Systolic Ventricular Dysfunction, a New Marker of Coronary Artery Disease in Patients With Aortic Stenosis Without Previous Myocardial Infarction

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Identification of clinical factors associated with coronary artery disease could obviate the need for coronary angiography in selected patients with severe aortic stenosis. We studied 315 patients (68 [8] years) with severe aortic stenosis without previous infarction who underwent coronary angiography. In the univariate analysis, age (P=.001), dyslipidemia (P=.003), angina (P=.018), aortic gradient (P=.001), and reduced ejection fraction (P=.006) were predictors of coronary artery disease. After multivariate analysis, age (OR=1.079, P=.01), ejection fraction <40% (OR=2.685, P=.02), angina (OR=2.518, P=.04) and dyslipidemia (OR=2.34, P=.008) were the factors independently associated with coronary artery disease. Left ventricular dysfunction correlated independently with the presence of coronary artery disease.

Key words: *Aortic valve stenosis. Coronary angiography. Coronary artery disease.*

Disfunción ventricular sistólica, un nuevo marcador de enfermedad coronaria en pacientes con estenosis aórtica sin infarto de miocardio previo

La determinación de factores clínicos predictivos de la presencia de enfermedad coronaria podría obviar la necesidad de realizar una coronariografía en pacientes seleccionados con estenosis aórtica severa. Se estudió a 315 pacientes (68 ± 8 años) sin infarto previo con estenosis aórtica severa a los que se realizó coronariografía.

En el análisis univariable, resultaron significativas la edad (p = 0,001), la dislipemia (p = 0,003), la angina (p = 0,018), el gradiente aórtico (p = 0,001) y la fracción de eyección (FE) reducida (p = 0,006). En el análisis multivariable las variables asociadas de forma independiente a la lesión coronaria fueron la edad (*odds ratio* [OR] = 1,079, p = 0,01), la FE < 40% (OR = 2,685, p = 0,02), la angina (OR = 2,518, p = 0,04) y la dislipemia (OR = 2,34, p = 0,008).

La disfunción ventricular se correlaciona de forma independiente con la presencia de lesiones coronarias.

Palabras clave: *Estenosis valvular aórtica. Coronariografía. Enfermedad coronaria.*

INTRODUCTION

Coronary artery disease (CAD) is frequently present in patients with valvular heart disease and is a predictor of perioperative mortality. The probability of suffering CAD is related to a series of known factors: type of valvular heart disease, age, presence of angina-type chest pain, and cardiovascular risk factors.[1]

The prevalence of CAD is greater in patients with aortic stenosis (AS) and mitral regurgitation than in those with mitral valve stenosis and aortic insufficiency, probably because this population is older. Aortic stenosis is the most common valvular heart disease in our area.[2,3] In Spain, the prevalence of CAD with AS is approximately 20%,[4,5] far lower than in the USA and Scandinavia (30%-50%).[6,7] Chest pain has less specificity in identifying CAD in the presence of severe AS than in the general population, since its appearance is explained by multifactorial mechanisms. Age is a significant predictive factor but at later ages than in Anglo-Saxon countries.[1] Coronary risk factors are cumulative such that the presence of 3 or more yields a 45% probability of CAD.[8]

Based on these factors, several authors have tried to carry out stratification to avoid coronary angiography before surgical intervention in a large population of patients.[4,5,8-10]

In patients with severe AS the presence of CAD and ventricular dysfunction are prognostic factors for surgical outcomes.[11-13] These 2 parameters could be interrelated. However, there is a lack of studies showing ventricular dysfunction as a predictor of CAD, especially in the absence of a previous myocardial infarction. Despite this, Spanish and North American clinical guidelines recommend preoperative coronary angiography in patients with systolic dysfunction of the left ventricle, especially from a certain age onwards.[1,14]

The aim of our study was to determine whether the presence of ventricular dysfunction prior to preoperative coronary angiography predicts significant coronary artery lesions in patients without previous myocardial infarction.

MATERIALS AND METHOD

All patients with severe AS who were candidates for surgery were retrospectively analyzed based on information taken from clinical histories. They had been recommended for coronary angiography, based on the clinical criteria in the Spanish Society of Cardiology[1] guidelines, at the Servicio de Cardiología del Hospital Clínico Universitario Virgen de la Victoria in Málaga between 1996 and 2002. Patients with previous myocardial infarction were excluded. Four percent of the patients were excluded due to poor acoustic window and the impossibility of calculating the ejection fraction (EF). Full demographic, clinical, echocardiographic, and hemodynamic variables were collected. Hypertension was defined as:

1. History of diagnosed hypertension treated with medication, diet or exercise.

2. Systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg on at least 2 occasions.

3. Standard drug therapy with antihypertensive medication.

Dyslipidemia was defined as: *a)* total cholesterol >200 mg/dL, or *b)* low-density lipoprotein ≥130 mg/dL, or *c)* high-density lipoprotein <40 mg/dL. Hypolipidemic treatment for low-density lipoprotein >100 mg/dL was also regarded as hypercholesterolemia in patients with known CAD. Diabetes mellitus, regardless of the duration of the disorder, was defined as the need for antidiabetic agents or fasting blood glucose >126 mg/dL. Significant CAD was considered present when there was a 70% or more reduction in the lumen diameter of the artery visualized in two orthogonal projections. Ejection fraction was determined by echocardiography visually and by the Teichholz's formula, using Simpson's method if there were changes in regional wall motion. Ventricular dysfunction was considered as significant when the EF was <50%

in the echocardiographic evaluation which was performed prior to coronary angiography, and as severe if EF was <40%.

The values of the continuous variables are expressed as mean ± standard deviation and those of the qualitative variables as percentages. The variables analyzed were compared in 2 groups according to the presence or not of coronary artery lesions. The χ^2 test was used for qualitative variables and Student s *t* test for continuous variables. A multivariate analysis was carried out with logistic regression to identify the variables independently predictive of significant CAD. To this end we analyzed the variables that were significant in the univariate analysis and the clinical factors recognized as predictors of significant CAD.

RESULTS

The sample consisted of 315 consecutive patients with severe symptomatic AS. The mean age was 68.8 years, there were more males (57%), and a broad range of cardiovascular risk factors were present. The main symptom was dyspnea (72%), followed by angina (41.9%) and electrocardiographic signs of left ventricular hypertrophy in 39.7% of patients. Significant ventricular dysfunction was present in 23.1% of patients and was severe (EF<0.40%) in 10.7%. There were 57 patients with significant coronary artery lesions (18.1%) (Table 1).

In the univariate analysis, in relation to the presence or not of CAD, age was statistically significant (67.5 years without CAD vs 71.8 years with CAD; *P*=.001), as well as angina (39.1% without CAD vs 56.1% with CAD; *P*=.018), dyslipidemia (25.2% without CAD vs 45.5% with CAD; *P*=.003), aortic gradient (82.8% without CAD vs 70.7% with CAD; *P*=.001) and EF (58.9% without CAD vs 54.2% with CAD; *P*=.006). No other differences were found among the remaining variables analyzed (Table 2). Differences were also found when analyzing the percentage of CAD in pa-

TABLE 1. **Baseline Characteristics of the Sample***

Mean age, years	68±8
Sex, males (%)	57
Maximum gradient (echocardiogram), mm Hg	80±23
Ejection fraction (echocardiogram), %	58±11
Dyslipidemia, %	28.6
Hypertension, %	46
Diabetes mellitus, %	24.5
Smokers, %	35
Angina, %	41.9
Syncope, %	15.6
Dyspnea, %	72
Functional class III-IV dyspnea, %	41.7

*Data are expressed as mean ± standard deviation for numerical variables and as percentages for qualitative variables.

TABLE 2. **Univariate Analysis: Baseline Characteristics in Relation to the Presence of Significant Coronary Artery Lesions**[*]

	With No Coronary Artery Lesions, n=258 (81.9%)	With Coronary Artery Lesions, n=57 (18.1%)	*P*
Age, years	67.5±9	71.8±6	.001
Sex, males (%)	56.2	61.4	NS
Angina, %	39.1	56.1	.018
Syncope, %	16.5	16.7	NS
Dyspnea, %	76	74.5	NS
Smoking habit, %	35.7	32.7	NS
Diabetes mellitus, %	22.9	34.5	NS
Hypertension, %	42	44	NS
Dyslipidemia, %	25.2	45.5	.003
Aortic gradient, echocardiogram	82.8±23	70.7±22	.001
Left ventricular hypertrophy, %	62.5	62.5	NS
Sinus rhythm, %	85.5	96	NS
Body surface area	1.77±.17	1.79±.17	NS
Ejection fraction (echocardiogram)	58.9±11	54.2±12	.006

*Data are expressed as mean±standard deviation for numerical variables and as percentages for qualitative variables.

tients with significant systolic ventricular dysfunction (EF<50%) versus patients with preserved systolic function (28.2% vs 15.2%, respectively; *P*<.01). The findings were similar (35% vs 17.4%; *P*<.05) when analyzing the patients with severe ventricular dysfunction (EF<40%).

In the multivariate analysis the variables associated with significant CAD were angina (odds ratio [OR]=2.518; 95% confidence interval [CI], 1.354-4.682; *P*=.04), dyslipidemia (OR=2.34; 95% CI, 1.250-4.382; *P*=.008), age (OR=1.079; 95% CI, 1.031-1.128; *P*=.01), and EF<40% (OR=2.685; 95% CI, 1.109-6.505; *P*=.02). On the other hand, the variables not associated with CAD were diabetes, hypertension, tobacco smoking, and aortic gradient (Table 3).

In our series the positive predictive and negative value of an EF<40% for the presence of significant CAD was 21% and 92.2%, respectively.

DISCUSSION

Significant ventricular dysfunction was present in 23.1% of our patients and was severe (EF<40%) in 10.7%. The prevalence of ventricular dysfunction with AS in our series matches that in other series.[12,13]

Systolic function in AS tends to be preserved and, according to Ross,[15] when this is reduced it is generally related to afterload mismatch and thus can be corrected after valve replacement. In a minority of cases it is related to an intrinsic defect in myocardial contractility.[16] In our study, all patients with a previous myocardial infarction were excluded to highlight the relevance of systolic function in patients in without manifestations of CAD.

In previous series, the variables age, angina[4,5,8-10] and coronary risk factors[4,8] were found to be positive independent predictors of significant coronary lesions

TABLE 3. **Variables Associated With Significant Coronary Artery Lesions in the Multivariate Analysis**[*]

	Odds ratio (95% CI)	*P*
Angina	2.518 (1.354-4.682)	.04
Age	1.079 (1.031-1.128)	.01
Dyslipidemia	2.34 (1.250-4.382)	.008
EF<40%	2.685 (1.109-6.505)	.02

*CI indicates confidence interval; EF, ejection fraction.

determined by coronary angiography in patients with valvular heart disease in general, and in aortic disease in particular. However, systolic function of the left ventricle has not been described as a significant predictor of preoperative coronary artery disease. This is even more striking when most guidelines for the management of patients with AS empirically recommend coronary angiography if there is preoperative ventricular dysfunction.

The preoperative study of patients with valvular heart disease is usually complemented by non-invasive tests which, in general, are limited to cardiac catheterization to study the coronary anatomy. This test can be avoided in a large group of patients; specifically, in those less than 60 years old, with no coronary risk factors, and without angina (in those in whom the estimated prevalence of significant CAD is less than 5%).[1]

In our series, univariate analysis showed that age, angina, dyslipidemia, EF, and aortic gradient estimated by echocardiography were statistically significant. No differences were found in the remaining variables analyzed. The positive result of the aortic gradient is in line with pathophysiology, since this decreases when systolic dysfunction is present (and, thus, significant CAD). In the multivariate analysis an EF less

than 40% correlated independently with the presence of significant CAD with an OR of 2.685 (95% CI, 1.109-6.505; *P*=.02), together with other previously recognized factors such as age, angina, and dyslipidemia.

From a pathophysiological viewpoint, in the absence of a previous myocardial infarction, the greatest percentage of ventricular dysfunction in patients with AS and coronary lesions is explained by the combination of an increase in oxygen demand due to afterload mismatch and a decreased in secondary flow to the diseased coronary artery. The combination of a high afterload situation, such as aortic stenosis, and a chronic flow deficit would probably imply a higher probability of ventricular dysfunction, due to myocardial adaptation to lower oxygen intake.

It is important to highlight that all the patients referred to coronary angiography for symptomatic severe AS with a history of previous myocardial infarction were excluded, given that the presence of CAD is already obvious in these patients. Likewise, we found a high negative predictive value, which increases interest in this variable as a predictor of coronary artery lesions. In other words, 92.2% of patients with an EF>40% do not present CAD. From a practical standpoint, this implies adding a new clinical factor to risk stratification for subclinical coronary artery disease in patients with significant AS.

Limitations

Our study is a retrospective analysis with its inherent limitations. However, since 1996, the presence of coronary risk factors and echocardiographic data prior to coronary angiography has been systematically collected in a database.

CONCLUSION

The presence of significant ventricular dysfunction in patients with symptomatic severe AS and with no history of previous myocardial infarction is a parameter associated with subclinical CAD. Therefore, this may be an adjunctive parameter to stratify for the risk of having CAD in this patient population and for the consequent indication for preoperative coronary angiography.

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