International Journal of Cardiology 128 (2008) 406 – 412

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Heart failure in patients with aortic stenosis: Clinical and prognostic significance of carbohydrate antigen 125 and brain natriuretic peptide measurement

Francesco Antonini-Canterin [a,*], Bogdan A. Popescu [b], Andreea C. Popescu [c], Carmen C. Beladan [b], Renata Korcova [a], Rita Piazza [a], Piero Cappelletti [a], Daniela Rubin [a], Matteo Cassin [a], Pompilio Faggiano [a], Gian Luigi Nicolosi [a]

[a] *Cardiologia, ARC, Azienda Ospedaliera S. Maria degli Angeli, Via Montereale, 24 33170 Pordenone, Italy*
[b] *"Prof. Dr. C. C. Iliescu" Institute of Cardiovascular Diseases Bucharest, Romania*
[c] *Cardiology Department, Elias Hospital Bucharest, Romania*

Received 11 October 2006; received in revised form 17 May 2007; accepted 26 May 2007
Available online 26 July 2007

Abstract

Background: Brain natriuretic peptide (BNP) is related to symptomatic status and outcome in aortic stenosis (AS) patients. Carbohydrate antigen 125 (CA125) demonstrated recently a BNP-like behaviour in patients with congestive heart failure (CHF) but has never been studied in AS patients. We aimed to assess the role of CA125 and BNP in AS patients.
Methods: CA125 and BNP blood levels, transthoracic echocardiography and independent evaluation of CHF symptoms were obtained in 64 consecutive patients (76±9 years; 35 males) with AS (valve area 0.9 ± 0.3 cm^2). A pre-specified combined end-point consisting of cardiac mortality, urgent aortic valve replacement and hospitalization for CHF was considered. The median follow-up was 8 months (interquartile range 4.5–10 months).
Results: Both CA125 and BNP have accurately identified patients with III–IV NYHA class: area under the ROC curve was 0.85 for CA125 and 0.78 for BNP (best cut-offs of 10.3 U/mL and 254.64 pg/mL respectively) and were independently correlated to left ventricular ejection fraction. Fifty-two percent of patients with CA125 ≥ 10.3 U/mL vs. 13% with CA125 < 10.3 U/mL ($p < 0.01$) and 65% patients with BNP ≥ 254 pg/mL vs. 7% with BNP < 254 pg/mL ($p < 0.001$) have reached the end-point.
Conclusions: Both CA125 and BNP levels are significantly correlated with NYHA class and outcome in patients with AS. CA125 blood level assessment (less expensive) may improve the clinical management in this setting.

Keywords: Aortic stenosis; Echocardiography; BNP; Carbohydrate antigen 125

1. Introduction

The natural history of aortic stenosis changes dramatically after the onset of symptoms with an extremely high mortality rate on medical therapy within 3 years [1,2]. Therefore, there is a general agreement on the recommendation of aortic valve replacement in clearly symptomatic patients [3,4]. Symptoms assessment, however, is frequently difficult, especially in elderly patients with aortic stenosis because of reduction of physical activity or under-reporting by the patients themselves. Furthermore, there is a wide overlap in all echocardiographic and hemodynamic measurements between symptomatic and asymptomatic patients [5–7]. Recent studies have shown that plasma levels of natriuretic peptides, well recognized markers of left ventricular hypertrophy and dysfunction in patients with congestive heart failure [8,9], are also related to disease

* Corresponding author. Tel.: +39 0434 399462; fax: +39 0434 399197.
E-mail address: cardiologia@aopn.fvg.it (F. Antonini-Canterin).

0167-5273/$ - see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2007.05.039

severity [10–13] and to symptoms [14,15] in patients with AS. In addition, it has been reported that natriuretic peptide levels predict symptom-free survival and postoperative outcome in patients with severe aortic stenosis [16–18]. An increase of serum levels of carbohydrate antigen 125 (CA125), a tumoural marker traditionally related to ovarian cancer, has been recently observed in patients with chronic congestive heart failure [19–22]. There is no information to date about the clinical usefulness of CA125 measurement in aortic stenosis patients. The purpose of the present study is then to evaluate the clinical and prognostic significance of both brain natriuretic peptide (BNP) and CA125 in patients with AS, correlating their blood levels with NYHA class, echocardiographic parameters and outcome.

2. Materials and methods

A total of 64 consecutive patients with isolated aortic stenosis referred to our adult echocardiography laboratory were enrolled in this prospective study. The exclusion criteria included more than mild associated aortic regurgitation, recent acute coronary syndrome (<1 month), prior cardiac surgery, chronic renal failure with a creatinine level >2 mg/dL. Patients with known malignant diseases were also excluded. The study protocol was approved by the local ethics committee, and all patients gave written informed consent.

Symptoms were assessed by experienced cardiologists blinded to echocardiographic results and CA125/BNP levels. Patients were grouped according to the New York Heart Association (NYHA) classification. The presence of coronary artery disease was defined as history of myocardial infarction or significant stenosis (>70% in a major epicardial coronary artery) in a previous coronary angiogram. The presence of angina and exertional syncope was also recorded. All patients were followed-up by means of scheduled clinical visits, by consulting the Regional Health Database and by phone call interviews. A pre-specified composite end-point consisting of cardiac death, urgent valve replacement and hospitalization for heart failure was considered to evaluate the prognostic value of CA125 and BNP levels. Echocardiographic data were obtained using commercially available ultrasound systems (Hewlett Packard Sonos 5500, Philips; Vivid 7, General Electric Inc.). All patients underwent a comprehensive examination including M-mode and 2-D echocardiography and continuous-wave, pulsed-wave and Color Doppler. Measurements were made according to the American Society of Echocardiography guidelines [23] and averaged from 3 to 5 cardiac cycles. M-mode echocardiograms were derived from 2-dimensional images and recorded at 50 mm/s. An optimized parasternal short-axis view at the mid-left ventricular level, just below the mitral valve leaflets was used to measure the following parameters: left ventricular end-systolic and end-diastolic dimensions, ventricular septum and left ventricular posterior wall thicknesses, and relative wall thickness. Left ventricular mass and LVMI (left ventricular mass indexed by body surface area) were measured with M-mode echocardiography using the Devereux formula [24]. Left ventricular volumes and ejection fraction were determined from a maximized apical 4-chamber view by measuring the end-systolic and end-diastolic volumes using the modified single plane Simpson's method or area-length method. Peak aortic velocity was obtained using continuous-wave Doppler from the window yielding the highest velocity signal. Mean aortic valve gradient was derived by the modified Bernoulli equation tracing the continuous-wave flow envelope across the aortic valve. The aortic valve area was calculated using continuity equation [25]. The assessment of left ventricular diastolic function was made from transmitral and pulmonary venous flow parameters, in patients in sinus rhythm, and classified as normal, impaired relaxation, pseudonormal, or restrictive pattern, as previously described [26]. Mitral and aortic regurgitation were evaluated by Doppler color-flow mapping [27,28]. All echocardiographic data were stored on high-quality S-VHS videotape for off-line analysis. Both CA125 and BNP levels were determined using commercially available kits (Bayer, ADVIA Centaur, chemiluminescent immunoassay). Venous blood samples were taken from an antecubital vein at the time of the echocardiogram from all patients into appropriate vacutainer test tubes, according to the manufacturer's instructions. Plasma samples were frozen at −70 °C until assay.

2.1. Statistical analysis

Continuous variables are presented as mean±standard deviation. Skewed data (such as CA125 and BNP values) were logarithmically transformed (ln), and the ln values were then used in analyses. Comparisons between groups for

Table 1
Patients' characteristics

	All (*n*=64)	NYHA I–II (*n*=40)	NYHA III–IV (*n*=24)	*p* value
Age (years)	76±9	74±9	79±8	<0.05
Female (%)	54.7	55.0	54.2	NS
Aortic peak velocity (m/s)	3.8±0.8	3.8±0.8	3.8±0.9	NS
Peak gradient (mm Hg)	61±27	61±25	61±30	NS
Mean gradient (mm Hg)	36±17	36±16	35±18	NS
Aortic valve area (cm^2)	0.92±0.31	0.96±0.33	0.84±0.27	NS
Ejection fraction (%)	54±10	59±6	47±11	<0.001
Coronary artery disease (%)	28.0	25.0	33.3	NS
Hypertension (%)	54.7	47.5	66.7	NS
Diabetes mellitus (%)	17.2	12.5	25.0	NS

Values are presented as mean±standard deviation or *n* (%) of patients.