Aortic Stenosis and Coronary Disease. Analysis of Risk Factors

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Objective

To analyze clinical laboratorial aspects of the presence of coronary disease in patients with aortic stenosis and evaluate the influence of risk factors in the development of obstructive coronary disease.

Methods

We studied 65 patients who had severe aortic stenosis with an indication for surgery, ages 51 to 85 years, 40 of them women. The coronary angiography assessment resulted in two groups: 26 (40%) with obstructive coronary disease and 39 (60%) with no coronary artery lesion. Personal antecedents for coronary disease (smoking, dyslipidemia, diabetes mellitus, arterial hypertension, family antecedents, sedentarism, and alcoholism) were analyzed. Additionally, the following assessments were made: electrocardiogram, echocardiogram with Doppler, and laboratory tests (blood glucose, total cholesterol and fractions, triglycerides, Apo-A1 and B, fibrinogen, lipoprotein (a) and fraction of triglycerides and cholesterol removal in both groups.

Results

In the age analysis, the group with obstructive coronary disease belonged to an older age range with statistical significance ($p<0.0001$). Signs of ischemia of the anterior wall identified on the electrocardiogram showed a significant relationship with the obstruction of an anterior interventricular artery ($p<0.002$). The univariate analysis showed a significant difference between the groups regarding averages of the aortic ($p= 0.041$), HDL ($p=0.042$), and fibrinogen ($p=0.047$) gradients. The group with coronary disease presented an average gradient and HDL level lower than the group without obstructive coronary disease. For the fibrinogen variable, the average in the group with no coronary disease was lower compared to that of the coronariopathy group. The multivariate logistic regression analysis showed fibrinogen levels as an independent variable for coronary disease ($p<0.039$).

Conclusion

Fibrinogen was an independent risk factor for the association between obstructive coronary disease and aortic stenosis.

Key words

Stenosis of aortic valve, coronary artery disease, risk factors.

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Aortic stenosis in adults is characterized by degenerative alterations of the valve leaflets that encumber the proper emptying of the left ventricle, leading to the development of muscular hypertrophy because of chronic and progressive pressure overload of the left ventricle. The main causes of aortic stenosis are congenital, rheumatic, and degenerative or senile.

The expression "risk factor"[1] describes characteristics that may be found in healthy individuals, which are independently associated with the manifestation of a given disease. In this sense, a risk factor can be defined as any measurable trait or characteristic in an individual that may lead to a greater probability of his manifesting a certain disease[2].

A meta-analysis of 33 studies showed a 37% prevalence of coronary disease in patients with calcified aortic stenosis[3]. There are still unanswered questions concerning risk factors for coronary artery disease in aortic stenosis patients. In the analysis of risk factors for coronary disease, it is not possible to assert what degree of participation these factors have in the development of coronary disease associated with aortic stenosis. In analyzing risk factors in an aortic stenosis patient, it would be extremely important from a clinical point of view to know the probability of this patient presenting an associated coronary disease. The answers to these questions could help in identifying the probability of the aortic stenosis patient also bearing an associated coronariopathy. We could determine the participation of each risk factor, alone or in combination, in the development of coronary disease in aortic stenosis patients and diminish the morbidity/mortality of this association.

Methods

Sixty-five patients participated in this research, 40 (61.5%) females, and 25 (38.5%) males. Patients were enrolled in the protocol according to the following inclusion criteria: presence of severe aortic stenosis, absence of any other valve disorder, age greater than or equal to 50 years, no previous cardiac surgery, and absence of clinically significant renal, hepatic, hemic, or neoplastic disease.

For each patient selected for the protocol, a case report form was completed that included age, gender, body mass index, risk factors for coronary disease, anamnesis data, electrocardiogram, and echocardiogram with Doppler. At the end of the interview, dates were scheduled for laboratory tests and cardiac catheterism.

In the body mass index evaluation, anthropometric measurements of weight and height were used for the Body Mass Index (BMI) calculation using the formula BMI = weight (Kg) / height2 (m^2)[4].

Selected risk factors were smoking (habit of smoking more than five cigarettes a day for at least six months)[5], HDL-cholesterol under 35 mg/dL, LDL-cholesterol over 130 mg/dL[6], diabetes mellitus (blood glucose levels over 140 mg/dL after 12-hour overnight fast)[7], systemic arterial hypertension (patients with systolic arterial pressure over 150 mmHg and diastolic pressure over 90 mmHg)[8], family antecedents (parents or siblings with history of coronary disease, and ages less than 55 years of age for men and less than 65 years of age for women)[2], sedentarism (patients who reported activities such as walking less than 30 minutes a week or sporadic participation in sports)[2], and alcoholism (men with intake of more than 4 doses a day or more than 20 doses a week and women with intake of more than 3 doses a day or more than 12 doses a week)[2].

Anamnesis data were defined by functional class according to the New York Heart Association classification[9], angina by the Canadian Cardiovascular Society[10], syncope and symptoms and signs compatible with congestive heart failure.

A 12-lead electrocardiogram was performed on all patients using Hewlett Packard equipment, model 1700, according to conventional criteria. Since there are classic electrocardiographic changes in aortic stenosis, we will analyze the association of anterior wall ischemia with significant damage of the anterior descending artery. We will not examine causal relationship with other affected coronary arteries, since they may be confused with the classic eletrocardiographic alterations that are present in severe aortic stenosis.

The echocardiogram with Doppler was performed on all patients with ATL equipment, HDI 3000 model; the maximal aortic valvar gradient was analyzed by applying BERNOULLI's modified equation[11], and the ejection fraction (EF) of the left ventricle by means of the Cube Method[12,13].

Blood test samples were drawn in the morning after a 12-hour fast. Measurements of blood glucose, triglycerides, total cholesterol and fractions, fibrinogen, apoA1, apoB and Lp (a) were carried out by the Clinical Laboratory of the Heart Institute. Also included in this study were the plasma removal kinetics of artificial chylomicrons, and this exam was performed by the Lipids Laboratory of the Heart Institute.

Cardiac catheterism was performed on all patients enrolled in the study as a pre-operative test in order to analyze coronary anatomy and evaluate the need for myocardial revascularization associated to aortic valve replacement. The test was carried out using the SONES and SHIREY technique[14]. Subjects were considered coronary patients when they had at least one subepicardial artery with an atherosclerotic process causing more than 50% reduction of the vessel lumen in comparison to the closest normal segment.

The classification variables are presented descriptively

on tables containing absolute (n) and relative (%) frequencies. The associations between these variables and the presence of coronary disease will be compared using the chi-square test, verisimilitude ratio test, or Fisher's exact test[15]. For the analysis of the incidence of coronary disease by age bracket, the ratio of verisimilitude test was used[15].

Continuous variables are presented descriptively in tables containing means and standard deviation. The means of these variables as to the presence of coronary disease were compared with Student's t-test[16]. Gradient, blood glucose, triglycerides, Lp (a), and FTR (Ch) variables were submitted to logarithmic transformation for parameter analysis.

Variables that showed statistical significance in the univariate analysis were used for the adjustment of a multiple logistic regression model with a stepwise variable selection procedure[16].

P values of $p < 0.05$ were considered significant.

Results

Ages of the 65 patients who participated in the study varied between 51 and 85 years (mean 68), and 40 (61.5%) of the subjects were women. Coronary angiography resulted in 26 (40%) patients with obstructive coronary disease and 39 (60%) without obstructive coronary disease.

We observed a greater proportion of coronary disease incidences in the older age ranges. There was a difference ($p<0.0001$) between the age brackets, i.e., the 71-80 year range had a larger proportion of patients with disease than the other age ranges.

A correlation between anterior ischemia seen on the electrocardiogram and damage of the anterior interventricular artery was observed. Of the 17 patients with lesions in this artery, 11 showed signs of anterior ischemia on the electrocardiogram (64.71%) with $p<0.002$ (Fisher's test). There was no significant association between the groups with and without coronary disease as to gender, number of risk factors, family antecedents, systemic arterial hypertension, diabetes mellitus, dyslipidemia, smoking, sedentarism, and alcoholism. No significant association was noted between the groups with and without coronary disease as to functional class, angina, syncope, and heart failure.

We did observe a significant difference between the groups in term of means of the maximal gradient ($p = 0.041$), HDL cholesterol ($p = 0.042$), and fibrinogen ($p = 0.047$) variables. Patients with coronary disease had lower values for the mean gradient and HDL than those without coronary disease. With the fibrinogen variable, patients without coronary disease had lower mean levels when compared to those with coronary disease as is shown on Table 1.

The influence of the parameters analyzed in the presence of coronary disease is described on Table 2. Only fibrinogen exerted a significant influence ($p = 0.039$) on the presence of coronary disease.

For the presence of coronary disease in the logistic regression model, the explanatory variables gradient, HDL, and fibrinogen were considered. These variables showed statistical significance in the univariate analysis. After the stepwise selection of variables, the fibrinogen

Table 1 - Mean and standard deviation of continuous variables per group (with and without coronary disease) and probability of significance (p) of student's t-test

Variable	Coronary disease						p
	+			-			
	n	Mean	DP	n	Mean	SD	
Age in years	26	70.46	9.02	39	65.9	8.38	0.250
BMI	26	21.54	4.39	39	19.62	3.070	0.078
GRAD* mmHg	26	77.35	26.77	39	87.54	24.40	0.041
EF (%)	26	0.665	0.099	39	0.696	0.085	0.174
Glucose* mg/dL	26	125.65	64.68	39	104.67	21.27	0.084
T. C. mg/dL	26	213.27	39.48	39	206.23	33.87	0.445
H.D.L. mg/dL	26	41.85	13.37	38	47.79	13.23	0.042
L.D.L. mg/dL	25	143.8	37.07	38	134.13	28.84	0.064
V.L.D.L. mg/dL	25	26.28	10.08	38	24.21	10.45	0.439
TG* mg/dL	26	146.15	90.67	39	128.38	69.27	0.371
APO-A_1 g/l	26	1.45	0.25	39	1.55	0.270	0.134
APO-B g/l	26	1.38	0.32	39	1.27	0.270	0.141
FIBRIN. mg/dL	26	377.96	72.16	39	341.82	69.45	0.047
Lp(a)* mg/dL	26	30.95	21.74	39	38.65	25.83	0.244
FTR (TG) min	26	0.036	0.021	39	0.040	0.023	0.553
FTR (Ch)* min	26	0.012	0.014	39	0.015	0.014	0.492

*SD = standard deviation; * submitted to logarithmic transformation*

Table 2 - Variables used in model adjustment: gradient, hdl, fibrinogen

Variable	Estimated Parameter	Standard Error	p	Odds Ratio	Confidence Interval (95%)	
Intercept	-3.280	1.439	0.023			
Fibrinogen	0.008	0.004	0.039	1.008	1.001	1.016

variable showed significance. Table 2 shows that the estimated parameter for fibrinogen is positive, indicating a positive correlation as to the probability of coronary disease (the greater the value of fibrinogen, the greater the probability of coronary disease).

Chart 1 shows the distribution of sensitivity and specificity values for different coronary disease probabilities. The maximum value point for both indices is the probability value of 0.42.

A 0.42 probability corresponds to a fibrinogen value of 370, that is, if the patients with values over 370 are classified as coronary patients and those with values under 370 are considered not ill, we have a 57.7% sensitivity and a 63.2% specificity (Charts 1 and 2)

Discussion

The incidence of coronary disease in patients submitted to aortic valve replacement is estimated between 7% and 66%[17,18]. A meta-analysis with 33 studies showed a 37% prevalence of coronary disease in patients with calcified aortic stenosis[3]. In our series, the 40% prevalence of coronary disease proved to be within the average of the above mentioned range, as had also been verified in well-conducted studies performed by LUND et al[19] Mautner et al[20] and Paquay et al[21].

The average age of 70 years was similar to those noted by other authors such as VEKSHTEIN[22] and BESSONE[23]. In our series, the age mean did not show a statistical difference between the two groups in spite of the older age

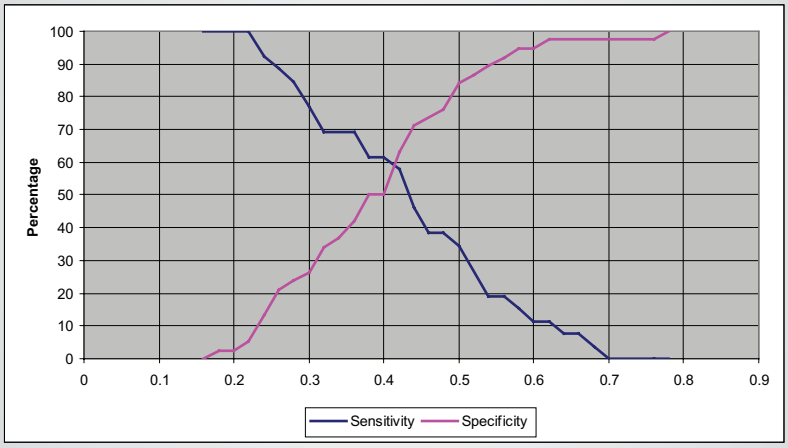

***Chart 1** - Dispersion of sensitivity and specificity of the logistic regression model*

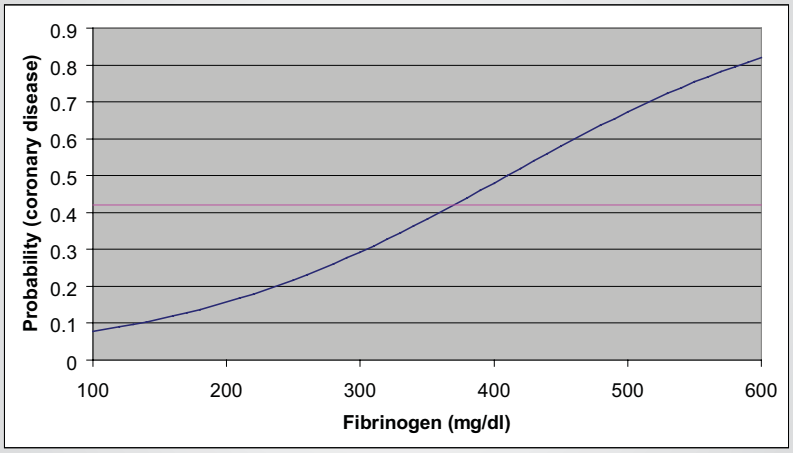

***Chart 2** - Dispersion of probability of coronary disease by fibrinogen level. The pink line represents the 0.42 probability that corresponds to 57.7% sensitivity and 63.2% specificity.*

range in the coronariopathy patients. A certain correlation was observed between age and coronariopathy rate, where the older age bracket has a greater probability of coronary disease associated with aortic stenosis[22,23]. Our highest age mean is in agreement with that found in most medical literature.

The presence of coronary disease in patients with aortic stenosis has been the focus of many studies, and some have suggested a correlation between risk factors and the presence of coronary disease in aortic valve disease patients[18,24-26]. The participation of risk factors for coronary disease has not been adequately appreciated as a predictive factor of coronary disease in patients with aortic stenosis[18,24,26,27]. In some studies, the absence of risk factors and angina were sufficient to exclude coronary disease associated with valve disorders[26]. On the other hand, Acar et al[28] and Pluta et al[18] found a high risk factor incidence in patients with coronary disease associated with aortic stenosis, while Carstens et al[29] and Exadactylos et al[30] did not observe a correlation between the presence of risk factors and the incidence of coronary disease associated with aortic stenosis. In our group of patients, the greater number of risk factors did not increase the incidence of coronary disease, a fact that concurs with the studies of Carstens[29] and Exadactylos[30].

Some authors[24,31,32] have observed that the aortic gradient tends to be smaller in patients with than in those without angina, especially when the angina is severe. This observation may be caused by the great prevalence of coronary disease associated with moderate aortic stenosis. Berndt et al[33] demonstrated that the aortic gradient was smaller in patients that had coronary disease, which was also a result noted in our study. Several authors[18,24,28,31,32] had this same result, which raises the hypothesis that myocardial ischemia or infarct could potentially diminish the gradient through the aortic valve.

Several studies in literature[34-38] observed that reduced levels of HDL-c increase the risk of coronary disease, especially if triglyceride levels are also elevated. Our study showed higher HDL-c levels in patients with aortic stenosis without coronary disease, reinforcing the concept of a protection factor for coronary disease. This aspect identified in our study is an important point because, when faced by a given patient's situation, it allows us, along with other factors, to determine the probability of his presenting coronary disease associated with aortic stenosis.

The level of plasmatic fibrinogen has been shown to be a predictor of coronary disease in several prospective studies[39,40]. Seven prospective studies[41,42] have noted an increase in the incidence of coronary disease when fibrinogen levels are high. The participation of fibrinogen as a risk factor in the coronary disease of a patient with a valve disorder has not yet been reported in literature.

In our research, this correlation was statistically significant on the univariate analysis (Table 1) and on the logistic regression model (Table 2). We studied it as an important factor in analyzing the probability of a patient with aortic stenosis having an associated coronary disease, since with the progressive increase of fibrinogen levels, the probability of this association also rises (Chart 2).

In conclusion, the observation of fibrinogen levels in clinical practice may be indicative of the increased prevalence of obstructive coronary disease in patients with aortic stenosis. This result was seen in our research, where the level of fibrinogen was an independent risk factor for the association of obstructive coronary disease and aortic stenosis, as the highest levels increased the probability of this association. This aspect, along with an analysis of the aortic gradient, age range, electrocardiogram, and HDL-c level, may be extremely important in the diagnosis and treatment of this group of patients, improving the clinical follow-up of this population.

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