

## Coronary Artery Disease in Patients with Rheumatic and Non-Rheumatic Valvular Heart Disease Treated at a Public Hospital in Rio de Janeiro

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### Summary

**Objective:** to estimate the prevalence of coronary artery disease (CAD) in valvular heart disease of rheumatic (RVHD) and non-rheumatic (NVHD) etiology, assessing possible predictive factors for the presence of CAD.

**Methods:** This is a cross-sectional study of a series of cases obtained from a pre-defined population, wherein 1,412 patients referred for heart surgery of any etiology were evaluated. Of these, 294 primary heart disease patients aged  $\geq 40$  submitted to cinecoronary arteriography (CA) were identified and studied.

**Results:** patients with RVHD presented lower prevalence of CAD (4%) when compared to NVHD (33.61%),  $p < 0.0001$ . The logistic regression analysis showed that age, typical angina-like chest pain (TACP), systemic arterial hypertension (SAH), diabetes and dyslipidemia were significantly related to CAD, and that the rheumatic etiology was not a disease determinant. Smoking and gender were clinically important in CAD, although not statistically significant. In the whole group, the Log-linear analysis showed that, regardless of the etiology, gender, age  $\geq 55$ , SAH, TACP, diabetes and dyslipidemia were all related directly to CAD, with the latter three being the most important variables for the disease.

**Conclusion:** the prevalence of CAD among RVHD patients is low, whereas it is high among NVHD patients; the rheumatic etiology does not seem to have any beneficial effects on the prevalence of CAD; gender, age, SAH, TACP, dyslipidemia and diabetes were identified as being strongly associated with the presence of CAD. It is possible to define the criteria that indicate the need for pre-surgical CA in heart valve replacements, so that the standard indication after the age of 40 years can be avoided. (Arq Bras Cardiol 2008; 90(3):197-203)

**Key words:** Coronary arteriosclerosis / epidemiology; rheumatic heart disease / diagnosis; heart valve diseases / diagnosis; coronary angiography.

### Introduction

The coronary angiography has been indicated as a routine procedure in the preoperative assessment of patients with valvular heart disease that meet the following criteria: males aged  $\geq 35$  years, pre-menopausal females aged  $\geq 35$  years with cardiovascular risk factors and post-menopausal females<sup>1,2</sup>. The procedure is justified by the diagnosis of coronary obstructions, especially the asymptomatic ones and the significant prevalence of coronary artery disease (CAD) in these patients. The diagnosis of associated coronary obstruction would indicate myocardial revascularization during the valve replacement, regardless of the clinical presentation and the presence or absence of symptoms. In our country, the coronary angiography has been indicated almost exclusively for patients

$\geq 40$  years. However, in clinical practice, we have observed a low prevalence of CAD among patients with valvulopathies, especially those with rheumatic etiology. It is noteworthy that although the non-rheumatic etiology of the valvulopathies is often found in our population, the rheumatic etiology still considerably outnumbers the first<sup>3,4</sup>.

The present study was developed considering these observations and in view of the restrictions regarding the rationale adopted for the very often indiscriminate indications of a costly, invasive and non-morbidity-free method. Our objectives were: to assess the prevalence of CAD in patients with orovalvular injuries with rheumatic and non-rheumatic etiology aged  $\geq 40$  years, referred to evaluation of surgical indication for valve replacement in a public hospital specialized in cardiology in the city of Rio de Janeiro and identify possible predictive factors of the presence of CAD in these patients, aiming at assessing the influence of the rheumatic etiology on the disease.

The present study was carried out based on clinical observations during the last 25 years of activities in a public

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hospital in the city of Rio de Janeiro. During this period, a broad experience was acquired on the treatment of patients with orovalvular injuries, especially adults aged  $\geq 40$  years, of low socioeconomic level, many of them with a history of acute episodes of rheumatic fever, referred to evaluation of surgical indication for valve replacement. All patients underwent coronary angiography.

## Methods

In a transversal case series study carried out in a pre-defined population between the years 1999 and 2005, a total of 1,412 patients were evaluated, after being referred with heart surgery indication due to any etiology. Of these, 294 patients with primary heart valve lesions were identified and selected for the study, with 175 presenting a rheumatic etiology and 119 a non-rheumatic etiology, aged  $\geq 40$  years, previously evaluated through coronary angiography. All patients met the clinical criteria for the diagnosis of stenosis, heart failure or double lesion of the aortic and/or mitral valves, supported by anamnesis and clinical assessment<sup>5</sup>. The echocardiogram was used to define the criteria of rheumatic and non-rheumatic etiology<sup>6</sup>.

To define the rheumatic valvular cardiopathy, the following criteria were considered: 1) in the mitral valve: thickening of the free border of the leaflets with or without commissure fusion and of the subvalvular apparatus with reduced mobility and posterior leaflet fixation, and 2) in the aortic valve: cusp thickening, from the border to the base. For the non-rheumatic valvular cardiopathy, the following degenerative disease criteria were considered: 1) in the mitral valve: leaflet thickening with preserved mobility in the free border; 2) in the aortic valve: fibrocalcific degeneration, characterized by calcification that started on the cusp bases and went towards their borders, and 3) in the bicuspid aortic valve: visualization of only two leaflets with cusp thickening.

The CAD was assessed by angiographic criteria of obstructive lesions  $\geq 50\%$  for the left coronary trunk (LCT) and  $\geq 70\%$  in the following arteries: anterior descending (AD), right coronary artery (RCA) and circumflex artery (CxA). For the marginal (MG) and diagonal (DG) arteries, or even an intermediate branch of anatomic importance (diagonalis – DI) the criteria considered were lesions  $\geq 70\%$  and arteries with a diameter  $> 3\text{mm}$ . Although only the severe lesions, of anatomically surgical nature, were considered in the present study, the mild and moderate lesions were classified for recording purposes, also by angiographic criteria. Mild lesions were classified as the obstructions  $< 50\%$  of the vessel lumen and moderate lesions were classified as those presenting obstruction between  $50\%$  and  $< 70\%$  of the vessel lumen<sup>7</sup>.

The studied variables were: age, sex, body mass index (BMI - patients with BMI  $< 25\text{kg/m}^2$  were considered normal; those with BMI between 25 and  $30\text{kg/m}^2$  were overweight and those with BMI  $> 30\text{kg/m}^2$  were considered obese), chest pain (typical, atypical and no pain), dyspnea, smoking and tobacco smoke load (number of years during which the patient smoked 1 pack a day), systemic arterial hypertension (SAH), considered systolic arterial pressure  $\geq 140\text{mmHg}$  or diastolic arterial pressure  $\geq 90\text{mmHg}$  or

use of anti-hypertensive medication, CAD, family history and diagnoses related to this disease, diabetes mellitus (considered when fasting glycemia was  $\geq 126\text{mg/dl}$  and dyslipidemia (considered when total cholesterol was  $\geq 200\text{mg/dl}$  and/or triglycerides  $\geq 150\text{mg/dl}$ ).

At the statistical analysis the Chi-square test was used for the comparison of proportions and the Student's *t* test was used for the analysis of the continuous variables, with *p* value being considered significant when  $\leq 0.05$ . The logistic regression model was used to estimate the influence of the selected variables on the outcome, i.e., the presence of coronary artery disease and the Log-linear model was used to analyze the interdependence relations of the first, second and third-degrees among the variables. The R System statistical program, version 2.3, was used for the statistical analyses. A database (Access) was created with the patients' clinical information and results of the complementary tests.

The study was approved by the Ethics Committee in Research of the Instituto Estadual de Cardiologia Aloysio de Castro, Rio de Janeiro, on 10/05/2005.

## Results

### 1. Analysis of the groups with rheumatic and non-rheumatic valvular cardiopathy.

Table 1 compares the variables of the groups with rheumatic and non-rheumatic valvular cardiopathy. The ones that presented statistical difference were: sex (predominantly female in the rheumatic group and predominantly male in the non-rheumatic group); age, older among the non-rheumatic patients; typically anginal chest pain (more frequent in the non-rheumatic group); absence of chest pain (higher frequency in the rheumatic group); SAH, diabetes mellitus, dyslipidemia and presence of coronary artery disease (more frequent in the non-rheumatic group). On the other hand, there was no significant difference between the two groups regarding the variables: BMI (normal, overweight and obese); atypical chest pain; dyspnea; family history of coronary artery disease; being a smoker and being an ex-smoker. Thus, these two groups presented heterogeneous clinical characteristics.

### 2. Correlation of coronary artery disease with the other variables.

To assess whether the valvulopathy etiology had any influence determining the presence of CAD, a logistic regression model analysis was carried out in which the disease was considered the dependent variable and the others were considered determinants. The variables included in this analysis were: sex, age, BMI (overweight and obesity), typical chest pain, SAH, diabetes mellitus, dyslipidemia, smoking and having a rheumatic etiology. Considering the median of 54 years, the cutoff for age was  $< 55$  and  $\geq 55$  years. The rheumatic etiology showed it was not a determinant variable in CAD, which allowed us to proceed with the analysis involving the 294 patients with valvulopathies, regardless of the etiology (Table 2). Considering its clinical importance in coronary artery disease, the variables smoking and sex were maintained in the model, although they did not present statistical significance.

**Table 1 - Characteristics of the rheumatic and non-rheumatic groups.**

	Variables	Rheumatic (n=175)	%	Non-rheumatic (n=119)	%	P value
Sex	male	54	30,86	85	71.43	<0.0001
	female	121	69.14	34	28.57	<0.0001
Age (mean)		50.87		63.66		
BMI	normal	147	84.00	89	74.79	0.072
	overweight	22	12.57	23	19.33	0.157
	obesity	06	3.43	7	5.88	0.470
Chest pain	typical pain	12	6.86	57	47.90	<0.0001
	atypical pain	34	19.43	22	18.49	0.959
	No pain	129	73.71	40	33.61	<0.0001
Clinical, history and laboratory variables	dyspnea	169	96.57	102	85.71	0.140
	SAH	52	29.71	70	58.82	<0.0001
	diabetes	07	4.00	17	14.29	0.003
	dyslipidemia	14	8.00	21	17.65	0.020
	CAD	07	4.00	40	33.61	<0.0001
	family history	76	43.43	66	55.46	0.056
	smoker and ex-smoker	87	49.71	58	48.73	0.789

*n* - number of patients; BMI - body mass index; SAH - systemic arterial hypertension; CAD - coronary artery disease.

**Table 2 - Demographic and clinical characteristics of the total population.**

Variables	N	%	
Age	≥ 55	146	49.65
	< 55	148	50.34
	mean	56	
	median	54	
Sex	male	139	47.30
	female	155	52.70
BMI	overweight and obesity	58	19.72
	typical	69	23.46
Chest pain	atypical	56	19.04
	no pain	169	57.48
	SAH	122	41.49
Clinical, history and laboratory variables	diabetes	24	8.16
	dyslipidemia	35	11.90
	CAD	47	15.98
	family history	142	48.29
	smoker and ex-smoker	145	49.31

*n* - number of patients; BMI - body mass index; SAH - systemic arterial hypertension; CAD - coronary artery disease.

Those variables that significantly correlated with the disease at the final model analysis were: age, typical chest pain, SAH, diabetes mellitus and dyslipidemia, as shown in (a)

(a) Final expression of the logistic regression model:

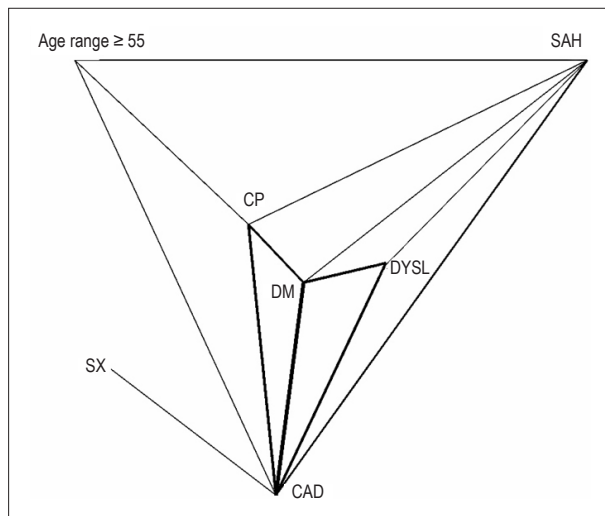
Logit (CAD) = -5.07 + 0.78 sex + 0.04 age + 2.05 typical chest pain + 0.91 SAH + 2.04 diabetes + 1.64 Dyslipidemia + 0.57 smoking; where:

$$\text{Logit (CAD)} = \ln\{ \text{Pr(CAD} = 1) / \text{Pr (CAD} = 0) \}$$

### 3. Interdependence Relations between coronary artery disease and the other variables

To support the results obtained at the logistic regression, the Log linear model was also used, which assessed the interdependence relations among the variables. It is a model of multivariate analysis, characterized by treating all variables with the same level of importance and not as outcome and explicative variables. The variables that showed to be significant in the model, when isolated, were: coronary artery disease, sex, age, typical chest pain, SAH, diabetes mellitus and dyslipidemia. At the interdependence relation (interaction) of the second-degree, an association was observed between coronary artery disease and male sex, age ≥ 55 years, typical chest pain, SAH, diabetes and dyslipidemia as well as an association between age ≥ 55 years and typical chest pain; age ≥ 55 years and SAH; typical chest pain and diabetes; SAH and diabetes; diabetes and dyslipidemia. At the interdependence relation of the third-degree, an association of coronary artery disease with typical chest pain and diabetes was observed, as well as an association between SAH and diabetes and of diabetes with dyslipidemia. In summary, the variables most strongly associated to coronary artery disease were typical chest pain, diabetes mellitus and dyslipidemia (Fig. 1).

### 4. Clinical characteristics of the population with and without coronary artery disease



**Fig. 1** - Interdependence of risk factors from CAD in the age range  $\geq 55$  years. CAD – Coronary Artery Disease; CP – chest pain; DM – Diabetes mellitus; DYSL – Dyslipidemia; SAH - systemic arterial hypertension.

Table 3 shows the clinical characteristics of the population according to the presence and absence of CAD. The findings are summarized as follows:

At the age range  $\geq 55$  years, 0 percentage of the disease prevalence was higher than in the age range  $< 55$  years. The frequency of the disease was higher in the male than in

the female sex. In the group with presence of the disease, significantly higher percentages were observed in the following variables: typical chest pain, SAH, diabetes, dyslipidemia, aortic stenosis and tobacco smoke load. In the group with absence of the disease, significantly higher percentages were observed for the variables: absence of pain and mitral stenosis. There was no significant difference between the groups regarding the following variables: overweight and obesity, family history, atypical pain, smoker and ex-smoker (although with a higher percentage in the group with coronary artery disease than in the group without the disease).

### Discussion

The present study analyzes the prevalence of CAD of rheumatic and non-rheumatic etiology in patients  $\geq 40$  years. In its severe form, the disease was considered not only when there was a trunk lesion as well as three-vessel lesions that affected simultaneously the main coronary arteries, but also the one-vessel and two-vessel lesions and the severe lesions that affected secondary branches of anatomical importance. Our criteria seem to be quite comprehensive, considering that most of the revised studies consider a trunk lesion to be severe when it is  $\geq 50\%$ , and the coronary artery lesions (CD, CX and DA) when they are  $> 70\%$ <sup>8,9</sup>. For some authors<sup>10</sup>, the ideal condition for the surgical indication of myocardial revascularization is that in which the patients exhibit proximal lesions of at least 70% in the main coronary arteries with good distal portions.

**Table 3** - Clinical characteristics of the population with CAD and without CAD

Variables	NO CAD		With CAD		P value
	(n=247)	%	(n=47)	%	
Age $\geq 55$ years	107	43.32	39	82.96	<0.0001
Age $< 55$ years	140	56.68	08	17.02	<0.0001
Male sex	106	42.91	33	70.21	0.0027
Female sex	141	57.09	14	29.79	0.0027
Overweight and obesity	47	19.03	11	23.40	0.79
Typical chest pain	37	14.98	32	68.09	<0.0001
Atypical chest pain	49	19.84	07	14.89	0.73
No pain	161	65.18	08	17.02	<0.0001
SAH	90	36.44	32	68.09	0.0003
Diabetes	11	4.45	13	27.66	<0.0001
Dyslipidemia	22	8.91	13	27.66	0.0013
Family history	115	46.56	27	57.45	0.30
Smoker and ex-smoker	116	46.96	29	61.70	0.18
Aortic stenosis	58	23.48	31	65.96	<0.0001
Mitral stenosis	78	31.58	4	8.51	<0.0001
Tobacco smoke load (number of years smoking 1 pack/day)	12		27.2		<0.0001

n - number of patients; SAH - systemic arterial hypertension; CAD - coronary artery disease.

Our findings show that it is possible to clinically identify aortic valvular patients with a lower probability of presenting CAD and based on that, we suggest that the coronary angiography should not be indicated indiscriminately for all patients, but for those presenting clear clinical evidence and predictive factors of the disease.

Regarding the etiology, we observed a low prevalence of severe CAD among the rheumatic patients<sup>11</sup>; it was initially thought that this etiology could confer some degree of protection against the development of coronary atherosclerosis, as observed by other investigators<sup>12</sup>. This was based on the fact that, in general, these patients receive the prophylaxis for rheumatic fever with the use of intramuscular antibiotics every 21 days for many years and this could have a protective antibacterial and antiinflammatory effect on the genesis of coronary atherosclerosis. However, our findings do not corroborate the idea. A review of the clinical history showed that most of the patients had never received prophylaxis for rheumatic fever, which seems to make sense, as if this had really been adequately performed, certainly their cardiac valves would not have reached such state of damage as commonly found in these patients.

The data showed an alternative explanation: that the low prevalence could be due to the demographic and clinical characteristics of this population<sup>13,14</sup>. In a group with predominantly young individuals of the female sex, and thus, with fewer comorbidities, it is reasonable to assume that the prevalence of the disease is lower than in another group, with predominantly older individuals of the male sex.

The prevalence of coronary artery disease was much higher in the non-rheumatic group, which was characterized by the predominance of the male sex and older age<sup>15,16</sup>, in opposition to what was observed in the rheumatic group. Other clinical characteristics significantly differed between these two groups: typically anginal chest pain and risk factors such as systemic arterial hypertension, diabetes and dyslipidemia<sup>17,18</sup>, more often found in the non-rheumatic group, with aortic stenosis due to fibrocalcific degeneration the most frequent diagnosis in this group<sup>19,20</sup> and mitral stenosis the most frequent one in the rheumatic group<sup>13</sup>.

The demographic and clinical aspects that characterized the patients from the CAD group were (as shown in Table 3): age  $\geq 55$  years, male sex, typical chest pain, SAH, diabetes, dyslipidemia, tobacco smoke load and the presence of two or more risk factors, with aortic stenosis being the diagnosis most often associated to the disease. Mitral stenosis was the least frequently associated diagnosis to CAD, similar to what has been described in other studies<sup>9,21,22</sup>.

Some aspects observed in our database data are noteworthy. Few patients with CAD were in the 40 to 60-year age range, but they presented clinical signs that suggested the presence of the disease. Thus, few of them would have been missed at a clinical stratification. Below the age range of 60 years, the prevalence of the disease was only 1.7%, i.e., it is almost non-existent within the range where most of the patients with rheumatic valvulopathy are concentrated, leading us to question the validity of indiscriminately perform coronary angiographies in this population. Regardless of the etiology,

the prevalence of the disease was 6.95% among the patients aged  $< 60$  years, increasing to 31.8% among those aged  $\geq 60$  years, which is expected, as the comorbidities increase with age. In a comparative analysis between the absence of risk factors with the presence of 1, 2, 3, 4 and 5 risk factors, respectively, we observed that patients who presented 2 or more risk factors were predominantly concentrated in the group with coronary artery disease, whereas in the group without CAD, higher percentages of patients with only one or no risk factors were observed.

Therefore, we considered that the hemodynamic study could be dispensed with in patients without typical angina and no associated risk factors. Regarding the coronary lesions, some considerations should also be made. According to our data, of 187 patients younger than 60 years, only 1 (0.53%) presented a trunk lesion and only 2 (1.06%) presented severe three-vessel lesions, that is, only three anatomical and truly surgical patients were identified below this age range. They presented typical angina and the association of 2 or more risk factors, and therefore, surely they would not be missed by a good clinical stratification.

In literature, the indication of routine preoperative catheterism has a level of evidence C<sup>4</sup>, which means that this evidence is based solely on the experts' opinion, on case studies or on the measure taken as a precaution, with no other well-established basis. For instance, patients with severe aortic failure who do not present symptoms of myocardial ischemia or risk factors, which are known to increase the prevalence of coronary artery disease, could safely dispense with the preoperative coronary angiography, according to some researchers<sup>23</sup>. Others<sup>24</sup> correlate the low prevalence of the disease and the valvulopathy, pointing out to the fact that the coronary angiography is unnecessary in these patients, except in the presence of risk factors or clinical findings such as angina and previous myocardial infarction.

## Conclusions

In our opinion, the routine indication of preoperative coronary angiography based solely on the age criterion must be reconsidered. Although the diagnostic coronary angiography is a low-mortality method, it has an incidence of complications that vary from less than 1% to close to 5%. However, when such complications occur, they can have a quite significant adverse effect. Among other complications, it is important to mention the occurrence of brain injuries due to gaseous and solid microembolisms that can result in the cognitive impairment of patients, particularly the predisposed ones<sup>25</sup>.

The myocardial revascularization surgery, when analyzed from a database that expresses the reality of clinical practice, shows mortality rates  $> 3.5\%$  in the United States<sup>26,27</sup>. In Brazil, these rates are  $> 5\%$ . In Rio de Janeiro, the hospital lethality at the myocardial revascularization surgery varies from 4.8%, among men with a diagnosis of chronic ischemic disease, up to 14% among women with angina<sup>28</sup>. In combined surgeries, these rates can be 5-fold higher than in the isolated valvular surgery<sup>29</sup>. In a study comparing previously revascularized patients with those who were not submitted to the procedure, no significant difference was observed during the evolution of



the two groups<sup>30</sup>. The authors did not consider an advantage to submit patients who were candidates to major valvular surgery, with coronary artery disease, to cardiac surgery and even to preoperative angioplasty. In our opinion, the same consideration applies to the investigation of coronary artery disease in patients with valvulopathies with low probability to present the disease, especially considering that the hemodynamic study brings an additional risk, many times with a higher likelihood of complications than those caused by the disease itself. However, we consider it reasonable to indicate the myocardial revascularization at the moment of the valve replacement, when this indication is made for the patients who present clinical evidence of ischemia, translated as the presence of chest angina associated to the predictive factors of coronary artery disease. Another aspect that we consider important is that the indication of revascularization associated to valve replacement is very often of "prophylactic" nature, considering that, in general, the coronary artery disease is randomly explored and casually found. In many cases, the surgical indication is made because a certain lesion was disclosed at the coronary angiography. Once the indication is

made due to the presence of the lesion, the surgical procedure is seen as an opportunity to revascularize the patient.

Our approach in the present study is based on the fact that there is no solid evidence that such management benefits the patients. In contrast, what is observed is that the valve replacement associated to the myocardial revascularization procedure significantly increases short- and mid-term mortality.

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

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