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ARTICLE

Determinants of pulse pressure amplification in hypertensive and diabetic patients

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Abstract

Hypertensive diabetic patients remain at high cardiovascular risk despite adequate blood pressure and glycemic control. Pulse pressure amplification (PPA) is expressed as the peripheral-to-central PP ratio and provides complementary information for use in assessing cardiovascular risk. The aim of our study was to determine the clinical and biological determinants of PPA in hypertensive and diabetic patients. A cross-sectional study was conducted in 624 patients. Applanation tonometry was used to determine hemodynamic parameters. Age, gender, and the association between hypertension and diabetes were the independent factors of PPA in our population ($N = 624$). A threshold of 55 years of age was chosen because of its link with menopause in our analysis. Multivariate regression analyses were performed to evaluate the independent determinants of PPA for hypertensive diabetic and hypertensive nondiabetic male and female patients. HbA1c level is the main factor of increased PPA regardless of age and gender ($P < 0.05$). Mean BP negatively regulates PPA in the overall study: men > 55 years ($P = 0.0001$) and women > 55 years ($P = 0.03$). The threshold calculated glomerular filtration rate (cGFR) < 60 mL/min/1.73 m2 was an independent and negative factor of PPA in hypertensive diabetic men regardless of age ($P < 0.05$) and in women > 55 years ($P = 0.04$). Mean BP negatively regulates PPA in hypertensive nondiabetic patients ($P < 0.04$) regardless of age and gender, except in women > 55 years, where cGFR < 60 ($P = 0.04$) negatively regulates the modulation of PPA. HbA1c and threshold cGFR < 60 have highly significant impacts on PPA in hypertensive diabetic patients, whereas mean BP appears as the main factor of PPA in hypertensive nondiabetic patients.

Keywords Pulse pressure amplification · hypertension · diabetes · HbA1c · glomerular filtration rate

Introduction

The diagnosis and treatment strategy of arterial hypertension are based on the measurement of brachial blood pressure (BP). It has been well established that brachial BP is a good predictor of cardiovascular risk, and BP-lowering therapeutics lead to reductions in cardiovascular risk, all-cause morbidity, and mortality [1]. Nevertheless, BP values and their amplitudes, such as pulse pressure (PP) and mean BP, depend on the caliber and elasticity of arterial vessels [2]. Mean BP corresponds to vascular resistance, such as that arising from small arteries, and steady pressure, whereas PP refers to pulsatile pressure (stroke volume, wave reflections and arterial stiffness). In large arteries, only wave reflections and arterial stiffness affect PP. Moreover, PP and SBP are higher in brachial than in carotid arteries for the same mean values of BP and DBP [3]. This phenomenon, called PP amplification, is related to changes in aortic stiffness and wave reflections along the arterial tree [3].

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Thus, the difference between carotid and brachial PP is defined as PP amplification (PPA) [3].

Several studies have shown the potential value of PP amplification in the prediction of cardiovascular (CV) [4, 5] and overall mortality risk [6]. Indeed, carotid BP is commonly represented as a main marker of cardiovascular risk and changes in carotid BP due to the use of antihypertensive treatments reduce cardiovascular mortality [7–9]. Furthermore, PP amplification is considered an independent factor of cardiovascular risk and mortality [6]. In hypertension and chronic kidney disease, PP amplification may appear as a stronger predictor of cardiovascular risk compared to carotid and brachial BP alone [10]. However, PP amplification and aortic stiffness are distinct and are not always strongly correlated [11].

The degree of PP amplification is related to hypertension, diabetes, and hypercholesterolemia [9, 12]. However, aging and gender are the main significant nonmodifiable factors leading to changes in PP amplification [13–15]. This may occur due to histological modifications in the elastic properties of conduit arteries, which lead to an increase in arterial stiffness and changes in wave reflections that occur with aging [9]. Substantial enhancement of central arterial stiffness appears, with the consequence of increased central PP and a reduction in peripheral PP augmentation. Collagen accumulation with a breakdown of elastin in the extracellular matrix occurs during aging vascular remodeling, leading to increased arterial stiffness [16].

Likewise, previous studies of pulsatile arterial hemodynamics have shown that men and women present different hemodynamic characteristics, especially in regard to PP [13]. CV mortality increases with age to a greater extent in women than in men. This phenomenon is largely increased in menopausal women over 55 years when compared with younger women. Moreover, at ages over 55 years, the impact of PP amplification evolution on CV mortality is threefold higher in women than in men [13]. The major putative cause of this gender difference is the menopausal change through its effects on large artery behavior and CV events [17]. The loss of estrogenic action in the carotid and brachial arterial wall might play a deleterious role by increasing arterial stiffness and reducing elasticity.

Numerous epidemiological studies have shown that hypertension and diabetes mellitus increase the risk of CV events [18] and modify PP amplification [11]. Nevertheless, a combination of treatments against hypertension and diabetes can be insufficient to cause a substantial reduction in CV mortality and morbidity despite adequate BP and glycemic control [19]. Thus, it is essential to better understand the different modifiable risk factors in high-risk populations that influence PP amplification degree. Several of these arterial factors may be investigated based on the noninvasive determination of PP amplification [6]. The presence of pulsatile and/or steady stress in hypertensive diabetic patients leads to increased SBP and PP from central (thoracic aorta, carotid artery) to peripheral (brachial artery) sites [20]. The factors affecting changes in PP amplification regardless of age and gender have been poorly studied thus far, especially in hypertensive diabetic patients [21]. Thus, the purpose of the present cross-sectional study was to determine the clinical and biological factors of PP amplification in hypertensive and diabetic patients after stratification based on age and gender.

Methods

Overall population

The present study included 646 consecutive patients from December 2012 to September 2017, men and women, with or without previous cardiovascular events. The patients were eligible for inclusion in this cross-sectional study during their follow-up at the Paris Hôtel-Dieu University Hospital. The patients were recruited after follow-up in the Diagnosis and Therapeutic Center of Hôtel-Dieu University Hospital. Most of the patients were in-hospital patients with routine cardiovascular follow-up, and the remaining patients were referred by their general practitioner for a cardiovascular checkup.

Informed consent for additional noninvasive hemodynamic measurements and data collection were provided by the patients during the day-hospital cardiovascular screening. The exclusion criteria were the following: age under 18, acute medical conditions, and atrial fibrillation.

The study complies with the Declaration of Helsinki. The study was registered with the French National Agency for Medicines and Health Products Safety (No. 2013-A00227-38) and was approved by the locally appointed ethics committee, the Advisory Committee for Protection of Persons in Biomedical Research.

Laboratory and clinical parameters

A form filled out at inclusion was used to compile information during the day-hospital for cardiovascular screening and included items on age, gender, weight, and height (which were, respectively, determined using a stadiometer affixed to a wall and a Tanita scale with a digital read-out), BMI (weight (kg) divided by height (m2)) obtained by standardized methods, family (first-degree relatives) history of premature cardiovascular events, personal history of dyslipidemia (defined as a total/HDL-cholesterol ratio > 5 after an overnight fast or the use of a hypocholesterolemic drug), hypertension, smoking habits, previous diseases, and use of medications including antidiabetics obtained through

patients files and self-reporting, lipid-lowering agents, and antihypertensive drugs. Previous cardiovascular events (at least one of coronary and heart disease, cerebrovascular disease, and peripheral vascular disease) were retrospectively assessed using CT-scan imaging; documented stroke for cerebrovascular disease; past medical history of documented myocardial infarction, coronary revascularization, or epicardial coronary artery disease diagnosed during coronary angiogram for patients with symptoms or typical electrocardiographic modifications for coronary heart disease; ankle-brachial pressure index of less than 0.90, imaging-documented atherosclerotic vascular disease, including asymptomatic severe carotid artery stenosis, peripheral vascular disease, and abdominal aortic aneurysm, arterial revascularization, or lower limb amputation were also recorded.

Hypertension status was defined as an SBP of at least 140 mmHg and/or a DBP of at least 90 mmHg, and/or use of an antihypertensive drug, according to European recommendations.

Diabetes mellitus was defined as a glycosylated hemoglobin (HbA1c) ≥ 6.5% and/or fasting glucose level ≥ mmol/l and/or the use of oral hypoglycemic agents or insulin therapy. A total/high-density lipoprotein cholesterol ratio greater than five or the presence of a hypocholesterolemic drug defined dyslipidemia.

Laboratory parameters were determined on the day of the hemodynamic measurements. These parameters included plasma glucose and glycated hemoglobin levels, cholesterol (total, low-density lipoprotein, and high-density lipoprotein) levels, triglyceride levels, plasma creatinine levels, and calculated glomerular filtration rate (cGFR) (calculated according to the MDRD formula, MDRD: modification of diet in renal disease, in units of mL/min/1.73 m2; cGFR < 60 mL/min/1.73 m2 signified kidney failure), as measured using standard methods on a venous blood sample, and the presence of albuminuria (on 24-h urine collection), recorded as normo-albuminuria (< 30 mg/24 h), microalbuminuria (30–300 mg/24 h), and proteinuria (> 300 mg/24 h), as measured from the urine sample.

Hemodynamic parameters

Hemodynamic measurements were performed in supine position in the morning after an overnight fast. Brachial SBP and DBP were measured in both arms using an automatic BP monitor (OMRON 705 CP II IT) with cuffs of appropriate sizes (3 sizes were utilized [22]) after 5 min of rest [23]. Five measurements 2 min apart were averaged, and heart rate was recorded. The first measurement was excluded to reduce the white-coat effect.

After BP determination, noninvasive applanation tonometry was used for measuring the structural and functional parameters of the artery. Application of a generalized transfer function was used to determine central BP components from radial artery applanation tonometry [24]. Mean BP ((systolic BP + 2 × diastolic BP)/3) was defined as the integral of the radial pressure waveform. Brachial SBP and DBP were utilized for radial pressure waveform calibration. PP was defined as the difference: systolic BP − diastolic BP, and PP amplification was represented by the ratio between brachial and carotid PP as follows: (brachial SBP − brachial DBP) / (central SBP − central DBP).

Abdominal aorta, carotid arteries, and lower limb arteries were scanned ultrasonographically for to detect atherosclerosis plaques. A localized echostructure encroaching into the vessel lumen was considered plaque if the common carotid artery intima-media thickness (CCA IMT) was > 50% thicker than that at neighboring sites [25].

Statistical analysis

Student's *t*-test was used for continuous variables (age, BMI, brachial, and central SBP and DBP, mean BP, and biological parameters). Pearson's χ^2 test was performed for categorical variables (gender, clinical parameters and drug treatments). Continuous variables are presented as the mean ± SD. Qualitative variables are expressed as frequencies with percentages.

A generalized linear model, based on significant univariate variables, was performed to highlight the independent factors of PP amplification in our overall study population ($N = 624$). We then stratified our study population into groups by age, gender, and association of hypertension and diabetes status. The effect of age was investigated by separating the population into two age groups (≤ 55 and > 55 years). The threshold of 55 years of age was chosen because of its link with menopause in this analysis [20, 21]. Relationships between the "age and gender" effect and the "hypertension and diabetes status" effect were analyzed using a generalized linear model.

To analyze the independent factors associated with PP amplification, a multivariate analysis was performed using generalized linear model regression. Regression models were obtained by stepwise selection and included all variables that were found to be significantly correlated in a univariate analysis ($P < 0.05$) and based on their pathophysiological plausibility. This forward selection involved starting with no variables in the model, testing the addition of each variable in turn, and adding a variable if its inclusion gives the most statistically significant improvement of the fit; this process was repeated until the inclusion of no variable improved the model to a statistically significant extent. Statistics were performed using SAS software (version 9.4; SAS Institute, Carry, NC). A P value < 0.05 was considered significant.

Table 1 Characteristics of the study population

	Men		Women		Age effect	Gender effect	Age and gender effect	Hypertension effect	Diabetes effect	Hypertension and diabetes effect
	≤55 years	>55 years	≤55 years	>55 years						
N	119	252	77	176						
Age (years)[a]	48 ± 6	67 ± 7	47 ± 6	66 ± 7	—	0.33	—	<0.0001	0.0007	<0.0001
Weight (Kg)[a]	82.1 ± 15.7	82.3 ± 13.5	73.8 ± 15.7	72 ± 15	0.48	<0.0001	<0.0001	<0.0001	<>0.0001	<0.0001
Height (cm)[a]	176 ± 7	173 ± 7	164 ± 7	160 ± 6	<0.0001	<0.0001	<0.0001	0.15	0.14	0.16
Body mass index (Kg/m2)[a]	26.6 ± 4.5	27.5 ± 4.54	27.4 ± 5.44	28.2 ± 5.97	0.06	0.07	0.02	<0.0001	<0.0001	<0.0001
Glycated hemoglobin[a]	6.08 ± 1.39	6.36 ± 1.23	5.9 ± 1.3	6.46 ± 1.51	0.003	0.96	0.006	0.001	<0.0001	<0.0001
Creatinine clearance[b, a]	86.5 ± 19.8	76.5 ± 21.7	86.7 ± 21.8	74.1 ± 19	<0.0001	0.67	<0.0001	0.0004	0.41	0.002
Microalbuminuria (n,%)[c]	15 (13)	49 (19)	6 (8)	18 (10)	0.73	0.21	0.002	0.006	<0.0001	<0.0001
Smokers (n, %)[d]	16 (17.20)	21 (8.90)	4 (6.35)	12 (7.32)	0.10	0.09	0.06	0.05	0.97	0.15
Dyslipidemia (n, %)[e]	32 (27)	102 (41)	15 (20)	56 (32)	0.32	0.003	0.002	0.01	<0.0001	<0.0001
Previous CV events (n, %)	14 (12)	74 (29)	7 (9)	23 (13)	0.001	0.01	<0.0001	0.02	0.28	0.51
Carotid plaques (n, %)	29 (24)	118 (47)	13 (17)	62 (35)	0.0006	0.005	<0.0001	0.03	0.01	0.004
LDL cholesterol (mM/L)[a]	2.01 (1.1)	1.93 (1.1)	1.98 (1.1)	2.34 (1.2)	0.20	0.05	0.01	0.71	0.81	0.91
Cholesterol total (mM/L)[a]	4.9 ± 1.2	4.4 ± 1	5.3 ± 1	5.2 ± 1.1	0.06	0.0001	<0.0001	0.0002	<0.0001	0.25
Systolic BP (mmHg)[a]	131 ± 15	134 ± 16	130 ± 17	134 ± 16	0.01	0.46	0.001	<0.0001	0.005	<0.0001
Diastolic BP (mmHg)[a]	81 ± 10	77 ± 9	78 ± 10	74 ± 9	<>0.0001	<0.0001	<0.0001	<0.0001	0.76	0.005
Mean BP (mmHg)[a]	98 ± 11	97 ± 10	96 ± 12	95 ± 10	0.11	0.02	0.007	<0.0001	0.62	<0.0001
Heart rate[a]	70 ± 13	67 ± 12	71 ± 11	71 ± 11	0.18	0.02	0.008	0.22	<0.0001	<0.0001
Brachial PP (mmHg)[a]	51.5 ± 8.5	57.3 ± 12.8	49.2 ± 11.4	57.8 ± 12.7	<0.0001	<>0.0001	<0.0001	<0.0001	0.0002	<0.0001
Carotid PP (mmHg)[a]	36.1 ± 8.9	43.5 ± 13	37.4 ± 13.4	45.2 ± 13.1	<0.0001	0.0009	<0.0001	<0.0001	0.001	<0.0001
PP amplification[a]	1.43 ± 0.17	1.32 ± 0.15	1.32 ± 0.17	1.28 ± 0.13	<0.0001	<0.0001	<0.0001	0.04	0.0004	0.0002
Hypertensive subjects (n, %)	70 (59)	193 (65)	44 (57)	135 (77)	<0.0001	0.86	<0.0001	—	0.0006	—
Hypertension duration[a]	3.6 ± 6.7	9.8 ± 10.1	4.4 ± 7.2	9.5 ± 10.4	< 0.0001	0.85	<0.0001	—	0.01	<0.0001
Diabetic subjects (n, %)	34 (29)	105 (42)	20 (26)	69 (39)	0.009	0.54	0.003	0.0006	—	—
Diabetes duration[a]	7.4 ± 10.6	11.2 ± 11.8	9.3 ± 12.5	11.1 ± 11	0.06	0.55	0.03	0.12	—	<0.0001
Hypertensive and diabetic subjects (n, %)	23 (19)	89 (35)	13 (17)	55 (31)	<0.0001	0.42	<0.0001	<0.0001	<0.0001	—

CV cardiovascular, *LDL* Low-density lipoprotein, *BP* blood pressure, *PP* pulse pressure

[a]Mean value ±SD

[b]Creatinine clearance using MDRD formula

[c]Microalbuminuria defined as urinary albumin excretion of 30–300 mg/day

[d]Current smokers

[e]Patients receiving lipid-lowering medication or classified as dyslipidemic

The "age effect" was estimated between ≤55 years patients versus >55 years patients. The "gender effect" as estimated between men patients versus women patients

Results

Study cohort

Of the total number of patients who entered into day-hospitalization for a cardiovascular checkup, 22 were excluded because of missing data. Therefore, the study cohort comprised 624 patients, of whom 371 were men (37.5% with diabetes) and 253 were women (35.2% with diabetes). Previous cardiovascular events were present in 118 patients: coronary artery disease in 103 (16.5%), cerebrovascular disease in 15 (3.4%), and myocardial infarction in 55 (8.8%) patients.

Age ($P < 0.0001$), gender ($P < 0.0001$), height ($P = 0.03$), association of hypertension and diabetes ($P = 0.02$), atherosclerosis ($P = 0.04$), and cGFR < 60 ($P = 0.05$) were associated with PP amplification in our overall study population ($N = 624$). In our multivariate analysis, gender ($P < 0.0001$), age ($P = 0.02$), and the association "hypertension and diabetes" ($P = 0.0002$) were independent factors of PP amplification (Supplementary file Table 1).

The characteristics of the overall study population divided by gender and age (threshold of 55 years) are described in Table 1. Mean BP was 97 (± 10.5) mmHg in men and 95 (± 10.7) mmHg in women ($P = 0.02$). PP amplification was 1.35 (± 0.16) in men and 1.30 (± 0.14) in women (< 0.0001). Younger men (≤ 55 years) presented the highest PP amplification (1.43 (± 0.17)), while older women (> 55 years) had the lowest PP amplification (1.28 (± 0.13)). Age and gender were associated with an increase of brachial PP ($P < 0.0001$) and carotid PP ($P < 0.0001$), but with a decrease of PP amplification ($P < 0.0001$) (Table 1). Hypertension and diabetes were associated with an increase of both brachial PP ($P < 0.0001$) and carotid PP ($P < 0.0001$) and with an increase of PP amplification (1.35 ± 0.16 vs. 1.32 ± 0.17, $P = 0.0002$).

The presence of carotid plaque was associated with the hypertensive status ($P = 0.02$), diabetes status ($P = 0.01$), and the association "hypertension and diabetes" ($P = 0.004$). The presence of microalbuminuria was significantly associated with hypertensive status ($P = 0.006$), diabetes status ($P < 0.0001$), and with the association "hypertension and diabetes" ($P < 0.0001$).

Brachial and carotid SBP and Mean BP were higher in hypertensive diabetic patients than in normotensive (diabetic or nondiabetic) patients. PP amplification was higher in patients with diabetes ($P = 0.0004$), with hypertension ($P = 0.04$), and with the association "hypertension and diabetes" ($P = 0.0002$).

Statin therapy was more frequently observed in hypertensive diabetic patients than in the other groups of patients ($P < 0.0001$). Treatment with beta-blockers ($P = 0.04$) or thiazide diuretic ($P = 0.005$) or angiotensin II receptor blockers (ARBs) ($P = 0.02$) were more frequent in hypertensive diabetic patients than in hypertensive nondiabetic patients. No significant difference was observed among hypertensive patients according to treatment with angiotensin-converting enzyme (ACE) or with aldosterone receptor antagonists or calcium blockers.

One hundred seventy-one (75%) diabetic patients with or without hypertension were on oral antidiabetic drugs, 63 (28%) were on insulin therapy alone and 34 (15%) were on both oral treatment and insulin therapy.

Determinants associated with PP amplification

Univariate analysis of determinants associated with PP amplification

Determinants associated with PP amplification in the different groups are presented in Supplementary file Table 2.

Women showed a significant decrease in PP amplification compared to men ($P < 0.0001$). In both men and women, hypertensive diabetic patients presented higher PP amplification than hypertensive nondiabetic patients after adjusting for age, height, and mean BP ($P = 0.01$, $P = 0.001$, respectively) (Fig. 1).

Multivariate analysis of determinants associated with PP amplification

In the overall study population, in both men and women, regardless of age (Table 2 and Table 3), HbA1c levels ($P < 0.05$) appeared as independent factors of PP amplification with a positive correlation. In men > 55 years ($P = 0.0001$) and women > 55 years ($P = 0.03$), PP amplification was correlated negatively with mean BP.

In hypertensive nondiabetic patients, mean BP appears as an independent factor of PP amplification with a negative correlation in men < 55 years ($P = 0.002$), in men > 55 years 0.04), and in women < 55 years ($P = 0.04$), whereas PP amplification was correlated negatively only with cGFR < 60 in women > 55 years ($P = 0.04$).

PP amplification was correlated positively with HbA1c levels in hypertensive diabetic men < 55 years ($P = 0.03$), men > 55 years ($P = 0.04$) and women < 55 years ($P = 0.04$), whereas mean BP was correlated negatively with PP amplification in hypertensive diabetic men > 55 years ($P = 0.0009$). cGFR < 60 appears as an independent factor of PP amplification with a negative correlation in hypertensive diabetic men < 55 years ($P = 0.03$), men > 55 years ($P = 0.04$) and women > 55 years ($P = 0.04$).

When antihypertensive treatment was included in the multivariate analysis, in hypertensive diabetic men > 55 years, ARBs treatment ($P = 0.03$) was correlated positively with PP amplification. No correlation was found

between the treatments and all hypertensive diabetic women or hypertensive diabetic men < 55 years.

Discussion

After stratification for age and gender, two factors (HbA1c levels and cGFR threshold) appear as independent modifiable risk factors of PP amplification in the high-risk population of hypertensive and diabetic patients. HbA1c levels appear as an independent factor of the modulation of PP amplification in the overall study population and in hypertensive diabetic men and younger women. Similarly, cGFR threshold may be considered an independent factor of PP amplification modulation in older hypertensive nondiabetic and hypertensive diabetic women, as well as in hypertensive diabetic men. However, mean BP is an independent factor of the modulation of PP amplification in hypertensive nondiabetic patients after stratification for age and gender.

Carotid BP and brachial BP are noninvasive methods for hemodynamic assessment, but each method is focused on one aspect of the regulation of BP and blood flow. In hypertensive patients, both blood flow and steady pressure are responsible for potential organ damage [26].

Pulsatile and dynamic hemodynamics are well represented by PP amplification as an indirect marker of forward and backward wave and circulatory volume. By integrating pulsatile and steady components of arterial circulatory system regulation, PP amplification may represent a superior noninvasive marker to brachial BP measurement for hemodynamic profiling.

Age had an important role in the modulation of PP amplification in our study by lowering PP amplification in our overall study population ($P < 0.0001$). Aging has numerous effects on the heart and arterial tree. The progressive loss of the elasticity of large arteries leads to an elevation of central PP and a reduction in PP amplification [27]. Carotid BP is negatively modulated by aging to a greater extent than brachial BP from young adults to elderly people [28, 29].

Previous studies have shown that women present a lower PP amplification than men; this was also true in our study (in the total population: −4.5%, $P < 0.0001$) [30, 31]. BP presents distinct characteristics in women and men [13, 32]. Body composition and the circulatory system differ between men and women. Women are shorter and have a higher heart rate leading to increased systolic central peak. Moreover, the body fat distribution and patterns of vascular reactivity to stress may play a role in the gender difference of hemodynamic regulation [17, 33].

HbA1c > 6.5% is associated with increased aortic stiffness [34, 35] but appears to have little association with central BP [36]. The association between HbA1c levels and

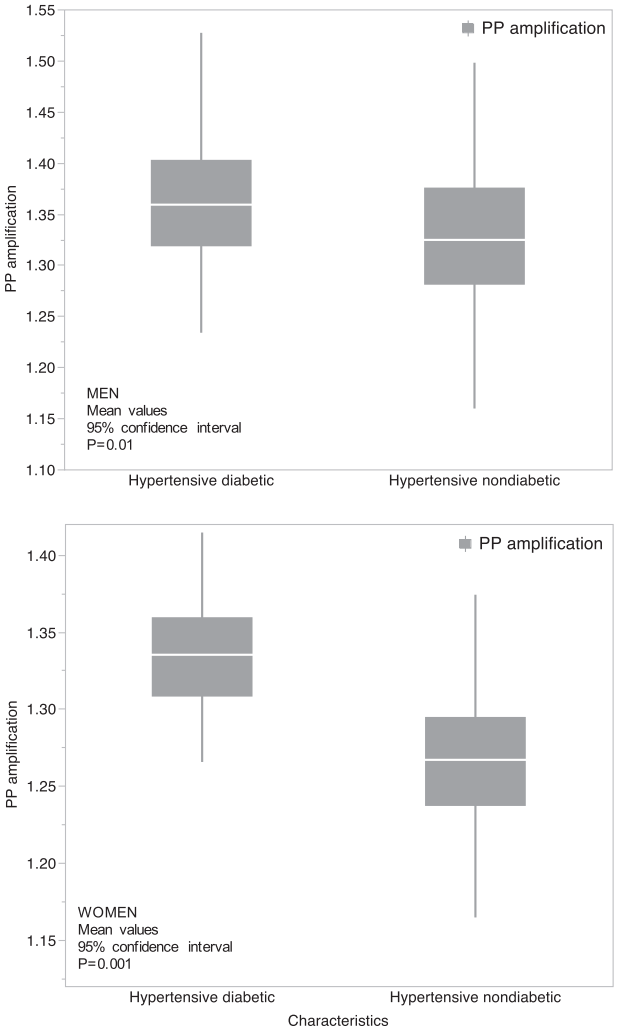

Fig. 1 Age-height and mean blood pressure-adjusted pulse pressure amplification in men and women.

the increase of PP amplification in our overall population is consistent with previous studies, which showed that type 2 diabetes is associated with increased PP amplification [11].

More specifically, in our hypertensive diabetic population, there was a significant correlation between HbA1c levels and PP amplification in comparison to the hypertensive nondiabetic population. Nevertheless, the mechanism relating type 2 diabetes and PP amplification remains unclear. However, increased plasma glucose levels stimulate the production of advanced glycation end-products (AGEs). These molecules contribute to the mechanism modulating the stiffening of arteries with age [37]. The stiffening of large arteries appears to contribute to the reduction of PP amplification ($P = 0.03$) [38].

Previous studies have shown that PP amplification was lower in patients with chronic kidney diseases (CKD) [39, 40], and this was observed regardless of age and gender in our study for the group of hypertensive and diabetic men with cGFR < 60 mL/min/1.73 m2 (< 55 years,

Table 2 Multivariate linear regression: significant factors of PP amplification in the different men groups of the study

Overall study population	≤55 years		R^2 model = 0.26		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.08	0.04 [0.005; 0.08]	0.03
		CV events (no)		−0.03 [−0.13; 0.06]	0.48
		cGFR(< 60)		−0.12 [−0.01; 0.25]	0.08
	>55 years		R^2 model = 0.34		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.08	0.02 [0.007; 0.04]	0.01
		Mean BP	0.04	−0.004 [−0.006; -0.001]	0.0001
		cGFR (< 60)		−0.02 [−0.05; 0.003]	0.07
		CV events (no)		−0.01 [−0.06; 0.007]	0.11
		Dyslipidemia (no)		−0.02 [−0.05; 0.01]	0.22
Hypertensive diabetic patients	≤55 years		R^2 model = 0.43		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.10	0.07 [0.06; 0.08]	0.03
		cGFR (< 60)	0.18	−0.14 [−0.23; −0.04]	0.03
		BMI		0.006 [−0.03; 0.01]	0.62
	>55 years		R^2 model = 0.42		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.15	0.03 [0.02; 0.04]	0.04
		cGFR (< 60)	0.08	−0.04 [−0.07; −0.02]	0.04
		Height		0.0004 [−0.005; 0.001]	0.80
		Waist circumference		0.002 [−0.001; 0.008]	0.11
		Mean BP		−0.007 [−0.002; 0.001]	0.12
		Atherosclerosis (no)		0.05 [−0.01; 0.08]	0.24
Hypertensive nondiabetic patients	≤ 55 years		R^2 model = 0.30		
		Term	Partial r^2	Coefficient (CI)	*P* value
		Mean BP	0.13	−0.009 [−0.015; −0.001]	0.002
		MI (no)		−0.04 [−0.08; 0.01]	0.62
		CAD (no)		−0.007 [−0.01; 0.002]	0.92
	>55 years		R^2 model = 0.69		
		Term	Partial r^2	Coefficient (CI)	*P* value
		Mean BP	0.10	−0.004 [−0.009; −0.001]	0.04
		Atherosclerosis (no)		−0.02 [−0.06; 0.02]	0.71

HbA1c glycated hemoglobin, *BP* blood pressure, *cGFR* calculated glomerular filtration rate, *CV events* cardiovascular events, *MI* myocardial infarction, *CAD* coronary artery disease, *BMI* body mass index

$P = 0.03$ and > 55 years, $P = 0.04$) and women (> 55 years, $P = 0.04$).

Several studies have shown that PP amplification is mainly decreased by an increase in central systolic BP in relation to an age-related increase of both arterial stiffness and wave reflections [39, 41]. In a recent study, patients with cGFR < 60 mL/min/1.73 m2 presented a higher central PP (43.0 ± 11.4 vs 39.7 ± 10.0 mmHg, $P < 0.001$) than the control group [42]. Stratification according to CKD stage has shown that PP amplification declines with advancing CKD, although the last stages present an elevation of PP amplification [39]. CKD may act through an accelerated vascular aging factor leading to an increase of PP amplification and can be considered a risk factor for CV morbidity and mortality [43]. However, the determinants of increased central hemodynamic parameters in moderate-to-severe CKD remain unclear even if vascular calcification appear to be a major mediator [44, 45]. Nevertheless, the increase of central BP could also participate in CKD progression [42]. As arterial stiffness increases, the low impedance and resistance of afferent arterioles lead to renal microcirculation. Pulsatile stress and wide variations of systolic and diastolic flows contribute to vasoconstriction and increased resistance [46, 47]. Arterial stiffness also increases BP

Table 3 Multivariate linear regression: significant factors of PP amplification in the different women groups of the study

Overall study population	≤55 years		R^2 model = 0.11		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.04	0.03 [0.02; 0.04]	0.04
		Dyslipidemia (no)		−0.01 [−0.06; 0.04]	0.68
	>55 years		R^2 model = 0.14		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.04	0.05 [0.04; 0.06]	0.0002
		Mean BP		−0.002 [−0.004; 0.001]	0.13
		CAD		−0.02 [−0.06; 0.02]	0.52
		Kaliuresis		−0.0006 [0.002; 0.0002]	0.38
Hypertensive diabetic patients	≤55 years		R^2 model = 0.43		
		Term	Partial r^2	Coefficient (CI)	*P* value
		HbA1c	0.20	0.02 [0.01; 0.03]	0.04
		cGFR (< 60)		−0.04 [−0.06; 0.01]	0.49
		Mean BP		−0.002 [−0.006; 0.001]	0.13
		Height		0.009 [−0.002; 0.01]	0.35
	>55 years		R^2 model = 0.21		
		Term	Partial r^2	Coefficient (CI)	*P* value
		cGFR (< 60)	0.08	−0.03 [−0.06; −0.02]	0.04
		Mean BP		−0.003 [−0.006; 0.001]	0.28
		Height		0.002 [−0.001; 0.005]	0.64
		Dyslipidemia (no)		−0.01[−0.03; 0.02]	0.54
		Atherosclerosis (no)		−0.02 [−0.04; 0.05]	0.57
Hypertensive nondiabetic patients	≤55 years		R^2 model = 0.19		
		Term	Partial r^2	Coefficient (CI)	*P* value
		Mean BP	0.12	−0.0001 [−0.002; −0.00001]	0.04
		Preious CV events (no)		−0.08 [−0.27; 0.02]	0.33
		Atherosclerosis (no)		0.04 [−0.05; 0.14]	0.88
	>55 years		R^2 model = 0.13		
		Term	Partial r^2	Coefficient (CI)	*P* value
		cGFR (< 60)	0.10	−0.05 [−0.08; -0.01]	0.04
		Previous CV events (no)		−0.03 [−0.06; 0.02]	0.28
		Mean BP		−0.001 [−0.02; 0.01]	0.31

HbA1c glycated hemoglobin, *BP* blood pressure, *cGFR* calculated glomerular filtration rate, *CV events* cardiovascular events, *MI* myocardial infarction, *CAD* coronary artery disease, *BMI* body mass index

variability by diminishing baroreflex sensitivity and arterial wall elasticity enhancing renal flow pulsatility and vascular damage. A recent study has suggested that aortic blood flow reversal caused by aortic stiffening can reduce blood flow into the kidney [48]. These results infer that central hemodynamic effects of arterial stiffness depend on CKD stages due to progressive parenchymal damage and structural remodeling. Moreover, in our study, CKD appears as an independent factor of decreased PP amplification in hypertensive diabetic patients but not in hypertensive nondiabetic patients. However, the relationship between CKD and PP amplification in patients with diabetes remains unknown. Type 2 diabetes is associated with enlarged brachial PP; however, when the age and CKD status of diabetic patients is taken into consideration, the values of brachial PP appear lower [49].

Class-effects of drugs on PP amplification

A recent study has shown that central PP and PP amplification can be modulated by pharmacological treatments wherein both wave reflections and heart rate account for the class-effect of antihypertensive drugs on PP amplification [50]. ARB therapy was positively correlated with PP amplification in hypertensive diabetic men > 55 years ($P = 0.04$). In this population, the use of ARB therapy was associated with increased PP amplification (no, PPA = 1.29 ± 0.11 vs yes, PPA = 1.35 ± 0.15, $P = 0.03$) according to other studies (the drug candesartan increased PP amplification, + 3.0% ± 14.6%, $P = 0.02$) [51].

Diabetes and PP amplification

In the present study, hypertensive diabetic patients presented with disproportionately increased PP amplification after stratification for age and gender when compared to the hypertensive nondiabetic patient groups. Similarly, several studies have shown that diabetic patients presented the highest increases in aortic stiffness [52]. These two parameters appear to be independently associated with the presence of previous cardiovascular events and numerous cardiovascular risk factors [53, 54]. However, they are partly not interrelated [11]. These findings may reinforce a global message on arterial

damage based on the evaluation of these two independent markers.

Limitations

The cross-sectional design of our study may appear as a limitation; for this reason, only simple correlations between factors and PP amplification, not causal interferences, are presented.

The pharmacological remodeling of small and large arteries can be characterized as a long-term process. In our study, the treatment duration of statin therapy and antihypertensive drug classes has not been considered because of a lack of relevant data. The prescription of a drug may reflect increased arterial damage and does not necessarily imply any direct effect on the amplification phenomenon described in the current study. This might explain why we were unable to find an association between lipid-lowering and more antihypertensive treatments with PP amplification, although these drugs have numerous effect on BP parameters [55].

Moreover, the potential confounding factor of antihypertensive drug class effects must be considered in relation to the hypertensive patients. PP amplification is a complex hemodynamic mechanism and is mainly related to heart rate and wave reflections. Additionally, the heterogeneity among beta-blocker therapies has not been considered. Indeed, newer beta-blocker treatments with peripheral vasodilatory effects might act differently on PP amplification and may reduce pressure wave reflection and partially counterbalance the effect of heart rate deceleration.

Conclusion

HbA1c level appears as a major factor that modulated the calculation of PP amplification in the overall study population and in hypertensive diabetic patients; however, this mechanism remains unclear. PP amplification may reflect pulsatile components of the arterial wall and vessel response to BP. PP amplification might represent one of the main candidates for central hemodynamic and cardiovascular risk assessment. However, PP amplification and aortic stiffness are partly independent and may appear as complementary factors of cardiovascular risk. In hypertensive diabetic patients, cGFR levels > 60 mL/min/1.73 m2 are correlated with a lower PP amplification. Also in hypertensive diabetic patients, the presence of chronic kidney disease, represented by the threshold cGFR value of < 60 mL/min/1.73 m2, may appear as a generator of increased cardiovascular risk, regardless of age and gender.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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