Effect of Correction of Anemia on Echocardiographic and Clinical Parameters in Patients With Aortic Stenosis Involving a Three-Cuspid Aortic Valve and Normal Left Ventricular Ejection Fraction

Miquel Gómez, MD, PhD[a,b,*], Mireia Ble, MD[a,b], Mercedes Cladellas, MD, PhD[a,b], Luis Molina, MD, PhD[a,b], Josep Comín-Colet, MD, PhD[a,b], Cristina Enjuanes, MD[a,b], Cristina Roqueta, MD, PhD[b,c], Cristina Soler, RN[a], and Jordi Bruguera, MD[a,b]

The objective of the study is to investigate the impact of anemia (defined as hemoglobin concentration of <12 g/dl in women and 13 g/dl in men) on prognosis and to study the effect of recovery from anemia on echocardiographic and clinical parameters in patients with aortic stenosis (AS). This was a prospective study in 315 patients with moderate or severe AS. Patients with anemia received oral iron (ferrous sulfate with mucoproteose, 160 mg iron/day) and erythropoietin, if needed, or intravenous iron, if necessary. The following tests were performed before and after normalization of hemoglobin values: echocardiogram, 6-minute walk test, N-terminal B-type natriuretic peptide, and measures of depression, cognitive impairment, and dependence. Patient mean age was 74 years (SD 9). Mean follow-up was 25 months (SD 8). Anemia prevalence in the overall group was 22% (n = 70). Patients who are anemic had a higher rate of complications at follow-up (mortality, hospital admission, or need for valve procedure; 80% vs 62%, p = 0.009). In total, 89% of patients recovered from anemia, with a mean time to recovery of 4.6 weeks (SD 1.4). Improvements were observed on echocardiographic parameters of peak velocity (4.1 to 3.7 m/s, p = 0.02) and mean gradient (44 to 35 mm Hg, p = 0.02). Performance on the 6-minute walk test improved from 235 to 303 m (p <0.001). Median N-terminal B-type natriuretic peptide value decreased from 612 to 189 pg/dl (p <0.001). In conclusion, patients with AS and anemia have a worse prognosis than those without anemia. Resolution of anemia is associated with improvements in echocardiographic parameters and functional status, suggesting that treatment of iron deficiency is a relevant option in the management of patients with AS, particularly in nonoperable cases. **(Am J Cardiol 2015;116:270−274)**

Anemia has been associated with poorer clinical status and prognosis in patients with aortic stenosis (AS).[1−3] In patients with chronic heart failure (CHF), iron deficiency (ID) has been associated with exercise intolerance[4] and the presence of depressive symptoms, whereas correction of ID has been linked with improvements in exercise capacity in several interventional studies.[5] Although there has been relatively little research into the effects of treating anemia and ID in patients with AS, in CHF a number of studies have shown a beneficial effect.[6−11] The detrimental effect of anemia and ID on prognosis and on clinical and functional status in patients with AS, coupled with a lack of research to date into how treatment of anemia and ID affects outcomes in these patients, makes further research in this area imperative. The aims of the present study were, first, to investigate whether patients with AS and concomitant anemia presented a worse prognosis than patients with AS without anemia and, second, to investigate whether recovery from anemia improves echocardiographic and clinical parameters in these patients.

Methods

This was a prospective study carried out in patients with moderate or severe AS attending the Cardiology Department of a large tertiary hospital in Barcelona, Spain. From 2007 to 2013, 315 patients with moderate or severe degenerative AS defined as peak velocity (V_{max}) >3.5 m/s and/or aortic valvular area (AVA) <1.25 cm^2 with normal ventricular function (defined as left ventricular ejection fraction >55%) were included consecutively in the study. Patients with bicuspid aortic valve and those with other significant associated valvular disease were excluded. All studies were performed at the Echo Lab with aVivid 9 echocardiograph (General Electric Medical Heakth, Waukesha, WI). The apical view was used to calculate transvalvular gradients. The aortic valve area was calculated using the continuity equation and indexed for body surface

[a]Cardiology Department, Heart Diseases Biomedical Research Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; [b]Department of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain; and [c]Geriatrics Department, Centre Forum-Parc de Salut Mar, Barcelona, Spain. Manuscript received December 29, 2014; revised manuscript received and accepted April 2, 2015.

See page 273 for disclosure information.

*Corresponding author: Tel: +34-932-483-118; fax: +34-932-483-398.
E-mail address: mgpcaelum@hotmail.com (M. Gómez).

0002-9149/15/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2015.04.020

Table 1
Baseline socio-demographic, clinical, and echocardiographic characteristics of the overall study sample and the anemia and non-anemia sub-groups

Variable	Overall (n=315)	Anemia		*p*-value
		No (n=245)	Yes (n=70)	
Age (years)	74.1±9.0	73.3±10.0	77.2±8.1	0.09
Women	154 (49%)	110 (45%)	45 (65%)	0.06
Hypertension	233 (74%)	176 (72%)	57 (78%)	0.24
Dyslipidemia	195 (62%)	149 (61%)	48 (68%)	0.63
Diabetes mellitus	88 (28%)	56 (23%)	31 (44%)	0.009
Smoker	35 (11%)	29 (12%)	7 (10%)	0.61
Chronic kidney disease	25 (8%)	17 (7%)	9 (13%)	0.09
Antiagregant/ anticoagulant therapy	94 (30%)	68 (27.9%)	24 (35%)	0.06
Atrial fibrillation	19 (6%)	17 (7%)	4 (5.5%)	0.15
NT-proBNP (pg/ml)*	291 (95-560)	126 (90-325)	402 (185-870)	0.001
Hemoglobin (g/dL)	13±6	14±1	11±1	0.001
Creatinine (mg/dL)	1±0.9	0.8±0.7	1±0.9	0.33
Surface area (m^2)	2±0.2	2±0.2	2±0.2	0.48
Peak velocity (m/s)	4±0.9	4±0.9	4±0.8	0.03
Mean gradient (mmHg)	43±16	39±17	45±17	0.01
Peak gradient (mmHg)	70±25	65±24	73±28	0.02
Aortic valve area (cm^2)	0.9±0.7	0.9±0.8	0.8±0.3	0.21
Aortic valve area index (cm^2/m^2)	0.5±0.1	0.5±0.1	0.5±0.2	0.67
Left Ventricle diastolic diameter (mm)	47±7	46±7	48±5	0.08
Left Ventricle systolic diameter (mm)	27±8	27±8	29±10	0.73
Left Ventricle mass (g)	232±83	229±80	242±93	0.87
Left Ventricle Ejection Fraction (%)	64±9	65±9	63±10	0.60

All values are presented as mean ± standard deviation unless otherwise indicated.

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg. Dyslipidemia was defined as LDL-Cholesterol > 160 mg/dl, HDL-Cholesterol < 35 mg/dl (men) or < 45 mg/dl (women).

NT-proBNP = N Terminal B-type natriuretic peptide.

* Median (interquartile range).

area. Blood tests were performed with the patient at rest and fasting to analyze N-terminal B-type natriuretic peptide (NT-proBNP) values in all patients 15 minutes before the echocardiogram. Patient-reported symptoms were used to determine the need for aortic valve replacement surgery, as recommended in clinical practice guidelines.[12,13] All patients provided informed consent, and the study protocol was approved by the center's Ethics Committee.

Data were collected on the following variables for all patients: age, gender, cardiovascular risk factors, and analytic variables (creatinine, hemoglobin [Hb], NT-proBNP, serum ferritin, transferrin, transferrin saturation index, haptoglobin, and lactate dehydrogenase). Echocardiographic variables recorded were V_{max} (m/s), mean gradient (mm Hg), peak gradient (mm Hg), AVA (cm^2), AVA index (cm^2/m^2), E/E' ratio, end-systolic and end-diastolic dimension of the left ventricle (mm), left ventricular mass (g), and the ejection fraction (%). Adverse events recorded were mortality, hospital admission, and need for a valve procedure. Data on adverse events were collected by review of the hospital clinical history in each patient or, if necessary, during a telephone interview with the patient or family.

The following tests were administered by a specialist nurse before and after normalization of Hb values in patients with a diagnosis of anemia: echocardiogram after recovery, 6-minute walk test, geriatric cognitive assessment tests (Mini-Mental State Examination and the Barthel Index), measures of depression (Yesavage test), and NT-proBNP.

Anemia was defined as an Hb concentration of <12 g/dl in women and 13 g/dl in men.[14] Patients with ID anemia were treated at our institution with oral iron (ferrous sulfate with mucoproteose, 80mg iron per tablet, 2 tablets/day, once in the morning in fasting state; Tardyferon Pierre Fabre, France). Once Hb recovery was attained, a 3-month treatment period with 1 daily tablet of ferrous sulfate with mucoproteose was established to replenish the body's iron stores. Patients with non-ID anemia or those with no improvement at the first follow-up visit (3 weeks) were treated with erythropoietin (EPO) 20,000 IU subcutaneously every 3 weeks. Patients with Hb <10 g/dl, those who were oral iron intolerant, or who showed no increase in Hb despite oral iron treatment received intravenous (iv) iron (100 mg of iron as iron sucrose per dose every 3 weeks until the administration of the total amount of calculated iron according to weight and initial level of Hb) and EPO every 3 weeks. In the case of side effects attributed to the oral iron supplement, the daily dose was divided over 2 administrations (1 tablet/12 hours) or reduced to 1 tablet/day; if discomfort persisted, the patient was switched to iv iron. Patients with a recurrence of anemia were treated with ferrous sulfate with mucoproteose (1 tablet/day). In cases of severe ID anemia, fecal occult blood testing was performed followed by digestive endoscopy if the fecal blood test was positive.

Continuous data were described using means and SD or medians and interquartile ranges, as appropriate. Categorical variables were described using measures of absolute frequency and distribution. Unpaired *t* tests were used for between-group comparisons of continuous variables when these showed a normal distribution, and Mann-Whitney U test was used when distribution was non-normal; categorical variables were compared using the chi-square test. Univariate analysis was used initially to identify risk factors associated with anemia, and variables that were statistically significant at $p < 0.10$ were included in a Cox multivariate regression analysis. Changes on variables used to assess response to anemia treatment were tested for statistical significance using paired *t* tests. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS 18.0 (Chicago, IL) and R, version 2.11.1 (R: a language and environment for statistical computing R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 315 patients were included in the study. Table 1 lists baseline patient sociodemographic, clinical, and echocardiographic characteristics for the study population as a whole and for patients with and without anemia. Patients were followed up for a mean of 25 months (8). Anemia was diagnosed in 22% (n = 70) of the study population: 57 had ID anemia, 12 anemia associated with chronic disease, and 1 had intravascular hemolysis.