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Significant coronary stenosis detected by coronary computed angiography in asymptomatic HIV infected subjects

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Summary *Objectives:* increased incidence of acute coronary events, high rate of abnormal surrogate markers of atherosclerosis and increased amount of coronary calcium have been described in HIV infected population.

To expand knowledge on coronary artery disease (CAD) in HIV patients, cardiac CT scan was performed in asymptomatic subjects with low cardiovascular (CV) risk.

Methods: A cross-sectional study using dual-source CT (MDCT) coronary angiography.was conducted in HIV-infected subjects with the following characteristics: Framingham Risk Score (FRS) $\leq$10, absence of metabolic syndrome, negative echocardiographic and ECG stress-test. A luminal narrowing exceeding 50% was defined as a clinically significant coronary stenosis.

Calcium score was quantified using the Agatston Calcium Score method.

Results: Fifty-five subjects were enrolled. Significant coronary stenoses, requiring coronary angiography, were found in 16/55 (29.1%). At multivariate analysis older age was the only variable independently associated with the presence of significant luminal narrowing ($p = 0.011$).

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Conclusions: MDCT showed an unexpected, age-associated high rate of significant coronary stenosis in asymptomatic HIV positive subjects with low CV risk. These findings suggest that aggressive screening programs for coronary artery disease may be appropriate in this population; further studies are recommended to assess the appropriateness of MDCT for this purpose.

Introduction

In the last few years increased cardiovascular morbidity and mortality has been reported in subjects with HIV infection,[1] even in countries where the rate of this complication is relatively low.[2] Commonly used tools to evaluate cardiovascular risk, such as the Framingham Risk Score (FRS), are inadequate in HIV + subjects,[3] in fact, elevated levels of high sensitive C-reactive protein, suggestive of an increased risk of acute coronary events, have been found in HIV + individuals with low FRS.[4] Markers of subclinical atherosclerosis, such as carotid artery intima-media thickness[5,6] and stiffness of femoral artery,[7] are altered in asymptomatic HIV + individuals, even if antiretroviral-naïve.[8] At the coronary level, high values of coronary artery calcium (CAC) suggest accelerated coronary ageing in HIV + patients.[9] To expand the current knowledge on subclinical coronary artery disease (CAD) in HIV + subjects, we performed a pilot study in a group of HIV + asymptomatic individuals with low cardiovascular (CV) risk and a negative echocardiographic and ECG stress-test. Dual-source CT (MDCT) coronary angiography scan[10,11] was used as a non-invasive test.

Materials and methods

Patients and methods

HIV-infected subjects recruited from the Department of Public Health and Infectious Diseases of the "Sapienza" University of Rome (Italy) were included in this cross-sectional study. The protocol was approved by the Ethics Committee of "Azienda Policlinico", Rome, and all the patients gave their informed consent to participate. Recruiting method was based on physician referrals and inclusion/exclusion criteria that were chosen to select a sample of the asymptomatic HIV infected population that had a low cardiovascular risk (see below). Multiple cardiovascular risk factor assessment was utilized for reducing the possibility of selection bias. The size of sample was determined by the availability of eligible patients consenting to participate.

The following criteria were needed for inclusion: FR risk score $\geq$10%, absence of metabolic syndrome (according to the definition of Adult Treatment Panel III − ATPIII[12]), negative echocardiographic and ECG stress-test. In addition, since HIV/HCV coinfection has been associated with an increased risk of cardiovascular disease, patients had to be negative for anti-HCV antibodies.[13]

Age, medical and family history, smoking, recreational drug use, duration of HIV disease (time from diagnosis), antiretroviral therapies, nadir of CD4+ cell count were collected. Body mass index (BMI) was calculated for each subject as weight divided by the square of height.

Serum glucose, cholesterol, triglycerides and HDL cholesterol were measured in blood samples. LDL was calculated according the Friedewald equation.

Current CD4+ and CD8+ cell count were determined by flow cytometric analysis. HIV-1 RNA plasma levels were measured by a quantitative reverse polymerase chain reaction (Amplicor HIV Monitor; Roche Diagnostic Systems, Branchburg, NJ version 1.5, l.o.d. 50 copies/ml). High sensitive C-reactive protein (hs-CRP) was measured using an Instant ELISA kit (Bender MedSystem, Inc Vienna, Austria) with l.o.d. 78 pg/ml. Cut-off values based on HIV-uninfected-populations were used to define 3 categories of cardiovascular risk: $<$ 1 mg/L: low risk; 1−3 mg/L: average risk: $>$3 mg/L: high risk.[14] As an internal control, serum hs-CRP was measured in 10 healthy uninfected controls (blood donors); mean value was 0.245 $\pm$ 0.319 mg/L.

Stress-test evaluation

Stress echocardiography and ECG were performed in all patients according to Guidelines.[15,16]

Multi-detector computed tomography protocol

All patients were examined by using a low-dose prospectively ECG-triggered CT coronary angiography protocol with a 64-slice multi-detector MDCT scanner (Somatom Definition Siemens Medical Solution, Forehheimen, Germany). In patients with heart rates $>$70 bpm, a single oral dose of a β-blocker (metoprolol 5 mg) was administered 1 h prior to the examination.

A preliminary unenhanced acquisition was performed for determination of coronary calcium score, followed by a contrast enhanced scan with 70 mL of high concentration iodine contrast agent (400 mgI/100 mL, Iomeron 400, Bracco, Milan, Italy) +40 mL of saline administered in the antecubital vein.

Calcium score was quantified using the Agatston Calcium Score method[17] from 3 mm non-overlapping sections by using a semi-automated software (Calcium Scoring CT; Siemens Medical Solutions).

Image analysis

MDCT dataset were transferred and analyzed on a dedicated cardiac workstation (Vitrea 2.6; Vital Images; USA).

For the analysis, the American Heart Association (AHA) coronary arteries segmentation model was adopted[18,19] and all segments with a diameter $\geq$1 mm at their origin were included. Two experienced cardiovascular radiologists (MF and AA) independently evaluated all coronary segments for the presence or absence of coronary plaques. Degree of luminal stenosis was classified as mild (grade I; 30−49%) moderate

(grade II; 50–69%), severe (grade III; 70–99%) or coronary occlusion (grade IV; 100%). A threshold of 50% luminal narrowing in any coronary segment greater than 1.5 mm in diameter was adopted to define clinically significant coronary stenosis.[20]

According to their CT attenuation values (Hounsfield Units; HU), significant lesions were semi-quantitatively classified as follows: non-calcified lesions (density <30 HU), fibro-calcified lesions (31–220 HU) and predominantly calcified lesions (>221 HU).[21,22]

Coronary angiography (CA)

All patients with coronary lesions ≥ Grade II at MDCT were considered for CA. This was performed using standard technique, with angiograms evaluated by two experienced readers (MM and FF) blinded to the MDCT results. The AHA segmentation model[23] was applied and degree of stenosis was quantified (quantitative coronary angiography, QCA) (Allura Xper FD 10, Philips Medical Systems). A significant stenosis was defined as a reduction in diameter ≥ 70%. The decision to perform coronary revascularization was made according to the recently redefined appropriateness criteria.[24]

Statistical analysis

Descriptive statistics were used to describe the sample. Values are given as mean ± SD. Presence of significant coronary lesions was considered as a dichotomized variable (yes/no). The chi square test was used to compare categorical variables, and the Student's test for continuous variables. Pearson correlation coefficient was used to determine correlations. Logistic regression analysis was used to perform adjusted analysis for binary outcome of the presence of plaques. A p-value <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using the SPSS version 17 software programs (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Fifty-five HIV + subjects with low CVD risk according to the above criteria were studied. Their main demographic, clinical and viroimmunological features are summarized in Table 1. 85.5% of them were males, mean (±SD) age was 47.6 ± 8.7 years, FR score was 4.1 ± 3.0 Six (10.9%) were HAART naïve; the remaining 49 had been on HAART for 9.4 ± 5 years. Of them 74.5% had less than 50 copies/ml of plasma HIV-1 RNA. Mean CD4+ cell count at study was 493 ± 223 cell/mmc; mean CD4+ nadir was 198.9 ± 126 cell/mmc.

CT coronary angiography

MDCT examination was successfully and safely performed in all patients.

Significant stenoses (i.e grade II–IV) were observed in 16/55 patients (29.1%). Of these 16, 9 (56.2%) had 1-vessel, 5 (31.3%) had 2-vessel and 2 (12.5%) had 3-vessel coronary disease. Considering the main coronary arteries, a significant obstruction was present in 28 of 64 examined arteries (43.8%). In 5 of these (17.9%) a significant stenosis involved the left main coronary artery (LMCA); in 14 (50.0%) the left anterior descending artery (LAD); in 7 (25.0%) the circumflex coronary artery (Cx); in 2 (7.2%) the right coronary artery (RCA).

When significant plaques were categorized according to density, in the 16 patients with ≥50% stenosis and detectable plaques, these were soft in 43.8% of cases, mixed in 37.5% and calcified in the remaining 18.8%. In subjects with non significant stenosis, these proportions were 52.9%, 35.3% and 11.8%, respectively ($p = 0.811$, not significant between the two groups).

As expected, number and extension of the lesions were higher in patients with more severe stenosis; multiple lesions were found in 87.5% of those with ≥50% stenosis and in 47.1% of subjects with non significant stenosis ($p = 0.026$) Their mean length was 16.66 ± 8.38 and 6 ± 4.33 mm, respectively ($p = 0.001$).

Calcium score

Mean Agatston score in the whole population was 21.25 ± 63.53. This value was 1.39 ± 5.35 in subjects without significant lesions and 103.200 ± 150 in the group with significant stenosis ($p = 0.016$). Values >100 were found in 6 of 55 (10.9%) patients, all of them with significant stenosis.

On the other hand, significant stenosis (due to soft, non-calcified plaques) was present in 5/16 patients (31.2%) with <1 Agatston score.

Agatston score progressively and significantly increased with patient's age ($r = 0.538$; $P = 0.001$).

CA results and patient's revascularization

At the time this paper is written, 13 of the 16 subjects with significant stenosis at CT have undergone CA; in 8 of them (61.5%) significant stenoses were found, The distributions of single-vessel, 2-vessel and 3-vessel disease were 4/8 (50.0%), 2/8 (25.0%), 2/8 (25.0%) respectively.

Eight patients underwent a percutaneous coronary intervention with application of 16 drug-eluting stents (Biosensors, Biomatrix® DES) (average number per patient: 2.0). MDCT and CA findings in an individual patient are reported in Fig. 1.

High sensitive CRP

Hs-CRP mean value was 0.988 ± 0.842 mg/L, consistent with a low CV risk. However, this value was significantly higher than value measured in healthy controls ($p < 0.001$). No values >3 mg/L were recorded. Twelve subjects had hs-CRP levels above 1 mg/L and no significant coronary stenosis. Four of them had detectable plasma HIV-1 RNA and 3 were CDC stage C at diagnosis. A statistically significant correlation was seen between hs-CRP values and severity of the obstruction ($r = 0.292$, $p = 0.038$). Mean value was 0.92 ± 0.84 mg/L in subjects with non significant stenosis and 1.29 ± 0.86 mg/L in those with ≥50% stenosis ($p = 0.177$).

Table 1 Demographic, clinical and viroimmunological characteristics of the whole population and of subjects with mild and moderate–severe stenosis. Values are expressed as mean ± SD or absolute number (percentage). Statistically significant values are reported in bold.

	All	CT grade of coronary stenosis		*p* values
		0–I (mild)	II–IV (moderate–severe)	
N	55	39 (70.9)	16 (29.1)	
Males, *n*, (%)	47 (85.5)	33 (84.6)	14 (87.5)	1.00
Age (mean + SD)	47.6 + 8.7	45.4 + 7.9	53.2 + 8.2	**0.002**
HIV diagnosis (years)	9.5 + 5.5	8.7 + 5.3	11.4 + 5.7	0.101
CD4 nadir (cell/μl)	193 + 126	197 + 121	183 + 140	0.726
Naive n, (%)	6 (10.9)	5 (12.8)	1 (6.3)	0.478
HAART (years)*	9.4 + 5.0	9.0 + 5.1	10.2 + 5.3	0.450
ABC (years)*	1.73 + 2.5	1.4 + 2.4	2.5 + 2.5	0.173
PI (years)*	4.4 + 3.8	4. 3 + 3.1	4.6 + 3.1	0.858
Framingham risk	4.1 + 3.0	3.2 + 2.5	6.3 + 3.3	**0.003**
BMI	22.2 + 2.5	22.1 + 2.6	22.5 + 2.6	0.631
HIV-RNA (log copies/ml)	2.3 + 1.1	2.5 + 1.2	1.8 + 0.5	**0.008**
Patients with HIV-RNA <50 copies/ml (%)	74.5	66.7	93.8	**0.045**

* Antiretroviral-treated patients.

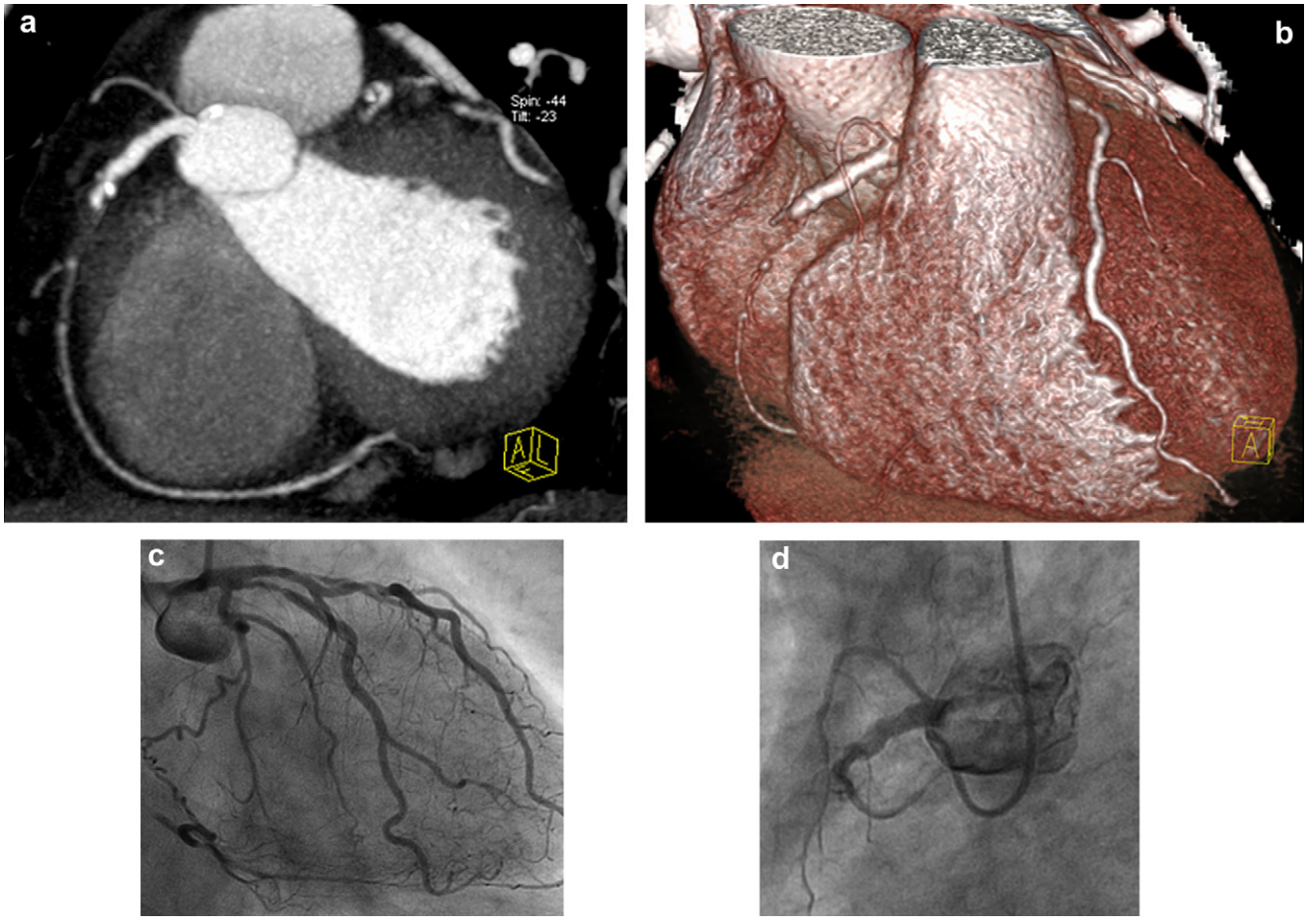

Figure 1 Chronic total occlusion of proximal right coronary artery in a 55-year-old female on HAART for 24 years. Multiplanar reformatting (MPR) and volume rendering reconstruction show proximal right coronary artery (RCA) occlusion with distal refilling from circumflex artery (a,b). Selective coronary angiography (SCA) confirms DSCT findings (c,d).

Patients with non significant and significant stenoses were compared for all the explored variables (Table 1). Age (45.4 ± 7.9 versus 53.2 ± 8.2, $p = 0.002$), Framingham risk score (3.2 ± 2.5 versus 6.3 ± 3.3; $p = 0.003$) and proportion of subjects with HIV-1 RNA below 50 copies (66.7% versus 93.8%; $p = 0.045$) were significantly higher in those with significant stenoses, consistently with lower HIV-1 RNA values in these latter (2.5 versus 1.8 log copies/ml). A significant correlation was found between age and grade of lesions ($p = 0.010$) (Fig. 2). In multivariate regression analysis, after adjusting for potentially confounding variables, age remained significantly associated with the presence of significant luminal narrowing ($p = 0.011$).

Discussion

In a recent paper Lo et al. performed coronary CT scan in young, asymptomatic HIV positive subjects, and found an increased prevalence of subclinical CAD respect to uninfected controls.[25]

In this paper we studied 55 HIV + individuals with low cardiovascular risk defined on the basis of FRS and additional parameters, including a negative exercise echocardiographic and ECG test. Using a cut-off value of 50% for defining significant stenoses, as in most published articles,[20,26–28] we found significant coronary obstructions in 29% of subjects. Five subjects with significant stenosis had low values (<1) of calcium score, due to the non-calcified nature of their plaques. This observation is of interest since a large number of acute coronary syndromes are caused by sudden ulceration in non-calcified vulnerable plaques.

According to the guidelines of the AHA, coronary angiography was planned in all the 16 patients with significant stenosis at CT scan, and performed in 13 of them. Eight out of 13 showed hemodinamically significant stenoses requiring revascularization.

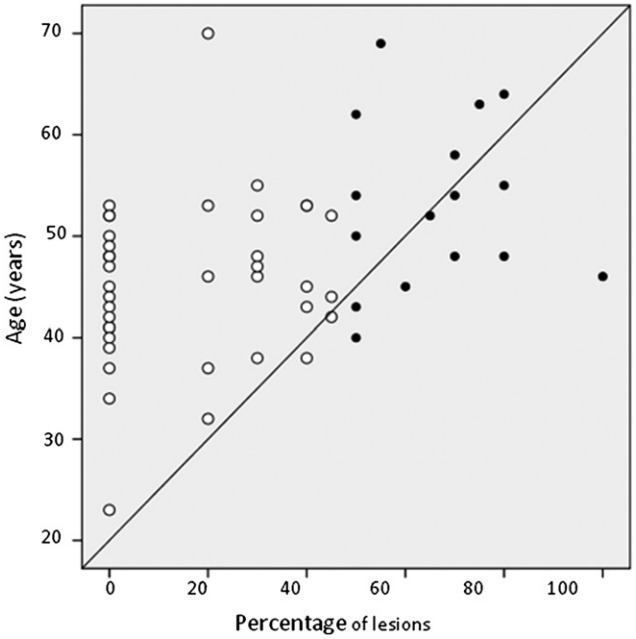

Figure 2 Correlation between age and grade of lesions ($r = 0.408$, $p = 0.002$). ○ grade 0–I patients; ● grade II–IV patients.

As a validated indicator of cardiovascular risk we measured hs-CRP[4]; the results were consistent with a low cardiovascular risk, as expected on the basis of inclusion criteria. However, the observed correlation between increasing hs-CRP levels and severity of coronary stenosis suggests that in HIV + population CAD can be present even with low hs-CRP values. Comparing the two patient groups (with/without significant coronary stenosis) for all the explored variables we found that age was the only factor independently associated with severity of coronary obstruction.

MDCT is an accurate tool for non-invasive assessment of coronary arteries.[29,30] Although it is not currently recommended in asymptomatic individuals,[31] a debate is ongoing about its use as a screening tool, mainly due to its.ability to identify non-calcified, potentially vulnerable, plaques.[32] Our findings seem to support this approach in older, asymptomatic HIV + subjects, and highlight the need for larger, longitudinal studies, where risks and benefits of heart CT scan are carefully evaluated. in individuals of different ages.

We acknowledge the limitations of our study, mainly the small size of the sample and the cross-sectional design, that does not provide follow up data. On the other hand, the strict criteria utilized for defining the low cardiovascular risk in our population (including negative stress ECG and echocardiography) may add further value to our observations.

Conflict of interest

The authors do not have a commercial or other association that might pose a conflict of interest. No financial support was received from private or public institutions.

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