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MR Characterization of Cardiac Abnormalities in HIV+ Individuals with Increased BNP Levels

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Abstract
Objective: To characterize cardiac abnormalities in HIV+ patients with increased serum B-type natiuretic peptide (BNP) by contrast-enhanced cardiac magnetic resonance imaging (MRI).
Design: Non-blinded prospective consecutive cohort evaluation.
Methods: More than 400 HIV+ patients were screened for potential BNP alterations. 16 met the inclusion criteria of elevated BNP levels and 12 patients could finally be enrolled. MRI analysis comprised function, oedema and late enhancement sequences.
Results: Patients exhibited a median serum BNP level of 249 pg/ml. Based on MRI, diagnosis of left ventricular hypertrophy (n = 3), myocarditis (n = 2), chronic myocardial infarction (n = 2), dilated cardiomyopathy (n=1) and right ventricular failure (n = 1) was made.
Conclusions: Although no specific MR pattern was found, MR allowed characterization of the underlying cardiac pathologies in 82% of HIV+ patients with elevated BNP levels.

Key words: HIV; AIDS; BNP; cardiac MRI; comorbidity

Introduction

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are known to be associated with cardiac involvement [1, 2]. Although life expectancy was dramatically reduced due to non-cardiac diseases, severe stages of HIV-related cardiomyopathy represented by NYHA functional classes III-IV could be frequently observed even in the pre-highly active antiretroviral therapy- (HAART-) era [3]. Nowadays, HAART has substantially improved the survival of patients with HIV disease resulting in a further increase of severe cardiac comorbidity [4, 5]. Additionally, HAART may independently contribute to cardiac impairment including acute onset heart failure, chronic dilated cardiomyopathy, coronary heart disease, and arrhythmias [6].

Extent, complexity and severity of cardiac involvement represent important factors influencing outcome and prognosis in HIV individuals. Therefore, early diagnosis and accurate staging of cardiac involvement are fundamental for appropriate management and therapy and remain an ongoing challenge. A subsectional program of the German heart failure network ("Kompetenznetz Herzinsuffizienz") currently analyzes the primary prevalence of heart failure in HIV+ patients [7]. Standardized examinations include patient history, clinical examination, ECG, 6-minutes-walk-test, B-type natiuretic peptide (BNP) measurement, and transthoracic echocardiography, where appropriate. As cardiac magnetic resonance imaging (MRI) is able to detect structural and functional myocardial and/or perimyocardial abnormalities, aim of our study was to determine different reasons for cardiac failure in HIV+ individuals with an increased serum BNP levels by means of cardiac MRI.

Material and Methods

Patients

Starting in 2003 a standardized non-invasive screening was performed in all HIV+ individuals treated in our departments (approximately 3 patients per week, together > 400 patients). The locally appointed ethics committee has approved the research protocol and informed consent has been obtained form all subjects. Until now, 16 HIV+ patients met the inclusion criteria of significantly elevated BNP levels (cut-off score > 100 pg/ml) [8]. Of these 16 individuals 3 patients refused to participate in the study and 1 patient died before the scheduled examination. Therefore, 12 patients (8 male, 4 female; age: 25-75 years; status: CDC/WHO A2-C3) were enrolled into the study in accordance with the regulations of the local ethics committee.

All patients were treated by a combination of nucleoside reverse transcriptase inhibitor and protease inhibitor resulting in a stable immunologic and virologic outcome. The most important clinical, laboratory and echocardiographic findings are summarized in Tables 1 and 2. Prior to the cardiac MR examination wall motion abnormalities, myocardial or valvular alterations were detected by echocardiography in 9

*Both authors contributed equally to this publication.

Table 1. Clinical and laboratory overview of 12 HIV+ patients with increased BNP levels and subsequent MRI assessment.

Patient [No]	Stage [CDC‡]	CVRF[]	ECG	CRP§ [mg/dL]	6-min-WTD* [m]	BNP† [pg/mL]	NYHA
1	B2	dyslip.¶	bradycardia, negative T-waves	0	400	122	II
2	C3	hypert. #, dyslip., diabetes	AV-block I°	0.5	n/a	134	I
3	A3	-	leftanterior hemiblock	1.1	380	141	I
4	B2	hypert.	left bundle-branch block	0	240	149	II
5	A3	dyslip., smoking	bradycardia, negative T-waves	0.1	240	152	III
6	B2	dyslip.	normal	0.1	320	208	I
7	A2	hypert., dyslip., diabetes	AV-block I°	0.7	n/a	254	II
8	B2	hypert., diabetes	normal	0.9	320	287	I
9	C3	-	normal	0.2	400	309	I
10	B3	dyslip.	left bundle-branch block	0.2	440	339	III
11	C3	hypert., dyslip.	right bundle-branch block	0.8	n/a	666	III
12	C3	dyslip.	normal	0.4	n/a	168	I

*6-min-WTD = 6-min-walk-test-distance; †BNP = B-type natiuretic peptide; ‡CDC = center of disease control; §CRP = c-reactive protein; []CVRF=cardiovascular risk factors; ¶dyslip. = dyslipidemia; #hypert. = hypertension

Table 2. Corresponding echocardiographic overview of 12 HIV+ patients with increased BNP levels and subsequent MRI assessment.

Patient [No]	Ejection fraction [%]	Regional wall motion	PAP* [mmHg]	Differential diagnosis
1	43	hypokinesia	27	unspecified
2	57	-	n/a	left ventricular hypertrophy
3	45	hypokinesia	30	left ventricular hypertrophy
4	52	dyskinesia	33	unspecified
5	32	hypokinesia	n/a	unspecified
6	62	-	21	normal
7	63	-	n/a	left ventricular hypertrophy
8	60	-	30	left ventricular hypertrophy
9	60	-	35	normal
10	28	akinesia	n/a	dilated cardiomyopathy
11	52	-	73	pulmonary hypertension
12	52	-	27	normal

*PAP = pulmonary artery pressure

patients.

MR Assessment

All examinations were performed on a 1.5T MR scanner equipped with high performance gradients (Magnetom Avanto, Siemens medical solutions, Erlangen, Germany). The MRI protocol included a steady state free precession cine sequence (TrueFISP, TR 3 ms, TE 1.5 ms, FA 60°) for the assessment of the myocardial function in all patients. For assessment of myocardial oedema a fat-suppressed T2-weighted turbo spin echo (TR 1600 ms, TE 49 ms, FA 180°) sequence was performed. Additionally, an inversion recovery fast low angle shot sequence (IR-turboFLASH: TR 8.0 ms, TE 4.0 ms, TI 180-240 ms, FA 20°) was acquired in short and long axis views 10 to 15 min after injection of a 0.2 mmol/ kg bodyweight of Gd-DTPA (Schering AG, Berlin, Germany) to detect delayed contrast enhancement.

Analysis

Volumetric measurements were performed based on contiguous short axis scans using the manufacturer provided software and semiautomatic contour detection (ARGUS software, Siemens medical solutions, Erlangen, Germany). Regional wall motion was characterized as normal, hypo-, a- or dyskinetic using the 17 segment model. For the detection of myocardial oedema the T2- weighted sequences were qualitatively eval-

Table 3. Screening results following MRI assessment in 12 HIV+ patients with elevated BNP levels.

Patient [No]	EF† [%]	Oedema	Regional wall motion	Myocardial mass [g/m²]	Late enhancement	Differential diagnosis
1	54	-	-	55	spotted/streaky	myocarditis
2	60	-	-	80	-	left ventricular hypertrophy
3*	n/a	n/a	n/a	n/a	n/a	n/a
4	52	-	dyskinesia	52	subendocardial	myocardial infarction
5	29	-	akinesia	76	transmural	myocardial infarction
6	60	-	-	53	-	normal
7	67	-	-	79	-	left ventricular hypertrophy
8	68	-	-	73	-	left ventricular hypertrophy
9	64	-	-	41	streaky, subepicardial	myocarditis
10	25	-	akinesia	71	-	dilated cardiomyopathy
11	60	-	-	54	-	pulmonary hypertension
12	64	-	-	50	-	normal

* data of patient no. 3 omitted due to inadequate image acquisition
† EF = ejection fraction

uated. Pattern and extent of late enhancement were assessed using short and long axes views.

All examinations were interpreted by 2 radiologists (K.N.; J.B.) and 1 cardiologist (F.B.) in consensus. Diagnosis was assessed using common criteria as described elsewhere [9-15].

Results

Patients exhibited a median serum BNP level of 249 ± 152 pg/ml. Six patients complained about cardiac symptoms in terms of dyspnoe following moderate to severe exercise (NYHA II-III) during the last six months prior to examination (Table 1).

Adequate MR image acquisition could be achieved in all but one patient (patient no. 3). After consideration of patient history, ECG, clinical appearance, laboratory parameters, 6-min-walk-test and echocardiographic evaluation alone, heart function and morphology of 3 patients was described as being normal (patients no. 6, 9, 12) and diagnosis in additional 3 patients displaying regional hypo- to dyskinesia remained unspecific (patients no. 1, 4, 5). MR evaluation could assign further diagnosis in all of the latter 3 patients as well as in 1 of the 3 patients, who were initially judged as normal (patient no. 9). Moreover, MR assessment was able to support the differential diagnosis in all of the remaining 5 patients (patients no. 2, 7, 8, 10, 11). Based on the MR findings the following diagnoses were finally suggested (Table 3):

a) left ventricular hypertrophy defined by concentric or asymmetric thickening of the left ventricle and increased myocardial mass (n = 3, Fig. 1a),
b) myocarditis and perimyocarditis (n = 2, Fig. 1b) characterized by diffuse non-segmented patchy spotted or streaky late enhancement,
c) chronic myocardial infarction (n = 2, Fig. 1c) defined by segmented subendocardial to transmural delayed enhancement pattern,
d) dilated cardiomyopathy characterized by dilated ventricles, regional or global contractility as well as reduced ejection fraction (n = 1, Fig. 1d), and
e) isolated right ventricular failure described by impaired right ventricular contractility and right ventricular volume overload (n = 1, Fig. 1e)

Only two patients did not show any pathologic abnormalities.

Discussion

This study performing contrast enhanced cardiac MR exams in HIV+ patients with elevated BNP levels carries three messages we believe to be important:

1. Functional abnormalities could be detected in 9 of 11 of the subjects using cardiac MRI.
2. Compared to other non-invasive examinations including echocardiography additional diagnosis could be obtained.
3. Although no specific pattern was found MRI allowed for a definite diagnosis in most of our patients.

The natriuretic peptides play a fundamental role in cardiovascular remodeling, volume homeostasis, and the response to myocardial injury [16, 17]. Current investigations have focused on their diagnostic usefulness for heart failure, left ventricular dysfunction and their prognostic usefulness after acute coronary syndromes and/or heart failure [18-20]. BNP is a cardiac neurohormone released as pre-pro-BNP, which is afterwards enzymatically cleaved to N-terminal-proBNP and BNP upon ventricular, especially the left ventricular, myocyte stretch. It acts via arterial dilatation, modulation of levels of vasoconstricting and sodium-re-

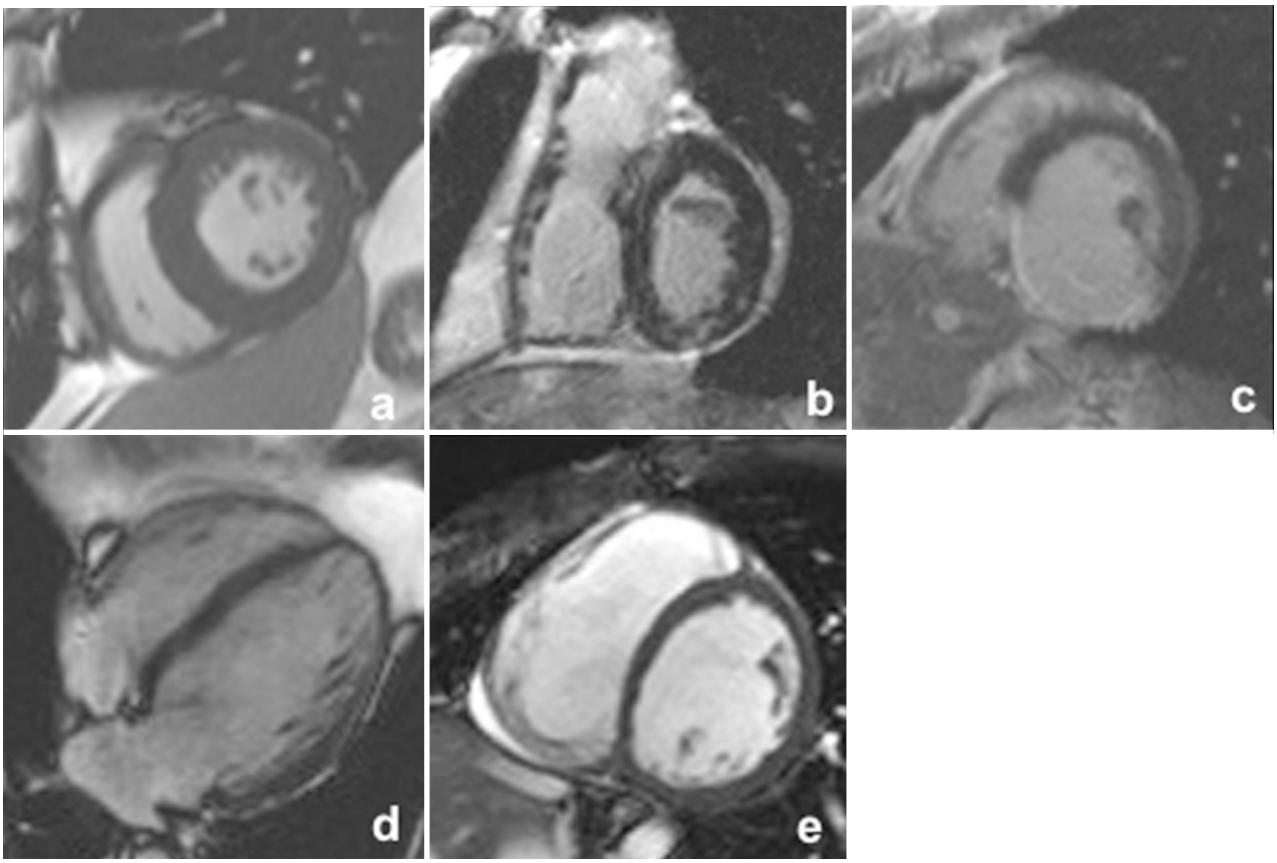

Fig. 1. a: Left ventricular hypertrophy. Steady state free precession cine sequence image in short axis demonstrates a hypertrophic left ventricle with pronouncement of the interventricular septum (patient No. 8).
b: Myocarditis/perimyocarditis. Breath-hold ECG-gated inversion recovery fast low angle shot sequence image in short axis view, obtained about 10 minutes after the injection of gadolinium contrast media, presenting delayed enhancement in a spotted streaky distribution (patient No. 1).
c: Chronic transmural myocardial infarction. Breath-hold short axis ECG-gated inversion recovery fast low angle shot sequence image, obtained about 15 minutes after the injection of gadolinium contrast agent, indicating transmural late enhancement in the right coronary artery territory (patient No. 5).
d: Dilated cardiomyopathy. Diastolic cine SSFP image revealing a significant dilatation of the left ventricle, global thinning of the left ventricular wall and a severely reduced ejection fraction (patient No. 10).
e: Right ventricular failure. Steady state free precession cine sequence image in the short axis view showing overall dilatation of the right ventricle accompanied by a thinning of the right ventricular wall (patient No. 11).

taining neurohormones as well as maintaining homeostasis by promoting diuresis and natriuresis [21]. To date, the BNP assay is especially used as a diagnostic and prognostic aid in congestive heart failure. In general, BNP levels exceeding 100 pg/mL have been proposed to be increased [19, 20, 22]. However, on the one hand, the above-mentioned cut-off score at least holds the limitation of lacking age normalization and adaptation to renal failure, on the other hand, BNP levels may also be increased in other cardiovascular diseases including ischemia, arrhythmias, fibrosis, cardiac hypertrophy, and coronary endothelial dysfunction [23]. Moreover, as to current literature, only slight elevations even below the cut-off point might already trigger an increased long-time risk for the development of such disorders [24]. Therefore, elevated BNP levels, which can easily be measured in routine clinical practice, seem to identify patients at risk for different cardiac disorders. However, elevated BNP levels alone remain an unspecific finding, and HIV+ patients may suffer from a variety of cardiac diseases. Of these, three major reasons, which might act independently or – even worse – in combination, have been proposed to be critical in the pathogenesis of secondary heart failure: direct HIV-induced myocardial changes, HIV-related cardiomyopathy and coronary artery disease. Additionally, a variety of further cardiac lesions have been reported in HIV infection including nonspecific or infectious myocarditis, pericardial disease with effusion or even tamponade, endocardial valvular disease due to marantic or infective endocarditis, arrhythmias, pulmonary hypertension and neoplastic invasion [1, 25].

Additionally, coronary artery disease resulting from therapy-induced dyslipidaemia and insulin resistance, drug-related cardiotoxicity, inflammation as well as cardiac autonomic dysfunction are getting increasingly prevalent in the post HAART-era. Whereas the connection between HAART and coronary artery disease is obvious the pathogenesis of HAART-induced sec-

ondary heart involvement is still poorly understood [26, 27]. However, at least as far as cardiotoxicity and therapy-induced cardiomyopathy are concerned, mitochondrial dysfunction due to the inhibition of the mitochondrial polymerase gamma by the NRTIs, such as it has been found in skeletal muscle myopathy, have been proposed [28, 29]. Studies performed in transgenic mice suggest that antiretroviral regimens are associated with diffuse destruction of cardiac mitochondrial ultrastructures and with an inhibition of mitochondrial DNA replication [30].

In our cohort of HIV+ patients displaying raised BNP levels, diagnosis other than normal was reached in 9 of 12 patients by echocardiography – but 3 of these just dislosed regional wall motion abnormalities, so finally only 6 of 12 were definitively diagnosed. On contrast enhanced cardiac MRI, 9 of 12 individuals showed different cardiac abnormalities. Pathological findings included left ventricular hypertrophy, (peri-) myocarditis, chronic ischemia, dilated cardiomyopathy and isolated right ventricular failure. Together, MR noted a new diagnosis in 1 of the echocardiographically normal individuals, and confirmed infarction in the 3 with regional wall motion abnormalities, therefore reaching a diagnosis in 9 of 11 (or 12) by MRI – one had inadequate imaging. Interestingly, patients exhibited a median BNP level of 249 pg/mL, which is more or less only a relatively slight increase of the BNP value. However, these slight increases are associated with a concommitant large percentage of BNP positive HIV individuals with NYHA functional class I. Due to the coexistence of an eminent HIV infection and ongoing HAART regimen in our patients, a direct HIV-related heart failure or therapy-induced cardiac impairment cannot be discriminated. Indeed the spectrum of cardiac diseases detected by MR imaging was quite heterogenous and may not solely be related to the underlying HIV disease. Although only a limited number of patients have been included so far, our data show that compared to echocardiography additional diagnosis may be achieved, resulting in a final diagnosis in 9/11 HIV patients with elevated BNP levels. These findings might have an impact on future therapy, as the differentiation between ischemic or non-ischemic alterations or between HIV- and HAART-associated impairments, respectively, may lead to different therapeutic consequences such as different schemes of oncoming medication (i.e. beta-blockers, ACE-inhibitors) or a potential change of current pharmaceutics (i.e. nucleoside reverse transcriptase inhibitors following resistogram) [5, 15, 16].

Limitations

In general, it is likely that cardiac MRI will provide insights not offered by other modalities. However, in our study the number of patients looked at is small. Further, there is a large variation of age ranging from 25 to 75 years as a possible bias of our observations. Due to its design resulting from a general screening, there is no indication to what extent their cardiac disease can be attributed to HIV or HIV therapy. The patients studied had clear cardiovascular risk factors that could explain at least some of the echocardiographic or MR findings. Additionally, without having a cardiac MRI study before starting medication, we cannot directly draw conclusions about the cardiac effects of the medication. Again, due to its design, the study further lacks an independent method confirming the MR diagnoses. For example, retrospectively no documented raise of cardiac enzymes could be evaluated in the individuals with assumed former myocarditis. However, for some diagnosis MR must be considered the clinical standard of reference, whereas in other cases an invasive procedure, e.g. myocardial biopsy was not justified in asymptomatic patients.

Together, it seems that the MRI is contributory increasing the diagnostic yield, nevertheless our data are yet not able to support a statistically significant advantage in contrast to echocardiography.

Conclusion

Taking our preliminary data into account, although no specific pattern of functional abnormalities or contrast enhancement were found, our study demonstrates that contrast enhanced MRI allows at least characterizing different underlying diseases in HIV+ individuals with elevated serum BNP levels. Even though these abnormalities cannot be directly linked to HIV as the underlying origin, as cardiovascular complications are important contributors to morbidity and mortality in HIV-infected patients, further studies are mandatory in order to assess a possible correlation between clinical stages of disease and prognosis and (peri-) myocardial involvement detected by native and/or contrast enhanced MRI for early detection and effective treatment. Further, assessment in HIV-infected naïve patients with increased BNP as controls would be of interest in order to exclude the possible interfering role of HAART in the assessment of clinical diagnosis.

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