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Invasive assessment of coronary flow reserve impairment in severe aortic stenosis and ecochadiographic correlations☆

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ABSTRACT

Objectives and background: Patients with aortic stenosis (AS) may have impaired coronary flow reserve (CFR) despite angiographically normal coronary arteries. This is the first report of invasive thermodilution-derived CFR and IMR in patients with AS and their associations with echocardiographic parameters for AS assessment.
Methods: Thirty-six consecutive severe AS patients and ten patients without AS underwent prospectively cardiac catheterization and coronary physiological parameters were determined in the left anterior descending (LAD). Mean transit time (Tmn), a surrogate of absolute coronary flow, was obtained from the coronary thermodilution curve.
Results: In AS patients we found a high LAD flow at rest (Tmn_{rest} 0.55 ± 0.3 vs 0.99 ± 0.4, p = 0.01) and a low flow at hyperemia (Tmn_{hyp} 0.44 ± 0.2 vs 27.7 ± 0.1, p = 0.02) and consequently a severe CFR impairment (1.4 ± 0.4 vs 3.8 ± 1.4, p < 0.001) compared with controls. An elevated index of microvascular resistance (IMR) (32.7 ± 16 vs 17.8 ± 6.5, p = 0.01) and a low baseline microvascular coronary resistance (48.1 ± 29 vs 84 ± 34, p = 0.02) were also found.
In AS patients there were significant correlations between CFR and left ventricular mass index (r = −0.32; p = 0.02), and the ratio of acceleration time to ejection time (AT/ET) (r = −0.4; p = 0.01) a non-flow dependent echocardiographic parameter for AS assessment. Multiple linear stepwise regression analysis showed that AT/ET (β = −0.441, p = 0.019) was the only independently variable associated with CFR
Conclusions: In severe AS, invasive CFR shows a progressive decrease with AS severity and a good correlation with echocardiographic parameters of AS, especially with flow-independent ones.

1. Introduction

Patients with aortic stenosis (AS) may have impaired coronary flow reserve (CFR) and microvascular dysfunction (MD) despite angiographically normal coronary arteries [1–3], which limits the ability of coronary circulation to increase flow to match myocardial oxygen demand [4].

The reduction of CFR is the key factor responsible for myocardial ischemia in AS patients, and may be associated with major adverse cardiac events [1,5].

However in previous studies in AS, the MD has been mainly assessed employing non-invasive techniques, and just in a few of studies, MD has been invasively assessed but not with the thermodilution technique [6, 7]. Otherwise only the most common echocardiographic variables associated with invasive CFR and coronary resistances have been previously characterized. The aim of the present study was to invasively assess the CFR and microvascular coronary resistances by the thermodilution method in severe AS patients and identify which echocardiographic variables were related to them, including some parameters that are not routinely assessed like the ratio of acceleration time to ejection time (AT/ET).

2. Methods

2.1. Patient population

A total of 46 patients were included in the study. 36 consecutive patients with severe AS (AVA < 1 cm^2) referred to cardiac catheterization prior to valve replacement signed the consent form and were prospectively included in the study.

Exclusion criteria were any previous coronary intervention in the study vessel (left anterior descending (LAD)); any concomitant severe valvulopathy or acute heart failure. One patient with AS and a FFR < 0.75 was excluded, except for IMR determination.

☆ All these authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Ten patients without AS with an angiographically unobstructed LAD who were scheduled for elective physiological assessment of epicardial disease severity formed the control group. Exclusion criteria for this control group were any previous coronary intervention in the LAD; FFR <0.8 in the LAD; a positive stress test for anterior ischemia or hypertrophic cardiomyopathy.

The study was approved by an institutional review committee and all the subjects gave informed consent.

2.2. Coronary angiography, aortography and physiological measurements

Coronary angiography was performed according to standard practice. A transradial approach with 6 Fr guiding catheters was performed in most cases (78%) and femoral approach in the other cases.

A coronary thermodilution curve was generated using a pressor sensory wire with a distal thermistor.

After diagnostic aortography and angiography, the mean distal coronary pressure (Pd, mmHg) and transit mean times (Tmns) were obtained using a 0.014″ wire (Pressure Wire™ Certus™; St. Jude Medical, St. Paul, MN, USA) positioned in the distal LAD. Tmn is a surrogate of absolute coronary flow and was measured from the coronary thermodilution curve as previously described [8,9].

Aortic pressure was concomitantly recorded through the guiding catheter (Pa, mmHg). Measurements were acquired both during resting conditions, as well as during hyperemia, induced by peripheral intravenous infusion of adenosine (140 μg/Kg/min). Three consecutive thermodilution curves were obtained by brisk injection of 3 mL of saline at room temperature into the coronary artery according to described methodology [8,9]. Data were displayed in real time (RadiAnalyzer Xpress; St. Jude Medical, St. Paul, MN, USA).

Patients were asked about any symptoms during adenosine infusion and symptoms were subjectively categorized in mild, moderate or severe. Severe were considered if the infusion had to be stopped.

2.3. Echocardiography

Two-dimensional transthoracic echocardiographic and doppler studies were obtained with clinical ultrasound machines equipped with 2.5- to 3–5-MHz transducers (iE33 Phillips Medical Systems, Best, The Netherlands). The echocardiogram was performed within 48 h before or after the catheterization following the AHA guidelines [10].

As a measure of global left ventricular (LV) afterload, we calculated the valvuloarterial impedance (Zva) as (systolic arterial pressure + mean gradient) / stroke volume index [11]; the systolic work loss (SWL) as (100 ∗ aortic mean gradient) / (aortic mean gradient + systolic blood pressure) [12]; and the AT/ET [13].

2.4. Data analysis

Fractional flow reserve (FFR) was calculated as the ratio of Pd to Pa at stable hyperemia. The inverse of Tmn strongly correlates to absolute coronary blood flow [8]. CFR was calculated as the ratio of resting Tmn (Tmn_{rest}) divided by mean hyperemic Tmn (Tmn_{hyp}) and was measured simultaneously with FFR using the thermodilution method, as described elsewhere [9]. IMR and baseline resistance (Br) were calculated as the product of Pd and Tmn at hyperemia and at rest respectively [8,14]

CFR corrected for changes in blood pressure as previously described by Pijls was calculated and was called CFR_c [15].

Coronary physiological data were collected blinded to echocardiography data.

2.5. Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables and compared using the unpaired *t*-test. Categorical variables were expressed as numbers or percentages and compared using chi-square analysis or Fisher's exact test. When a variable was not normally distributed, a logarithmic transformation was performed. The Spearman test was used to assess the relation between two quantitative variables. The independent correlation of CFR was assessed with the multiple linear regression analysis. A stepwise multiple logistic regression analysis was performed to identify independent predictors of severely reduced AVA (≤0,4 cm^2/m^2). Variables related to the dependent variable in univariate analysis ($p < 0.1$) were included in the multivariate models. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics

Clinical characteristics of the overall study population stratified by the presence of AS are shown in Table 1.

In the AS group most of the patients were symptomatic (94%). The most common symptom was dyspnea (78%).

Table 1
Baseline characteristics stratified by the presence of aortic stenosis (AS).

Total (n = 48)	AS (36)	Controls (10)	P value
Clinical variables			
Age (yrs)	72 ± 7	66 ± 8	0.056
BMI (Kg/m$^{2)}$	29 ± 4	26 ± 2	0.16
Hypertension	21(58.3)	3(37)	NS
Diabetes mellitus	11 (30.6)	3(33)	NS
Hypercholesterolemia	13(36.1)	3(37)	NS
CKD	4(11)	1(10)	NS
Smoking	5(13.9)	4(44)	0.06
Syncope	6(16.7)	0(0)	NS
Chest pain	11(30.6)	9(90)	0.001
Sex (male)	17(47.2)	4(44)	NS
Epicardial LAD disease	1(3)	0(0)	NS

Values are n (%) or mean ± SD; ACE angiotensine-converting enzyme; CKD chronic kidney disease.

3.2. Echocardiographic characteristics

The etiology of AS was degenerative in most cases (86%) and bicuspid aortic valve in the other cases.

Two patients (5%) had LV dysfunction with low gradient but confirmed severe AS after dobutamina stress echocardiogram. Only one patient had severe ventricular dysfunction.

We divided the patients in two group based in aortic valve area (AVA): 50% of the patients had a very severely reduced AVA (aortic valve area index (AVAi) ≤ 0,4 cm^2/m^2). A severe increase in left ventricular mass index (LVMi) was found in 47% of the patients (≥122 g/m^2 in woman and ≥149 g/m^2 in men).

Echocardiographic parameters are summarized in Table 2.

3.3. Coronary physiological findings and adenosine

The variability of Tmn within each set of three consecutive measurements was 11.7 ± 7.5% at baseline and 12.2 ± 8% at hyperemia. Because maximal flow during hyperemia is directly related to perfusion pressure at that time, we calculated the drop in blood pressure induced by hyperemia for both groups without finding significant differences (12.3 ± 5.9 vs 10.6 ± 9, p = 0.096) and the CFR corrected by pressure (CFR_c). CFR_c was increased by 11% compared to CFR. All the statistical analysis performed with CFR were repeated using CFRc leading to the same results and conclusions.

Patients with severe AS had a high baseline LAD flow (Tmn_{rest} 0.537 ± 0.23) and a low hyperemic LAD flow (Tmn_{hyp} 0.47 ± 0.37) compared with controls and consequently we found a severe impairment of CFR (1,4 ± 0.4). An elevated IMR (32.7 ± 16) and a low Br (47.7 ± 29) were also found (Table 3).

Most of the patients had a severely impaired CFR, there were only five patients with a CFR higher than 2, and three of these patients had an IMR below 25. The highest CFR value was 2.8 and the median was 1.5.

During adenosine infusion, there was a statistically significant drop in blood pressure in both groups but it did not correlate to clinical side effects. A trend for more frequents side effects in AS patients (81% vs 60%, $p > 0.2$) was found. However all symptoms referred were mild (39%) or moderate (42%) and no infusion had to be stopped early for side effects. Chest pain (42%) and heat sensation (42%) were the most frequent side effects registered

3.4. Relationship between measured parameters

Table 4 summarizes the main correlations. CFR correlated significantly with LVMi (r = −0.32; p = 0.02), and AT/ET (r = −0.4; p = 0.01). IMR correlated with CFR but did not correlate with any other variable, although showed a non-significant trend with an association with echocardiographic parameters of AS ($p < 0.1$).