Am J Cardiovasc Dis 2011;1(2):176-184
www.AJCD.us /ISSN: 2160-200X/AJCD1107001

Original Article

Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study

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Received July 2, 2011; accepted July 27, 2011; Epub July 30, 2011; published August 15, 2011

Abstract: Aims: The aim of the current study was to assess cardiac structure and function as well as cardiac abnormalities in a large patient-population based multicenter study of HIV-infected subjects. Materials and methods: We enrolled 803 HIV-positive adults (83.4% men, mean age: 44.2 ± 10.3 yrs) in this prospective, cross-sectional cohort study. The study protocol included a standardized documentation of patient history, medical treatment and clinical examination. All subjects underwent a standardized transthoracic echocardiographic examination protocol including Doppler and tissue Doppler imaging. Results: Echocardiographic measurements revealed a structural dilatation of the left ventricle in 10.1% of all HIV-infected subjects. Interventricular septum and posterior wall thickness were increased in 18.0% and 11.1%, respectively, with elevated muscle mass in 14.3% male and 19.4% female patients. Of all participants 13.5% exhibited a pathologic contraction characteristic of one or more myocardial segments. Prevalence of systolic and diastolic dysfunction was 34.3% and 48.0%, respectively. However, severe forms of ventricular dysfunction were rare. Conclusions: In conclusion our results demonstrate the relevance of echocardiography in this patient-population in the era of antiretroviral therapy. Above all, left ventricular wall thickness and function should be controlled regularly in HIV-infected subjects. (ClinicalTrials.gov number, NCT01119729).

Keywords: Echocardiography, HIV-Infection, AIDS, cardiomyopathy

Introduction

Survival has markedly improved in HIV-infected patients over the last years, but not without significant adverse events. Cardiovascular disease has been reported as one of the leading cause of death in HIV-infected patients [1-4]. However, this patient population is at risk not only due to an elevated rate of classic cardiac risk factors [5,6]. Unfortunately, various metabolic abnormalities related to antiretroviral treatment (ART), such as diabetes and hyperlipidemia, are being implicated in the increased incidence of cardiovascular disease in this patient population [7,8]. Even the onset of ART has been associated with adverse effects on the cardiovascular system [7]. Other factors that may contribute independently to cardiovascular risk include uncontrolled HIV replication [9], the effects of HIV and ART on vascular endothelial function [9,10] and inflammatory cytokines [11].

Although these cardiotoxic effects have led to a growing concern that HIV-infected patients may be predisposed to the development of clinically significant and progressive cardiomyopathy, there is a lack of large prospective studies of structural and functional abnormalities in this patient population. Determining the deleterious effects of HIV may prove echocardiography to be a useful, non-invasive tool to assess cardiac function and monitor for cardiac abnormalities. Hence, the present study examined a large population of HIV-infected patients both receiving ART and non-treated patients by a comprehensive non-invasive cardiology diagnostic procedure, using conventional echocardiography and new echocardiographic techniques, includ-

ing tissue Doppler imaging. All analyses data are part of the HIV-HEART study, a prospective, cardiology driven, cross-sectional multicenter trial.

Methods

Study design

The HIV-HEART study was funded by the Federal Ministry of Education and Research (FKZ 01GI0205). An operations committee is responsible for the design, conduct and reporting of the study. The study has been regularly evaluated from an international and independent steering committee.

The HIV-HEART study was designed to define the significance of myocardial dysfunction and heart failure in a HIV-infected urban population and classify appropriate methods for identifying high-risk patients, the basis for risk stratification and therapy [12]. The HIV-HEART study population included adult outpatients (≥ 18yrs), who had a known HIV-infection and exhibited a stable disease status within 4 weeks before participation. Patients were recruited during a twenty-month time period in a consecutive manner. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board and performed in compliance with the GCP (good clinical practice) guidelines and the Declaration of Helsinki. Appropriate national regulatory authorities and regional ethics committees further approved this study.

Clinical data collection

Baseline examinations included a patient history, medication treatment and clinical examination, taking of blood samples for comprehensive laboratory tests (including HIV specific parameters, i.e. CD4-cell counts and virus load). Furthermore, non-invasive cardiac tests such as subsequent heart rate and blood pressure measurements, a resting 12-lead electrocardiogram (ECG) and a standardized echocardiography examination were part of the study protocol. Transthoracic echocardiography was performed as described below.

Echocardiographic examination

Transthoracic echocardiography was performed by two not blinded, experienced operators using Toshiba PowerVision 8000 echocardiographic equipment. Both operators were trained before joining the study. Participants were placed in the left lateral supine position and examined in standard parasternal and apical views. Measurements were made in accordance with recommendations of the American Society of Echocardiography [13]. Normal chamber measurement values were defined according to current guidelines [14,15] including the measurement of ejection fraction (EF) by quantitative biplane method of disk. Each patient underwent pulsed-wave Doppler examination of mitral inflow before and during Valsalva maneuver and of pulmonary venous inflow and Doppler tissue imaging of the mitral annulus. Diastolic function was categorized according to the progression of diastolic dysfunction as follows: normal; mild, defined as impaired relaxation without evidence of increased filling pressures; moderate, defined as impaired relaxation associated with moderate elevation of filling pressures or pseudonormal filling, and severe, defined as advanced reduction in compliance or reversible or fixed restrictive filling. Participants were required to have two Doppler criteria consistent with mild, moderate or severe DD to be so classified [16-18]. Additionally, pulsed Doppler pulmonary venous flow and TEI-Index were measured [19]. Left ventricular mass was calculated by the equation of Devereux [15,20,21].

Statistical analysis

Analysis was performed using SPSS (release 17.0.0, August 2008). Data are expressed as mean ± SD, mean value and interquartile range (IQR) from 25%-75% quartile. Continuous variables were analyzed by Wilcoxon's signed rank test and categorical variables by Fisher's exact or χ 2 as appropriate. Echocardiography parameters were normalized to body surface area and afterwards compared with reference values, described by the German Society of Cardiology and the American Society of Echocardiography [15,22,23].

Results

Study patients

A total of 803 eligible patients were enrolled in the study and underwent standardized cardiac examination. Of the 803 patients in this study,

Table 1. Characteristics of enrolled patients

Demographic characteristics	
Mean Age [yrs (IQR)]	44.2 ± 10.3 (37,50)
Gender [n (% Male)]	670 (83.4)
Body-mass index [kg/m^2]	24.1 ± 3.7
Systolic blood pressure [mmHg]	128.4 ± 20.7
Diastolic blood pressure [mmHg]	83.2 ± 12.4
Heart rate [bpm]	70.7 ± 12.2
HIV disease characteristics	
HIV-type 1 (%)	99
CD4$^+$ cell count [cells/mm^3]	509 ± 301
CD4$^+$ / CD8$^+$ - ratio	0.62 ± 0.53
RNA-virus load < 50 copies/µl [%]	65.6
Antiretroviral therapy [%]	85.2
- NRTI [%]	96.8
- NNRTI [%]	45.7
- PI [%]	48.5
Not exposed to ART [%]	14.8

IQR: Interquartile range; bpm: beats per minute; NRTI: nucleoside reverse-transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors

711 (88.7%) were of Caucasian origin. In our population the most common risk factor for HIV-infection was man-having sex with man in 478 of 803 (59.5%) patients. Other ways of transmission were heterosexual contacts in 163 (20.3%) and intravenous drug abuses in 75 (9.4%) of the 803 patients. Only a minority was infected due to blood transfusion, living in epidemic areas or could give no reliable information about risk factors. In correspondence with epidemiological data, this distribution is representative for HIV-infected patients in most industrial countries. The mean age of participants was 44.2 ±10.3 years (83.4% men). Women were younger than men (age 40.3 ± 9.2 vs. 45.0 ± 10.3 years, p<0.0001) and 119 (14.8%) of the total population were over 55 years of age. Duration between first diagnosis of HIV-infection and enrollment was in mean 7.6 ± 5.8 years. Further characteristics of the study population are presented in **Table 1**.

Cardiac dimensions

Germane parameters of echocardiography examination are presented in **Table 2**, including dimensions of atria, ventricle, wall thickness and vessel diameter. 94% of the evaluated parameters were in the reference range, however, some parameter exhibited a higher rate of pathologic results.

In particular, the interventricular septum and the posterior wall thickness were increased in 18.0% and 11.1%, respectively. Furthermore, an elevated rate of pathologic results were present for E-Septum-Separation (EPSS) with 28.2% and in the four chamber view examining the end-diastolic and end-systolic left ventricular dimension with 10.1% and 20.1%, respectively.

Based on body surface, the myocardial mass was 103.9 ± 29.7g/m^2 in male (reference range: 49-115g/m^2) and 90.2 ± 26.5g/m^2 in women (reference range: 43-95g/m^2) [15]. Due to an increase of wall thickness and left ventricular dimension, an elevated myocardial muscle mass was present in 14.3% in male and 19.4% in women of patients with HIV-infection.

Cardiac function

One of the most important clinical parameter of systolic function is the echocardiography quantification of the left ventricular ejection fraction (LVEF) using method of disk on the basis of the left ventricular end-diastolic and end-systolic volume. The mean LVEF was 57.5 ± 7.3% and 65.7% of all measurements were in the reference range (**Table 3**). However, a large proportion of almost one third of the study participants (32%) exhibited a mild reduction of LVEF (45 -

Table 2. Structural echocardiographic findings of HIV-infected patients

Parameter	Mean ± SD	Median	IQR
Long – axis (M-Mode)			
Aorta [mm]	28.8 ± 5.1	29	25 -32
Aorta Dilatation§	1.4% with an aortic diameter > 4 cm		
LVD_{ED} [mm/m²]	26.3 ± 3.4	26.3	24.1 -28.4
LVD_{ED} – Dilatation	4.1% mild LVD_{ED} – Dilatation (W: 3.3-3.4; M: 3.2-3.4 mm/m²)		
	0.6% middle LVD_{ED} – Dilatation (W: 3.5-3.7; M: 3.5-3.6 mm/m²)		
	0.5% severe LVD_{ED} – Dilatation (W: ≥3.8; M: ≥3.7 mm/m²)		
LVD_{ES} [mm/m²]	17.2 ± 3.3	17.1	15.1 – 19.0
LVD_{ES} – Dilatation	10.5% with LVD_{ES} > 21 mm/ m²		
LA_{ES} [mm/m²]	18.1 ± 2.6	18.0	16.3 – 19.7
LA_{ES} – Dilatation	2.0 % mild LA_{ES} – Dilatation (2.4-2.6 mm/m²)		
	0.4% middle LA_{ES} – Dilatation (2.7-2.9 mm/m²)		
	0% severe LA_{ES} – Dilatation (≥ 3.0 mm/m²)		
IVS_{ED} [mm]	10.6 ± 2.3	10.0	9.0 – 12.0
IVS_{ED} – Hypertrophy	18.0% with IVS_{ED} > 12 mm		
PW_{ED} [mm]	10.2 ± 2.0	10.0	9.0 – 11.0
PW_{ED} – Hypertrophy	11.1% with PW_{ED} > 12 mm		
EPSS [mm]	6.5 ± 3.0	6.0	5.0 – 8.0
EPSS – Enlargement	28.2% with EPSS ≥ 7 mm		
$RV_{crosswise}$ [mm]	30.1 ± 5.3	30.0	26.5 – 33.0
$RV_{crosswise}$ – Dilatation	2.7% with RV_{CW} ≥ 40 mm		
Four chamber view (B-Mode)			
LVV_{ED} [ml/m²]	58.2 ± 13.6	56.6	49.3 – 65.9
LVV_{ED} – Dilatation	7.3% mild LVV_{ED} – Dilatation (76-86 ml/m²)		
	1.8% middle LVV_{ED} – Dilatation (87-96 ml/m²)		
	1.0% severe LVV_{ED} – Dilatation (≥ 97 ml/m²)		
LVV_{ES} [ml/m²]	25.2 ± 11.5	23.9	19.6 – 29.2
LVV_{ES} – Dilatation	14.1% mild LVV_{ES} – Dilatation (31-36 ml/m²)		
	3.7% middle LVV_{ES} – Dilatation (37-42 ml/m²)		
	2.3% severe LVV_{ES} – Dilatation (≥ 43 ml/m²)		
$RA_{crosswise}$ [mm/m²]	19.2 ± 3.2	19.0	17.0 – 21.2
$RA_{crosswise}$ – Dilatation	2.7% mild RA-Dilatation (2.6-2.8 mm/m²)		
	0.5% middle RA-Dilatation (2.9-3.1 mm/m²)		
	0% severe RA-Dilatation (≥ 3.2 mm/m²)		

SD: standard deviation; IQR: interquartile range; LVD: left ventricular diameter; LVV: left ventricular volume; ES: endsystolic; ED: enddiastolic; LA: left atrium; IVS: interventricular septum; PW: posterior wall; EPSS: mitral valve E point-septal separation; RV: right ventricle; RA: right atrium; §: age 20–39yrs: 0.97+1.12×KOF±2×0.24; age >40yrs: 1.92+0.74×KOF±2×0.37

54%). Moderate to severe impairment was seen in 2.3% of HIV-infected patients (minimal value was 20%).

Fractional shortening (FS) of less than 25% was present in 10.6% of all participants. Furthermore, 13.5% of HIV-infected subjects exhibited a regional wall motion abnormality of one ore more myocardial segments. While most of these abnormalities were hypokinetic segments, also akinetic and dyskinetic segments were detected (79.6%, 13.9% and 6.5%, respectively).

The diastolic function was achieved by pulsed-waved Doppler measurements and Doppler tissue imaging of the mitral annulus. Diastolic dys-

Table 3. Functional echocardiography findings of hiv-infected patients

Parameter	Mean ± SD	Median	IQR
LVEF [%]	57.5 ± 7.3	57.0	53.0 – 62.0
LVEF – Reduction		32% mild LVEF-Reduction (45-54%)	
		1.9% middle LVEF -Reduction (30-44%)	
		0.4% severe LVEF -Reduction (<30%)	
SVI [ml/m²]	33.4 ± 8.5	32.8	27.8 – 38.3
SVI – Reduction		< 24 ml/m²: 10.5%	

IQR: interquartile range; LVEF: Left ventricular ejection fraction; SVI: stroke volume; ml: millilitre.

Table 4. Doppler measurements of hiv-infected patients

Characteristic	HIV-Infected Patients		
	Mean ± SD	Median	IQR
PW-Doppler (Mitralvalve)			
E-Wave [cm/sec]	66.8 ± 15.7	67	55 -77
E-Wave impairment	15.4% E-Wave flow < 50 cm/sec		
A-Wave [cm/sec]	61.6 ± 14.6	59	51 -71
A-Wave enlargement	25.4% A-Wave flow > 70 cm/sec		
E/A-Wave [cm/sec]	1.14 ± 0.4	1.16	0.8 -1.4
E/A-Wave impairment	38.7% E/A-Ratio < 1		
Deceleration time [ms]	162.6 ± 41.3	156	136 -184
Enlargement of deceleration time	7.8% deceleration time > 220 ms		
Tissue-Doppler (Mitralring)			
E'-Wave [cm/sec]	18.2 ± 5.7	18	14 - 22
A'-Wave [cm/sec]	16.4 ± 5.4	15	13 - 19
E/E'-Wave [cm/sec]	3.9 ± 1.2	3.7	3.1 -4.5
E/E'-Wave impairment	0.3% E/E' of > 10		

IQR: interquartile range; PW: pulsed wave; E-Wave, A-Wave and E/E' ratio is standard Doppler parameters utilized to quantify and categorize diastolic function; cm: centimeter; ms: milliseconds.

function was present in 48% of all HIV-infected subjects. Diastolic dysfunction was characterized mild, moderate and severe in 36%, 9%, and 3%, respectively. Further values of Doppler measurements in our cohort are presented in Table 4.

A global assessment of systolic and diastolic function could be achieved by the TEI-Index. Overall participants, the mean value of the TEI-Index was 0.37 ± 0.14. However, 19.4% of all HIV-infected patients exhibited a pathologic TEI-Index of more than 0.49. Signs of a right ventricular failure, indicated by liver vein congestion, were rare with 0.9% of all patients.

Discussion

Our results provide an overview of echocardiographic findings in HIV-infected patients and make pathologic alterations obvious. In particular, our results highlight the importance of cardiac alterations in terms of systolic and diastolic abnormalities in a cohort of HIV-infected patients.

The frequency of cardiac abnormalities associated with HIV-infection has been described previously. One of the largest studies is the prospective P2C2 HIV Study, which enrolled 205 HIV-infected children [24]. More than 20% of these patients developed myocardial dysfunction and left ventricular dilatation. Patients, who developed symptomatic heart failure, had a 1-year mortality in this trial of over 50%. Together with previous studies these results demonstrate the clinical relevance of cardiac disorders in the HIV-infected patient population [25].

Our results underline an increased rate of car-

diovascular disorders in HIV-infected subjects. As previously described by our research group, left ventricular dilatation is a notable cardiac structural disorder [26]. Recently, Schuster et al. demonstrated cardiac abnormalities to be frequent in HIV-positive patients. Importantly, in this study the changes went along with a decreased exercise tolerance compared to controls, demonstrating the possible heterogeneous side-effects of ART and the HIV-infection itself [26]. These findings are consistent with *in vitro* studies describing a dilated cardiomyopathy or a decompensated heart failure due to the influence of HIV-specific proteins or the use of antiretroviral drugs [27].

An increase of the left ventricular mass is described to be an independent predictor of cardiovascular events and cardiovascular mortality [28,29]. In our study, the interventricular septum and posterior wall thickness were increased in 18.0% and 11.1%, respectively, with elevated muscle mass in 14.3% in male and 19.4% of HIV-infected women. A relevant rate of elevated ventricular mass in HIV-positive patients has been described previously. However, it is still unknown if this is significantly different to non HIV-infected subjects of same age and gender [30,31].

Left ventricular diastolic dysfunction seems to be a common cardiac disorder in HIV-infected patients and is often associated with myocardial hypertrophy. Using a multiparametric echocardiographic approach for the evaluation of diastolic function (see above), we diagnosed a prevalence of 48%. Hence, our results confirm the results of previous studies with smaller patient groups also presenting a pathologic rate of 37-50% of patients with at least mild diastolic dysfunction [31,32]. This was as high as in a HIV-negative high-risk population [32]. Even more relevant seems to be the rate of patients with pathologic contraction pattern and global systolic malfunction in this patient population; even most of these were mild forms of myocardial dysfunction. However, *in vitro* studies still have evaluated a variety of pathologic mechanism that could impair myocardial function [33] and it could be assumed, that left ventricular function will become an even more relevant topic in this patient population in the near future.

There are more HIV-associated cardiac diseases, which we have not considered, yet. In particular, cardiac neoplasm was the first manifestation of acquired immunodeficiency syndrome in a female patient in a state of severe immunodeficiency virus infection [34]. However, in our study no participant had a susceptive result of a cardiac tumor. Another important cardiac manifestation of HIV-infection is pulmonary arterial hypertension as recently described by our group [35].

The present trial is a prospective, multicenter, epidemiological study of over 800 patients. Due to the quality of the study design, the echocardiography examination and the amount of patients, there are only a few limitations that have to be discussed. One limitation might be the sensitivity to determine cardiac disorders. The present study was performed with a standardized echocardiography protocol, and well trained stuff. Therefore, we believe that the present results are reliable and reflect reality. Another limitation might be the exclusion of hospitalized patients. In fact, this group might have lead to a further increased rate of pathologic cardiac findings. Though we had a large population size, there was no comparator control. However, the aim of our work was to analyse the frequency of cardiac disorders in the group of outpatient, which is the biggest part in HIV-community since effective antiretroviral therapy was developed.

Conclusions

Summarizing the data of our cross-sectional multicenter trial, we could demonstrate a relevant number of systolic and diastolic abnormalities in a HIV-infected population. The usefulness of a systematic non-invasive screening for cardiac abnormalities using standardized echocardiographic examination in this population should be considered. Large epidemiologic studies seem to be necessary to determine long-term cardiac outcome associated with echocardiography abnormalities in HIV-infected patients.

Acknowledgement

This work was supported by the Competence Network of Heart Failure funded by the Federal Ministry of Education and Research (BMBF), FKZ 01GI0205. The authors give their respect and thanks to all participating and supporting

persons of the present study, including the staff of the recruiting centers, i.e. the team of Dr. Becker-Boost (Duisburg), Dr. Rudolph (Essen), Dr. Hower (Dortmund), Prof. Dr. Brockmeyer (Bochum), and Dr. Esser (Essen).

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References

[1] Mocroft A, Brettle R, Kirk O, Blaxhult A, Parkin JM, Antunes F, Francioli P, D'Arminio Monforte A, Fox Z, Lundgren JD; EuroSIDA study group. Changes in the cause of death among HIV-positive subjects across Europe: results from the EuroSIDA study. AIDS 2002; 16: 1663–71.

[2] Bonnet F, Morlat P, Chêne G, Mercié P, Neau D, Chossat I, Decoin M, Djossou F, Beylot J, Dabis F; Groupe d'Epidémiologie Clinique du SIDA en Aquitaine (GECSA). Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy. HIV Med 2002; 3: 195–9.

[3] D:A:D Study Group, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Møller N, Kirk O, Pradier C, Weller I, Phillips AN, Lundgren JD. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. Lancet 2008; 371: 1417-26.

[4] Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, Fichtenbaum CJ, Gerschenson M, Mitchell CK, Murphy RL, Squires K, Stein JH; ACTG 5152s Study Team. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy. J Am Coll Cardiol 2008; 52: 569-76.

[5] Barbaro G, Klatt EC. HIV infection and the cardiovascular system. AIDS Rev 2002; 4: 93-103.

[6] Neumann T, Woiwoid T, Neumann A, Miller M, Ross B, Volbracht L, Brockmeyer N, Gerken G, Erbel R. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: part I. Differences due to the acquisition of HIV-infection. Eur J Med Res 2003; 8: 229-35.

[7] Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiébaut R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003; 349: 1993-2003.

[8] Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD; DAD study group. Cardiovascular disease risk factors in HIV patients - Association with antiretroviral therapy. Results from the DAD study. AIDS 2003; 17: 1179–93.

[9] Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fätkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport C. CD4+ count- guided interruption of antiretroviral therapy. N Engl J Med 2006; 355: 2283–96.

[10] Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, Fichtenbaum CJ, Gerschenson M, Mitchell CK, Murphy RL, Squires K, Stein JH. Antiretroviral therapy improves endothelial function in individuals with human immunodeficiency virus infection: A prospective, randomized multicenter trial (Adult AIDS Clinical Trials Group Study A5152s). J AM Coll Cardiol 2008; 52: 569-76.

[11] Mu H, Chai H, Lin PH, Yao, Q, Chen C. Current update on HIV-associated vascular disease and endothelial dysfunction. World J Surg 2007; 31: 632–43.

[12] Neumann T, Esser S, Potthoff A, Pankuweit S, Neumann A, Breuckmann F, Neuhaus K, Kondratieva J, Buck T, Müller-Tasch T, Wachter R, Prettin C, Gelbrich G, Herzog W, Pieske B, Rauchhaus M, Löffler M, Maisch B, Mügge A, Wasem J, Gerken G, Brockmeyer NH, Erbel R; HIV-HEART Study Investigative Group.. Prevalence and natural history of heart failure in outpatient HIV-infected subjects: rationale and design of the HIV-HEART study. Eur J Med Res 2007; 12: 243-8.

[13] Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smit. 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003; 16: 1091-110.

[14] Erbel R, Schweizer P, Henn G, Meyer J, Effert S. Apical two-dimensional echocardiography: normal values for single- and bi-plane determi-

nation of left ventricular volume and ejection fraction. Deutsche Medizinische Wochenschrift 1982; 107: 1872–7.
[15] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–63.
[16] Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539–2550.
[17] Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998; 32:865–875.
[18] Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, Döring A, Broeckel U, Riegger G, Schunkert H. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J 2003; 24: 320–8.
[19] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: Causal mechanisms and treatment. Circulation 2002; 105: 1503–8.
[20] Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450–8.
[21] Jafary FH: Devereux formula for left ventricular mass—be careful to use the right units of measurement. J Am Soc Echocardiogr 2007; 20: 783.
[22] Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J: Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989; 64: 507–12.
[23] Buck T, Breithardt OA, Faber L, Fehske W, Flachskampf FA, Franke A, Hagendorff A, Hoffmann R, Kruck I, Kücherer H, Menzel T, Pethig K, Tiemann K, Voigt JU, Weidemann F, Nixdorff U. Manual zur Indikation und Durchführung der Echokardiographie. Clin Res Cardiol Suppl 2009; 4: 3–51.
[24] Starc TJ, Lipshultz SE, Easley KA, Kaplan S, Bricker JT, Colan SD, Lai WW, Gersony WM, Sopko G, Moodie DS, Schluchter MD. Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: The prospective P2C2 HIV study. J Pediatr 2002; 141: 327-34.
[25] Schuster I, Thöni GJ, Edérhy S, Walther G, Nottin S, Vinet A, Boccara F, Khireddine M, Girard PM, Mauboussin JM, Rouanet I, Dauzat M, Cohen A, Messner-Pellenc P, Obert P. Subclinical cardiac abnormalities in human immunodeficiency virus-infected men receiving antiretroviral therapy. Am J Cardiol 2008; 10: 1213-7.
[26] Breuckmann F, Neumann T, Kondratieva J, Wieneke H, Ross B, Nassenstein K, Barkhausen J, Kreuter A, Brockmeyer N, Erbel R. Dilated cardiomyopathy in two adult human immunodeficiency positive (HIV+) patients possibly related to highly active antiretroviral therapy (HAART). Eur J Med Res 2005; 10: 395-9.
[27] Hruz PW, Yan Q, Struthers H, Jay PY. HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. FASEB J 2008; 22: 2161-7.
[28] Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 2001; 141: 334–41.
[29] Benjamin EJ, Levy D. Why is left ventricular hypertrophy so predictive of morbidity and mortality? Am J Med Sci 1999; 317: 168–75.
[30] Hsue PY, Hunt PW, Ho JE, Farah HH, Schnell A, Hoh R, et al. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail 2010; 3: 132-9.
[31] Mansoor A, Golub ET, Dehovitz J, Anastos K, Kaplan RC, Lazar JM. The association of HIV infection with left ventricular mass/hypertrophy. AIDS Res Hum Retroviruses 2009; 25: 475-81.
[32] Nayak G, Ferguson M, Tribble DR, Porter CK, Rapena R, Marchicelli M, Decker CF. Cardiac diastolic dysfunction is prevalent in HIV-infected patients. AIDS Patient Care STDS 2009; 23: 231-8.
[33] Chaves AA, Mihm MJ, Schanbacher BL, Basuray A, Liu C, Ayers LW, Bauer JA. Cardiomyopathy in a murine model of AIDS: evidence of reactive nitrogen species and corroboration in human HIV/AIDS cardiac tissues. Cardiovasc Res 2003; 60: 108-18.
[34] Iwahashi N, Nakatani S, Kakuchi H, Yamagishi M, Fukuchi K, Ishida Y, Hirooka K, Koretsune Y, Ueta C, Shirasaka T, Kitakaze M. Cardiac

tumor as an initial manifestation of acquired immunodeficiency syndrome. Circ J 2005; 69: 243-5.

[35] Reinsch N, Buhr C, Krings P, Kaelsch H, Kahlert P, Konorza T, Neumann T, Erbel R; Competence Network of Heart Failure. Effect of gender and highly active antiretroviral therapy on HIV-related pulmonary arterial hypertension: results of the HIV-HEART Study. HIV Med 2008; 9: 550-6.