Aortic stiffness and central hemodynamics in treatment naïve HIV infection: A cross-sectional study

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Abstract

Background: Human immunodeficiency virus (HIV) infection is associated with a greater risk of cardiovascular disease (CVD). HIV infection causes a chronic inflammatory state and increases oxidative stress which can cause endothelial dysfunction and arterial stiffness. Aortic stiffness measured by carotid femoral-pulse wave velocity (cfPWV) and central hemodynamics are independent cardiovascular risk factors and have the prognostic ability for CVD. We assessed cfPWV and central hemodynamics in young individuals with recent HIV infection diagnosis not receiving antiretroviral therapy. We hypothesized that HIV individuals would present greater cfPWV and central hemodynamics (central systolic blood pressure and pulse pressure) compared to uninfected controls.

Methods. We recruited 51 treatment naïve HIV individuals (HIV(+)) without previous CVD and 51 age- and sex-matched controls (HIV(-)). We evaluated traditional CVD risk factors including metabolic profile, blood pressure (BP), smoking, and immune state. Arterial stiffness and central hemodynamics were evaluated by cfPWV, central systolic BP and central pulse pressure (cPP) via applanation tonometry.

Results. HIV(+) individuals presented a greater prevalence of smoking, reduced high density lipoprotein cholesterol, and body mass index. 65.9% of HIV(+) individuals exhibited lymphocytes <500 cell/μL. There was no difference in brachial or central BP between groups; however, HIV(+) individuals showed significantly lower cPP. We observed a greater cfPWV (mean difference= 0.5 m/s; $p<0.01$) in HIV(+) compared to controls, even after adjusting for heart rate, mean arterial pressure and smoking.

Conclusion: In the early stages of infection, non-treated HIV individuals present a greater prevalence of traditional CVD risk factors, arterial stiffness, and normal or decreased central hemodynamics.

1. Introduction

Cardiovascular disease (CVD) is one of the most common causes of death among individuals infected with human immunodeficiency virus (HIV), with greater risk for myocardial infarction[1], ischemic stroke[2], and heart failure[3]. Furthermore, an accelerated rate of arterial stiffening has been reported after HIV infection, possibly due to the acute[4] and chronic inflammatory response[5], lipid disorders[6, 7], oxidative stress[8], and the adverse effects of some antiretroviral therapies (ART). The complex associations between chronic infection, inflammation, and endothelial function have long been studied, but the underlying mechanisms by which HIV infection per se increases the risk for CV disease are not completely understood. HIV is capable to penetrate and to initiate inflammatory and biochemical intracellular reactions in the endothelial cells of the coronary arteries[9], the cerebral vasculature[10], and the aortic wall[11]. Moreover, aortic stiffness is associated with coronary artery disease[12, 13] and is an independent predictor of coronary events[14], but there are contradictory findings on aortic stiffness measured by carotid-femoral pulse wave velocity (cfPWV) in the setting of recent HIV diagnosis without ART.

Identification of subclinical changes in the CV system, such as arterial stiffness and central hemodynamic assessment, is essential for a more accurate CV risk classification. Numerous studies have shown that arterial stiffness measured by cfPWV is an independent risk factor for CV events[15] and all-cause mortality[16, 17]. In addition, central hemodynamic assessment (central systolic blood pressure [cSBP] and central pulse pressure [cPP]), better reflect the load imposed on the left ventricle. The non-invasive central hemodynamic assessment has been reported to have a stronger relationship to organ and vascular damage, as well as to better predict CV events compared to peripheral pressures[18, 19]. A significant amount of available literature looking at cfPWV in HIV combines both individuals on ART and treatment naïve [20-22]. As a result, the impact of HIV infection per se on arterial function is not clear. For this reason, the objective of this study was to non-invasively assess and compare arterial stiffness and central hemodynamic in non-previously treated (treatment naïve) HIV positive patients versus HIV negative individuals.

2. Material And Methods

2.1 Study population

Between January 2015 and August 2019, HIV infected patients were enrolled from the “Antiguo Hospital Civil de Guadalajara” in Guadalajara, Mexico. Uninfected volunteers were recruited from our local network of researchers and volunteers within the University of Guadalajara. Informed consent was obtained from every participant. The study complies with the Declaration of Helsinki and was approved by the ethics committee of the Hospital Civil Fray Antonio Alcalde. Inclusion criteria included: a) Patients with 18 years of age or older with confirmed HIV infection and without previous ART, b) Absence of current or previous rheumatological, neoplastic, or CVD; c) Without opportunistic infections at the time of enrolment. At study entry, participants' past medical history and demographic information were obtained.

2.2 Arterial stiffness

Arterial stiffness was measured by cfPWV as described previously[23] by applanation tonometry (PulsePen, Diatechne, Milan, Italy). cfPWV was calculated as the time delay between the arrival of the pulse wave at the carotid and the femoral artery, divided by the distance between carotid and femoral arteries, with previous subtraction of the segment between the carotid and the sternal notch. All measurements were performed by a single trained technician in a temperature-controlled room. The participants rested in a supine position for 15 minutes before the assessment and were instructed to abstain from smoking, alcoholic, or caffeinated beverages 24 hours before the evaluation. Two consecutive measurements were performed, and the average cfPWV was used if the difference was lower than 0.5 m/s. Otherwise, a third measurement was obtained, and the median of the three measurements was used for analysis[24]. cSBP was estimated by applanation tonometry on the right carotid artery and calibrated with brachial diastolic blood pressure (pDBP) and mean arterial pressure (MAP) obtained by an automated sphygmomanometer (Omron HEM-907XL). MAP was calculated as MAP = pDBP + peripheral pulse pressure (pPP)0.33. cPP was determined as cPP = cSBP - pDBP.

2.3 Immune state evaluation and serum lipids

A venous blood sample was obtained from the antecubital vein after 8-hour fasting. T $CD4^+$ lymphocyte count was performed by flow cytometry (FACScalibur System, Becton Dickinson) and viral count with real-time polymerase chain reaction with retro transcription (Cobas AmpliPrep/Cobas Taqman, Roche Diagnostics). Serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG) were determined by colorimetric quantification (AU5800 autoanalyzer, Coulter Beckman, USA). Plasma glucose was determined by photometry ((AU5800 autoanalyzer, Coulter Beckman, USA).).

2.4 Statistical analyses

Values are presented as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the data distribution. Continuous data were compared using unpaired t-test or Mann-Whitney's test if normally or not normally distributed, respectively. A Chi-square test was used to compared categorical variables. A generalized linear model was used to adjust cfPWV to confounding factors. Statistical analysis was performed using SPSS v.24 (IBM Chicago, IL) and for graphical representation, we used GraphPad Prism version 6.0 (Graph Pad Software, San Diego, California, USA). We calculated the sample size to be 35 in each group at an alpha of 0.05 and a power of 90%, based on the study conducted by Schillaci et al.[25]. Power calculation was performed using GPower 3.1.9.2.[26]. A two-sided p-value of <0.05 was considered significant.

3. Results

We recruited 102 participants; 51 treatment-naïve HIV(+) individuals and 51 HIV negative (-) participants. HIV(+) individuals did not show evidence of opportunistic infections on the day of the assessment. Serum lipids and immune assessment were obtained from 51 individuals in the HIV(+) group and from 35 individuals in the control group. Clinical characteristics and hemodynamic values are shown in Table 1. There were no significant group differences regarding age, TG, or LDL-c. We observed a significantly higher prevalence of smoking, greater heart rate (HR) ($p<0.05$), and lower body mass index (BMI) ($p<0.05$) in HIV(+). We also found a tendency for lower TC ($p=0.08$) but significantly lower HDL-c in the HIV(+) group compared to HIV(-). Regarding the immune state, 65.9% of HIV(+) presented lymphocytes <500 cell/µL. We did not observe differences in peripheral (pSBP, MAP, and pDBP) or cSBP between groups. In the HIV(+) group, pPP showed a tendency to be lower, and cPP was significantly reduced compared to the HIV(-) group (Figure 1). HIV(+) individuals exhibited greater cfPWV (mean difference= 0.5 m/s; 95% CI 0.2 to 0.86) compared to the uninfected group, even after adjustment for MAP, HR and current smoking (Table 2).

Table 1. Demographic, hemodynamic, metabolic and immune characteristics of the study groups.

	HIV(-) (n=51)	HIV(+) (n=51)	P value
Age, years	31.9 ± 10.2	33.4 ± 9.9	0.44
Male sex, n (%)	45 (86)	45 (90)	0.56
Weight, kg	74 ± 13	66 ± 10	**<0.01**
Cigarette smoking, n (%)	12 (23.5)	32 (62.7)	**<0.01**
BMI, kg/m^2	24.8 ± 3.3	23.2 ± 4.0	**0.04**
Hemodynamic			
pSBP, mmHg	117.8 ± 10.3	115.1 ± 12.9	0.24
pDBP, mmHg	64.5 ± 8.7	65.4 ± 8.8	0.59
MAP, mmHg	82.7 ± 8.3	82.3 ± 8.8	0.82
HR, bpm	65.7 ± 11.9	71.2 ± 13.7	**0.03**
pPP, mmHg	53.2 ± 9.4	49.6 ± 9.2	0.05
Metabolic profile			
TC, mmol/L	4.1 (3.5 to 4.7)	3.7 (3.1 to 4.4)	0.05
LDL-c, mmol/L	2.5 (1.9 to 2.9)	2.2 (1.8 to 2.7)	0.29
HDL-c, mmol/L	1.1 (1.0 to 1.3)	0.8 (0.7 to 0.9)	**<0.01**
TG, mmol/L	1.2 (0.9 to 1.6)	1.4 (0.9 to 2.1)	0.25
Glucose, mmol/L	5.0 (4.7 to 5.3)	4.7 (4.4 to 5.2)	**0.04**
Immune profile			
T CD4, cel/µL	-	496 ± 298	
Viral load, copies/mm^3	-	70,250 (1173 to 2'279,000)	

Values are mean±SD and median (IQR). BMI, body mass index; pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure, MAP, mean arterial pressure; HR, heart rate; pPP, peripheral pulse pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; T CD4, lymphocytes T CD4.

Table 2. Central hemodynamics and arterial stiffness between groups.

	HIV(-)	HIV(+)	p-value
cSBP, mmHg	107.6 ± 9.8	105.3 ± 12.4	0.23
cPP. mmHg	42.5 (36 to 52)	39 (31 to 47)	**0.03**
cfPWV, m/s	6.7 ± 1.0	7.3 ± 1.1	**0.04**
cfPWV, m/s (SE)[a]	6.8 (0.14)	7.4 (0.14)	**<0.01**

Values are mean±SD and median (IQR). cSBP, central systolic blood pressure; cPP, central pulse pressure, cfPWV, carotid-femoral pulse wave velocity. [a]Adjusted for MAP, HR, and current smoking. SE, standard error.

4. Discussion

In this study, we found that treatment-naïve HIV(+) individuals present greater arterial stiffness compared to age- and sex-matched controls. This difference remained significant after adjusting for HR, MAP, and current smoking. Despite a greater cfPWV, we paradoxically also found a tendency for lower brachial and central pulse pressure in the HIV(+) group. The results of this study replicate previous findings on the harmful effect on HIV infection itself on the arterial vasculature. Furthermore, this is the first study assessing arterial stiffness in HIV infected Mexican individuals. It is important to establish the effect of chronic infectious diseases in different populations such as HIV, given that the immune activation has been reported -in some studies- to vary between ethnicities[27]. For example, compared to Caucasians, Hispanic individuals have been reported to present a greater prevalence of diabetes and insulin resistance[28] and greater average years of life lost after HIV infection[29]. Currently, it unknown whether Latin-American individuals with HIV infection could develop, to a greater degree, metabolic abnormalities secondary to inflammation and accelerated arteriosclerosis[30].

4.1 Arterial stiffness

In our study, cfPWV was significantly greater in HIV treatment-naïve individuals, which agree with the findings reported by other groups in non-treated HIV infection[31-34], while others have reported similar cfPWV in non-treated HIV individuals versus controls[21, 35, 36]. Schillaci et al.[37] found a lower BMI, HDL-c, and a higher TG and cfPWV in HIV(+) individuals without ART. A greater aortic stiffness in the setting of recently diagnosed HIV infection could be a combination of functional and structural changes in the arterial wall. The development of arterial stiffness is a complex phenomenon where different factors intervene, such as endothelial dysfunction, smooth muscle vascular tone, and structural changes. For example, one of the mechanisms that regulate endothelial function is nitric oxide (NO). NO produces vasodilation, inhibits inflammation, and prevents thrombosis[38]. Chronic inflammation and greater oxidative stress impair NO by reducing its bioavailability; both processes present during HIV infection[39, 40]. For instance, Clapp et al.[8] reported that after the administration of the typhoid vaccine, inflammatory cytokines increase, and anti-oxidant capacity decreases, resulting in endothelial

dysfunction. Furthermore, Zhou et al. conducted a study in antioxidant (superoxide dismutase) knock-out mice where they found that the mice lacking the antioxidant exhibited progressively greater PWV over time compared to the wild type mice[41]. In individuals with HIV, it has been reported a reduction of the antioxidant glutathione in the early stages of infection[42], total antioxidant capacity, and increased peroxidation potential[43]. Furthermore, in a previous study from our laboratory, we had similar findings as Schillaci et al.[25], where serum gamma-glutamyl transpeptidase, a serum enzyme associated with insulin resistance, liver disease, and oxidative stress, was positively correlated with arterial stiffness[44].

One of the mechanisms by which non-treated HIV infection may cause arterial structural changes is through the dysregulation of matrix metalloproteinases (MMPs). MMPs are a group of endopeptidases that degrade components of the extracellular matrix, including the arterial wall's collagen, elastin, laminin, and fibrillin. Specifically, MMP-9 (gelatinase B) and MMP-2 have been associated with vascular remodeling [45]. Both endopeptidases can break down the elastic component of the arterial wall (i.e., elastin) and have been positively associated with aortic PWV in individuals with isolated systolic hypertension[46]. One in vitro study reported that HIV-infected macrophages upregulate the secretion of MMP-9 by 3.1-fold compared to non-infected macrophages. More specifically, the HIV-derived proteins, envelope glycoprotein 120 (gp120), and Tat protein have been reported to stimulate MMP-9 expression[47, 48]. Although these endopeptidases were not assessed in our study, this mechanism could partially explain our findings regarding greater cfPWV.

The degree of immunosuppression has been linked to the development of atherosclerosis, due to impairment of cholesterol efflux in HIV infected macrophages and arterial stiffness[49]. In our HIV cohort, we observed that 63.6% of individuals had a lymphocyte T $CD4^+$ count <500 cell/mm3, which may indirectly indicate a long-standing HIV infection before diagnosis; thus, a chronic and more detrimental effect on the vasculature.

4.2 Central hemodynamics

Regarding central hemodynamics, we found a significantly lower cPP but only a tendency in pPP in HIV(+) compared to the uninfected group. These results are likely caused by a combination of a slightly reduced cSBP and pSBP and higher pDBP in HIV(+). A slight decrease in cSBP, despite greater PWV, may be explained by peripheral vasodilation (small and medium-sized arteries), possibly due to the vasodilating effect of prostaglandins[50, 51] through a NO-independent mechanism[52] and inflammatory cytokines (i.e., interleukin 1beta)[53] which are increased after HIV infection. This vasodilation effect on peripheral reflection sites (e.g., arterial bifurcations) might cause a decreased reflection of the backward wave and reduced contribution to cSBP[54]. However, Maloberti et al.[55] found no difference in cPP between controls and HIV(+) receiving ART or treatment naïve. Only HIV individuals who received ART and presented chronic kidney disease had significantly greater cPP compared to HIV(-). The lack of difference in their study might be due to underpowered sample size to detect differences in cPP, as their HIV subgroup comparison was relatively small. Likewise, Vlachopoulos et al.[35] reported similar cPP and cfPWV; however, they observed a reduced cSBP compared to uninfected individuals.

4.3 Lipid metabolism

Abnormal lipid metabolism after HIV infection can be caused by the HIV infection itself, chronic inflammation, and ART. The greater arterial stiffness could be explained by dyslipidaemia observed in the HIV(+) naïve group. Alterations in lipid metabolism have been mainly associated with ART, specifically protease inhibitors[56, 57]. However, lipid abnormalities have also been reported in HIV treatment-naïve individuals, identified as low HDL-c and TC, and increased TG.[6] In this study, we found a tendency for lower TC and significantly lower HDL-c compared to uninfected controls. The majority of HIV(+) individuals in our study presented low HDL-c (<1.04 mmol/L) (78.2% vs. 21.8%) and TC below 5.2 mmol/L (60.8% vs. 39.2%) compared to the HIV(-) group, respectively. From the traditional risk factor point of view, HDL-c plays an essential role in the development of CVD in HIV. HDL-c provides atherogenic protection, defends the vasculature against inflammation[58] and oxidative stress[59], and helps to preserve endothelial function[60, 61]. A large cohort study in the U.S. found that HDL-c levels <1.04 mmol/L were associated with greater carotid stiffness compared to patients with normal or >1.04 mmol/L HDL-c levels[49].

Previous findings of the effect of HIV on arterial stiffness have not been consistent. This can be due to several causes, including a pooled comparison of individuals receiving and not receiving ART and different methodologies to assess arterial stiffness such as ultrasound-based carotid-brachial PWV[53] and one point PWV[62, 63]. By exploring treatment-naïve HIV infected individuals, this study allowed us to exclude the negative effect of ART on the arterial system and evaluate the impact of HIV infection itself and traditional risk factors as potential etiologies. However, our study has several limitations. Due to its cross-sectional design, we were unable to establish a causal relationship. The smoking history was statistically adjusted, and we were not able to assess biomarkers of inflammation or vascular disease, which have been associated with future CV events, like highly-sensitive C-reactive protein[64, 65]. Additionally, waist measurements were not available to establish the presence of metabolic syndrome. Prospective studies are needed to further clarify the molecular mechanisms involved in CVD after HIV infection and the effect of different ART combinations to reduce cardiovascular mortality in this population.

5. Conclusion

Our study provides evidence that, in the early stages, non-treated HIV infected individuals present greater arterial stiffness and prevalence of traditional CVD risk factors compared to non-infected controls. Paradoxically, central hemodynamics appears to remain unchanged or present a favourable profile.

Abbreviations

HIV: Human Immunodeficiency virus; CVD: cardiovascular disease; cfPWV: carotid-femoral pulse wave velocity; HIV(+): HIV positive; HIV(-): HIV negative; ART: antiretroviral therapy; MAP: mean arterial pressure; BP: blood pressure; SBP: systolic blood pressure; pDBP: diastolic blood pressure; cPP: central pulse

pressure; pPP: peripheral pulse pressure; HDL-c: high density lipoprotein cholesterol; TC: total cholesterol; LDL-c: low density lipoprotein cholesterol; TG: triglycerides; HR: heart rate; BMI: body mass index; CI: confidence interval.

Declarations

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Author’s contributions

PM-A, GAA-S, CR-B, DC-M, LAG-H, JFA-V, ST-S and EGC-M conceptualized and designed the study methodology. DAC-Z, CR-B and GAA-S performed the vascular assessments. GAA-S, RIC-S, KS-R, MA-Z, MR-S, and DAC-Z performed data curation and formal analysis was conducted by GAA-S, PM-A, CR-B, and RIC-S. GAA-S and PM-A drafted the original manuscript. PM-A, RIC, KS-R, MA-Z, LAG-H, EGC-M , JFA-V reviewed and edited the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The University of Guadalajara ethics committee approved the study and full informed written consent was obtained for all participants. Approval number 208/15.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

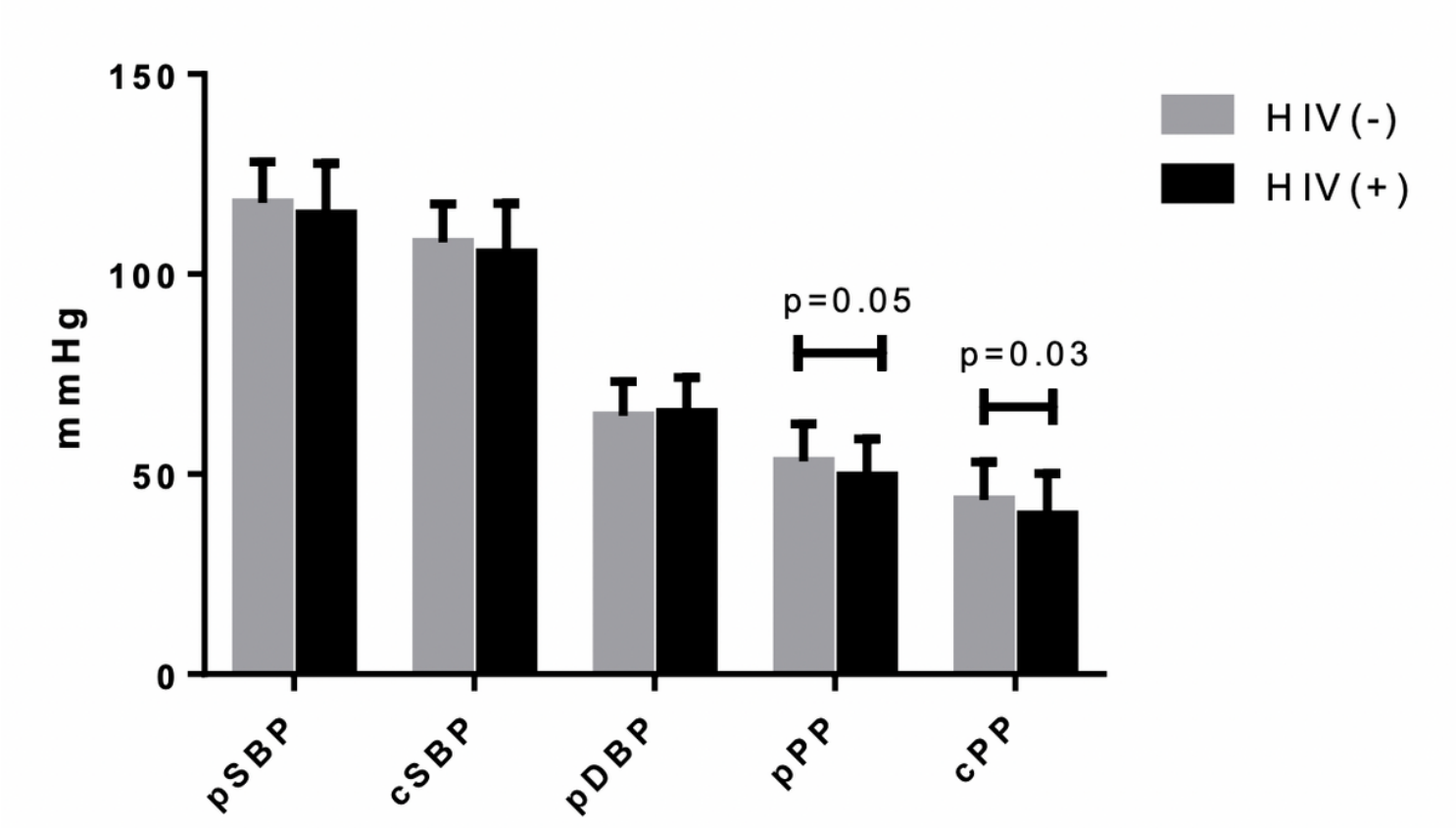

Figure 1

Peripheral and central hemodynamic parameters between HIV(+) and HIV(-) controls. pSBP, peripheral systolic blood pressure; cSBP, central systolic blood pressure; pDBP, peripheral diastolic blood pressure; pPP, peripheral pulse pressure; cPP, central pulse pressure.