Justification for the Use of CA 125 Levels After Cardiac Surgery

R. Oktay PEKER[1], Tülay T. PEKER[2], Ercan VAROL[3], Mehmet ÖZAYDIN[3], Şenol GÜLMEN[1], Osman GÖKALP[4], Savaş KAYA[5], Şahin KAPAN[1], Doğan ERDOĞAN[3], Recep SÜTÇÜ[6], Ahmet ÖCAL[1]

[1] Süleyman Demirel University Faculty of Medicine, Department of Cardiovascular Surgery
[2] Süleyman Demirel University Faculty of Medicine, Department of Anaesthesiology and Reanimation
[3] Süleyman Demirel University Faculty of Medicine, Department of Cardiology, Isparta
[4] Dicle University Faculty of Medicine, Department of Pharmacology
[5] Dicle University Faculty of Medicine, Department of Medical Biology and Genetics, Diyarbakır
[6] Süleyman Demirel University Faculty of Medicine, Department of Biochemistry, Isparta, TURKEY

ABSTRACT

CA 125, a tumor marker has been found to be elevated in malign conditions as well as in some benign conditions like heart failure. Cardiac surgery has been shown to cause a systemic inflammatory response. In this study, we investigated alterations in serum levels of CA 125 during cardiac surgery with cardiopulmonary by-pass. Thirty nine patients with a mean age of 54.7 years who underwent either coronary bypass surgery or valvular heart surgery were prospectively recruited to the study. We measured plasma levels of CA 125 preoperatively and on postoperative days 1 and 7. Comparing with preoperative values, CA 125 levels were similar on postoperative day 1 (5.26 [6.89] U/ml vs 5.74 [4.54] U/ml) but elevated significantly on postoperative day 7 (42.1 [34] U/ml, $p< 0.0001$) (data in median interquantile range). CA 125 levels were found to be elevated after cardiac surgery. The elevations are more in patients undergoing valvular heart surgery than coronary bypass graft surgery. Although CA 125 can be considered a reliable tumor marker in the diagnosis and follow up of patients with malignant diseases, the presence of a recent cardiac surgery with cardiopulmonary bypass must be taken into account when asking for the cause of elevated CA 125 plasma level.

Key Words: Tumor marker CA 125, Cardiac surgery, Cardiopulmonary by-pass

ÖZET

Kardiyak Cerrahi Sonrası CA 125 Belirtecinin Kullanımı

Bir tümör belirteci olarak bilinen CA 125'in, malign hastalıkların yanısıra kalp yetmezliği gibi bazı benign durumlarda da yükseldiği bildirilmiştir. Kalp cerrahisi sistemik iltihabi bir cevap oluşturur. Çalışmamızda kardiyopulmoner bypass kullanılarak gerçekleştirilen kalp cerrahisinde plazma CA125 düzeylerindeki değişimleri araştırdık. Koroner baypass veya kapak cerrahisi planlanan ve yaş ortalaması 54.7 olan 39 hasta çalışmaya prospektif olarak dahil edildi. Preoperatif dönemde, postoperatif 1. ve 7. günlerde plazma CA 125 seviyesi için kan örnekleri alındı. Preoperatif dönem ve postoperatif 1. günde CA 125 düzeyleri benzer bulundu (5.26 [6.89] U/ml'ye 5.74 [4.54] U/ml). Postoperatif 7. günde ise bazal düzeylere göre anlamlı olarak yükseldi (42.1 [34] Ü/ml, $p < 0.0001$). CA125 seviyelerinde kapak cerrahisi yapılan hastalarda koroner cerrahisi geçiren hastalara göre daha belirgin artış tespit edildi. CA 125, malign hastalıkların teşhis ve takibinde güvenilir bir tümör belirteci olmakla birlikte, yüksek CA 125 tespit edilen hastalarda yakın zamanda kardiyopulmoner baypass kullanılarak geçirilmiş kalp cerrahisi sorgulanmalıdır.

Anahtar Kelimeler: Tümör belirteci CA125, Kalp Cerrahisi, Kardiyopulmoner Baypass

INTRODUCTION

Carbohydrate Antigen 125 (CA 125) is a high molecular weight glycoprotein most appropriately used for monitoring treatment response and recurrence of ovarian carcinoma, with concentrations >35 units/mL indicating residual tumor.[1] The recent observational studies has shown increased CA 125 levels in patients with heart failure, related to severity of congestive heart failure and pleural fluid involvement.[2-7] During cardiac surgery, blood is circulated in extracorporeal cardiopulmonary bypass system, which consists of a membrane oxygenator, polyurethane tubing set, and mechanical pump.[8] The non-biological surfaces of cardiopulmonary bypass system induce an inflammatory response.[9] In present study, we investigated if the coronary artery by-pass surgery (CABG) or mitral valvular heart surgery with cardiopulmonary bypass alter plasma level of CA 125. We also studied the correlation between serum CA 125 levels and preoperative New York Heart Association (NYHA) functional class of the patients.

MATERIAL AND METHODS

With local research ethics committee approval, 39 patients (Men: 20, Women: 19) with a mean age of 54.7 years were recruited to the study in Suleyman Demirel University Medical School, Isparta, between May and September 2006. Patients underwent either CABG or valvular heart surgery with cardiopulmonary by-pass. The patients with a diagnosis of acute coronary syndrome, cancer, pneumonia, sepsis, severe hepatic disease or end-stage renal disease undergoing dialysis treatment were excluded from the study. All patients underwent physical examination, ECG , chest X-ray, complete blood count, erythrocyte sedimentation rate, C-reactive protein, biochemical examinations including renal and hepatic function tests, ultrasonography and echocardiography. Symptoms such as rales on chest auscultation and the presence of pretibial edema were also recorded. Additionally, the presence of pulmonary congestion and pleural fluid on chest X-ray were evaluated. No malignant or other additional pathologies were found. The left ventricular ejection fraction was calculated using the Simpson method from the apical four-chamber view. Blood samples were collected preoperatively and on postoperative days 1 and 7. Polypropylene tubes were used for serum storage. Immulite 2000 (Diagnostic Products Corporation, Los Angeles, USA) automated analyzer was used for CA 125 assays. The normal reference range of CA 125 was 0-21 U/mL. All patients received the same anesthetic regimen. Anesthetic induction consisted of fentanyl (5 $\mu g\ kg^{-1}$), etomidate (1.5 mg kg^{-1}) and vecuronium (0.1 mg kg^{-1}) was used for muscular relaxation. Anesthetic maintanence consisted of propofol (2-3 mg $kg^{-1}\ h^{-1}$), remifentanyl (0.5-1 $\mu g\ kg^{-1}\ h^{-1}$), and vecuronium (0.3-0.5 mg $kg^{-1}\ h^{-1}$) infusions. The patients were ventilated to maintain normocapnia without positive end-expiratory pressure (PEEP) and FiO_2 between 50% and 60%. Conventional midline sternotomy and standard aortic canulation was performed in all patients. All the patients received 300 U kg^{-1} heparin to achieve an activated clotting time (ACT) over 450 seconds (Hemochron 401, International Technidyne Corporation, Edison, N.J.). Cardiopulmonary bypass was performed using a membrane oxygenator (Dideco, compactflo evophisio Mirandola, Italy). The extracorporeal circuit was primed with Ringer solution, mannitol and heparin at a dose of 5000 U. Patients were cooled to 28^0C during cardiopulmonary bypass and were rewarmed to a core temperature of 36^0C. Cold blood cardioplegia was used for myocardial preservation. Cardioplegia was delivered 10 mL kg^{-1} antegrade way and continued intermittently antegrade 5 mL kg^{-1} every 20 minutes. Hot shot cardioplegia was administered before declamping the aorta. After cardiopulmonary bypass, the heparin was reversed by protamine administration.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL). Normal distribution of CA 125 was checked with Kolmogorov-Smirnov test. Due to the fact that measure data of CA 125 were markedly skewed, all values are expressed as median interquartile range. Analysis of the differences between subgroups was performed using the nonparametric Mann-Whitney U test. Correlations between CA125 and clinical, laboratory and echocardiographic parameters were measured using Spearman's rho method. A p value < 0.05 was considered statisticaly significant.

Table 1. Demographics and clinical characteristics of patients (n= 39)

Age (yrs)	54.79±14.72
Men/women	20/19
NYHA functional class	
I (%)	2 (%5.1)
II (%)	25 (%64.1)
III (%)	12 (%30.8)
LVEF (%)	53.25±9.27
Etiology (%)	
CABG surgery	22 (%56.4)
Valvular surgery	17 (%43.6)
Rhythm (%)	
Sinus	29 (%74.4)
AF	10 (%25.6)
X Clamp time (min)	54.23±23.07
CPB time (min)	96.46±30.86
ESR (mm.h^{-1})	23.77±20.49

Data are presented as the mean value ± SD or number (%) or percentage of patients. NYHA= New York Heart Association, LVEF= left ventricular ejection fraction, CABG= coronary artery bypass grafting, AF= atrial fibrillation, Xclamp: cross clamp, CPB: cardiopulmonary bypass, ESR: erythrocyte sedimentation rate.

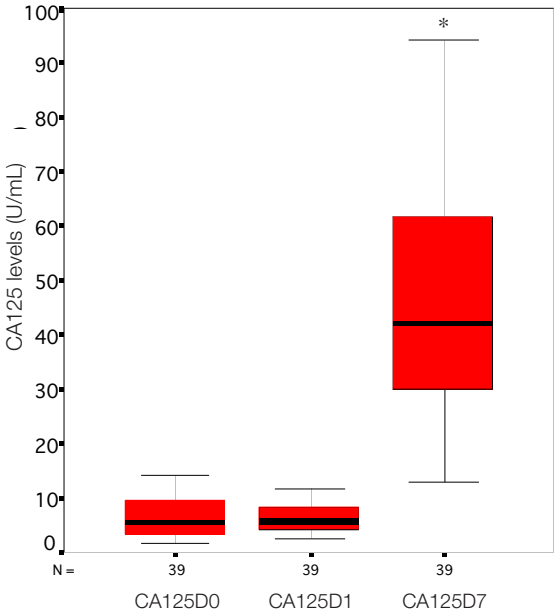

Figure 1. Serum levels of CA125: pre and postoperative periods

CA125D0: Preoperative levels of CA 125,
CA125D1: Postoperative day 1 levels of CA 125,
CA125D7: Postoperative day 7 levels of CA 125.
*p< 0.0001 compared with preoperative levels of CA 125

RESULTS

Clinical and demographic characteristics of patients were outlined in Table 1. The mean age in our sample was 54.7 years. The study population consisted of 17 mitral valve surgery and 22 CABG patients. The mean cardiopulmonary bypass time was 96.46±30.86 and cross clamp time was 54.23±23.07 minutes. The preoperative and postoperative day 1 CA 125 values were similar. However all patients had significantly elevated CA 125 levels on postoperative day 7 compared to baseline value (Table 2) (Figure 1). A higher proportion of valvular surgery patients were in NYHA class III, whereas most of the CABG patients were NYHA class II. The distribution of patients according to NYHA was shown in Table 3. CA125 elevation was more in valvular surgery patients (p< 0.01). CA 125 levels were significantly higher during all the periods of the study in valvular surgery patients (p< 0.01) (Table 4). In patients undergoing valvular heart surgery two patients had moderate pulmonary congestion and three patients had minimal right pleural fluid in preoperative period. No early postoperative complications, such as infection, renal and hepatic insufficiency, pleural and pericardial effusion were observed postoperatively in any of the patients. Postoperative atrial fibrillation responding to amiodarone infusion within 24 hours was observed in two patients who had CABG surgery.

Table 2. Serum levels of CA125 (U/ml)

Preoperative	5.26 (6.89)
Postoperative day 1	5.74 (4.54)
Postoperative day 7	42.1 (34)*

Data are presented median interquartile range.
*p<0.0001 compared with preoperative levels of CA 125.

DISCUSSION

The two important sources of CA 125 are epithelium of the ovary and peritoneum. However, there is also a contribution of the pleura, pericardium, cervix, endometrium, fallopian tube, colon, kidneys, and epithelial cells of the stomach.[1] Elevated

Table 3. NYHA Classification of CABG and valvular surgery patients

	NYHA Class I	NYHA Class II	NYHA Class III
CABG (n= 22)	1 (4.5%)	18 (81.8%)	3 (13.6%)
MVR (n= 17)	1 (5.9%)	17 (41.2%)	9 (52.9%)
Total (n= 39)	2 (5.1%)	25 (64.1%)	12 (30.8%)

Data are presented as the number or percentage (%) of patients. CABG = coronary artery bypass grafting, MVR= mitral valve replacement, NYHA = New York Heart Association, p= 0.026.

CA 125 levels have also been reported in hemodialysis patients with pleural fluid and in heart failure patients with accompanying pleural fluid.[1,7,10]

In present study, we investigated the alterations in plasma level of CA 125 after CABG or valvular heart surgery with cardiopulmonary bypass. CA 125 levels were found to be elevated on postoperative day 7 compared to preoperative stage. The elevations were more prominent in valvular surgery patients than CABG patients. To the best of our knowledge this is the second study related with CA125 and cardiac surgery. The first study was done just on CABG patients with or without cardiopulmonary bypass.[8] However we performed our study on both CABG and valvular surgery patients with cardiopulmonary bypass.

There are many cardiac markers that can be used for risk stratification and prognostic purposes in congestive heart failure. It has been reported that serum levels of CA125, which are in parallel to natriuretic peptides and norepinephrine, are elevated due to cardiac dysfunction, and it has been associated with congestion and the clinical course of the heart failure.[2,7] The role of CA 125 as a cardiac biomarker has only emerged in recent observational studies that have found CA 125 to be increased in patients with heart failure and to have potential role as a prognostic factor. Heart failure is associated with an excessive and increasing mortality, generating an extreme burden on our healthcare system.[11] Heart failure may be a challenging problem also in patients undergoing routine cardiac surgery or in end-stage patients bridge to transplantation. We think that CA 125 levels can be considerable in cardiovascular surgery clinics for prognostic evaluation and risk assessment of heart failure.

According to the results of our study, CA 125 levels were found to be significantly higher in valvular surgery patients whose NYHA classes were higher than CABG surgery patients (Table 3). A higher proportion of valvular surgery patients were in NYHA class III, whereas most of the CABG patients were NYHA class II. There are only 3 CABG patients in NYHA class III. Moreover, five mitral surgery patients in our study had mild congestion according to chest X-ray and auscultation findings. These suggest that preoperative serum CA125 levels may correlate significantly with congestion and NYHA class of the patient.

We found that both CABG and valvular heart surgery with cardiopulmonary bypass increased CA 125 levels. The non-biological surface of cardiopulmonary bypass system induces a systemic inflammatory response and cause increased levels of inflammatory mediators.[9,12,13] It has been reported that CA 125 is produced and released from ovarian cancer cells and lymphoma cells when stimulated with cytokines such as tumor necrosis factor and

Table 4. CA125 levels of CABG and valvular surgery patients

	CABG	MVR	p
Preoperative	4.06 (5.18)	9.2 (9.94)	0.003
Postoperative day 1	4.14 (3.37)	7.7 (12.1)	0.009
Postoperative day 7	32.1 (25.35)*	64 (83.85)*	0.000

Data are presented median interquartile range.
* p< 0.001 compared with preoperative levels of CA 125.

interleukin-6.[14] A recent study performed by Kosar et al. reported that CA 125 levels are elevated and positively correlated with serum tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6) and Interleukin-10 (IL-10) levels in heart failure patients.[15] In an our previous study, we have found elevated CA 125 levels in symptomatic hypertrophic cardiomyopathy patients with high functional class without congestion. We speculated that certain inflammatory cytokines especially in severely symptomatic hypertrophic cardiomyopathy patients with high functional class may stimulate expression of CA 125 from nonmesothelial cells.[16] We considered that the systemic inflammatory response of cardiac surgery might be the cause of elevated levels of CA 125 in patients undergoing CABG or valvular surgery with CPB.

It has been shown that cardiac surgery with or without CPB causes elevated CA 125 levels on day 7 and day 12 after CABG.[8] Cardiac surgical intervention employing extracorporeal circulation induces a systemic inflammatory response by triggering the production and release of a multitude of inflammatory mediators.[9] Besides the effect of cardiopulmonary bypass, our results indicate that the elevation of CA125 may be directly correlated with the degree of inflammation due to the extent of surgical trauma, which is more intense in mitral valve surgery than CABG surgery. Therefore increased inflammatory response in relation to the degree of surgical trauma in mitral valve surgery might be the cause of more elevation of CA 125 than CABG surgery.

The low cost, wide availability and easy determination of this biomarker make it a potential tool for using prognostic purposes in cardiac dysfunction. This study has some limitations, since the patient number is small. Also another limitation was that we did not measure the amount of pericardial fluid during preoperative echocardiography and at the time of operation. Currently CA125 is not a specific biomarker. If tissue specific CA125 subtypes are identified this will lead us more reliable and accurate diagnosis for various pathologies. The biological role of CA 125 in cardiac surgery must be evaluated in further studies.

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Correspondence
Dr. Recep Oktay PEKER
Süleyman Demirel Üniversitesi Tıp Fakültesi
Kalp Damar Cerrahi Anabilim Dalı
32100 ISPARTA
TÜRKİYE

E-mail: ropeker@hotmail.com
Fax. (+90.246) 218 01 63