

Evaluation of left ventricular systolic function by Myocardial Deformation Imaging in asymptomatic HIV patients

Kunjang Sherpa¹, Ram Kishor Sah¹, Arun Maskey², Rabi Malla², Deewakar Sharma², Sujeeb Rajbhandari², Man Bahadur KC², Rikesh Tamrakar², Sushil Shakya³, Birat Krishna Timilsina¹, Anish Hirachan¹, Prabha Chapagain Koirala¹, Ajay Adhikari¹, Shaneez Nazmy¹

¹Department of Cardiology, National Academy Of Medical Sciences, Bir hospital, Kathmandu, Nepal

²Department of Cardiology, Sahid Gangalal National Heart center, Kathmandu, Nepal

³Department of General practice and Emergency medicine / ART clinic, Bir Hospital, Nepal

Corresponding Author: Kunjang Sherpa,
Department of Cardiology, National Academy of Medical Sciences,
Bir hospital, Kathmandu, Nepal
Email: sherpakunjang7@gmail.com
ORCID ID NO: 0000-0003-1136-6983

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Abstract

Background and Aims: Despite improvements in clinical care, evidence from both industrialized and developing countries indicates that the prevalence of subclinical cardiac dysfunction in individuals with well-controlled HIV infection may approach 50% and represent a newly recognized comorbid condition. The aim of our study was to reveal abnormalities in cardiac function using conventional transthoracic echocardiography and left ventricular strain imaging in HIV infected patients without cardiovascular disease.

Methods: This was a hospital based, single center descriptive cross-sectional comparative study conducted in National Academy of Medical Sciences (NAMS), Bir Hospital which included HIV patients with baseline examination including a patient medical history, clinical examination, baseline CD4 count, viral load and a standardized transthoracic echocardiography and strain imaging examination and the findings were compared among age and sex frequency matched healthy adult population.

Results: Our study enrolled 142 patients out of which 95 HIV positive patients (mean age 36.7±9.2 years with 58% female) and 47 healthy control (mean age 33.7±8 years with 57.4% female). The median duration of HIV diagnosis was 7 years (IQR 2, 10) and median CD4 count was 464 cells/mm³ (IQR 259,750). There was no significant difference in conventional echocardiographic parameters between two groups except for transmitral E velocity that was lower in HIV group (p value of 0.001). The HIV population has lower mean global longitudinal strain (GLS) value of -19.92% ± 2.54 SD compared to the healthy control population with mean of -21.39% ± 1.54 SD (p value of 0.001) and patients with CD4 count less than 300 cell/mm³ had GLS value significantly lower than -18% (p value of 0.05).

Conclusion: HIV infected population without established cardiovascular disease have subclinical left ventricular dysfunction revealed by GLS imaging technique.

Keywords: Global Longitudinal strain, HIV Infection, LV systolic dysfunction.

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Introduction

Despite improvements in clinical care, evidence from both industrialized and developing countries indicates that the prevalence of subclinical cardiac dysfunction in individuals with well-controlled HIV infection may approach 50% and represent a newly

recognized comorbid condition^{1, 2}. Many studies reported a strong association between human immunodeficiency virus (HIV) infection and cardiac abnormalities, which are closely associated with high morbidity and mortality^{3, 4}. Cardiovascular manifestations have two clinical patterns: 6–7% of HIV-infected patients have significant

cardiac disease while the remainder is asymptomatic. Among asymptomatic patients, 8–10% develop symptomatic heart disease over a two- to five-year period, which constitutes an independent predictor of mortality^{5,6}.

HIV infection itself is accompanied by subclinical left ventricular systolic dysfunction, which is not apparent to standard echocardiography, which can be unmasked through using sensitive echocardiographic techniques. Global longitudinal strain (GLS) echocardiographic imaging, allows for more direct assessment of myocardial muscle shortening and lengthening throughout cardiac cycle by assessing myocardial strain that can unmask left ventricular dysfunction in asymptomatic patients^{7,8}. As heart failure is often recognized late in HIV infected patients, early detection of left ventricular function is crucial.

There are very few studies done around the globe studying GLS imaging showing that it can unmask LV systolic dysfunction in asymptomatic HIV patients not apparent to standard transthoracic echocardiography and there are no any studies done in our part of the world. Hence, the present study aim to examine population of asymptomatic HIV-infected patients with GLS imaging for early detection of left ventricular systolic dysfunction.

Methods

The study was a hospital based, single center descriptive cross-sectional comparative study conducted for 6 months (December 2018 to May 2019) in National Academy of Medical Sciences (NAMS), Bir hospital which included HIV patients visiting the anti-retroviral therapy (ART) clinic of Bir hospital with the baseline examination including a patient history, medication treatment, baseline CD4 count and viral load. Furthermore, noninvasive cardiac test such as heart rate, blood pressure, and a standardized transthoracic echocardiography and strain imaging examination was a part of the study protocol. To compare the findings, we also included age and sex frequency matched healthy adult population. We recruited 95 HIV patients by sample size calculation based on estimated prevalence of systolic cardiac dysfunction of 34.3% by a large, prospective multicenter HIV-heart study¹. The inclusion criteria were patient with HIV -infection and age >18 years and the exclusion criteria were patients with pre-existing cardiac disease, pregnant women, patients with diabetes, hypertension, dyslipidemia, renal disease, liver disease, Centers for Disease Control and Prevention (CDC) Class C patients and refusal to give consent. We also included control group in 1 : 2 case ratio with total of 47 healthy adults with age and sex frequency matched group to compare our findings between HIV vs. Non- HIV patients. Formal permission for the study was taken from the institutional review board of the NAMS and informed consent was taken from the study population.

Transthoracic echocardiography was performed with a commercially available imaging system with PHILLIP Affiniti 50c Echocardiography machine using a 2.5 MHz phased array transducer. Cardiac dimension and cardiac function was measured according to the recommendations of the American Society of Echocardiography⁹. Global longitudinal strain (GLS) was calculated by the mean longitudinal strain of the six walls (basal, mid and apical segments) in apical view. The software automatically displayed an epicardial tracing to include the entire myocardial width, and was later adjusted manually for optimal tracking. GLS value less than – 18% was considered abnormal for detecting LV systolic dysfunction as a value above –20% with a standard deviation of $\pm 2\%$, the value cited by the American Society of Echocardiography, is likely to be normal¹⁰. Intra-observer reproducibility was determined by an echocardiographer's own analysis and inter-observer reproducibility was determined by the analyses of two echocardiographers for strain imaging after 2

weeks on stored offline images of 15 random study population.

Statistical analysis

All data were entered into an electronic spreadsheet (Microsoft Excel, Redmond) and the statistical analysis was done using the SPSS version 20 software (SPSS INC, Chicago, III). Categorical variables were analyzed as percentage, continuous variable with normal distribution presented as mean \pm SD and continuous variable with skewed distribution presented as median and interquartile range (IQR). After processing of all available information, statistical analysis of their significance was done. Dichotomous variable were compared using Chi-Square test or Fischer's exact test, as appropriate and independent t test for means of continuous variable. 'P' value of less than 0.05 was considered to be significant. Coefficient of variation analysis were performed for intra- and inter-observer reproducibility of strain imaging echocardiography

Results

Our study enrolled 142 patients out of which 95 were HIV positive patients with mean age 36.7 ± 9.2 , 58% female and 47 healthy control with mean age 33.7 ± 8 , with 57.4% female population. The clinical characteristics of the HIV-infected population are presented in table 1 and comparison with control group are presented in table 2. The median duration of HIV diagnosis was 7 years (IQR 2, 10) and median CD4 count was 464 cells/mm³ (IQR 259,750). Among the HIV patients 71.6% had viral copies <50 copies/ml and 87.4% were taking antiretroviral therapy (ARV). The median duration of ARV duration was 5 years (IQR 1, 10). With respect to age, sex and blood pressure there were no significant differences among the two groups, however the HIV group has mean BMI of 22.5 ± 2.87 significantly lower than control group (BMI 23.79 ± 3.13) (p value of 0.02).

Table 1: Baseline Clinical Characteristics of the HIV-Infected Population

Variable	HIV group (n= 95)
Age in years (mean \pm SD)	36.7 \pm 9.2
Female (N/%)	55 (58%)
BMI (weight in kg/height in mm ²) (mean \pm SD)	22.5 \pm 2.87
Systolic BP in mmHg (mean \pm SD)	114 \pm 11
Diastolic BP in mmHg (mean \pm SD)	73.2 \pm 6.7
CD4 count (cells/mm ³) [Median (IQR)]	464 (IQR 259,750)
Viral load (< 50 Copies/ml)	68 (71.6%)
Duration of HIV diagnosis (years) [Median (IQR)]	7 (IQR 2,10)
ARV use (N/%)	83 (87.4%)
Duration of ART therapy (years) [Median (IQR)]	5 (IQR1,10)

The conventional and strain echocardiographic parameters of HIV infected population and healthy control population are shown in table 3 and 4 respectively. There was no significant differences in conventional echocardiographic parameters between HIV population and healthy population except for transmittal E velocity which were

significantly lower in HIV group (p value of 0.001).

In strain imaging, the asymptomatic HIV population with normal Left ventricular ejection fraction (LVEF) have significantly lower mean GLS value of $-19.92\% \pm 2.54$ SD compared to the healthy control population with mean GLS value of $-21.39\% \pm 1.54$ SD (p value of 0.001).

In HIV patients, the relationship of GLS value to different baseline CD4 count and HIV viral load, duration of HIV diagnosis, HAART (highly active antiretroviral treatment) therapy and HAART

Table 2: Clinical Characteristics of HIV Infected Population and Control Group

Variable	HIV group (n=95)	Control group (n=47)	p value
Age in years (mean \pm SD)	36.7 \pm 9.2	33.7 \pm 8	0.062 ^a
Female (N/%)	55 (58%)	27 (57.4%)	0.959 ^b
BMI (weight in kg /height in mm ²) (mean \pm SD)	22.5 \pm 2.87	23.79 \pm 3.13	0.02 ^a
Systolic BP in mmHg (mean \pm SD)	114 \pm 11	113 \pm 10	0.69 ^a
Diastolic BP in mmHg (mean \pm SD)	73.2 \pm 6.7	72.92 \pm 7.1	0.85 ^a

^ap value from t test, ^bP-value from χ^2 test

Table 3: Conventional echocardiographic parameters of the HIV-infected population and the control group.

Echo Parameters	HIV group (Mean \pm SD)	Control (Mean \pm SD)	P- value
LVEDD (mm)	4.39 \pm 0.447	4.47 \pm 0.438	0.291 ^a
LVEDS (mm)	2.84 \pm 0.45	2.96 \pm 0.422	0.137 ^a
IVS (mm)	0.978 \pm 0.16	0.95 \pm 0.121	0.251 ^a
PW (mm)	0.80 \pm 0.13	0.76 \pm 0.12	0.07 ^a
LV mass index (gm/m ²)	117 \pm 31	115 \pm 21.6	0.81 ^a
FS (%)	33 \pm 4.24	34 \pm 2.95	0.604 ^a
EF (%)	63.12 \pm 4.3	63.3 \pm 2.9	0.748 ^a
E _{max} (cm/s)	73.6 \pm 16.3	89.09 \pm 19.04	0.001 ^a
A _{max} (cm/s)	66.04 \pm 16.32	65.7 \pm 14.85	0.941 ^a
Average E/e'	7.39 \pm 1.86	8.06 \pm 1.86	0.051 ^a
LA volume (ml/m ²)	18.38 \pm 3.81	17 \pm 2.7	0.234 ^a
RV basal dimension (mm)	2.7 \pm 0.41	2.9 \pm 0.34	0.06 ^a
IVC	1.42 \pm 0.21	1.45 \pm 0.11	0.115 ^a
TAPSE (cm)	2.07 \pm 1.3	1.88 \pm 0.14	0.342 ^a
Lateral S' (cm/s)	12.5 \pm 2.1	13.4 \pm 1.2	0.370 ^a

^ap value from t test

Table 4: Strain Parameters in the HIV-Infected Population and the Control Group

	HIV group	Control	p-value
GLS in % (mean \pm SD)	-19.92 \pm 2.54	-21.39 \pm 1.54	0.001 ^a

Table 5: Relationship of LV Function with GLS to Baseline CD4 Count.

CD4 count (cells/mm ³)	Global Longitudinal strain (GLS)		p value
	<-18%	\geq -18%	
CD4<300 (n=25) N (%) [*]	8 (32%)	17 (68%)	0.05 ^a
CD4>300 (n=70) N (%) [*]	10 (14.2%)	60 (85.8%)	
CD 4<500 (n=49) N (%) [*]	12 (24.5%)	37 (75.5%)	0.155 ^a
CD 4>500 (n=46) N (%) [*]	6 (13.1%)	40 (86.9%)	

*N (%) represents number and percentage within row, ^ap value by χ^2 test

Table 6: Relationship of LV Function with GLS with Baseline HIV Viral Load, Duration of HIV Diagnosis, HAART Therapy and HAART Therapy Duration

Clinical Parameters	Global longitudinal Strain (GLS)		P- value
	< -18%	\geq -18%	
HIV viral load (N/%) [*]			0.134 ^a
Undetectable (<50copies/ml) (n=68)	10 (14.8%)	58 (85.2%)	
Detectable (>50 copies/ml) (n=9)	4 (44.4%)	5 (55.6%)	
Duration of HIV diagnosis in years (N/%)			0.179 ^a
< 1 (n=19)	6 (31.5%)	13 (68.5%)	
1 to 5 (n=18)	4 (22.2%)	14 (77.8%)	
5 to 10 (n=35)	3 (8.5%)	32 (91.5%)	
>10 (n=23)	5 (21.8%)	18 (78.2%)	
HAART therapy (N/%)			0.174 ^a
Yes (n=83)	14 (16.8%)	69 (83.2%)	
No (n=12)	4 (33.3%)	8 (66.7%)	
Duration Of HAART therapy in year (N/%)			0.356 ^a
<1 (n=14)	3 (21.4%)	11 (78.6%)	
1 to 5 (n=27)	6 (22.2%)	21 (77.8%)	
5 to 10 (n=28)	2 (7.1%)	26 (92.9%)	
>10 (n=15)	4 (26.6%)	11 (73.4%)	

* N(%) represents number and percentage within row, ^ap value by Fischer's exact test.

therapy duration are as shown in table 5 and 6 respectively. Patients with CD4 count less than 300 cell/mm³ had significantly lower GLS value of less than -18% compared with higher CD4 count (p value of 0.05). However, there were no significant differences in GLS value with baseline HIV viral load, duration of HIV diagnosis, HAART therapy and its duration.

Intra-observer and inter-observer coefficients of variation were < 10% in strain imaging echocardiography.

Discussion

HIV infection itself is accompanied by subclinical systolic dysfunction, not apparent to standard echocardiography that can be unmasked though using sensitive echocardiographic techniques. When present, early management of cardiovascular abnormalities in these patients may improve their well-being and survival. Currently, left ventricular ejection fraction is one of the most commonly used markers to evaluate LV systolic function, as assessed by conventional echocardiography¹. However, this method has several limitations such as geometric assumptions, foreshortening, load dependency, interobserver variability, and the influence of the heart rate. Strain imaging (SI) has been able to detect subclinical myocardial dysfunction at an earlier stage compared with conventional imaging in a number of diseases¹¹. This method has also been shown to evaluate LV systolic functions more comprehensively and reliably than conventional echocardiography methods^{12, 13}. It is an important marker to detect subclinical LVSD with a high sensitivity and specificity rate¹⁴. There are very few studies done evaluating GLS for detecting subclinical dysfunction in asymptomatic HIV patients.

The main analysis of the present study showed that asymptomatic HIV-infected patients without cardiovascular disease had significantly lower GLS value despite having normal LV systolic function compared to the that of healthy individuals which were similar to previous study done by Mendes et al¹⁵ and Cetin et al¹⁶. There were also very few study done with Doppler/TDI strain imaging and strain rate done by Sims A et al¹⁷, Onur et al¹⁸ and Karavidas et al¹⁹ which all have demonstrated impaired strain and strain rate despite having normal systolic function in HIV patients compared to the healthy control group.

Our study evaluate the relationship of LV function with GLS in HIV patients to baseline CD4 count, HIV viral Load, duration of HIV diagnosis, HAART therapy and HAART therapy duration showed patients with CD4 count less than 300 cell/mm³ had significantly lower GLS value less than -18% compared with higher CD4 count. Previous study done by Onur et al¹⁸ and Karavidas et al¹⁹ found no relationship between CD4 T-cells and systolic strain. But later study done by Cetin et al¹⁶ showed positive correlation between reduced CD4 count and GLS value, though there were no significant difference between different CD4 level group below and greater than 300.

There was no significant differences in conventional echocardiographic parameters between HIV population and healthy population except for transmitral E velocity (P value of 0.001) which were significantly lower in the HIV group and this finding were similar to the study done by Karavidas et al¹⁹ and Mendes et al¹⁵. The diastolic function abnormalities such as reduced transmitral E velocity, an increased peak of A velocity, and an increased isovolumetric relaxation time and early filling duration has been described in HIV patients with wide variability in its incidence.^{20,21} In our study only the reduced transmitral E velocity was found to be significantly lower probably because of impairment of LV contraction as detected with strain imaging, could precede the development of diastolic function abnormalities or small-sized study sample including only asymptomatic young HIV patients may have prevented us from reaching significant differences in other

diastolic parameters.

The strength of the present Study was that our study population included 57% female with larger sample size and younger age population compared to the previous study done by Karavidas et al¹⁹, Mendes et al¹⁵ and Cetin et al¹⁶. Our study had tried to overcome the limitation of previous study of underrepresented female population and less sample size.

Limitation of the study

The study was a descriptive cross-sectional study, CD4 T-cell counts were only measured in HIV-infected patients, but not in healthy individuals and indicators of myocardial fibrosis such as MRI imaging and biochemical variables as were unable to be investigated.

Conclusion

GLS imaging technique is a valuable tool for detecting subclinical LV dysfunction in asymptomatic HIV which is often overlooked by conventional echocardiography. It is likely that the subclinical LV dysfunction may later progress with higher incidence of cardiomyopathy and heart failure in HIV-infected patients. Thus, a low threshold for using these technique should be applied in asymptomatic HIV patients especially in patients with lower CD4 level for early detection of subclinical LV dysfunction. Although our study revealed that early subclinical dysfunction can be unmasked by GLS imaging, further large scale, long term follow up studies are needed to address the mechanisms involved in it and could also determine whether the reported low GLS value abnormalities would translate into a worse prognosis.

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Conflict of interest: None

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