Elevated carbohydrate antigen 125 levels in patients with aortic stenosis: relation to clinical severity and echocardiographic parameters

Aort darlığı hastalarında artmış karbonhidrat antijen 125 düzeyleri: Klinik ciddiyet ve ekokardiyografik değişkenlerle ilişkisi

Ercan Varol, M.D., Habil Yücel, M.D., Akif Arslan, M.D., Mehmet Özaydın, M.D., Doğan Erdoğan, M.D. Abdullah Doğan, M.D.

Department of Cardiology, Süleyman Demirel University Faculty of Medicine, Isparta

ABSTRACT

Objectives: Carbohydrate antigen 125 (CA 125), known as a tumor marker for ovarian cancer, has been reported to increase in relation to disease severity in heart failure patients with systolic dysfunction. Aortic stenosis (AS) has a wide clinical spectrum that often includes heart failure symptoms. The purpose of the present study is to evaluate the serum levels of CA 125 in patients with AS and its relation to clinical severity and echocardiographic parameters.

Study design: The study group consisted of 42 patients (20 males, 22 females, mean age 62.5±14.9 years) with AS and 35 healthy controls (17 men, 18 women; mean age 59.0±9.1 years). All patients and control subjects underwent chest X-ray and echocardiographic evaluation. We measured serum CA 125 values in patients with AS and control subjects.

Results: The median (interquartile range) CA 125 level was significantly higher among AS patients than in the control group in covariate analysis (9.4 [2.5-38.1] vs. 6.8 [4.4-13.9] U/ml respectively; p=0.001). Spearman correlation analysis in the whole group indicated that CA 125 was positively correlated with aortic mean gradient (p=0.007, r=0.30) and creatinine levels (p=0.02, r=0.26).

Conclusion: We found that CA 125 levels were elevated in patients with AS and were correlated with mean gradient and creatinine levels.

ÖZET

Amaç: Over kanserleri için tümör belirteci olarak bilinen karbonhidrat antijen 125'in (CA 125) sistolik disfonksiyonu olan kalp yetersizliği hastalarında arttığı ve klinik ciddiyetle ilişkili olduğu bildirilmiştir. Aort darlığı (AD), kalp yetersizliği bulgularının da içinde olduğu geniş klinik yelpazeye sahiptir. Bu çalışmada, AD'li hastalarda serum CA 125 düzeylerinin, klinik ve ekokardiyografik bulgularla ilişkisi değerlendirildi.

Çalışma planı: Çalışmaya 42 AD hastası (20 erkek, 22 kadın, ort. yaş 62.5±14.9) ve kontrol grubu olarak 35 sağlıklı gönüllü (17 erkek, 18 kadın; ort. yaş 59.0±9.1) alındı. Bütün hastalar ve kontrol grubu göğüs filmi ve ekokardiyografik değerlendirmeden geçirildi. AD'li hastalarda ve kontrol grubunda CA 125 düzeyleri ölçüldü.

Bulgular: Median (dörttebirler aralığı) CA 125 düzeyleri kovaryans analizinde AD'li hastalarda kontrol grubundan daha yüksekti (sırasıyla, 9.4 [2.5-38.1] ve 6.8 [4.4-13.9] U/ml; p=0.001). Bütün grupta yapılan Spearman korelasyon analizinde CA 125 düzeyleri ortalama gradiyent (p=0.007, r=0.30) ve kreatinin düzeyleri ile pozitif korelasyon gösteriyordu (p=0.02, r=0.26).

Sonuç: CA 125 düzeylerinin AD'li hastalarda arttığını ve ortalama gradiyent ve kreatinin düzeyleri ile pozitif korelasyon gösterdiğini belirledik.

Carbohydrate antigen 125 (CA 125) is a high-molecular-weight glycoprotein produced by epithelial ovarian tumors and by mesothelial cells and is normally used as a tumor marker of ovarian cancer.[1,2] In addition, it has been shown that CA 125 is increased in patients with heart failure,[3-9] and related to congestive heart failure severity,[4-8] short-term prognosis,[5] and pleural fluid involvement.[9] CA 125

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Correspondence: Dr. Ercan Varol. Süleyman Demirel Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Isparta, Turkey.
Tel: +90 246 - 232 44 79 e-mail: drercanvarol@yahoo.com

levels have also been shown to be increased in severe symptomatic mitral stenosis patients with normal left ventricular ejection fraction (EF) and dimensions.[10] Recently, it has been shown that both CA125 and brain natriuretic peptide levels were significantly correlated with New York Heart Association (NYHA) class and outcome in patients with aortic stenosis (AS).[11]

The purpose of the present study is to evaluate the levels of CA125 in patients with AS and to study the relationship between the levels of CA 125 and functional class and echocardiographic parameters.

PATIENTS AND METHODS

Subjects and study design

Patients with isolated AS referred to our echocardiography laboratory between August 2006 and July 2010 were enrolled in this prospective study consecutively. Control subjects were selected from individuals who were admitted to our outpatient clinic due to suspicion of heart disease and whose examinations, including echocardiography, showed normal cardiac findings. All patients and control subjects underwent medical history, physical examination, electrocardiogram, chest X-ray, and echocardiographic evaluation. Patients with AS admitted during this period, with the exception of patients having one or more exclusion criteria, were included in our study. None of the patients had pleural or pericardial effusion, or ascites. Symptoms were assessed by experienced cardiologists blinded to echocardiographic results and CA 125 levels.

Patients were grouped according to the NYHA classification. As a concomitant valvular disease, only mild ortic/mitral/tricuspid/pulmonary regurgitation without mitral/tricuspid/pulmonary stenosis was allowed. Exclusion criteria were left ventricular systolic dysfunction, known coronary artery disease, acute coronary syndrome, previous myocardial infarction, atrial fibrillation, history of renal or liver disease, malignancy, hematological disorders, acute or chronic infection. The study was approved by the institutional ethics committee and all patients gave their informed consent.

Echocardiography

The M-mode, two-dimensional, and Doppler echocardiographic examinations were obtained using a GE VingMed System FiVe (Norway) to asses left atrial diameter, left ventricular systolic and diastolic dimensions, left ventricular EF, aortic velocity and transaortic pressure gradient.

Abbreviations:

AS	*Aortic stenosis*
CA 125	*Carbohydrate antigen 125*
DT	*Deceleration time*
EF	*Ejection fraction*
IVRT	*Isovolumic relaxation time*
LVM	*Left ventricular mass*
MPI	*Myocardial performance index*
NYHA	*New York Heart Association*

Left atrial and ventricular dimensions and left ventricular EF were measured by M-mode echocardiography in the parasternal long axis view using the American Echocardiography Society M-mode technique.[12] Peak aortic velocity, peak aortic gradient and mean aortic gradient were derived by Doppler.[13] Aortic and other valvular regurgitation were evaluated by Doppler color flow mapping. Left ventricular mass (LVM) was calculated using a simple and anatomically validated formula: LVM = 0.8 × 1.04 [(IVS + LVEDD + LVPW)3 −LVEDD3] +0.6.[14] LVM was corrected for height[2,7] and LVM index (LVMI) was calculated.[15] The left ventricular diastolic function was estimated with PW-Doppler measurement of transmitral flow patterns, E and A velocities, E/A ratio, early filling deceleration time (DT), and isovolumic relaxation time (IVRT). The left ventricular myocardial performance index (MPI) was calculated as (isovolumic contraction time + IVRT)/aortic ejection time using PW-Doppler. The normal adult MPI is 0.39±0.05 and increases with worsening left ventricular dysfunction. Global left ventricular dysfunction was defined as a MPI ≥0.50.[16]

Biochemical measurement

Blood samples were drawn from the antecubital vein by careful vein puncture in a 21 G sterile syringe without stasis at 08.00-10.00 AM after a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods. CA 125 was measured with chemiluminescent enzyme immunoassay methods by using an OM-MA commercial kit (DPC, Los Angeles, CA, USA; upper normal limit 21 U/ml).

Statistical analysis

Data was analyzed with the SPSS software version 10.0 for Windows. Continuous variables from the study groups were reported as mean ± standard deviation, categorical variables as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared with Student's t-test. Categorical variables were compared using the chi-squared

Table 1. Comparison of clinical and laboratory findings in aortic stenosis patients and control subjects

	Aortic stenosis (n=42)			Control (n=35)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			62.5±14.9			59.0± 9.1	0.23
Sex							
Male	20			17			0.93
Female	22			18			
Body mass index (kg/m^2)			26.9±5.0			28.7±4.5	0.12
Systolic blood pressure (mmHg)			126.4±20.4			121.5±22.1	0.32
Diastolic blood pressure (mmHg)			78.8±8.8			76.2±9.1	0.22
Smoking (%)	10	24		4	11		0.16
Glucose (mg/dl)			102.3±18.2			95.8±15.1	0.10
Creatinine (mg/dl)			0.9±0.1			0.9±0.1	0.15
Total cholesterol (mg/dl)			194.1± 40.1			192.4±38.8	0.86
Triglycerides (mg/dl)			147.6± 69.4			140.6±70.0	0.67
LDL-cholesterol (mg/dl)			114.0±33.4			108.8±29.0	0.47
HDL-cholesterol (mg/dl)			50.3± 11.3			54.3±16.5	0.22

LDL: Low density lipoprotein; HDL: High density lipoprotein; p value is for comparison between control and study population.

test. CA 125 was not normally distributed. We firstly performed Mann-Whitney U test to compare mean and medians of CA 125 with other variables. Afterwards, MPI and LVMI are taken as covariates, and covariate analysis (ANCOVA) was performed for CA 125 comparison. One-way analysis of variance with post- hoc Scheffé correction was used to compare the variables between controls, functional class I/II patients, and functional class III patients. LVMI was different between groups. Because of this observation, LVMI was taken as covariate and covariate analysis (ANCOVA) was performed for CA 125 comparison between three groups. Correlations between CA 125 and the baseline characteristics were sought by the Spearman correlation test in whole group. Statistical significance was defined as $p<0.05$.

RESULTS

Clinical features and laboratory findings of the study and control groups are summarized in Table 1. There were forty-two patients (20 males, 22 females, mean age 62.5±14.9 years) with AS in the study group and there were thirty-five healthy volunteers (17 men, 18 women; mean age 59.0± 9.1 years) in the control group. There were no statistically significant differences between the two groups with respect to age, gender, body mass index, systolic and diastolic blood pressures, and levels of glucose, creatinine, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high density lipoprotein cholesterol. Comparison of the echocardiographic findings and CA 125 levels of the AS patients and control subjects are shown in Table 2. Aortic peak velocity, aortic peak gradient and aortic mean gradient were significantly higher in patients with AS than in controls. The MPI and LVMI were significantly higher in patients with AS than in controls. Because of this, they are taken as covariates and covariate analysis (ANCOVA) was performed for the CA 125 comparison to eliminate the effects of these variables. We found that median CA 125 level was significantly higher among AS patients than control group (9.4 [2.5-38.1] vs. 6.8 [4.4-13.9] U/ml respectively; p=0.001) and MPI and LVMI has no effect on CA 125 levels (p=0.14 and p=0.23 respectively) in covariate analysis (ANCOVA).

Echocardiographic findings and serum CA 125 levels in AS patients classified according to NYHA functional class and in the control group are shown in Table 3. LVMI was different between groups. Because of this, LVMI was taken as a covariate and covariate analysis (ANCOVA) was performed for CA 125 comparison to eliminate the effect of this vari-

Table 2. Comparison of the echocardiographic findings and CA 125 levels of the aortic stenosis patients and control subjects

	Aortic stenosis (n=42)	Control (n=35)	
	Mean±SD	Mean±SD	*p*
Aortic peak velocity (m/s)	3.6±0.7	1.3±0.2	0.001
Peak gradient (mmHg)	57.5±23.4	7.9±2.7	0.001
Mean gradient (mmHg)	32.8±15.4	3.7±1.1	0.001
Ejection fraction (%)	62.8±5.5	64.0±3.8	0.31
E/A	0.9±0.3	0.9±0.2	0.76
Isovolumic relaxation time (msec)	101.4±24.1	97.0±18.8	0.38
Deceleration time (msec)	210.8±65.2	193.0±50.8	0.19
Myocardial performance index (MPI)	0.59±0.18	0.52±0.09	0.03
Left ventricular mass index (LVMI) (g/m$^{2.7}$)	58.0±15.5	45.7±8.9	0.001
CA 125 (U/ml)	9.4 [2.5-38.1]	6.8 [4.4-13.9]	**0.001***

LCA 125: Carbohydrate antigen 125; p value is for comparison between control and study population.
*Covariance analysis (ANCOVA) was performed. MPI and LVMI were taken as covariates.

able. We found that LVMI has no effect on CA 125 levels (p=0.25) in covariate analysis (ANCOVA). The median CA 125 level in functional class I/II patients was significantly higher than that of the control group (9.0 [2.5-38.1] vs. 6.8 [4.4-13.9] U/ml, p= 0.04) and the median CA 125 level in functional class III patients was significantly higher than that of the control group, independent of LVMI (13.0 [2.8-32.6] vs. 6.8 [4.4-13.9] U/ml, p=0.001). There was no difference between the median CA 125 levels between functional class III patients and functional class I/II patients (13.0 [2.8-32.6] vs. 9.0 [2.5-38.1] U/ml, p= 0.16).

Spearman correlation analysis in whole group indicated that CA 125 was positively correlated with mean gradient (p=0.007, r=0.30) and creatinine (p=0.02, r=0.26).

DISCUSSION

In the present study, we investigated the CA 125 levels and its relation to functional status and echocardiographic parameters in patients with AS. We found that CA 125 levels were higher in patients with AS than that of control subjects. CA 125 levels in func-

Table 3. Comparison of the echocardiographic findings and CA 125 levels of the aortic stenosis patients and control subjects

	Control (n=35)	NYHA class I/II (n=29)	NYHA class III (n=13)	*p*
Mean gradient (mmHg)	3.7±1.1	28.7±14.8	42.0±12.7	**0.001**
E/A	0.9±0.2	1.0±0.3	0.8±0.2	0.15
Isovolumic relaxation time (msec)	97.0±18.8	102.5±26.3	98.9±19.2	0.60
Deceleration time (msec)	193.0±50.8	200.7±56.2	232.4±79.4	0.12
Myocardial performance index	0.52±0.09	0.60±0.19	0.56±0.16	0.08
Left ventricular mass index (g/m$^{2.7}$)	45.7±8.9	58.5±16.5	57.2±13.5	**0.001**
CA 125 (U/ml)	6.8 (4.4-13.9)	9.0 (2.5-38.1) $^{\#}$	13.0 (2.8-32.6) $^{\&}$	**0.001***

LCA 125: Carbohydrate antigen 125; NYHA: New York Heart Association.
*p=0.001 among all three groups; $^{\#}$ p=0.04 between NYHA class I/II and control; $^{\&}p$=0.001 between NYHA class III and control.
Covariance analysis (ANCOVA) was performed for CA 125 comparison. LVMI was taken as covariate.

tional class I/II patients were significantly higher than in the control group. However, there was no significant difference between functional class I/II patients and functional class III patients. CA 125 was positively correlated with mean gradient and creatinine.

CA 125 is a sensitive, but nonspecific, tumor marker and it was initially described in women affected by ovarian carcinoma, especially with peritoneal involvement.[1,2] High CA 125 values have also been observed in patients with lung, breast, uterine, and gastrointestinal tract cancer.[17] Subsequently, It was found to be increased in some other nonmalignant diseases, especially those with serosal involvement (which represents an important site of production) such as hepatic cirrhosis, nephrotic syndrome, and chronic renal diseases on hemodialysis with pleural, peritoneal, or pericardial effusion.[18-20]

Involvement of CA 125 and other tumor markers in heart diseases has gained interest in recent years. CA 125 has been shown to be increased in patients with moderate to severe heart failure[3-9] and related to congestive heart failure severity,[4-8] short-term prognosis,[5] and pleural fluid involvement.[9] Furthermore, Duman et al.[10] reported that CA125 levels, but not serum levels of other tumor markers (CA19.9, CA15.3, CEA) were elevated in severe symptomatic patients with mitral stenosis and normal left ventricular size and function. They suggested that elevated CA 125 levels in this patient group might be due to venous congestion and activation of peritoneal mesothelial cells or increased signal peptides. Recently, it has been shown that both CA125 and BNP levels were significantly correlated with NYHA class and outcome in patients with AS.[11] They found that CA125 levels increased significantly from NYHA class I-II to NYHA class III-IV. However, they did not compare CA125 levels in AS patients with control subjects. In the present study, we have compared the CA 125 levels in AS patients with a control group.

Immunohistochemical studies shows that CA 125 is released from the pleura and peritoneum.[21,22] It has been suggested that mesothelial cells are able to produce CA125, possibly as a consequence of inflammation, stasis, or other stimulatory mechanisms.[8] Previous studies showed that serum CA 125 levels were elevated in heart failure patients without fluid accumulation in the pleural, peritoneal, or pericardial space as well as in heart failure patients with fluid accumulation.[4,5,8] Therefore, it was thought that CA 125 might be produced from mesothelial cells even in the absence of classic stimuli (such as fluid accumulation) and/or that other cell lines may secrete CA 125. According to another hypothesis, CA 125 may be produced as a consequence of cytokine network activation or increased signal peptides. It has been reported that CA 125 is produced and released from ovarian cancer cells and/or peritoneal mesothelial cells when stimulated by cytokines such as interleukin-6 (IL-6).[23,24]

In a previous study, we found that CA 125 levels were elevated in severe symptomatic hypertrophic cardiomyopathy patients with NYHA functional class III and we also found that CA 125 levels increased as the level of diastolic dysfunction increased.[25] We speculated that elevation of certain inflammatory cytokines (TNF-α, IL-6, and IL-10) in severe symptomatic hypertrophic cardiomyopathy patients with high NYHA functional class may stimulate expression of CA 125 from nonmesothelial cells or predispose to contributory factors for production of CA 125.

High serum levels of inflammatory markers like high sensitivity C-reactive protein and soluble adhesion molecules were also detected in patients with severe AS indicating an inflammatory process in AS.[26,27] This inflammatory process might also have a role in the elevation of CA 125 levels in AS patients.

It has been shown that CA125 levels increased significantly as NYHA functional class increased in heart failure patients,[4-8] mitral stenosis patients[10] and AS patients.[11] Although CA 125 levels increased in our AS patients as functional class increased, the difference did not reach a statistically significant level. This could be due to low sample size, especially severe AS (functional class III) patient group.

Recently, we studied CA 125 levels and some inflammatory mediators including tumor necrosis factor-α (TNF-α), IL-6, and interleukin-10 (IL-10) in heart failure patients.[28] We reported that CA 125 levels were elevated and positively correlated with serum TNF-α, IL-6, and IL-10 levels in heart failure patients. Therefore, an increase in inflammatory mediators that have been shown to be elevated in AS patients may cause an increase in CA 125 levels. We can say that CA 125 levels may increase in patients with AS with normal left ventricular size and function without fluid accumulation in the pleural, peritoneal, or pericardial space.

The small sample size, and especially small number of severe AS patients, was the primary limitation of the study. Also, we did not measure inflammatory mediators and cytokines in the same setting.

In conclusion, we have shown that CA 125 levels were higher in patients with AS than in control subjects. CA 125 level was correlated with mean gradient and creatinine.

This study shows that AS is one of the nonmalignant conditions in which CA 125 levels are elevated. Further studies with larger patient population are needed to establish the pathophysiological and clinical significance of increased CA 125 in patients with AS.

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Key words: Aortic valve stenosis/blood/complications; biological markers; CA-125 antigen; heart failure/diagnosis.

Anahtar sözcükler: Aort kapak darlığı/kan/komplikasyonlar; biyobelirteçler; CA 125 antijen; kalp yetersizliği/tanı.