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Higher pulse pressure and risk for cardiovascular events in patients with essential hypertension: The Campania Salute Network

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Abstract

Background: Increased pulse pressure is associated with structural target organ damage, especially in elderly patients, increasing cardiovascular risk.

Design: In this analysis, we investigated whether high pulse pressure retains a prognostic effect also when common markers of target organ damage are taken into account.

Methods: We analysed an unselected cohort of treated hypertensive patients from the Campania Salute Network registry ($n = 7336$). Participants with available cardiac and carotid ultrasound were required to be free of prevalent cardiovascular disease, with ejection fraction $\geq$50%, and no more than stage III Chronic Kidney Disease. The median follow-up was 41 months and end-point was occurrence of major cardiovascular events (i.e. fatal and non-fatal stroke or myocardial infarction and sudden death). Based on current guidelines, pulse pressure $\geq$60 mm Hg was classified as high pulse pressure ($n = 2356$), at the time of the initial visit, whereas pulse pressure $<$60 mm Hg was considered normal ($n = 4980$).

Results: High pulse pressure patients were older, more likely to be women and diabetic, while receiving more antihypertensive medications than normal pulse pressure (all $p < 0.0001$). High pulse pressure exhibited greater prevalence of left ventricular hypertrophy, and carotid plaque than normal pulse pressure (all $p < 0.0001$). In Cox regression, high pulse pressure patients had 57% increased hazard of major cardiovascular events, compared to normal pulse pressure (hazard ratio = 1.57; 95% confidence interval: 1.12–2.22, $p = 0.01$), an effect that was independent of significant prognostic impact of older age, male sex, diabetes, left ventricular hypertrophy, carotid plaque and less prescription of anti-renin–angiotensin system therapy.

Conclusions: High pulse pressure is a functional marker of target organ damage, predicting cardiovascular events in hypertensive patients, even independently of well-known structural markers of target organ damage.

Keywords

Hypertension, target organ damage, pulse pressure, cardiovascular events, arterial stiffness

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Introduction

With advancing age, conduit vessels decrease their compliance and elasticity due to elastin degeneration, and collagen deposition.[1] As a consequence, left ventricular (LV) pulsatile load increases, with substantial burden especially in patients with left ventricular dysfunction.[2] Variation of pulsatile load may be clinically appreciated

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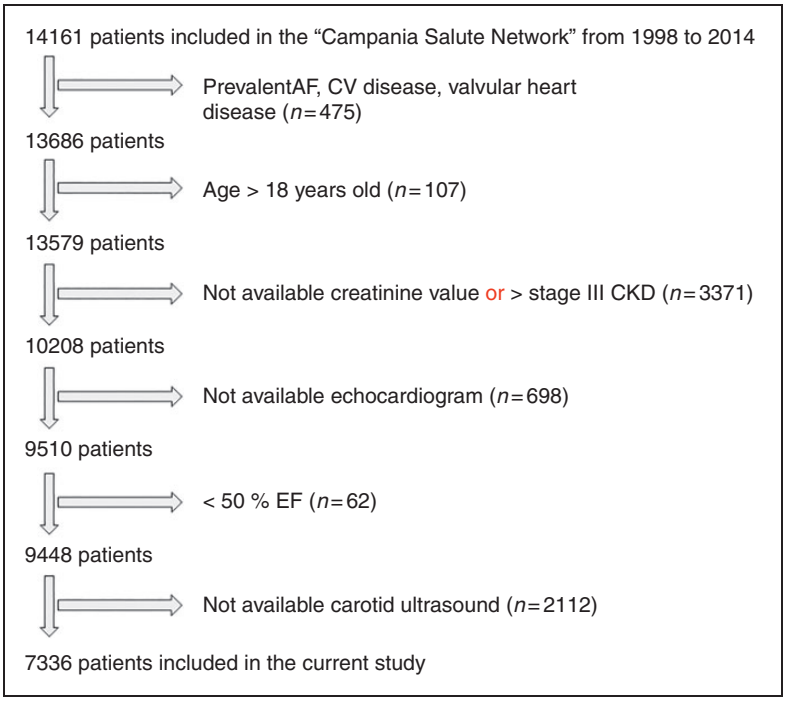

Figure 1. Selection of the study population. CV: cardiovascular; CKD: Chronic Kidney Disease; EF: ejection fraction.

as pulse pressure (PP). Thus, the structural changes beyond the increase in PP indicate that high PP is a surrogate functional sign of target organ damage (TOD)[3,4] in elderly patients, associated with increased cardiovascular (CV) events.[4]

Specifically, estimated central pulse pressure has been reported to be independently associated with adverse CV outcome in the cohort of the Strong Heart Study.[5] More recent evidence suggests that increased brachial PP is associated with adverse CV outcome, also independently of mean arterial pressure, in high-risk patients with atherosclerosis[6] and in patients with type 2 diabetes.[7]

However, whether high PP influences outcome also independently of structural markers of TOD, such as LV hypertrophy (LVH) and carotid atherosclerosis, is unknown. Accordingly, we evaluated whether increased PP impacts on incident CV events even independently of LVH and carotid plaque, in a large registry of hypertensive patients.

Methods

Patient population

The Campania Salute Network (CSN) is an open electronic registry on arterial hypertension, networking 23 community hospital-based hypertension clinics, and 60 general practitioners to the Hypertension Research Center of Federico II University Hospital in Naples,[8] from the Campania district in Southern Italy (ClinicalTrials.gov Identifier: NCT02211365). As previously reported in detail,[9,10] subjects recruited by participating hospitals or general practitioners are referred for CV imaging to the Hypertension Research Center. The registry currently includes over 15,000 subjects.

For the present analysis 7336 hypertensive patients without prevalent coronary or cerebrovascular disease, valvular heart disease, with ejection fraction $\geq$50%, no more than stage III chronic kidney disease (based on estimation of glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration formula.)[11] and with baseline echocardiogram and carotid ultrasound were selected (Figure 1).

The database generation of the CSN was approved by the Federico II University Hospital Ethic Committee. All participants signed written informed consent for the possibility of using the data for scientific purposes.

CV risk factor assessment

Prevalent CV disease was defined at the first examination in the outpatient clinic and included previous myocardial infarction (MI), angina pectoris, coronary revascularization procedures, stroke, transitory ischaemic attack, or congestive heart failure.[12] Office systolic and diastolic blood pressures (SBP and DBP) were measured in triplets after at least five minutes of rest in the sitting position, following current guidelines.[4] The average of the two last measurements was taken

as the clinical blood pressure (BP). In the CSN the measurement of BP has been always attended by a physician, using a regularly calibrated aneroid sphygmomanometer. Follow-up (FU) BP was considered controlled when the average clinic BP values during FU < 140/90 mm Hg.[8]

High PP was classified when PP ≥ 60 mm Hg.[4] High systolic BP was ≥140 mm Hg. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2.[13] Fasting glucose and lipid profile were measured by standard methods. Diabetes was defined as history of diabetes, use of any anti-diabetic medication or presence of a fasting blood glucose ≥126 mg/dl.[14] Diabetes was defined controlled if the average value of all glycaemic measurements during FU were <126 mg/dl, and uncontrolled if mean value of all glycaemic measurements during FU was ≥126 mg/dl.

Echocardiography

Echocardiography was performed using commercially available phased-array machines following a standardised protocol. All final readings were performed off-line by a single highly experienced reader and supervised by a senior faculty member. Quantitative echocardiography was performed following the joint European Association of Echocardiography and American Society of Echocardiography recommendations.[15] LVH was identified by prognostically validated sex-specific cut-off values for LV mass/height, >47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men, respectively.[16] Consistent with our approach to normalization for body size, LV end-diastolic dimension was normalised by height. Relative wall thickness was calculated as the ratio between posterior wall thickness and LV internal radius at end-diastole and considered increased if ≥0.43.[15] LV volumes were estimated by the z-derived method.[17,18] Left atrial (LA) volume (eLAV) was estimated from LA antero-posterior diameter in cm (LAd), measured in the longitudinal parasternal window, using a validated non linear equation:

$$\text{eLAV} = 2.323 \times \text{LAd}^{2.071}$$

and normalised by height in m^2 (eLAVi).[19]

Carotid ultrasonography

Carotid ultrasonography was performed using a commercially available ultrasound scanner equipped with a 7.5-MHz high-resolution transducer with an axial resolution of 0.1 mm. B-mode ultrasonography was performed with subjects in the supine position with the head turned away from the sonographer and the neck extended in mild rotation. Images were recorded on super video home system tapes for off-line analysis. The standardised comprehensive scanning and reading protocol has been previously published.[20] The maximal arterial intima media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation and proximal internal carotid artery, according to European Society of Hypertension/European Society of Cardiology guidelines.[4] The average and the maximum IMT was reported in the individual patient. Carotid plaque was defined as IMT ≥ 1.5 mm in accordance with previous studies.[21]

Endpoints

Major adverse cardiovascular end-points (MACEs) at their first presentation were considered fatal or nonfatal MI or stroke, and sudden death. Secondary analyses were also performed using composite major and minor end-points, also including first presentation of heart failure requiring hospitalization, incident coronary revascularization, angina, transient ischaemic attack, carotid artery stenting and atrial fibrillation. Both prevalent and incident CV and cerebrovascular events were adjudicated by the Committee for Event Adjudication in the Hypertension Research Center and were based on patient history, contact with the reference general practitioner, and review of hospital medical records.[22]

Statistical analysis

Statistical analysis was performed using IBM SPSS 23 (IBM Corporation, Armonk, New York, USA). Data are presented as mean ± one standard deviation for continuous variables and as percentages for categorical variables. Patients were categorised into two groups according to the absence (normal pulse pressure (NPP); $n = 4980$) or the presence of high PP (HPP; $n = 2356$):

Analysis of variance was used to compare continuous variables. The χ^2 distribution was used to compare categorical variables. As previously reported,[22,23] to account for antihypertensive therapy during FU, single classes of medications were dichotomised according to their overall use during the individual FU, based on the frequency of prescriptions at the control visits during FU. All medications prescribed for more than 50% of control visits in an individual patient during FU were considered as covariates in the Cox analyses.[22,23]

Kaplan–Meier survival curves were used to compare outcome of HPP vs NPP for MACEs. The outcome was also analysed in relation to LVH and carotid

Table 1. General characteristic of the study population.

Variable	HPP ($n = 2356$)	NPP ($n = 4980$)	p
Age (years)	57 ± 12	52 ± 11	0.0001
Women (%)	50	39	0.0001
Systolic blood pressure (mm Hg)	159.6 ± 17	135 ± 13	0.0001
Diastolic blood pressure (mm Hg)	88.5 ± 12.5	88.9 ± 10.4	0.221
Mean blood pressure (mm Hg)	112.1 ± 13.1	105 ± 11.1	0.0001
Heart rate (bpm)	74.7 ± 11.1	74.2 ± 11	0.104
Obesity (%)	25	26	0.256
Diabetes (%)	14	8	0.0001
Estimated glomerular filtration rate (ml/min/1.73m^2)	78.7 ± 15.8	82.1 ± 14.9	0.0001
Total serum cholesterol (mg/dl)	208 ± 39.6	206.4 ± 38.9	0.111
Serum HDL cholesterol (mg/dl)	51.2 ± 13.4	50.5 ± 12.9	0.075
Serum non-HDL cholesterol (mg/dl)	129 ± 36.2	128.4 ± 35.6	0.444
Serum triglycerides (mg/dl)	136 ± 78.4	135.7 ± 75.6	0.870
Number of antihypertensive drugs during FU	1.8 ± 1.1	1.5 ± 1.0	0.0001
Anti-RAS during FU (%)	82	77	0.0001
Beta-blockers during FU (%)	29	24	0.0001
Calcium-blockers during FU (%)	33	22	0.0001
Diuretics during FU (%)	49	39	0.0001

GFR: glomerular filtration rate; FU: follow-up; HDL: high density lipoprotein; RAS: renin–angiotensin system.

plaque in combination with high PP in Cox regression analyses for either categories of PP or PP as continuous variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. In a first Cox model, the condition of high PP was adjusted for age and sex; in a second model, presence of diabetes, LVH and carotid plaque were forced. A third model also included all classes of antihypertensive medications used during FU. Finally Model 4 was additionally adjusted for mean arterial pressure $((2 \times \text{DBP} + \text{SBP})/3)$. The same analysis was done for PP as a continuous variable.

All variables used in the Cox models were analysed for multicollinearity, by computing linear variance inflation factor (VIF). VIF was always less than 1.5.

A two-tailed p-value < 0.05 was considered statistically significant in all analyses.

Results

HPP patients were older, more likely to be women and diabetic, and exhibited higher SBP and lower GFR, while receiving more of each class of antihypertensive medications than NPP (all $p < 0.0001$, Table 1). No difference was observed in lipid profile.

Table 2 shows that HPP patients exhibited greater LV chamber dimension and stroke index, with greater LV mass and relative wall thickness, greater prevalence of LVH, concentric geometry, and carotid plaque than NPP patients (all $p < 0.0001$).

Incident MACEs

During the median FU of 41 months (interquartile range = 15–88 months), 157 incident MACEs occurred. Consistent with the risk profile displayed in Tables 1 and 2, HPP patients exhibited 86% greater risk of MACEs than NPP patients (HR = 1.86; 95% CI: 1.36–2.56, $p < 0.0001$, Figure 2).

In sequential Cox regression models, the hazard of HPP was slightly reduced after adjusting for age and sex (Table 3, Model 2). HPP remained a significant predictor of MACEs, also when diabetes, LVH, carotid plaque and antihypertensive therapy were added to the Cox model (Table 3, Model 3). Further control for classes of medicines did not alter the impact of HPP, but revealed that anti-renin–angiotensin system (RAS) medicines were less likely to be prescribed in patients with incident MACEs. Finally, consideration of mean BP did not alter the risk profile (Table 3, Model 4). Even when including control of diabetes in Model 4 displayed in Table 3 the effect of high PP did not change (HR = 1.58, 95% CI 1.12–2.23, $p = 0.01$). With further adjustment for the presence of obesity and stage III CKD (found in 671 participants), high PP maintained an HR of 1.57, (95%

Table 2. Target organ damage among study population.

Variable	HPP ($n = 2356$)	NPP ($n = 4980$)	p
LV end-diastolic dimension (cm/m)	3.00 ± 0.19	2.95 ± 0.18	0.0001
Stroke index (ml/beat $\times$ $m^{2.04}$)	26.35 ± 3.5	25.61 ± 3.3	0.0001
Relative wall thickness	0.39 ± 0.04	0.38 ± 0.04	0.0001
LV mass index (g/$m^{2.7}$)	49.4 ± 9.9	45.7 ± 8.4	0.0001
Intima media thickness (mm)	1.8 ± 0.8	1.5 ± 0.7	0.0001
Concentric LV geometry (%)	12	9	0.0001
LV hypertrophy (%)	49	31	0.0001
Carotid plaque (%)	57	39	0.0001

HPP: high pulse pressure; LV: left ventricular; NPP: normal pulse pressure.

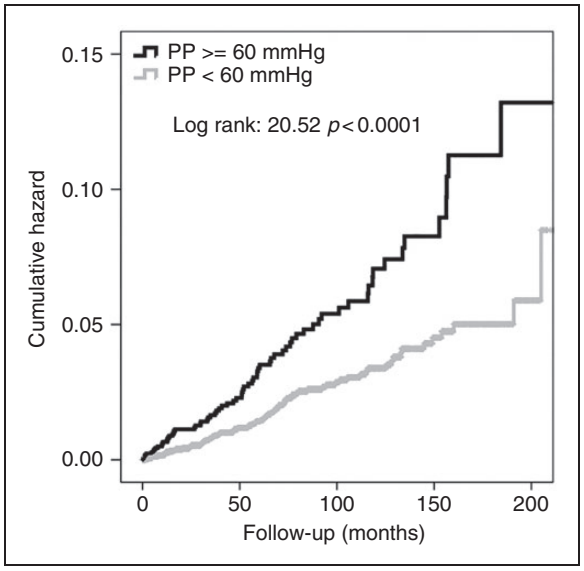

Figure 2. Kaplan–Meier plot of cumulative hazard of major adverse cardiovascular end-points (MACEs) in patients with high vs normal pulse pressure (PP).

CI 1.11–2.21, $p = 0.01$). Model 4 in Table 3 has been further adjusted for haemoglobin level, estimated GFR, LA volume index and stroke volume index with high PP maintaining a significant prognostic impact (HR 1.55, 95% CI 1.10–2.20, $p = 0.013$). To verify whether the introduction of a classical cut-off value of high baseline systolic BP (>140 mm Hg) could influence the prognostic impact of high PP we have run a new model changing mean BP with high systolic BP. As shown in Table 4 the prognostic impact of high PP was not influenced by the introduction of high systolic BP in the model (HR 1.69, 95% CI 1.15–2.49, $p = 0.008$).

To verify whether the introduction of high PP in a traditional TOD-based model influences the hazard of CV events due to structural TOD, another Cox analysis was run forcing the condition of high PP into a model including age, sex, LVH and plaque. The age and sex-adjusted hazard of LVH and carotid plaque were respectively 1.54 (1.11–2.13) and 1.66 (1.17–2.35), decreasing to the value of 1.42 and 1.63 when high PP coexisted in the model (all $p < 0.0001$).

Analysis of PP as a continuous variable yielded similar results (HR 1.15/10 mm Hg (95% CI 1.05–1.25), $p = 0.003$) independently of confounders.

A similar model as displayed in Table 3, Model 3, was run changing PP with its two components, SBP and DBP. In this model, both SBP and DBP were independent predictors of CV events, but in opposite directions, because SBP exhibited a direct relation with probability of events (HR = 1.08/5 mm Hg, 1.05–1.13, $p < 0.001$), whereas the relation of DBP was negative (HR = 0.89/5 mm Hg, 0.80–0.99, $p < 0.03$).

The fourth Cox regression in Table 3 was also run in a subgroup of patients with controlled BP during FU (3910 patients with 91 MACEs) and high PP retained a tendency for increased CV risk (HR 1.60; 95 CI 1.00–2.55, $p = 0.05$).

Incident composite MACEs and minor end-points

During FU, 313 incident composite MACEs and minor end-points occurred. HPP patients exhibited 66% greater risk of composite end-points than NPP patients (odds ratio (OR) = 1.66; 95% CI: 1.32–2.01, $p < 0.0001$, Figure 3).

Similar to analysis with MACEs, in Cox regression analysis, HPP patients maintained a 33% increased hazard, compared to NPP patients (HR 1.33 (95% CI 1.04–1.70), $p = 0.024$), independently of significant effect of old age, male gender, LVH, carotid plaque and less anti-RAS therapy, without significant effect for mean BP and the other classes of medicines (not shown).

Table 3. Sequential models of proportional hazard analysis for major adverse cardiovascular end-point (MACE) adjusting for group of covariates for high pulse pressure (PP). Significant predictors are highlighted in bold.

	Model 1			Model 2			Model 3			Model 4		
Predictors	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI
Age (years)	**0.0001**	**1.05**	**1.03–1.06**	**0.0001**	**1.03**	**1.01–1.05**	**0.0001**	**1.03**	**1.02–1.05**	**0.0001**	**1.04**	**1.02–1.05**
Male sex	**0.001**	**1.76**	**1.25–2.48**	**0.002**	**1.72**	**1.22–2.42**	**0.002**	**1.75**	**1.24–2.48**	**0.002**	**1.75**	**1.23–2.47**
High PP (≥60 mm Hg)	**0.001**	**1.72**	**1.24–2.39**	**0.007**	**1.58**	**1.14–2.20**	**0.004**	**1.63**	**1.16–2.27**	**0.01**	**1.57**	**1.12–2.22**
Diabetes (n/y)				**0.34**	**1.59**	**1.04–2.46**	**0.019**	**1.68**	**1.09–2.59**	**0.017**	**1.69**	**1.01–2.61**
LV hypertrophy (n/y)				**0.031**	**1.43**	**1.03–1.99**	**0.016**	**1.51**	**1.08–2.11**	**0.019**	**1.50**	**1.07–2.1**
Carotid plaque (n/y)				**0.009**	**1.59**	**1.12–2.26**	**0.004**	**1.68**	**1.19–2.39**	**0.004**	**1.68**	**1.18–2.39**
Anti–RAS (n/y)							**0.0001**	**0.36**	**0.24–0.53**	**0.0001**	**0.35**	**0.24–0.53**
Beta blockers (n/y)							0.51	1.13	0.79–1.61	0.536	1.12	0.78–1.60
Calcium-channel blockers (n/y)							0.83	0.96	0.68–1.36	0.782	0.95	0.67–1.35
Diuretics (n/y)							0.82	0.96	0.68–1.36	0.794	0.96	0.68–1.35
Mean BP (mm Hg)										0.475	1.01	0.99–1.02

BP: blood pressure; CI: confidence interval; HR: hazard ratio; LV: left ventricular; PP: pulse pressure; RAS: renin–angiotensin system.

Table 4. Cox model of proportional hazard analysis for major adverse cardiovascular end-point (MACE) adjusting for group of covariates for high pulse pressure (PP) including high systolic blood pressure (BP). Significant predictors are highlighted in bold.

Predictors	Sig.	HR	95.0% CI	
Age (years)	**0.000**	**1.034**	**1.016**	**–1.052**
Male sex	**0.002**	**1.753**	**1.238**	**–2.482**
High PP (≥60 mm Hg)	**0.008**	**1.689**	**1.147**	**–2.487**
Diabetes (n/y)	**0.019**	**1.682**	**1.091**	**–2.594**
LV hypertrophy (n/y)	**0.015**	**1.517**	**1.085**	**–2.122**
Carotid plaque (n/y)	**0.004**	**1.684**	**1.184**	**–2.393**
Anti-RAS (n/y)	**0.000**	**0.356**	**0.239**	**–0.530**
Beta-blockers (n/y)	0.510	1.128	0.788	–1.613
Calcium-channel blockers (n/y)	0.839	0.965	0.682	–1.365
Diuretics (n/y)	0.828	0.963	0.683	–1.357
High systolic BP (≥140 mm Hg)	0.700	0.925	0.623	–1.374

CI: confidence interval; HR: hazard ratio; LV: left ventricular; RAS: renin–angiotensin system.

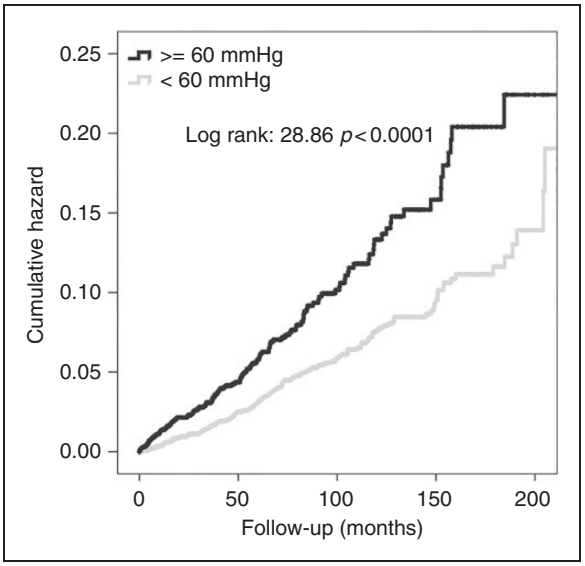

Figure 3. Kaplan–Meier plot of cumulative hazard for composite major adverse cardiovascular end-points (MACEs) and minor events in patients with high vs normal pulse pressure (PP).

Discussion

This analysis is the first direct demonstration that high PP is a functional equivalent of a structural TOD, also independent of other commonly measured TODs. This finding is particularly relevant, because it was revealed in a context of primary prevention in a real-world context.

PP is the measure of the combined LV ability to expel blood, depending on the capacitance and distensibility of the conduit arterial system.[1] Thus, PP represents the pulsatile component of circulatory physiology, a consequence of the balance between systolic and diastolic components which sustain the peripheral circulation. Mean BP estimates the continuous peripheral flow, which is the physiological consequence of the combination of systolic flow with the diastolic arterial run-off at the aortic valve closure. With the progressive stiffening of the conduit arteries, the ability of arterial run-off is lost and consequently the diastolic component of the peripheral flow decreases; if the final goal

is to preserve peripheral continuous flow (i.e. mean BP), any increase in stiffening of conduit arteries needs a corresponding increase in the systolic component of peripheral flow (i.e. SBP), which participates to widening of pulse pressure.[24] Model 4 of Table 3, with the strong prognostic effect of high PP and the evidence that mean BP does not independently contribute to outlining risk, indicates that the way to maintain peripheral blood flow is substantially important for cardiovascular health. Combining information of both components of BP (SBP + DBP) has been demonstrated to better predict outcome in several studies, especially in the middle-aged population.[25,26] The widening of PP due to the diverging of SBP and DBP with aging carries an adverse CV prognosis that includes effects of both higher SBP and lower DBP, which may be more easily identified using PP as a prognostic maker.

In addition to BP components, aging is strongly associated with HPP, mainly due to age-related alterations in collagen to elastin ratio and disruption of elastic fibres[27] in the conductance arteries.

In our outpatient setting of adult hypertensive patients, HPP was also associated with greater prevalence of TOD, suggesting that HPP is another sign of established CV damage in the setting of arterial hypertension.[3] This association has been also confirmed on the large cohort of patients of the Multi-Ethnic Study of Atherosclerosis (MESA), where increased PP was correlated with markers of subclinical CV disease and this association was stronger with advancing age.[28] Recent data from the Hypertension Genetic Network (HyperGEN) study highlighted the importance of PP for the development of subclinical cardiac target organ damage, in both hypertensive and non-hypertensive patients.[29]

Other studies have demonstrated that both subclinical TOD and CV prognosis were related to increased PP, suggesting a specific cut-off (>60 mm Hg) in study populations older than 60 years.[30,31]

The prognostic impact of PP on CV disease has been recently demonstrated in a population-based study with high prevalence of obesity and hypertension.[6] A pulse pressure ≥70 mm Hg increased risk of CV events, even after adjustment for multiple confounders such as age, sex, smoking, hypercholesterolemia and other confounders. Comparing with our study, the Reach Registry included also patients with prevalent CV diseases who were not included in our study, focused on primary prevention. Another large longitudinal cohort study indicated that PP higher than 65 mm Hg was an independent risk factor for acute coronary heart disease even after adjustment for SBP.[32] Particularly interesting is the observation that when the classical cut-off value of high systolic BP coexists in the same Cox regression model with high PP the risk associated with systolic BP ≥ 140 mm Hg is completely obscured by risk represented by a PP ≥ 60 mm Hg. No study, however, verified whether the prognostic impact of PP was independent of other markers of TOD, since no ultrasound data were reported.

Taking advantages of our large registry of hypertensive outpatients, we could demonstrate that increased PP is a potent predictor of CV events, and this prognostic power was maintained not only in addition to a large number of confounders and antihypertensive therapy, but also independently of common markers of TOD, such as LVH and carotid plaque. This outcome effect independent of structural TOD could be documented either with MACEs or with composite MACEs and minor events.

It should be underlined that, in the exploratory analysis, patients with high PP were more likely to be women and more treated with anti-RAS therapy during FU. However, in Cox regression, those who suffered with MACEs were more frequently men and had a reduced probability of having been treated with anti-RAS therapy.

The modification of HRs of LVH and carotid plaque when there is high PP in the Cox model suggests that all three factors explore different aspect of the pre-clinical CV disease pointing towards pathophysiologic links. Exposure to risk factors represents the initial stimulus to induce biological changes leading to structural abnormalities in the arterial system and at cardiac level.[33] Arteriosclerosis and consequent stiffening of conduit arteries reduce the arterial run-off due to elastic recoil, with consequences on maintenance of DBP, a process that is also proposed to change the initial presentation of hypertension and lead to isolated systolic hypertension.[34,35] LVH develops as the consequence of haemodynamic modifications and takes the geometry determined by the balance between pressure and volume overload.[16,22] PP increases as the consequence of merging reduced arterial compliance with maintained or even increased stroke volume, regulated by the dominant haemodynamic workload and the availability of contractile mass.[16,36] Atherosclerosis, manifested by the presence of carotid plaque, is a particularly severe manifestation of the arterial system impairment.

Based on the evidence provided by the present analysis, and on the recalled considerations, the link between structural TOD (i.e. LVH and carotid atherosclerosis) and PP is evident in the process of defining a specific risk profile. We propose considering 'high PP' in the range of age analysed in the CSN as a 'functional' TOD to merge with structural TOD.[37]

As a functional marker of TOD, increased PP identifies a status in which the vascular ventricular interaction is no longer working properly,[38] especially in

older age, when the amplification of the pulsatile wave toward peripheral arteries substantially attenuates and, therefore, cuff PP is closer to central PP.[39]

In a large registry of hypertensive patients free of prevalent CV disease, high PP is a potent marker of TOD, predicting CV events independently of LV hypertrophy and carotid plaque with a cut off value of 60 mm Hg. High PP is a functional marker of TOD paralleling the effect of structural TOD.

Limitations

The CSN is an observational registry which can be influenced by bias, a limitation that is difficult to eliminate despite the extensive multivariable adjustment that we performed. However, we paid particular attention to minimising both selection and observational bias, by receiving all hypertensive patients seen in our network and applying substantially the same protocol to everyone. It needs to be underlined that observational studies cannot demonstrate any cause–effect relationship, but are useful for the generation of hypotheses to be tested in prospective studies and/or clinical trials.

The measurement of PP is a rough method to estimate arterial stiffness. However, there is evidence that what is thought to be the gold standard to measure arterial stiffness, pulse wave velocity, is closely related to pulse pressure especially with advancing age.[40] In addition, our findings have direct, easy clinical applicability in daily clinical practice, with the implicit recommendation to doctors to consider PP in addition to SBP and DBP, a practice that is not yet very common.

Author contribution

CM and GdS contributed to the conception and design of the work. MAL, RI, GC, MVC, GA contributed to the acquisition, analysis and interpretation of data for the work.
CM and NDL drafted the manuscript. BT critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflicting interests

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