffness, expressed as AI, increases with age in younger individuals (<50 years), whereas this relation disappears over age 50 years (26,31).

In our study population, LV structure and function were not independently related to CV events, and no significant relation was found between LV ejection fraction and carotid stiffness expressed as AI. Our findings are at variance with those reported by the Cardiovascular Health Study (32,33). However, in the Cardiovascular Health Study, the study sample was larger, the observation time was longer, and the number of events was greater. Moreover, in the Cardiovas-

cular Health Study, LV functional parameters predicted new-onset congestive heart failure specifically, whereas we evaluated total fatal and nonfatal CV events. Our fatal CV events comprised mostly fatal acute coronary syndromes and strokes (33% and 29%, respectively), and nonfatal events included mostly strokes or transient ischemic attacks and acute coronary syndromes (34% and 24%, respectively), which might explain why indicators of atherosclerosis were more powerful predictors of CV rather than LV structural and functional abnormalities in our study.

Whether central BP is related to CV events more strongly than brachial BP is debated (8,9,23,24,34–36). In the CAFE (Conduit Artery Function Evaluation) study, central PP was associated with clinical outcomes more strongly than brachial PP (37). In contrast, Dart et al. (8) found a greater prognostic impact of brachial than central PP. In a population of patients who underwent coronary angiography for established coronary artery disease, Chirinos et al. (38) found that central but not brachial PP was an independent predictor of all-cause death, whereas the association of increased central PP with incident CV events was borderline ($p = 0.057$). In our study, we separately and specifically evaluated whether carotid PP predicted higher CV morbidity and mortality more strongly than brachial PP. We found that central PP predicted incident CV events, whereas brachial PP did not, independent of age and gender, similar to the study of Safar et al. (36) in patients with end-stage renal disease. Our results in an elderly population provide additional support to the recent Strong Heart Study findings (9) that increased central PP is associated with greater LV and vascular remodeling as well as carotid atherosclerosis. In fact, subjects with increased PP have a higher LV mass/body surface area and carotid atherosclerosis, and these abnormalities lead to an increased risk of CV events. In a previous study in a less elderly population, higher brachial PP, indicative of increased arterial stiffness, was found to be associated with higher CV mortality independent of LV hypertrophy (39). In the present study, we demonstrated that central BP, more than brachial BP, predicted CV events, independent of carotid atherosclerosis.

Study limitations. The hypertensive subjects included in the present analysis were untreated at the time of enrollment in the ICARe Dicomano study (1995), but no data are available regarding antihypertensive treatment initiated during follow-up. However, as previously demonstrated in a different subset of the ICARe Dicomano study, treated hypertensive subjects with optimal BP control (brachial BP <140/90 mm Hg) had higher carotid PP than in normotensive subjects (62 ± 20 mm Hg vs. 50 ± 14 mm Hg, $p = 0.004$), despite normalized brachial PP (52 ± 9 mm Hg vs. 48 ± mm Hg, p = NS). Thus, the association between carotid PP and adverse outcome might be less affected by the impact of antihypertensive treatments. A further limitation of our study is that the prognostic importance of cardiac and vascular remodeling was not a primary outcome of the ICARe Dicomano study; thus, the sample size might be too limited to avoid type 2 errors. However, this study has the advantage of analyzing an unselected population of elderly subjects of an entire town. Finally, both fatal and nonfatal events were classified as CV or non-CV on the basis of the data recorded in the electronic database of the Regional Ministry of Health without an independent review of medical records; thus, we cannot exclude that some event would be erroneously attributed to the wrong cause.

Conclusions

Our prospective study in an unselected geriatric population of normotensive and untreated hypertensive subjects demonstrated that CV disease burden predicts CV events independent of age and BP. Moreover, we demonstrated the superior prognostic importance of carotid BP over brachial BP, indicating that central BP should be taken into account in the evaluation of the impact of therapeutic strategies on outcomes.

Reprint requests and correspondence: Dr. Riccardo Pini, Unit of Geriatric Cardiology, Via delle Oblate, 4, 50141 Florence, Italy. E-mail: rpini@unifi.it.

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