Hypertension Research (2015) 38, 405–412

www.nature.com/hr

ORIGINAL ARTICLE

Brachial and central blood pressure in HIV-infected subjects

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HIV infected subjects present an unfavorable cardiovascular (CV) risk profile that is determined by the infection itself, highly active anti-retroviral therapy (HAART) and other factors, such as chronic kidney disease (CKD). Information is scant and contradictory on whether these factors are associated with arterial stiffness and blood pressure (BP) alteration. Our study aimed to evaluate those parameters in HIV-positive subjects both with and without HAART and with and without CKD, which was defined as the presence of microalbuminuria with a normal glomerular filtration rate. We enrolled 94 HIV-infected subjects without known CV risk factors and compared them with 37 control subjects. We recorded brachial and central BP (pulse wave analysis) and pulse wave velocity (SphygmoCor). HIV-positive subjects of similar ages and with similar BP values showed central pulse pressure values that were significantly greater than those of controls; this was also the case for the Aix value. Central systolic and pulse pressure values and Aix were significantly greater in HIV-positive subjects with HAART and CKD than in the other HIV-positive subgroups and control subjects. PWV was also superimposable between groups when the data were analyzed relative to the presence of HAART and CKD. Our study shows that the unfavorable CV risk profile associated with HIV infection includes an increase in both central BP and Aix. The central BP increase seems to be favored by renal damage, which apparently has a role in the early stages of the disease.
Hypertension Research (2015) **38,** 405–412; doi:10.1038/hr.2015.25; published online 5 March 2015

Keywords: arterial stiffness; central blood pressure; HIV infection; highly active anti-retroviral therapy; pulse wave analysis; pulse wave velocity

INTRODUCTION

Highly active anti-retroviral therapy (HAART) has strikingly reduced the incidence of death in HIV positive subjects. Concomitantly, it has markedly altered the incidence of comorbidities and the causes of death associated with HIV infection, which now result primarily from non-HIV-related diseases, many of which are of a cardiovascular (CV) nature.[1–7] Because of the extended survival of patients, classic CV risk factors can now exert their harmful effects over a longer time span.[8] However, some evidence suggests that HIV infection itself promotes or accelerates the progression of atherosclerosis via direct (molecular viral products) or indirect (chronic inflammation) mechanisms.[9–11] Furthermore, HAART is also believed to contribute, by aggravating dyslipidemias and diabetes.[12–19]

Although the association of HIV infection and HAART with metabolic CV risk factors has been studied extensively, limited information is available on the association of this condition with central blood pressure (BP) alterations, which are more important than peripheral BP alterations.[20–25] Furthermore, information is scant and contradictory on whether HIV infection and HAART are associated with a reduction in large artery distensibility,[26–39] which is an alteration of paramount importance as both a predictor of systolic hypertension and a determinant of systolic BP levels in individuals with an isolated systolic BP elevation.[40–45]

Our study aimed to add information on these issues in a relatively large group of HIV-positive subjects. BP was measured not only in the brachial artery but also as central BP, and large artery stiffness was measured using the gold standard method of aortic pulse wave velocity (PWV). Data were collected from HIV-positive subjects with and without HAART and in patients with and without chronic kidney disease (CKD). The latter is of particular interest because the prevalence of CKD in HIV infections has markedly increased over the past few years.[46]

METHODS

Study population

A total of 94 HIV-positive patients followed by the Infectious Disease Department of San Gerardo Hospital were studied, and their data were compared with those for 37 HIV-negative control subjects, who were selected from the hospital's blood donor list. The HIV-positive patients had serologically confirmed presence of HIV infection, and the control subjects were

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Received 16 September 2014; revised 21 December 2014; accepted 31 December 2014; published online 5 March 2015

serologically excluded. For both groups, the exclusion criteria were as follows: age less than 18 years; pregnancy; a history of CV disease (myocardial infarction, angina pectoris, heart failure, stroke, transient ischemic attacks or claudication); use of antiaggregants, anticoagulants or any other CV drugs except antihypertensive agents; diabetes mellitus (defined as a fasting plasma glucose $>126\,mg\,dl^{-1}$ on two occasions or the use of antidiabetic drugs); uncontrolled hypertension (defined as a systolic BP $\geqslant 140\,mm\,Hg$ and a diastolic BP $\geqslant 90\,mm\,Hg$ under treatment); and dyslipidemia (defined as LDL cholesterol $\geqslant 160\,mg\,dl^{-1}$, serum triglycerides $\geqslant 400\,mg\,dl^{-1}$ or the use of lipid-lowering drugs). In HIV-positive subjects, the information collected included the status of the infection, the degree of disease progression and the use of current HAART.

In all subjects, we measured height and body weight, which allowed calculation of body mass index (BMI, $kg\,m^{-2}$), serum creatinine, glucose, triglycerides and total and fractionated cholesterol. Additionally, in the HIV-positive subjects, CD4 cell count and HIV RNA level were measured. Proteinuria was measured by dipstick on the morning urine and considered positive if $\geqslant 1+$. In the case of a positive dipstick, proteinuria was quantified over the next 24 h, and the subjects were included in the HAART CKD subgroup (see below) if a value higher than 30 mg per 24 h was confirmed. Control subjects with proteinuria were excluded.

Glomerular filtration rate was estimated (eGFR) by using the modification of diet in renal disease equation.[47]

CKD was defined as the presence of structural (proteinuria) and/or functional (eGFR lower than $60\,ml\,min^{-1}$ per $1.73\,m^2$) renal alteration.

Subjects agreed to participate in the study after being informed of its nature and purpose. The study protocol complies with the Declaration of Helsinki (as revised in 2004)[48] and was approved by the ethics committee of the institutions involved.

Protocol

Subjects were asked to come to the outpatient clinic of the San Gerardo Hospital in the afternoon. After 10 min of rest in a quiet room, in which the temperature was maintained at 22 °C, brachial BP was measured three times in the right arm, using an oscillometric device (Omron Healthcare Europe, Hoofddorp, The Netherlands). With the subject remaining in the supine position, the brachial BP measurements were followed by central BP assessment via pulse wave analysis (PWA) and PWV (see below).

Table 1 Demographic and clinical characteristics of HIV+ patients and controls

	HIV+	*Controls*	P (*t-test*)
Number	94	37	—
Age (years)	44.3±5.8	44.9±7.8	0.62
Female (%)	17.0	24.0	0.33
Current smoker (%)	54.2	10.8	**<0.001**
Number of former smoker (%)	14.9	2.7	**<0.001**
BMI ($k\,m^{-2}$)	24.2±3.8	24.8±2.9	0.41
Brachial SBP (mm Hg)	125±9.7	122±8.9	0.09
Brachial DBP (mm Hg)	75.2±7.4	75.7±6.3	0.71
Heart rate (b.p.m.)	74.9±11.7	64.8±10.7	0.32
Serum creatinine ($mg\,dl^{-1}$)	0.85±0.16	0.88±0.16	0.37
eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	102.1±19.5	95.5±16.5	0.07
Serum triglyceride ($mg\,dl^{-1}$)	155.8±81.6	102.2±56.3	**<0.001**
Serum total Ch. ($mg\,dl^{-1}$)	175±42.6	192.5±22.8	**0.02**
Serum LDL Ch. ($mg\,dl^{-1}$)	101.9±36.6	118±22.2	**0.01**
Serum HDL Ch. ($mg\,dl^{-1}$	41.9±12.4	56.7±13.7	**<0.001**
Serum glucose ($mg\,dl^{-1}$)	89.6±13.6	88.2±9.9	0.59
Hypertension (%)	7.4	0	0.08

Abbreviations: BMI, body mass index; Ch., cholesterol; DBP, diastolic blood pressure; eGFR, estimated glomerual filtration rate; HIV, human immunodeficiency virus; SBP, systolic blood pressure.
Data are shown as means±s.d. or percentage. Bold numbers show statistically significant difference.

Pulse wave velocity

Aortic (carotid-to-femoral) PWV was obtained using an automatic applanation tonometry-based device, the SphygmoCor Vx system (AtCor Medical, Sydney, NSW, Australia). ECG-gated pulse waveforms were obtained sequentially over the common carotid and femoral arteries, and PWV was automatically provided as the ratio (meters per second) of the delay between the feet of the pressure wave at the second vs the first point to the distance between the vessels measured on the surface of the body with a rigid ruler and corrected by 0.8.[49,50] Each instance of data acquisition included at least ten consecutive cardiac beats so that the information would include a complete respiratory cycle. The mean of two acquisitions was used for the analysis.

In our laboratory, the intra-session within- and between-operator variability of PWV had a mean coefficient of variation value of 2 and 4%, respectively, and the corresponding value for the inter-session between-operator variability was 4%.

Pulse wave analysis

PWA is used to determine central BP via a Millar piezoresistive pressure transducer connected to a device (SphygmoCor)[51,52] that allows measurement of the arterial waveform from the applanation of the radial artery at the site of its maximum pulsation. The central systolic, diastolic and pulse pressures are then calculated using a validated transfer function[53] that is based on a previous software calibration performed using values obtained sphygmomanometricaly at the brachial artery site. The collected data included the augmentation index (AIx), which is the supplementary increase in systolic BP as determined by the reflected pressure waves, according to the following formula:

$$\mathrm{Aix} = (\mathrm{AP}/\mathrm{PP}) \times 100$$

where AP is the pressure difference between the shoulder of the wave and the peak systolic pressure and PP is the pulse pressure. Because of their dependence on heart rate, the data are automatically normalized to 75 b.p.m. (called AIx @ HR75).[50,54]

In our laboratory, the intra-session within- and between-operator variability of the Aix values (coefficient of variation of the mean) was 3 and 5%, respectively, and the inter-session within-operator variability was 4%.

Statistical analysis

The data obtained for each subject were averaged, and the individual data were summed and expressed as the means (±s.d.) separately for the HIV-positive and control groups.

Table 2 Demographic and clinical characteristics of HIV+ patients with or without HAART

	HIV+/HAART	*HIV+/no HAART*	P (*t-test*)
Number	63	31	—
Age (years)	44.7±5.7	43.4±5.8	0.29
Female (%)	15.8	19.3	0.30
Current smoker (%)	58.7	45.2	0.33
Former smoker (%)	17.4	9.6	0.35
BMI ($k\,m^{-2}$)	24±3.4	24.7±4.4	0.38
Brachial SBP (mm Hg)	124.1±10	126.8±9	0.23
Brachial DBP (mm Hg)	74.4±7.6	76.8±6.7	0.14
Heart rate (b.p.m.)	74.2±12.0	76.4±11.0	0.40
Serum creatinine ($mg\,dl^{-1}$)	0.85±0.16	0.85±0.17	0.94
eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	101.6±18.5	103.2±22.3	0.72
Serum triglyceride ($mg\,dl^{-1}$)	174.1±88.7	118.6±47.3	**0.001**
Serum total Ch. ($mg\,dl^{-1}$)	176.8±42.9	171.5±42.5	0.57
Serum LDL Ch. ($mg\,dl^{-1}$)	99.9±36.7	105.8±36.4	0.47
Serum HDL Ch. ($mg\,dl^{-1}$)	41.8±13.0	41.9±11.3	0.97
Serum glucose ($mg\,dl^{-1}$)	89.3 ±15.1	90±10.2	0.81
Hypertension (%)	4.7	12.9	0.23

Abbreviations: BMI, body mass index; Ch., cholesterol; DBP, diastolic blood pressure; eGFR, estimated glomerual filtration rate; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; SBP, systolic blood pressure.
Data are shown as means±s.d. or percentage. Bold number shows statistically significant difference.

The subgroup analysis involved HIV patients with and without HAART and with and without CKD. Between-group differences were assessed by Student's *t*-test with Bonferroni correction, Wilcoxon and χ^2-tests (or Fisher exact test when needed) for normally distributed, non-normally distributed and categorical variables, respectively. One-way analysis of variance was used for multiple comparisons, and Pearson's or Spearman's correlation coefficients were used, as appropriate, to test the association between variables. We performed linear regression by using the additive model and adjusting for covariates as determined by stepwise regression. The covariates used for multivariate adjustments were age, sex and BMI.

Sample size was calculated for the central BP to demonstrate a significant difference of 4 mm Hg with an SD of 5 mm Hg, a type 1 error of 0.05 and a power of 0.80; thus, a minimum number of 47 cases was needed.

SPSS 13.0 (SPSS, IBM, Armonk, NY, USA) was used for the statistical analyses, and a *P*-value <0.05 was taken as the level of statistical significance.

Table 3 Demographic and clinical characteristics of HIV+ patients on HAART with or without CKD

	HIV+ HAART/CKD	*HIV+ HAART/no CKD*	P (*t-test*)
Number	33	30	—
Age (years)	44.8±5.7	44.7±6.0	0.97
Female (%)	12.1	20	0.75
Current smoker (%)	57.6	60	0.90
Former smoker (%)	15.1	20	0.82
BMI ($k\,m^{-2}$)	23.8±3.4	24.6±3.5	0.58
Brachial SBP (mm Hg)	124.4±10.7	123.9±9.4	0.83
Brachial DBP (mm Hg)	75.8±6.7	73±8.5	0.15
Heart rate (b.p.m.)	73.2±11.5	75.4±12.7	0.48
Serum creatinine ($mg\,dl^{-1}$)	0.92±0.17	0.78±0.1	**<0.001**
eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	93.9±18.2	110.1±14.3	**<0.001**
Serum Triglyceride($mg\,dl^{-1}$)	195.4±83.7	150.6±89.5	**0.04**
Serum Total Ch. ($mg\,dl^{-1}$)	181±45.8	172.2±39.8	0.42
Serum LDL Ch. ($mg\,dl^{-1}$)	102.3±41.7	97.4±31.0	0.60
Serum HDL Ch. ($mg\,dl^{-1}$)	39.4±13.2	44.5±12.5	0.12
Serum glucose ($mg\,dl^{-1}$)	86.4±16.0	92.5±13.7	0.11
Hypertension (%)	3.0	6.6	0.47

Abbreviation: BMI, body mass index; Ch., cholesterol; CKD, chronic kidney disease; DBP, diastolic blood pressure; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; SBP, systolic blood pressure.
Data are shown as means±s.d. or percentage. Bold numbers show statistically significant difference.

RESULTS

Population characteristics

As shown in Table 1, the mean age was similar in the control and HIV-positive groups, which showed a slight and non-significant prevalence of females. The BMI, brachial BP, blood glucose, serum creatinine and eGFR values were all within the normal range and were similar between groups. Compared with the control group, HIV-positive subjects showed a greater prevalence of smokers (current and former) as well as higher serum triglycerides and lower serum total cholesterol, LDL-cholesterol and HDL-cholesterol values. A small percentage of HIV-positive subjects were hypertensive (eight patients, all on treatment); no hypertension was observed in the control group.

Table 2 shows the demographic and clinical data for HIV-positive patients with and without HAART, and the corresponding data for HIV-positive patients without and with CKD are shown in Table 3. Compared with HIV-positive patients with HAART, the only significant difference exhibited by those without HAART was a much

Table 4 Immunological status, virological status and HAART details for HIV+ patients

	HIV+ HAART/CKD	*HIV+ HAART/no CKD*	*HIV+ no HAART*	P (*ANOVA*)
Number	33	30	31	—
CD4 ($cell\,mm^{-3}$)	409.6±234.7	520.9±294.9	466.5±237.4	0.24
$<200\ cell\,mm^{-3}$ (%)	15.1%	10%	6.5%	0.11
Nadir ($cell\,mm^{-3}$)	368.4±205.4	443.3 ±268.4	326.9 ±154.6	0.14
HIV RNA titer (Log10 $copies\,ml^{-1}$)	5.3±5.8	5±5.3	4.8±5	0.47
Undetectable	72.7%	63.3%	6.65%	**0.02**
$>50.000\ copies\,ml^{-1}$	6%	3.3%	25.8%	**0.01**
Time on HAART (month)	76.9±75	78.8±59.2	—	0.32
NRTI	93.9%	96.7%	—	0.59
Abacavir	45.5%	30%	—	0.21
Zidovudin	9%	26.6%	—	0.06
Lamivudin	51.5%	50%	—	0.90
Emtricitabin	39.4%	46.7%	—	0.56
Tenofovir	39.4%	46.7%	—	0.56
NNRTI	15.1%	46.7%	—	**0.02**
Nevirapin	0%	6.7%	—	0.22
Efavirenz	15.1%	40%	—	**0.006**
PI	78.8%	50%	—	**0.01**
Atazanavir	18.2%	13.3%	—	0.43
Fosamprenavir	18.2%	13.3%	—	0.43
Darunavir	12.1%	6.6%	—	0.38
Saquinavir	3%	3.3%	—	0.73
Indinavir	0%	3.3%	—	0.47
Lopinavir	27.3%	10%	—	0.07
Raltegravir	9%	6.7%	—	0.54
Maraviroc	3%	0%	—	0.52

Abbreviations: ANOVA, analysis of variance; HAART, highly active anti-retroviral therapy; NRTI, nucleoside reverse trascriptase inhibitors; NNRTI, non-nucleoside reverse trascriptase inhibitors; PI, protease inhibitors.
Data are shown as means±s.d. or percentage. Bold numbers show statistically significant difference.

lower serum triglyceride value. As expected, HAART patients with CKD showed a higher serum creatinine and a lower eGFR compared with the HAART patients without CKD although in both groups the mean values were still in the normal range. HAART patients also showed a slightly higher serum triglyceride value than that in patients with HIV infection and no anti-retroviral therapy.

The patients' immunological, virological and detailed HAART data are shown in Table 4. No difference was observed in the CD4+ cell count and HIV RNA level between the HAART-treated patients with CKD, the HAART-treated patients without CKD and the non-HAART-treated HIV-positive patients. HAART-treated patients with CKD were given nephrotoxic drugs (tenofovir, nevirapin and efavirenz) less frequently and were given protease inhibitors more frequently compared with HAART-treated patients without CKD.

Pulse wave velocity, pulse wave analysis and central blood pressure

Figure 1 shows that PWV was not significantly different between control and HIV-positive patients and that no difference was observed when the data were analyzed relative to the presence of HAART with or without CKD vs the absence of any treatment (Figure 2).

Despite similar augmentation pressure and Aix values, standardizing the latter at a heart rate of 75 b.p.m. (Aix@HR75) resulted in higher values in the HIV-positive subjects than in the controls (Figure 1). However, this difference disappeared when the subgroup analysis was performed and multiple comparison methods were used (Figure 2). In all HIV-positive subjects, the central systolic and diastolic BP values were similar to those in the control group, whereas the central pulse pressure values were significantly greater (Figure 1). Both the central systolic and pulse pressure values were significantly greater in HIV-positive subjects with HAART and CKD than in the other HIV-positive subgroups and control subjects. This was also the case when the statistical analyses were corrected using Bonferroni's method (Figure 2).

DISCUSSION

In our HIV-positive patients, the brachial artery systolic and diastolic BP values were similar to those exhibited by age-matched controls. This was also the case for brachial pulse pressure. By contrast, central systolic BP was greater in HIV-positive patients than in controls, and the difference was statistically significant for the central pulse pressure value (11.7% higher in HIV-positive patients than in controls). This was also the case for the Aix value, which was 43% higher in HIV-positive patients than in controls. Based on these observations, we can conclude that the unfavorable CV risk profile known to be associated with HIV infection includes an increase in BP. This increase may not be detected when BP is measured peripherally, but it appears to be significant and quantitatively non-marginal when BP is obtained at the central site.

Our study provides an additional piece of information, that is, the extent of BP alterations in treated or untreated HIV-positive patients and in HIV-positive patients with or without renal damage. The central pulse pressure values were superimposable in patients

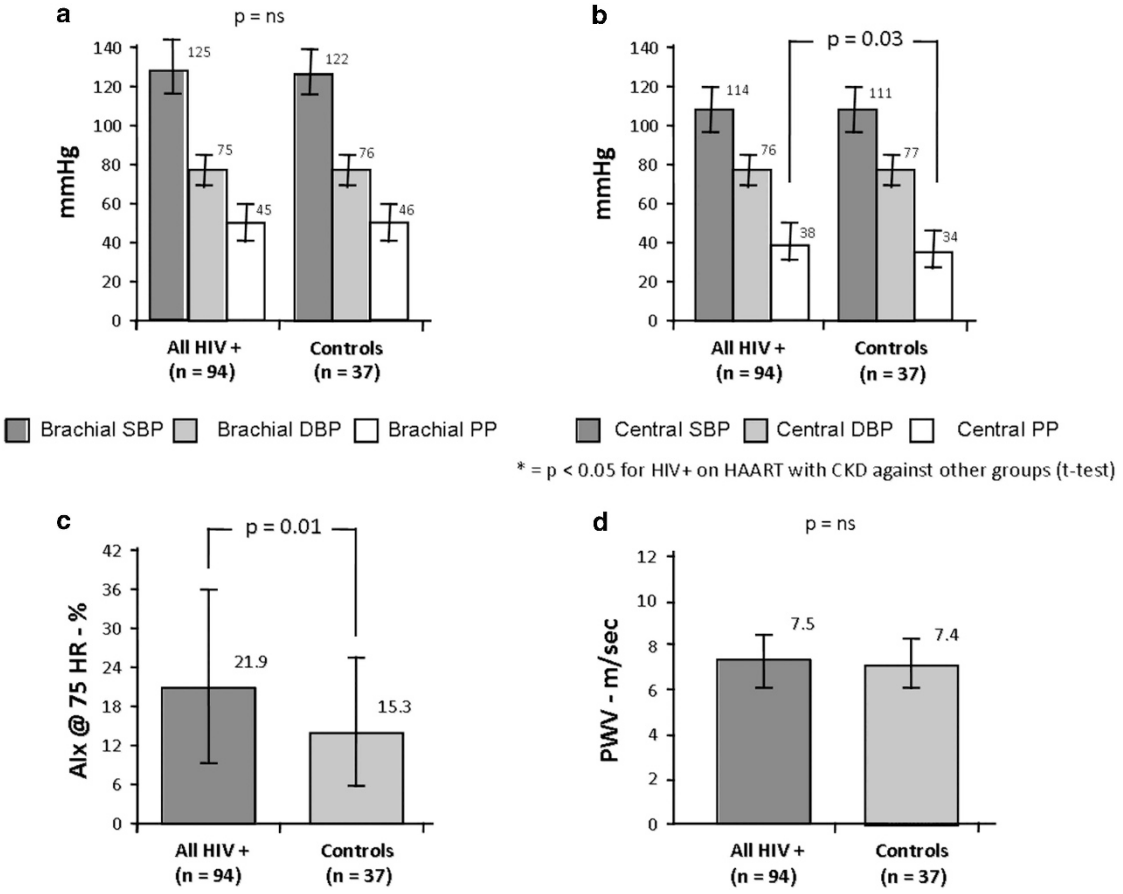

Figure 1 Brachial BP (**a**), central BP (**b**), Aix (**c**) and PWV (**d**) of all HIV+ patients and controls. Aix, augmentation index; CKD, chronic kidney disease; DBP, diastolic blood pressure; HAART, highly active anti-retroviral therapy; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

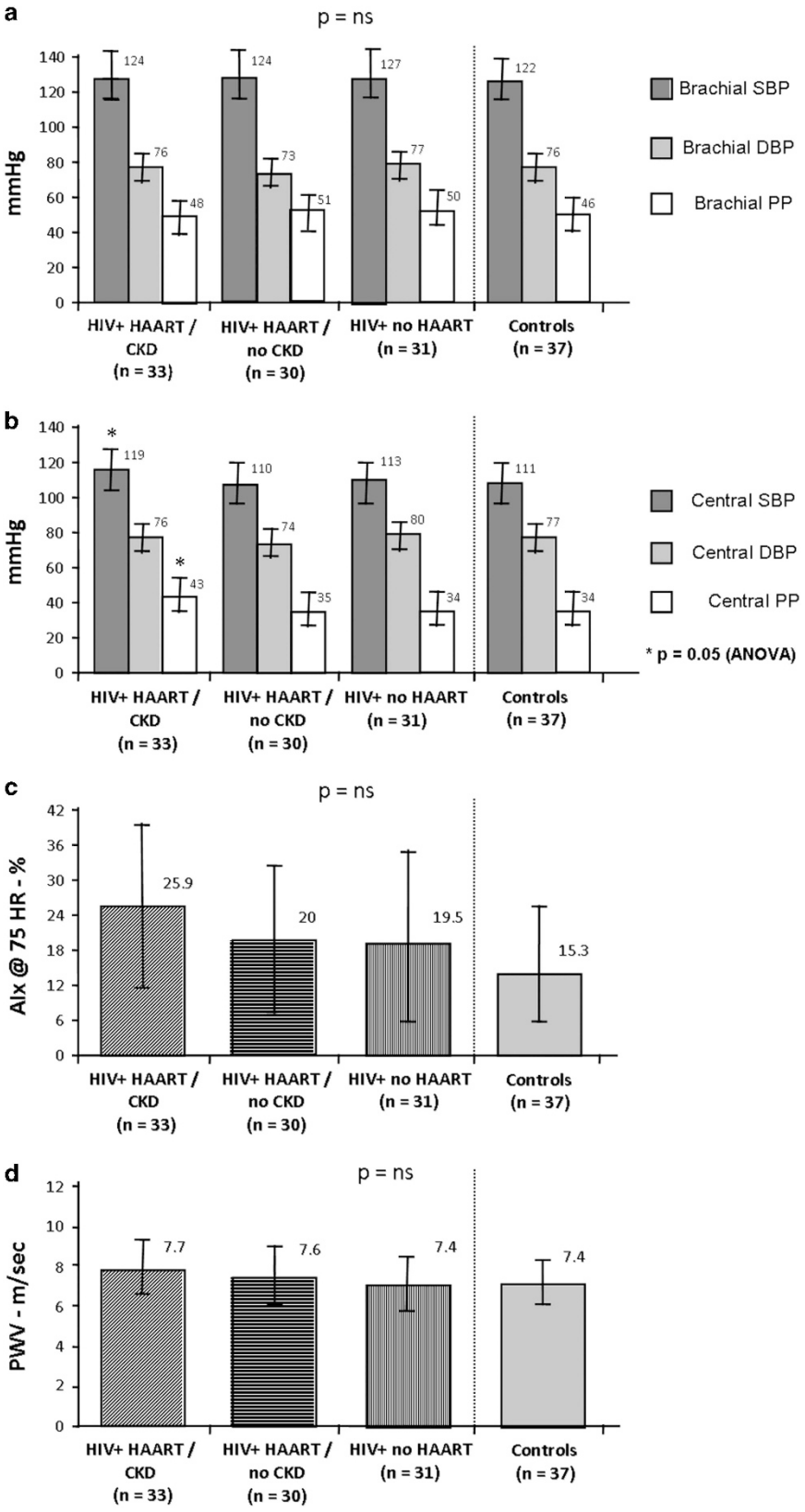

Figure 2 Brachial BP (**a**), central BP (**b**), Aix (**c**) and PWV (**d**) of HIV+ patients (when divided by the presence of HAART and CKD) and controls. Aix, augmentation index; CKD, chronic kidney disease; DBP, diastolic blood pressure; HAART, highly active anti-retroviral therapy; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

under HAART and in those without HIV treatment but were significantly greater (and extended not only to pulse but also to systolic BP) in patients under HAART who showed evidence of renal damage because of increased urinary protein excretion. These data suggest that HIV treatment does not contribute to the central BP increase observed in HIV infection. Instead, the increase seems to be favored by renal damage. The 'renal factor' apparently plays a role at an early stage because in our patients the increased urinary protein excretion was associated with a renal filtration level that was still within the normal limits. The role played by this renal factor in the central BP alteration is in line with the conclusions of several studies of HIV patients showing that renal damage was the precipitating factor for CV disease.[55–59] Additionally, the reverse causality—that hypertension can determine microalbuminuria instead of the hypothesis that renal damage can determine augmented central BP—may be true. Only a small proportion of our population had hypertension; it was treated and well controlled in all cases, with all patients presenting with BP levels lower than 140/90 mm Hg. As such, no clinically relevant BP acted on the kidney and could influence its function, thus favoring our hypothesis that renal damage determines an increase in central BP. However, more studies are needed to disentangle this difficult argument.

In our patients, arterial stiffness as assessed by PWV was not significantly different between the HIV-positive patients and controls. Furthermore, arterial stiffness did not show any noticeable difference when the comparison was made between HAART and untreated patients or individuals with or without renal disease. This observation is not in line with the results of some previous studies, which have reported an increase in PWV, and thus a reduction of large artery distensibility, in HIV-infected patients.[20–23] It may also appear to be in opposition to the finding that, in general, there is arterial stiffening in individuals with kidney disease.[60–70] However, in our patients renal damage was probably in its incipient phase (as shown by the normality of their eGFR value), which allows us to suggest that in HIV-positive patients this alteration becomes evident in a somewhat more established phase of renal involvement. This is not inconsistent with an earlier increase in central BP because central BP has been shown to have only a limited relationship to the ability of large arteries to distend in response to intravascular pressure.[50] Therefore, the major determinant of its increase is probably a reflected wave phenomenon that allows forward and background waves to coalesce at the large artery level.[50]

Our study has some limitations. First, it was cross-sectional, which means that it does not provide evidence pertaining to the progression of the abnormalities of central BP and arterial stiffening with the duration of the HIV disease. Furthermore, we used eGFR instead of directly measured glomerular filtration rate, and we assessed both proteinuria and eGFR only once. Thus, there was no possibility of addressing the natural variability of these measures. Additionally, we did not obtain a comprehensive assessment of CV risk profile and therefore could not identify the relationship between alterations of central BP and large artery stiffness with CV risk factors. Third, the HIV patient group had a higher proportion of smokers compared with the controls; this might have influenced the final results in terms of accurately reflecting the true epidemiology of HIV subjects regarding their smoking habits. Fourth, a second control group with CKD but without HIV would surely add important information to our results. Finally, because of the limited number of our HIV-infected patients, some of the subgroups were small, limiting the power to detect some associations or changes, particularly regarding anti-retroviral drugs.

However, our study also had strengths. First, the careful CV selection and the absence of between-group differences regarding the principal confounders allowed us to draw clear conclusions, at least concerning the impact of CKD on central blood pressure. Second, the central blood pressure and PWV were measured using a state-of-the-art technique. Finally, our controls were blood donors who were free from any CV or metabolic overt disease and thus represented an excellent control population for the comparisons.

In conclusion, the determinants of the unfavorable CV risk profile associated with HIV infection are actually not fully understood, and HIV infection itself, HAART and other factors have been advocated. Our study found that in HIV-infected patients an increase in central BP can be part of this risk profile. Moreover, another factor known to have an impact on arterial vessels in the general population was identified, that is, renal damage, which seems to have an important role, even at an early stage.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank the participating patients, nurses (Poli Anna, Marzia Fiorino) and research coordinators (Elena Cappelletti and Valeria Pastore).

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