

Indices of Cardiovascular Function Derived from Peripheral Pulse Wave Analysis Using Radial Applanation Tonometry in HIV Positive Patients from Mthatha District of South Africa

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Abstract

Background: HIV patients are suspected to have increased arterial stiffness which may contribute to a higher risk of coronary atherosclerosis. Invasive techniques are of limited value, hence in this study, the use on a non-invasive method was applied. The objective of the study was to see if there is increased arterial stiffness in HIV patients using applanation tonometry of the radial artery, consequently leading to cardiac dysfunction resulting in myocardial ischemia.

Methods: 169 participants took part in the study between December 2012 and June 2013. There were 63 HIV positive participants, 52 HIV negative participants, and 54 HIV treatment naïve participants. Augmentation index (AIx (75)), Ejection duration index (ED%) and sub-endocardial variability ratio (SEVR) and other parameters of interest were measured using arterial wave reflection in these participants.

Results: SEVR was highest in the HIV negative participants and lowest in HAART naïve HIV participants ($p < 0.001$). In both groups, the HIV positive participants had significant arterial stiffness compared to HIV negative participants ($p = 0.024$). The HIV positive participants also had higher ejection duration index (ED %) with the highest values being observed in those that were not on treatment ($p < 0.001$). Both SEVR and ED% had negative correlation with HR using Pearson's correlation and Stepwise Linear regression $p < 0.001$. There was no significant correlation with age $p = 0.143$. No significant differences in both the systolic and diastolic blood pressures between the three groups were observed, although heart rate was lower in the HIV negatives participants.

Conclusion: HIV patients are prone to having systolic dysfunction which may lead to myocardial ischemia.

Keywords: HIV; Subendocardial variability ratio; Ejection duration index; Arterial stiffness; Cardiac function

Introduction

Arterial stiffness is considered a composite measure of vascular health and a predictor of cardiovascular events independent of traditional risk factors. It is caused by structural changes in the vascular wall, including fibrosis, medial smooth muscle cell necrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules into the arterial wall [1,2].

One particularly promising non-invasive method for assessing arterial stiffness and cardiovascular function that has emerged is the novel technique of pulse wave analysis (PWA) using applanation tonometry [3,4]. Wilkinson [5], reported that PWA is a simple and reproducible technique to measure Pulse Wave Velocity (PWV) and Augmentation index AIx (75). AIx (75) is the most widely researched index of PWA, with several studies indicating that AIx is independently predictive of adverse cardiac events [4,5]. Augmentation Index is the measure of arterial stiffness derived from the ascending aortic waveform (Figures 1a and 1b). Thus, by calculating the augmentation index, the degree of arterial stiffness can be calculated by which cardiac risk to the patient can be diagnosed.

The SphygmoCor system converts the peripheral waveform to a central waveform using a proprietary algorithm ('general transfer function') [5,6]. PWA permits the non-invasive measurement of three main indices of cardiovascular function: augmentation index adjusted to a heart rate of 75 beats per minute AIx (75), subendocardial viability ratio (SEVR), and the ejection duration index (ED%). In the peripheral arteries, the outgoing systolic pulse wave is reflected back towards the heart and adds to ('augments') the central aortic pressure in late systole [3-5]. The amount by which the aortic pressure is increased by this phenomenon is the 'augmentation pressure' (AP) (Figure 1a). AIx is the aortic AP expressed as a percentage of the aortic 'pulse pressure' (PP) [3-5]. AIx (AP/PP) indicates the combined influence of large artery pulse wave velocity, peripheral pulse wave reflection and vascular function [3-6]. Since AIx varies with heart rate it is commonly adjusted to a 'standard heart rate of 75 beats per minute AIx (75) [4-6].

PWA can provide important information about hemodynamic parameters including augmentation index AIx (75) and subendocardial viability ratio which is an indicator of myocardial workload and perfusion (O_2 supply vs. demand) [7,8].

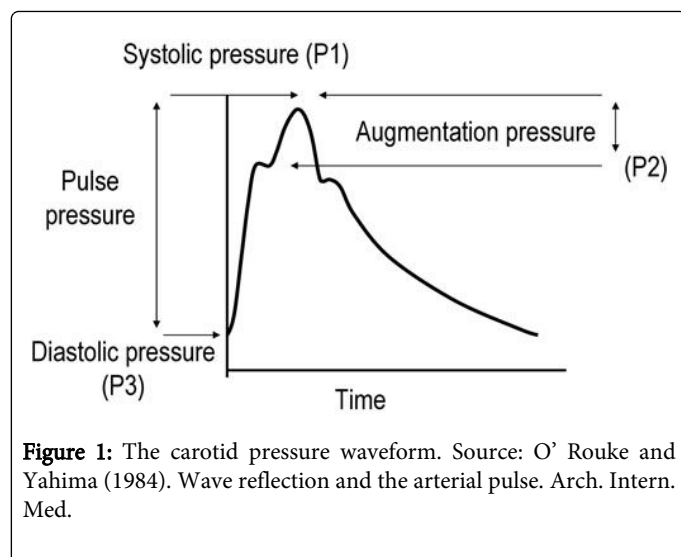


Figure 1: The carotid pressure waveform. Source: O' Rouke and Yahima (1984). Wave reflection and the arterial pulse. *Arch. Intern. Med.*

Low SEVR has been shown to be associated with coronary artery disease. Decreased coronary blood flow is observed in patients with healthy coronary arteries, severity of type I and type II diabetes, decreased renal function, and a history of smoking [7-10]. These are also associated with low SEVR. Myocardial ischemia occurs when there is an imbalance between myocardial oxygen supply and demand and the ischemia is usually entirely or predominantly subendocardial. Animal models have shown that relative subendocardial ischemia can be predicted from the ratio of two pressure time areas (or integrals): the area between diastolic aortic and left ventricular (LV) pressures (DPTI) and the area beneath the systolic LV pressure curve (SPTI) (Figure 2). Increased arterial stiffness increases wave reflection amplitude and aortic systolic BP, which prolongs mechanical systole (or ejection duration) and decreases diastolic pressure time. These pressure changes negatively influence myocardial perfusion and reduce the myocardial oxygen (MVO_2) supply/demand ratio, which promotes subendocardial ischemia [9,10].

Not much work has been done in HIV patients using wave reflections and systolic functions. Augmentation index using PWA is suitable for large-scale population and intervention studies investigating the clinical relevance of vascular stiffness.

With 6.1 million people living with HIV and a prevalence of 17.9 percent in South Africa, South Africa has the largest HIV epidemic than any other country. The remaining countries in Southern Africa have prevalence rates of between 10 and 15 percent [11-13]. In sub-Saharan Africa, like many parts of the world, the HIV epidemic disproportionately affects women, often as a result of social and economic inequality. In 2012, 59 percent of all people living with HIV in the region were female [11-14].

There have been a massive scale-up in access to HIV treatment with dramatic effects on the lives of people living with HIV. As these treatments have their adverse effects, it is envisaged that HIV infected subjects and the treatments being used might lead to cardiovascular complications of which arterial stiffness is one of them [15,16]. Not much work has been done in HIV patients using wave reflection and systolic functions in South Africa. Previous work done has been mainly on diastolic function in HIV using echocardiography [16]. Hsue et al. [17] found that HIV-infected patients had a higher prevalence of diastolic dysfunction and higher left ventricular mass

index compared with controls. These differences were not readily explained by differences in traditional risk factors and were independently associated with HIV infection. These results suggest that contemporary asymptomatic patients with HIV manifest mild functional and morphological cardiac abnormalities, which are independently associated with HIV. The objective of this study was to investigate the extent of arterial stiffness in HIV infected subjects using applanation tonometry of the radial artery and examine its association with cardiac systolic dysfunction.

Material and Methods

The design of the study was a descriptive and analytical cross sectional study and was conducted from December 2012 to June 2013. The study comprised patients diagnosed with HIV who were attending Infectious Disease Clinic in Mthatha which is a semi-rural town in the Eastern Cape of South Africa. Included were undiagnosed HIV patients with minor ailments attending the Gateway Clinic and Stamford Terrace Clinic also in Mthatha. The HIV seronegative participants included patients with minor ailments attending both the Gateway Clinic and Stamford Terrace Clinics in Mthatha. The clinics catered for patients in Mthatha and its environs. They were all of African descents and lived mostly in the rural areas of the Eastern Cape.

Sampling and recruitment of patients

A convenient sampling method was used. 300 participants were recruited because of envisaged dropout rate, with 169 completing the study. There was a high dropout rate of 41% because of socio economic reasons, the main one being lack of a steady source of income. Death, drug side effects, change of address and phone numbers, lack of compliance contributed to this high dropout rate of patients from 300 to 169. Participants were told to abstain from alcohol and caffeine and the use Viagra for at least 72 hours before the study as these might affect the functioning of the blood vessels.

Inclusion and exclusion criteria

Exclusion criteria for the study were breast feeding mothers, pregnant mothers and those below the age of 18 years. Furthermore, participants who were on regular cardio protective medications or were acutely ill were excluded.

Informed consent was obtained from the participants after due explanation of the procedures to them. They were informed that they may refuse to participate or withdraw from the study at any time without fear of victimization. Ethical clearance certificate number 0043/009 was obtained from the Ethics Committee, Faculty of Health Sciences, Walter Sisulu University. Translated questionnaires were administered to the participants by someone who spoke fluent Xhosa.

Measurements

Augmentation index and cardiac functions were assessed in 169 participants using applanation tonometry of the radial artery to derive central arterial waveform by a validated transfer function. Aortic augmentation index (AIx) was used as index of wave reflection. Indices of cardiac function were measured by Ejection duration (ED %), and Subendocardial variability ratio (SEVR).

The SphygmoCor system using applanation tonometry evaluated PWA, SEVR, and ED%. Aortic augmentation index was used as

indices of arterial stiffness, (ED%), and SEVR as cardiac function parameters. For PWA, an average radial pressure waveform was generated from 30 sequential radial pressure waveforms. The procedure took place in a quiet cool room and participants were not allowed to talk. Participant's personal details such as the name, date of birth and gender were entered into the patient screen. Height, weight and blood pressure of the participants were measured and again entered into the corresponding SphygmoCor software fields. The participants sat comfortably beside a table with their arm on the table and their palms facing upward in a quiet room. The location of the strongest pulse was felt on top of the skin and the tonometer placed directly on that location. Peripheral pressure waveforms were recorded from the right radial artery using applanation tonometry.

After 30 sequential waveforms had been acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform, from which the augmentation index was obtained AIx (75) (Figures 1a and 1b). This was calculated as the ratio between augmentation pressure and pulse pressure. Larger values of AIx (75) indicate increased wave reflection from the periphery or early return of the reflected wave as a result of increased pulse wave velocity due to increased arterial stiffness. Only high-quality recordings, defined as an in-device quality index 85% (derived from an algorithm including average pulse, height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform and acceptable curves on visual inspection) were included in the analysis.

Anthropometric measurements

Height was measured twice using the Harpenden stadiometer (Holtain Ltd, Crymch, Dyfed, United Kingdom). For weight measurement, the participant stood in the middle of the scale without touching anything and had minimal clothing. The weight was read to the nearest 100 gm (0.1 kg) and recorded. The average of the weights measured was taken. Body Mass Index (BMI) was calculated using the following formula: Weight (in Kilograms) divided by height (in meters) squared= $wt (kg)/ht (m)^2$. Blood pressure was measured using the Omron sphygmomanometer (Omron, Guangdong, China). Three blood pressure measurements were taken 5 minutes apart, and the average of these readings was used in the analysis.

Laboratory analysis

Blood of patients were tested for CD4 count in the NLHS laboratory using the flow cytometry method. The test is considered an essential part of HIV care, since this parameter is used to stage disease and guide clinical management.

Statistical analysis

Data was analyzed using the statistical program SPSS version 19. All quantitative variables in the text are expressed as means \pm SD. (P values <0.05 will be significant for statistical differences). Data was tested for normal distribution. Statistically, ANOVA was used for variables with normal distribution and non-parametric tests were used for variables with skewed distribution. Post Hoc test (Tukey and LSD) were administered to establish which of the 3 groups is the cause of the significance difference observed within and between the 3 groups. Data were expressed as means and standard deviations. Results were expressed as mean \pm SD or as proportion (%) for the different parameters.

Results

Table 1 shows the General characteristics of the participants and their cardiac functions. The mean ages were as follows: HIV negative participants 30.34 ± 10.65 years, HIV positive participants not on treatment 36.25 ± 10.79 years, and HIV positive on treatment 40.21 ± 9.56 years. The mean values of all anthropometric parameters were similar ($P>0.05$) across the HIV status groups (Table 1). The highest mean age was in HIV positive participants on treatment. Of the 169 participants, there were 62 males and 107 females. There were 88 participants below the age of 35 years, and 81 above the age of 35 years. The differences between the systolic, diastolic and mean arterial pressures were not significant (Table 1), but the heart rate in HIV negatives was lower than those of the HIV positives. The means of the cardiac functions in the three groups of participants were compared and they showed significant differences in the three groups of participants in all the variables examined. Table 1 also shows a significant difference in the levels of ED, SEVR, HR and AIx (75) in the three groups of participants ($p<0.05$). Figures 3 and 4 showed plots depicting the differences in the cardiac functions in the three groups of participants.

Variables	HIV-ve n=63	HIV+ve not on treatment n=54	HIV+ve on treatment n=52	P-value ANOVA
Age in years	30.34 \pm 10.646	36.25 \pm 10.785	40.21 \pm 9.554	<0.000
Weight (kg m)	71.35 \pm 15.45	71.31 \pm 19.64	68.50 \pm 13.72	0.583
Height (cm)	164.77 \pm 8.40	162.87 \pm 7.61	162.72 \pm 8.03	0.322
WC (cm)	85.43 \pm 15.32	85.84 \pm 21.41	90.39 \pm 10.58	0.209
HC (cm)	105.44 \pm 14.02	102.12 \pm 13.94	103.69 \pm 10.30	0.439
BMI (kgm/m ²)	33.10 \pm 38.57	26.38 \pm 5.80	25.78 \pm 4.79	0.17
WHR (%)	0.83 \pm 0.09	0.80 \pm 0.19	0.88 \pm 0.21	0.13
SBP (mm/hg)	121.25 \pm 14.52	123.40 \pm 21.99	126.44 \pm 17.83	0.312
DBP (mm/hg)	79.72 \pm 9.57	82.88 \pm 12.05	84.63 \pm 11.60	0.059
PBP (mm/hg)	75.43 \pm 11.88	77.29 \pm 18.27	79.33 \pm 18.69	0.458
HR (b/min)	67.58 \pm 9.50	73.31 \pm 11.54	72.83 \pm 14.40	0.017
MP (mm/hg)	92.76 \pm 15.34	98.22 \pm 11.25	97.33 \pm 12.62	0.063
ED (%)	33.71 \pm 3.80	36.31 \pm 3.56	36.15 \pm 4.431	0.001
AIx (75)	15.56 \pm 13.20	19.92 \pm 12.20	21.87 \pm 12.26	0.024
SEVR (%)	176.16 \pm 29.55	155.04 \pm 24.55	159.80 \pm 28.559	0
In all the participants not differentiating the ages HR, AIx(75).SEVR%,ED% within the three groups of participants				

Table 1: General characteristics and cardiac functions of the participants.

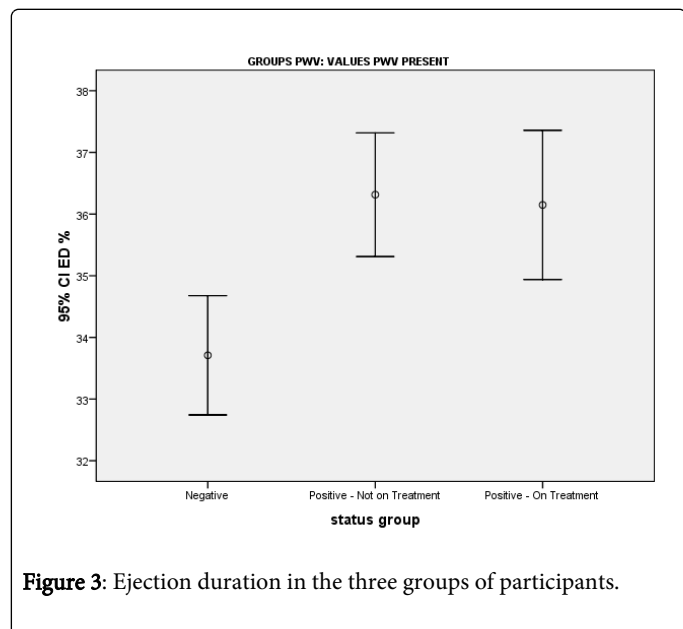
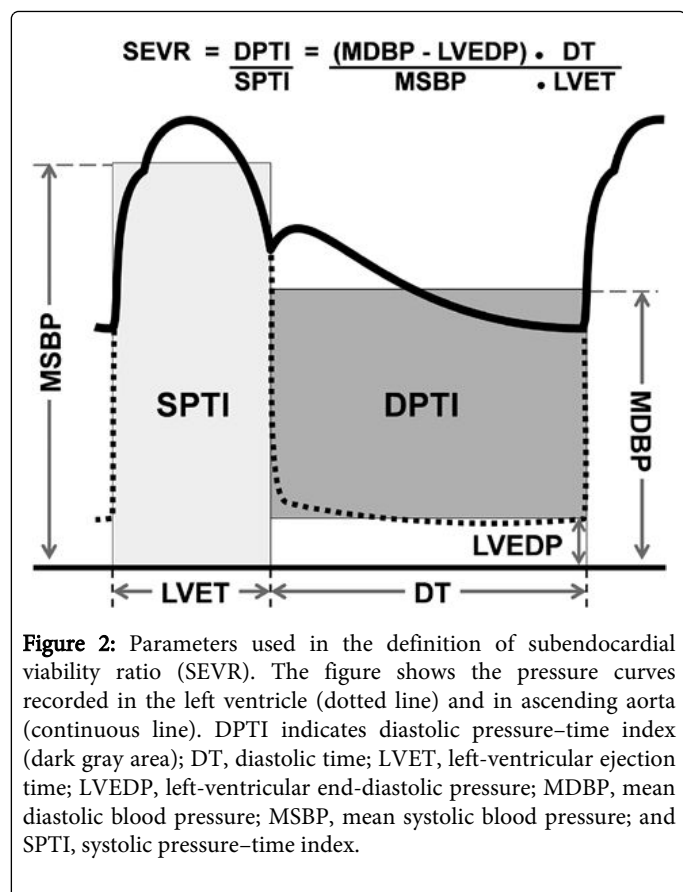


Table 2 illustrates cardiac functions in participants who are less than 35 years and those who are older than 35 years. There was significant difference in the means of AIx (75) in participants aged below 35 years and above 35 years with $p < 0.001$). Table 2 shows the means of certain indices of cardiac function using SphygmoCor variables in participants aged below and above 35 years. Augmentation index in those above 35 years was more than those less than 35 years

$p < 0.001$. There was no significant difference in the means of the Ejection duration and Subendocardial viability ratio in those over 35 years and those over 35 years of age.

The systolic, diastolic blood pressures and mean arterial pressure were not significant when both males and females were taken into account. In contrast, compared with males, females had higher levels of ED% and AIx(75), ($P < 0.05$), but lower values for SEVR% (Table 3).

Variables	Age more than 35 years	Age less than 35 years	p-value ANOVA
ED (%)	35.30 ± 3.99	35.30 ± 4.21	0.888
AIx (75)	24.52 ± 11.06	14.34 ± 12.22	0
SEVR (%)	162.71 ± 26.72	165.7 ± 30.95	0.42
SBP (mmHg)	127.78 ± 20.10	120.30 ± 15.13	0.007
DBP (mmHg)	84.82 ± 10.58	80.31 ± 10.97	0.012
PBP (mmHg)	78.54 ± 19.74	76.36 ± 12.88	0.403
MP (mmHg)	99.04 ± 12.42	93.68 ± 13.43	0.006

No significant difference in the values of SEVR%, ED% in those participants who are less than 35 years and those who are over 35 years in the total group of participants. There was significant difference in AIx (75) and the blood pressures with the exception of the pulse pressure in these participants.

Table 2: The means of some cardiac functions using some Sphygmocor variables in participants aged below 35 years and above 35 years in all the groups combined.

Variables	Males	Females	P-value
ED (%)	33.73 ± 4.16	36.15 ± 3.81	< 0.000
AIx (75)	14.64 ± 11.78	21.15 ± 12.81	0.001
SEVR (%)	177.10 ± 31.02	157.52 ± 25.47	<0.000
SBP (mmHg)	126.22 ± 18.34	121.96 ± 17.58	0.151
DBP (mmHg)	81.42 ± 10.64	82.78 ± 11.39	0.459
PBP (mmHg)	74.91 ± 16.79	78.60 ± 15.72	0.177

Females had higher SEVR% higher AIx (75) and lower ED% whereas there were no significant changes in the blood pressures

Table 3: The means of AIx (75) and cardiac functions between male and female participants.

Table 4 shows correlations between AIx (75) and some cardiac functions. There were no significant correlations with AIx (75) in all the variables i.e. SEVR, ED% and HR with the exception of MAP (mean arterial pressure) in all the three groups of participants There was also a negative correlation of heart rate with Augmentation index within the 3 groups of participants but this was not significant using simple linear regression.

Table 5 shows correlations between SEVR and some variables. There was negative correlation with heart rate and SEVR in all the groups. Ejection duration index also correlated negatively with SEVR in all the groups. There was a slightly negative correlation with SEVR with age in the 3 groups of participants but they were not

significant. For HIV negative ($r=-0.127$, $p=0.321$), HIV positive on treatment ($r=0.113$, $p=0.143$), with treatment naïve HIV participants ($r=0.652$, $p<0.001$). With all the groups combined there was a non-significant negative correlation with age ($r=-0.113$ and $p=0.143$). There was a significant positive correlation in all the three groups of SEVR with heart rate ($r=-0.749$, $p<0.001$). It is interesting to also note that in the groups combined there was also a significant negative correlation of SEVR with smoking ($r=-0.253$, $p<0.005$).

Variables	HIV-ve		HIV+ve not on treatment		HIV+ on treatment	
	r-value	P-value	r-value	P-value	r-value	P-value
SEVR%	0.001	0.993	0.062	0.668	0.033	0.814
ED%	0.02	0.826	0.053	0.717	0.03	0.833
HR b/min	-0.14	0.277	-0.038	0.793	-0.059	0.676
MP (mm/hg)	0.377	0.003	0.372	0.008	0.348	0.011

Ejection duration fraction (ED %) between the groups $p<0.001$. Augmentation index (AIx (75) between the two groups $p=0.024$ and $p<0.001$ for SEVR between groups.

Table 4: Simple correlations between cardiac functions and AIx (75) in the three groups of participants.

Variables	HIV-ve		HIV+ve treatment naïve		HIV+ on treatment	
	r-value	P-value	r-value	P-value	r-value	P-value
Age (yrs)	-0.127	0.321	0.017	0.908	0.223	0.104
Smoke	-0.404	0.001	-0.23	0.137	-0.023	0.873
CD4	-0.184	0.202	0.131	0.427	0.088	0.589
ED%	-0.875	0	0.94	0	-0.955	0
AIx (75)	0.793	0	0.055	0.699	-0.031	0.825
HR b/min	-0.833	0	-0.682	0	-0.732	0
MP (mmHg)	-0.5	0	-0.129	0.363	-0.16	0.943

Heart rate had negative correlation with SEVR in all the groups. ED% also had negative correlation with SEVR in all the groups. AIx (75) and smoking had negative correlation with SEVR in all the groups.

Table 5: Simple correlations between cardiac functions with SEVR in the three groups of participants (All ages).

Table 6 and 7 depicts the general characteristics of participants 35 years and below in the three groups of participants. Almost the characteristics including age were similar. The CD4 count and SEVR were decreased in the HIV positive. Heart rate and ejection duration index were significantly increased in the HIV positives.

Variables	HIV-ve N (37)	HIV+ve treatment naïve N (32)	HIV+ve on treatment N (25)	p value
Age (yrs)	27.67 ± 3.70	28.31 ± 4.371	29.72 ± 3.16	0.062
CD4	919.85 ± 299	485.33 ± 323.478	364 ± 223	0

BMI kg/m ²	27.98 ± 20.54	27.963 ± 18.89	27.37 ± 5.27	0.173
MP (mm/hg)	90.76 ± 15.436	95.02 ± 12.02	96.62 ± 9.87	0.165
HR b/min	67.80 ± 9.68	73.15 ± 9.18	76.33 ± 12.04	0.005
ED%	33.61 ± 3.93	36.50 ± 3.18	38.00 ± 4.45	0
AIx (75)	12.82 ± 12.76	16.12 ± 12.39	16.83 ± 11.58	0.378
SEVR%	177.88 ± 31.22	155.27 ± 23.32	148.72 ± 27.63	0

Significant differences observed in SEVR%, ED%, HR, CD4, and AGE in the three groups of participants who are 35 years and below.

Table 6: Characteristics of participants 35 years and below 35 years in the 3 groups.

Variables	SEVR%		ED%	
	r	p	r	p
Age (yrs)	0.073	0.371	0.116	0.265
Smoke	-0.291	0.006	0.276	0.011
Alcohol	-0.291	0.006	0.302	0.004
CD4	0.168	0.164	-0.159	0.19
MP (mmHg)	-0.129	0.213	-0.837	0
HR (b/min)	-0.978	0	0.867	0

Slight negative correlation of smoking and alcohol consumption with SEVR% and ED%. Significant negative correlation of HR and SEVR%. No significant correlation of age with either SEVR% or ED% in participants 35 years and below.

Table 7: Simple correlations between SEVR% and ED% and some anthropometric and laboratory data groups of participants whose ages are below 35 years.

Figure 2 depicts the parameters used in the definition of subendocardial viability ratio (SEVR). The figure shows the pressure curves recorded in the left ventricle (dotted line) and in ascending aorta (continuous line). With the subendocardial viability ratio the myocardial perfusion relative to left ventricle workload has been indirectly estimated by SEVR (Figure 2). It is calculated using the following formula: $SEVR = DPTI/SPTI$. DPTI which represents the area between the aortic and left-ventricular pressure curves in diastole: $DPTI = (\text{mean diastolic aortic pressure} - \text{mean diastolic left ventricular pressure}) \times \text{diastolic time}$. SPTI represents the area under the aortic pressure curve in systole: $SPTI = \text{mean systolic aortic pressure (corresponding to left-ventricular mean systolic pressure)} \times \text{left-ventricular ejection time}$. The 2 areas, thus, reflect blood flow supply (DPTI) and demand (SPTI) and their ratio (i.e., SEVR) indirectly gives information on the adequacy of subendocardial blood flow. Hence the value of over 100% in our result on Table 1.

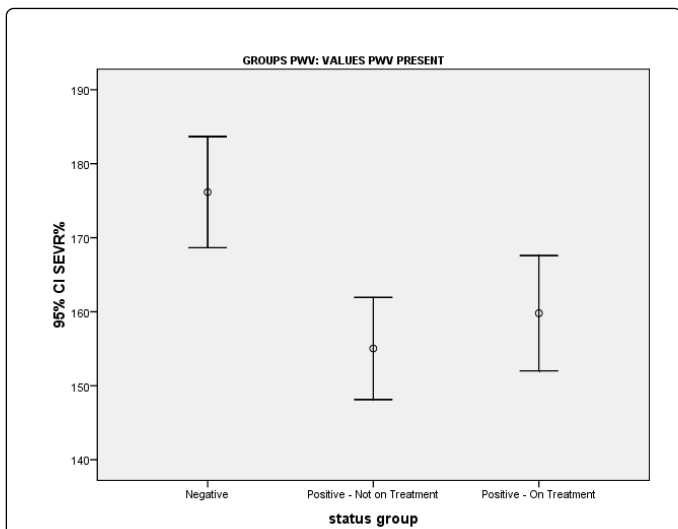


Figure 4:

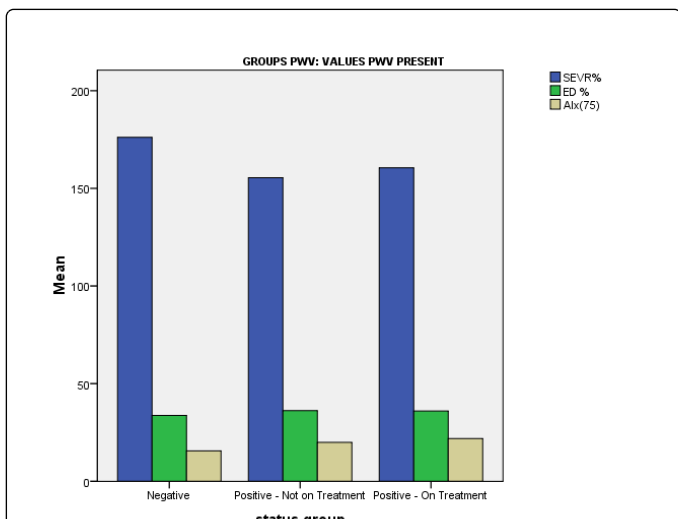


Figure 5: Histogram comparing the cardiac functions in 3 groups of participants. SEVR% increased in HIV negative participants whilst AIx (75) is decreased relatively in HIV negatives when all the participants were taken into account.

Discussion

Arterial stiffness AIx (75) was significantly raised in HIV patients both treated and treatment naïve compared to HIV negatives when all the participants were taken into account (Table 1 and Figure 5). This is in agreement by the study reported by Falasca [18], who compared HIV patients and non-infected subjects. Compared with uninfected subjects, HIV-infected subjects in their study had higher PWV and AIx (75) values.

We also took note of the fact that the groups had significant differences in their age groups. When we looked at the age range 35years and below, the AIx in the differences in the Augmentation

index were not significant and the significance in the overall participants might be due to the age differences. Some other studies have also referred to arterial stiffness as being affected by age [19,20]. The present study showed positive correlations of arterial stiffness with age in the controls and HAART naïve participants. These findings are also in agreement with studies previously reported in HIV children by measuring their carotid arterial stiffness [21].

Charakida [21] studied 83 HIV-infected children with a mean age of 1.0 ± 3.1 years and 59 controls aged 12.2 ± 2.8 years. Among the HIV-infected children, 48 were receiving HAART (23 including a protease inhibitor). HIV-infected children had increased arterial stiffness compared with healthy children. These changes were more pronounced with increasing age in HIV-infected children particularly in those who were receiving HAART. Mitchell [22] in the Framingham study reported that with advancing age, arterial stiffness and wave reflections increase and elevate systolic and pulse pressures. Mention must also be made of the fact that the Augmentation index in the females were also increased, This might be due to reduced height in females compared to males which leads to increased augmentation index.

In this study, SEVR% was highest in the HIV negative participants and lowest in HAART naïve participants (Table 1 and Figure 5). The decrease in SEVR in the two groups of HIV positive patients ($p < 0.001$) observed in the present study may be due to endothelial dysfunction affecting the coronary arteries. Increased immune activation and inflammation reported in chronic HIV-infection as well as the characteristic dyslipidemia associated with HIV infection and antiretroviral therapy (ART) also contribute to an increased risk of atherosclerotic vascular disease among HIV-infected adults [22].

In the older age group, this might be due to atherosclerosis. There is also premature biological aging in HIV-infected patients [23]. This will now cause decreased myocardial perfusion [24]. In normal coronary arteries, subendocardial ischemia occurs when SEVR% falls below 50% [25]. The findings of this study were that SEVR was decreased significantly in the two groups of HIV participants ($p < 0.001$) whilst ED% was higher in the HIV participants. Low SEVR% has been shown to be associated with coronary artery disease [23,24]. Estimation of SEVR by using applanation tonometry may provide a reliable tool for the assessment of coronary microcirculation in essential hypertensives with indications of myocardial ischemia and normal coronary arteries [23,24]. This might also be used in HIV positive subjects. To rule out the effect of aging on these results, participants who were aged 35 years and below were analysed. After adjusting for confounding factors (MP, waist-Hip ratio, study status group-HIV negatives-HIV positives on ART-HIV positives on ART, and ages) and using multiple linear regression analysis, only increase in HR ($P < 0.0001$) and female gender ($P = 0.048$) significantly and independently predicted decrease in SEVRs% as follows. Thus, the effect of age was sort of cancelled $Y = 292.688 - 0.727 \times HR - 0.162 \times \text{Gender}$ (Male=1 and Female=2). Thus increase in heart rate decreased the SEVR. Females were also found to have a lower SEVR than males ($p < 0.000$).

Although age is a predictor for all the participants including those that are over 35 in our study it is not a determining factor in participants below the age of 35 years. The fact that females can also predict SEVR having a lower value makes females more prone to myocardial ischemia. Women have smaller and stiffer blood vessels resulting in an earlier return of the reflected wave, which is likely due to an increased pulse wave velocity in women contributing to their increased augmentation index compared to males (Table 4), This can

lead to increased arterial stiffness [25]. The tonometric sub-endocardial viability ratio (SEVR) is impaired in the HIV positive participants in this study. In HIV positive participants there was also significant arterial stiffness compared to HIV negative participants. This shows that increased aortic stiffness and decreased subendocardial viability ratio predisposes to myocardial ischemia by increasing the systolic tension-time index and by decreasing aortic pressure throughout diastole. Thus the HIV positive participants are prone to having myocardial infarction or stroke because of the impaired oxygen supply to the heart.

Endothelial dysfunction has emerged as one of the major mechanisms underlying the increased cardiovascular disease risk seen in the HIV population [26]. Endothelial progenitor cells, circulating endothelial cells, endothelial micro particles, and platelet micro particles are all now considered as biomarkers of cardiovascular disease risk in otherwise healthy individuals [26]. In normal coronary arteries, subendocardial ischemia occurs when SEVR% falls below 50% [27,28]. The findings of this study were that SEVR was decreased significantly in the two groups of HIV participants ($p < 0.001$) whilst ED% was higher in the HIV participants.

The ratio of the duration of systolic ejection to the total duration of a cardiac cycle is the ejection duration index (ED %) [29]. The HIV positive participants in this study have higher ejection duration index ED%. The ED% was lowest in the HIV negative participants and highest in those that are not on treatment ($p < 0.001$). This might indicate that the HIV positive participants not on treatment were at a higher risk of developing cardiovascular problems such as systolic dysfunction. ED% was also higher in females than males [29]. This might be because females have higher Augmentation index therefore lower heart rate and therefore lower ejection index [30]. This shows that increased aortic stiffness and decreased subendocardial viability ratio predisposes to myocardial ischemia in HIV positive participants. This could be due to increasing the systolic tension-time index and by decreasing aortic pressure throughout diastole. Thus the HIV positive participants are prone to having myocardial infarction or stroke because of the impaired oxygen supply to the heart. From this study there was also no significant correlation in healthy subjects, in the SEVR between the age groups and in both males and females ($p < 0.05$ for both). There was also no correlation between SEVR and age, CD4 count in all the groups. We also observed significant arterial stiffness in HIV positive participants when compared to HIV negative participants ($p = 0.024$) (Table 1).

Smoking both had negative correlations on SEVR in the HIV negative participants (Table 5); Heart rate also had negative correlation with SEVR in all the groups of participants. This was more with HIV participants who were already on treatment ($p = 0.000$ and $p = 0.02$). This could be because those on treatment knew they were already positive, whereas the other group is not aware until they were tested. They might be using the smoking habit and alcohol intake to allay their fears.

The study has some limitations. First, the cross-sectional design did not allow the investigation of some abnormalities in arterial properties. Longitudinal studies are needed to clarify this. Also matching for age and gender and other potential risk factors was not successful in all cases. The study started with 300 enrolled participants of which only 169 finished although this was anticipated. Although the duration of anti-retrovirals used were asked in the questionnaire many of the participants could not give the exact date of commencement and hence it was not used in the study. Though exercising habit was

recorded it was also not included in the analysis. This study has shown that HIV virus contributes to arterial stiffness and cardiac functions. This could be prevented if these indices are monitored and preventive measures such as statins given to these patients. It is also possible that in the older age group, age is a predictor of SEVR but not a determining factor in those participants under 35 years.

Conclusion

These findings suggest HIV infection as a potentially relevant contributor to arterial stiffness and certain indices of cardiac dysfunction such as systolic dysfunction and provide a conceptual background for the increased cardiovascular risk observed among HIV-infected individuals regardless of antiretroviral treatment. It also demonstrated that gender and age were factors that should be considered that affected cardiac functions. This affected the cardiac functions such as ED% and SEVR which might lead to myocardial ischaemia, and heart failure. This was more obvious when those that were 35 years and below were assessed in all the groups which made the ages in the groups almost the same. Close, non-invasive evaluation of preclinical atherosclerotic disease should be considered for HIV patients, especially those with additional risk factors for cardiovascular diseases. Lifestyle modification and pharmacological interventions should be instituted to reduce cardiovascular risks in these patients.

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