The Brazilian Journal of
INFECTIOUS DISEASES

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Original Article

Angina pectoris in patients with HIV/AIDS: prevalence and risk factors

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ARTICLE INFO

Article history:
Received 14 January 2011
Accepted 17 February 2011

Keywords:
Acquired immunodeficiency syndrome
Angina pectoris
Coronary disease
Risk factors

A B S T R A C T

Introduction: The incidence of ischemic heart disease is higher in patients with HIV/AIDS. However, the frequency of angina pectoris in these patients is still not known. Literature about this subject is still scarce.

Objective: To evaluate the prevalence of angina pectoris and risk factors for coronary disease and to examine the association between traditional risk factors and HIV-related risk factors and angina pectoris.

Method: An epidemiological cross-sectional study, analyzed as case-control study, involving 584 patients with HIV/AIDS. Angina pectoris was identified by Rose questionnaire, classified as definite or possible. Information regarding risk factors was obtained through a questionnaire, biochemical laboratory tests, medical records and anthropometric measures taken during consultations at AIDS treatment clinics in Pernambuco, Brazil, from June 2007 to February 2008. To adjust the effect of each factor in relation to others, multiple logistic regression was used.

Results: There was a preponderance of men (63.2%); mean ages were 39.8 years for men, 36.8 years for women. The prevalence of definite and possible angina were 11% and 9.4%, respectively, totaling 20.4%, with independent associations between angina and smoking (OR = 2.88; 95% CI: 1.69-4.90), obesity (OR = 1.62; 95% CI: 0.97-2.70), family history of heart attack (OR = 1.70; 95% CI: 1.00-2.88), low schooling (OR = 2.11; 95% CI: 1.24-3.59), and low monthly income (OR = 2.93; 95% CI: 1.18-7.22), even after adjustment for age.

Conclusion: This study suggests that angina pectoris is underdiagnosed, even in patients with medical monitoring, revealing lost opportunities in identification and prevention of cardiovascular morbidity.

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Introduction

The knowledge that human immunodeficiency virus (HIV) infection could harm the heart goes back to 1983 when the first case of cardiac Kaposi's sarcoma was described.[1] Since then, a number of studies have identified the relationship between heart disease and AIDS in adults and this association is being increasingly reported as a cause of death.[2]

In 1996, with the introduction of highly active antiretroviral therapy (HAART), with the resulting reduction of morbidity and mortality and improvement of quality of life of HIV-infected subjects,[3] the description of atherosclerotic cardiovascular alterations[4] became increasingly frequent in prospective studies. In this connection, a reduction in the frequency of heart alterations caused by opportunistic agents has been reported as well as an increase in atherosclerotic coronary events in patients with HIV/AIDS.[5,6] The action of HIV itself,[7] exposure to traditional risk factors for coronary heart disease (CHD),[8] and the adverse effects of antiretroviral drugs in the cardiovascular system[9-12] have all been suggested as the determining factors in these atherosclerotic alterations.

In a 3-year observational study with a cohort of 900-infected subjects, a fourfold incidence of myocardial infarction (MI) in HIV-positive patients treated with protease inhibitors (PI) was detected.[13] On the other hand, some studies suggest the participation of non-PI antiretrovirals [reverse transcriptase inhibitors analogous to nucleosides (NRTI)] in the common metabolic alterations among HIV/AIDS subjects, said to result in cardiovascular disease.[14]

An increase in coronary events has also been observed in infected populations that have never used antiretrovirals, suggesting a direct effect of the virus itself on the atherogenic process[7] and/or individual exposure to smoking, hypertension, diabetes mellitus, dyslipidemia and traditionally recognized risk factors associated with the development of coronary atherosclerosis.[15]

However, despite the above mentioned, the association of risk factors with atherosclerotic ischemic cardiopathy in these patients is still controversial. With this in mind, the present study was carried out with the aim of establishing the prevalence of angina pectoris as a clinical manifestation of ischemic heart disease and the risk factors associated with its appearance in a HIV-infected population, seen at two reference hospitals for HIV/AIDS treatment in Pernambuco, Brazil. The following potential risk factors for CHD were analyzed: time elapsed since diagnosis of HIV/AIDS infection, use and type of antiretroviral regimen, CD4 lymphocyte count and the commonly known risk factors.

Methods

A cross-sectional study, analyzed as a case-control, was conducted from June 2007 to February 2008 involving 584 HIV-infected patients aged over 20 years treated at two hospitals (Hospital Universitário Oswaldo Cruz and Hospital Estadual Correia Picanço) in Recife, Pernambuco, Brazil; both are reference centers for the treatment of AIDS. Subjects reporting acute or chronic CHD, myocardial infarction or revascularization surgery at any time before the HIV-infection/AIDS diagnosis, and patients with signs of active AIDS or hospitalization in the previous three months of the study were excluded.

The frequencies of angina pectoris and risk factors for CHD were studied, as well as the association between angina pectoris and traditional risk factors for CHD [sex, age, ethnicity, sedentarism (< 4 times a week, 30' minimum), monthly income (minimum wage), schooling (studied years), alcohol use (classified according to a specific questionnaire), smoking (all patients who declared themselves as smokers, regardless of the amount of smoked cigarettes), family history of CHD – sudden death and heart attack –, obesity [body mass index (BMI) > 25 kg/m^2], central obesity (> 102 cm for men, and > 88 cm for women), arterial hypertension (systolic BP > 140 mmHg and diastolic BP > 90 mmHg), hyperglycemia (≥ 100 mg/dL), hypercholesterolemia (> 200 mg/dL), hypertriglyceridemia (≥ 150 mg/dL), low HDL (< 40 mg/dL) and high LDL cholesterol (> 130 mg/dL), time elapsed since diagnosis of HIV (< 24 and ≥ 24 months), use and type of antiretroviral regimen (with and without protease inhibitors) and CD4 lymphocyte count (< 350 and ≥ 350 cells).

Patients with angina pectoris were those who presented definite or possible angina, as classified by Bodegard.[16] In this classification, definite angina is the report of pain or discomfort located on the central or left chest region that occurs when walking fast or uphill, and making it necessary to stop or slow down, and disappears in less than 10 minutes after stoping the activity. Possible angina is considered when the patient reports pain or discomfort that occurs when walking fast or uphill but without accomplishing all the other requirements for definite angina. Identification of angina pectoris was made by means of the Rose questionnaire, accredited and adopted by the World Health Organization for this purpose,[17] and the controls were those over the age of 20 who did not report chest pain or discomfort.

Patients were selected from the HIV/AIDS outpatient clinics of the two hospitals (HUOC, HCP) at the time of their clinical consultation after agreeing to participate in this study by signing the free and informed consent form.

Risk factors information were obtained as follows: 1) administration of a structured and encoded questionnaire designed to collect information on the presence of risk factors; 2) assessment of blood glucose, triglycerides, total cholesterol and its HDL and LDL fractions, after a 12-hour fasting period; 3) from the hospital records, CD4 lymphocyte count, use of antiretrovirals and type of regimen used; 4) anthropometrical measurements and blood pressure (mean diastolic and systolic measurements of the superior members taken two times during the consultation).

Considering an expected frequency of angina pectoris of 6.7% and also a plus or minus 2% margin of error with a 95% confidence level, the sample size was estimated at 600 individuals.

Time elapsed since HIV/AIDS diagnosis, the type of antiretroviral (ARV) regimen, smoking and obesity were

the items of comparison selected for their association with angina pectoris.

The data were stored in a specific database, following a review of the completed questionnaires, in order to avoid any information bias.

Odds ratios with 95% confidence intervals were used to measure the magnitude of the associations, using the statistical package STATA version 9.0. Multiple logistic regression was used to adjust the effect of each factor over the others.

The present study was approved by the Ethics in Research Committees (protocol number 052/05).

Results

The study comprised 584 HIV-infected patients, of whom 369 (63.2%) were men with a mean age of 39.8 years (range, 20 to 74 yr) and 215 (36.8%) women with a mean age of 36.8 years (range, 20 to 67 yr).

A total of 56.1% (325/579) of the patients reported low schooling (up to 8 years) and 81.2% (385/474) reported low income (less than two minimum wages) (1 minimum wage = US$ 194.87).

A history of heart attack and sudden death in first-degree relatives was reported in 164/549 (29.9%) and 76/519 (14.0%) patients, respectively.

Alcohol use was admitted by 239/557 (42.9%) patients, smoking by 140/583 (24.0%) and 358/582 (61.5%) were sedentary.

Overweight/obesity was present in 207/581 (35.6%) patients and only 113/584 (19.3%) presented central obesity. A total of 154/549 (26.7%) patients reported hypertension. Glucose levels in 87/575 (15.3%), triglyceride levels in 278/575 (48.3%), overall cholesterol in 167/575 (29.0%) and LDL in 102/541 (18.8%) patients were increased. HDL levels were below the lower limit of normal in 517/575 (89.9%) of the patients.

In 393 subjects (67.4%) HIV infection had been diagnosed more than 24 months earlier (Table 1) and 467 (81.2%) were on ARV, of whom 256 (54.8%) were on a protease-inhibitor (PI) regimen and 211 (45.2%) were not, according to their medical records.

Of the total sample population, 119/584 (20.4%) presented angina pectoris (65 definite – 11%, and 54 possible – 9.4%), diagnosed by the Rose questionnaire. Of these, 95.8% were under 55 years old, 63.9% were black or mulatto, 37.9% reported smoking (45/119), 72.3% (86/119) had been diagnosed with HIV infection more than 24 months earlier, and 77.1% (91/118) used ARV, of whom 52.2% were on a PI-containing regimen and 47.7% were on no PI.

An independent association was found between angina pectoris and smoking (OR = 2.88; 95% CI: 1.69-4.90), obesity (OR = 1.62; 95% CI: 0.97-2.70), family history of heart attack (OR = 1.70; 95% CI: 1.00-2.88), and low schooling (OR = 2.11; 95% CI: 1.18-7.22) in the multivariate analysis, even after adjusting for age (Table 2). The variables used for this analysis were those with statistical significance in the univariate analysis – sex, smoking, low schooling, low monthly income, CD4 lymphocytes, ethnicity, alcohol use, family history of CHD/heart attack in first-degree relatives, obesity, low HDL, ARV use, and type of ARV regimen (Tables 1, 3 and 4).

Table 1 - Frequency distribution and univariate analysis of the association between time elapsed since diagnosis, CD4 lymphocyte level, use and type of ARV regimen with angina pectoris

Variables			Pain		No pain		OR (95% CI)	p
	n	%	n	%	n	%		
Time elapsed since diagnosis								
Up to 24 months	190	32.6	33	17.4	157	82.6	1	
> 24 months	393	67.4	86	21.9	307	78.1	1.33 (0.85-2.07)	0.206
ARV use								
No	109	18.8	27	24.8	82	75.2	1	
Yes	472	81.2	91	19.3	381	80.7	0.72 (0.44-1.18)	0.200*
ARV type								
Without ARV	109	18.9	27	24.8	82	75.2	1	
Without PI	211	36.7	43	20.4	168	79.6	0.77 (0.44-1.34)	0.368
With PI	256	44.4	47	18.4	209	81.6	0.68 (0.40-1.17)	0.165*
CD4 level**								
> 350 cells/mm^3	250	59.9	54	21.6	196	78.4	1	
< 350 cells/mm^3	167	40.1	22	13.2	145	86.8	0.55 (0.32-0.94)	0.030*

*Multivariate analysis; **Brazilian Ministry of Health.[27]

Table 2 - Final multivariate model of the association between risk factors and angina pectoris

Variables	OR (95% CI)	p
Age	0.96 (0.94-0.99)	0.020
Schooling		
Less than 8 years	2.11 (1.24-3.59)	0.006
More than 8 years	1.0	-
Smoking		
Smoker	2.88 (1.69-4.90)	0.000
Non-smoker/ex-smoker	1.0	-
Monthly income		
Low (< 2x minimum wage)	2.93 (1.18-7.22)	0.019
High (> 2x minimum wage)	1.0	-
Family history of CHD/attack		
Present	1.70 (1.01-2.88)	0.046
Absent	1.0	-
Overweight/obesity		
Present	1.62 (0.97-2.70)	0.063
Absent	1.0	-

*Sex, ethnicity, alcohol use, CD4 level, ARV use, type of ARV regimen and HDL have been omitted from the model. The model was adjusted for age.

Table 3 - Frequency distribution and univariate analysis of the association between traditional risk factors* and angina pectoris

Variables			Pain		No pain		OR (95% CI)	p
	n	%	n	%	n	%		
Sex								
Female	215	36.8	55	25.5	160	74.5	1	
Male	369	63.2	64	17.3	305	82.7	1.64 (1.09-2.46)	0.018†
Age								
20-54 yr	548	93.8	114	20.8	434	79.2	1	
> 55 yr	36	6.2	05	13.9	31	86.1	0.61 (0.23-1.61)	0.323
Schooling								
< 10 years	254	43.9	34	13.4	220	86.6	1	
> 10 years	325	56.1	84	25.8	241	74.1	2.25 (1.45-3.49)	0,000†
Monthly income								
> 2x minimum wage	89	18.8	06	6.7	83	93.3	1	
< 2x minimum wage	385	81.2	90	23.4	295	76.6	4.22 (1.78-9.98)	0.001†
Ethnicity								
White + Yellow + Indigenous	180	30.9	43	23.9	137	76.1	1	
Black + Brown	403	69.1	76	18.9	327	81.1	0.74 (0.48-1.13)	0.165†
Smoking								
Non-smoker	443	76.0	74	16.7	369	83.3	1	
Smoker	140	24.0	45	32.1	95	67.9	2.36 (1.53-3.64)	0.000†
Alcohol use								
Absent	318	57.1	57	17.9	261	82.1	1	
Present	239	42.9	55	23.0	184	77.0	1.36 (0.90-2.07)	0.139†

(Cont.)

Table 3 - Frequency distribution and univariate analysis of the association between traditional risk factors* and angina pectoris (cont.)

Variables			Pain		No pain		OR (95% CI)	p
	n	%	n	%	n	%		
Sedentarism								
Absent	224	38.5	45	20.0	179	800	1	
Present	358	61.5	73	20.4	285	79.6	1.01 (0.67-1.54)	0.930
Family history of CHD/death								
Absent	443	85.4	85	19.2	358	80.8	1	
Present	76	14.6	17	22.4	59	77.6	1.21 (0.67-2.18)	0.520
Family history of CHD/attack								
Absent	385	70.1	70	18.2	315	81.8	1	
Present	164	29.9	40	24.4	124	75.6	1.45 (0.93-2.25)	0.097†

*Sex, age, schooling, monthly income, ethnicity, smoking, alcohol use, sedentarism, family history of CHPD; †multivariate analysis.

Table 4 - Frequency distribution and univariate analysis of the association between traditional risk factors* and angina pectoris

Variables			Pain		No pain		OR (95% CI)	p
	n	%	n	%	n	%		
Overweight/obesity** BMI = [weight(kg)]/[h(m)]²								
Absent (≤ 25 kg/m²)	374	64.4	69	18.4	305	81.6	1	
Present (> 25 kg/m²)	207	35.6	49	23.7	158	76.3	1.37 (0.90-2.07)	0.135†
Central obesity**								
Absent (≤ 102 cm men; ≤ 80 cm women)	471	80.7	92	19.5	379	80.5	1	
Present (> 102 cm men; > 80 cm women)	113	19.4	27	23.9	86	76.1	1.29 (0.79-2.10)	0.302
Hypertension (JNC 7)[28]								
Absent	425	73.4	88	20.7	337	79.3	1	
Present	154	26.6	30	19.5	124	80.5	0.92 (0.58-1.47)	0.746
Fasting glucose**								
Normal	480	84.7	94	19.6	386	80.4	1	
High	87	15.3	14	16.1	73	83.9	0.78 (0.42-1.45)	0.446
Cholesterol**								
Normal	408	71.0	81	19.8	327	80.2	1	
High	167	29.0	29	17.4	138	82.6	0.84 (0.53-1.35)	0.491
HDL-C**								
Normal	58	10.1	07	12.1	51	87.9	1	
Low	517	89.9	103	19.9	414	80.1	1.81 (0.79-4.11)	0.155†
LDL**								
Normal	439	81.1	81	18.4	358	81.6	1	
High	102	18.9	21	20.6	81	79.4	0.87 (0.57-1.35)	0.561
Triglycerides**								
Normal	297	51.6	62	20.9	235	79.1	1	
High	278	48.4	48	17.3	230	82.7	0.79 (0.52-1.20)	0.272

*Obesity, central obesity, arterial hypertension, glucose, overall cholesterol, triglycerides, HDL, LDL; †multivariate analysis; **NCEP-ATPIII.[29]

Discussion

Although ischemic cardiovascular alterations in patients with AIDS have been exhaustively studied, in the review of the literature no studies were identified dealing specifically with stable angina in patients with AIDS, hence the exploratory nature of the present study. On the other hand, since the identification is based on the clinical history, the Rose questionnaire adopted by WHO[17] was used for epidemiological reasons to identify angina pectoris.

In our study, the prevalence of definite angina pectoris (with all the typical symptoms) in HIV-infected patients was 11%, representing, for ischemic heart diseases (myocardial infarction and angina pectoris), a prevalence two and a half times higher than in the general Brazilian population (4.1%; 95% CI: 2.9-6.7), and three times greater than in the population of Recife (3.7%; 95% CI: 2.1-5.2), identified by a home-based survey conducted in fifteen Brazilian capitals (2000-2003).[18] It likewise represents almost twice the angina pectoris prevalence found in a major meta-analysis carried out by Hemingway[19] comprising 74 studies, with a total population of 201,821 men and 199,494 women from 31 different countries. Among the latter, the prevalence of definite angina, diagnosed by the Rose questionnaire, was 6.7% for women and 5.7% for men. In our study, when the patients with possible angina (chest pain on exertion without fulfilling all the classical angina characteristics included in the Rose questionnaire) were added to the definite angina patients, this frequency rose to 20.4%.

The inclusion of possible angina patients, as defined by Bodegard,[16] is based on his important study that reported higher mortality from cardiovascular disease after 26 years of monitoring in patients diagnosed with angina by the Rose questionnaire, but who did not meet all the criteria for classical angina.

Our findings become even more significant when patients are analyzed by age: the mean age for our patients was 39.8 for men and 36.8 for women. In Hemingway's meta-analysis[19] the prevalence of angina in populations under 45 years of age was even lower, namely between 3.2 and 3.8%.

Finally, it is important to emphasize that none of our patients reported any specific cardiological complaint in the HIV/AIDS clinic or underwent any process of prior selection. In other words, none of them had been identified by their doctors as having angina pectoris, a situation that is true for many HIV/AIDS health services.

Regarding the traditional risk factors for CHD, it was found that smoking, overweight/obesity, a family history CHD in first-degree relatives, low schooling and low monthly income (< 2x minimum wage) all turned out as independent factors associated with a high risk of developing angina pectoris.

Smoking was the risk factor most strongly associated with angina pectoris among our patients, more than tripling the chance of developing the condition (OR = 2.22; 95% CI: 1.37-3.58). Its frequency (24.0%) in the overall population of this study was similar to that found in the population of Recife (24.4%) (2000-2003 survey),[18] in general, and represented half the smoking frequency reported by Friis-Møller et al.[20] in 17,852 AIDS patients studied at the DAD study (51.5%). Also, our results are in contrast to the findings of Neumann et al.,[21] who reported 67% and 52%, respectively, in homosexuals and heterosexuals, obtained in 309 infected patients.

On the other hand, overweight/obesity (BMI ≥ 25 kg/m^2), present in 35.6% of the patients, represented a 62% increase in the chance of developing stable angina in the sample population (OR = 1.62), but central obesity was not statistically significant (frequency = 19.4%).

A family history of CHD/heart attack increased in 70% the risk of developing angina pectoris (OR = 1.70) in our patients, confirming the positive relationship between family history of CHD and coronary heart diseases in patients with AIDS, similar to the relation reported in the general population, as presented by Moraes and Souza.[22]

In addition, low schooling (up to 8 years) and low monthly income (≤ 2x US$ 194.87), respectively, doubled (OR = 2.11) and tripled (OR = 2.93) the risk of developing angina pectoris in the population studied. These results are similar to those found in other studies covering the overall Brazilian population (association between CHD and these risk factors).

Unlike population-based studies which show that an increased glucose level (> 99 mg/dL), arterial hypertension (PAS ≥ 140 mmHg and/or PAD ≥ 90 mmHg) and sedentarism are associated with increased risk for CHD among men and women,[23] in our study these factors were not associated with the development of angina pectoris. Increased levels of glucose, hypertension and sedentarism were found in 15.3%, 26.6% and 61.5% of the subjects, respectively.

Despite the many studies indicating the association between dyslipidemia and coronary events[24] in the overall population and in the HIV-infected population, no associations between angina pectoris and hypercholesterolemia (≥ 200 mg/dL), hypertrygliceridemia (≥ 150 mg/dL), high LDL (≥ 130 mg/dL) and low HDL (≤ 45 mg/dL) were observed in our study.

Agreeing with Spósito et al.,[25] who state that some lipid abnormalities are common in HIV patients, indicating that the infection itself change these profiles, we found a high frequency (90%) of low HDL-c. However we did not find similar results regarding LDL-C (19%) and triglycerides (50%).

Another important result to be emphasized is that, in the case of Pernambuco, despite the fact that the time elapsed since HIV diagnosis reflects the type of ARV regimen, since the majority of the patients who seek AIDS treatment at reference centers are at advanced stages of the disease, in our sample this variable was not associated with angina pectoris. Likewise, we did not find any positive association between ARV use and CD4 lymphocyte levels.

The prevalence of angina pectoris was 18.4% and 20.4% in patients receiving ARV with and without PI, respectively,

a difference not statistically significant, similarly to the findings of Coplan et al.,[26] who found no significant differences in myocardial infarction rates between individuals receiving ARV with and without PI.

In our study, it is important to point out that many patients had already used several types of ARV regimens (with and without PI), which prevent a correct evaluation of the association between the type of ARV regimen and the risk of developing angina pectoris.

Conclusion

The present study showed that around 20.4% of the patients with HIV/AIDS have a potential risk of ischemic coronary disease not identified by their doctors, despite their regular attendance at health services. Thus, simple and well-defined questions, such as the ones in the Rose questionnaire, might be useful in identifying this clinical condition and for selecting patients that need detailed cardiological investigation and referral to experts in this area.

Our results also corroborate the influence of the traditional risk factors (smoking, obesity, family history of heart attack) in the development of angina pectoris in HIV-infected patients.

From this perspective, our study not only presents a starting point for the identification of ischemic coronary disease in such patients but also, most importantly, points to the real possibility of including the constant and systematic monitoring of these patients as part of routine clinical work within the framework of an early preventive and therapeutic approach.

Aknowledgements

We would like to thank Hospital Correia Picanço and Hospital Oswaldo Cruz for all the support granted in our research. All the financial support was granted by National STD/AIDS Program of the Brazilian Ministry of Health.

Conflict of interest

All authors declare to have no conflict of interest.

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