

# Elevation of the serum total and free prostate specific antigen levels after stent implantation in patients with coronary artery disease

Turkay Ozcan<sup>a</sup>, Murat Bozlu<sup>b</sup>, Necati Muslu<sup>c</sup>, Kerem Han Gozukara<sup>b</sup>, Sabri Seyis<sup>a</sup>, Burak Akcay<sup>a</sup>

Departments of Cardiology<sup>a</sup>, Urology<sup>b</sup> and Biochemistry<sup>c</sup>, University of Mersin School of Medicine, Mersin, Turkey

## Summary

**Background:** Prostate specific antigen (PSA) is the most important biochemical marker in the diagnosis and follow-up of patients with prostate cancer. In recent years, a relationship between PSA levels and cardiovascular conditions has been described. However, no study has investigated the PSA levels after coronary stenting.

**Aim:** To investigate the impact of coronary stent implantation on serum total PSA (tPSA) and free PSA (fPSA) levels.

**Methods:** This study involved 60 men who underwent coronary angiography for suspected coronary artery disease. Of these, 25 were diagnosed as having angiographically normal coronary arteries (Group 1) and 35 underwent coronary stent implantation (Group 2). Serum tPSA and fPSA levels and f/tPSA ratios were determined in all patients immediately before the intervention and 24 hours and 30 days after the procedure.

**Results:** In Group 1, there was no statistically significant change in the values of tPSA, fPSA and f/tPSA ratio before and after coronary angiography ( $p > 0.05$ ). In Group 2, tPSA and fPSA values 24 hours after stent implantation were significantly higher than the values at the baseline ( $p < 0.01$ ), whereas f/tPSA ratio did not change ( $p > 0.05$ ). Compared with the baseline, there was no statistically significant difference in the PSA values 30 days after stent implantation ( $p > 0.05$ ).

**Conclusions:** This study demonstrated that serum tPSA and fPSA levels are increased after coronary stent implantation, but f/tPSA ratio is not affected. The findings suggest that serum tPSA and fPSA levels should not be used for the diagnosis of prostate cancer during the first 30 days after coronary stenting.

**Key words:** prostate specific antigen; stent implantation; coronary artery disease

## Introduction

Prostate specific antigen (PSA) is a kallikrein-like serine protease produced exclusively by the epithelial cells of the prostate. Although increased PSA levels have been found to be closely associated with prostate cancer, there can be different reasons for an elevated PSA level, including benign prostatic hyperplasia, prostatitis, prostatic trauma, and prostatic infarction [1–3].

In recent years, a relationship between PSA levels and cardiovascular conditions has been described [4]. It has been reported that prolonged cardiopulmonary resuscitation is frequently asso-

ciated with increases of PSA serum level [5]. Cardiogenic shock due to acute myocardial infarction and coronary artery bypass surgery are associated with a rise in serum PSA levels [6–10]. Therefore, the results of the previous studies suggest that PSA cannot be used for diagnosis of adenocarcinoma of the prostate during the first few weeks after these events. However, no study has investigated the PSA levels after coronary stenting. The aim of the present study was to investigate the impact of coronary stent implantation on serum total PSA (tPSA) and free PSA (fPSA) levels.

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## Materials and methods

The study population were selected from 60 male patients who underwent coronary angiography in our hospital for suspected coronary artery disease. Of these, 25 were diagnosed as having angiographically normal coronary arteries (Group 1) and 35 underwent coronary stent implantation (Group 2). Serum tPSA and fPSA levels and f/tPSA ratios were determined in all patients immediately before the intervention and 24 hours and 30 days after the procedure. None of the patients had a urinary catheter during the study period. Serum tPSA and fPSA were measured with the electrochemiluminescence immunoassay "ECLIA" (Hitachi Modular Analytics E170, Roche Diagnostic GmbH, Mannheim, Germany).

The indications and methods of coronary angiography and stent implantation have been previously described [11]. Briefly, coronary angiography was performed by a femoral approach using the standard Judkins technique. Coronary arteries in left and right oblique planes and cranial and caudal angles were demonstrated. Left ventricular and aortic pressures were obtained. During coronary angiography, Iomeron-400 (Bracco s.p.a.) and Lopromide (Ultravist-370, Schering AG) were used as contrast agents and were manually injected (6–8 mL of contrast agent at each position). Patients were eligible for stent implantation if there was an-

giographic evidence of single or multivessel disease with a target lesion stenosis of  $\geq 70\%$  in a  $\geq 2.25$  mm vessel. Stent size was chosen according to the angiographic arterial diameter. A high pressure technique was used for final in-stent dilatation. Multiple stents were deployed if necessary, to cover the full extent of the target lesion or the dissection, if it occurred.

Patients were excluded from the study if they had a history of prior coronary angiography, stent implantation, prostate biopsy, malignancy of prostate, medical or surgical treatment of benign prostatic hyperplasia, urethral catheterization or instrumentation, prostatitis or a documented urinary tract infection and had PSA levels  $> 2.5$  ng/mL and f/tPSA  $< 25\%$  before the procedure. The institutional ethical committee approved this study, and all study participants read and signed an informed consent form.

### Statistics

All data are expressed as mean  $\pm$  standard deviation. Statistical analyses were done using the paired *t* test to compare the PSA values before and after the intervention, and the Mann-Whitney *U* test to compare the values between the two groups. A *p* value less than 0.05 was considered statistically significant.

## Results

No statistically significant differences were found between the groups with regard to the baseline characteristics (table 1). The PSA values for both groups are presented in table 2. The baseline values of tPSA, fPSA and f/tPSA ratio did not reveal any statistically significant differences between the groups ( $p > 0.05$ ). For Group 1, there was no statistically significant change in the values of tPSA, fPSA and f/tPSA ratio before and after coronary angiography ( $p > 0.05$ ) (table 2). For Group 2, tPSA and fPSA values 24 hours after

stent implantation were significantly higher than the values at the baseline ( $p < 0.01$ ), whereas f/tPSA ratio did not change ( $p > 0.05$ ) (table 2). Nineteen patients in Group 2 had a tPSA value of greater than 2.5 ng/mL at 24 hours after stent implantation. Compared with the baseline, there was no statistically significant difference in the PSA values 30 days after stent implantation ( $p > 0.05$ ) and no patients had diminished serum PSA levels after the procedures.

**Table 1**

Baseline characteristics of the patients in Group 1 (coronary angiography) and Group 2 (coronary artery stenting). Data presented as mean  $\pm$  standard deviation.

	Group 1 (n = 25)	Group 2 (n = 35)	p value
Age (years)	57.50 $\pm$ 6.75	58.55 $\pm$ 6.45	0.699
Residual urine volume (ml)	45.65 $\pm$ 20.2	45.25 $\pm$ 22.52	0.578
Prostate volume (ml)	45.36 $\pm$ 15.35	46.75 $\pm$ 16.55	0.964
Transition zone volume (ml)	22.5 $\pm$ 12.25	24.55 $\pm$ 12.45	0.706

**Table 2**

PSA values (mean  $\pm$  SD) of the patients in Group 1 (coronary angiography) and Group 2 (coronary artery stenting). Data presented as mean  $\pm$  standard deviation.

	Group 1			Group 2		
	Baseline	Postprocedure		Baseline	Postprocedure	
		24th hour	30th day		24th hour	30th day
tPSA (ng/mL)	1.59 $\pm$ 0.44	1.63 $\pm$ 0.48	1.66 $\pm$ 0.38	1.62 $\pm$ 0.55	3.35 $\pm$ 0.95*	1.73 $\pm$ 0.52
fPSA (ng/mL)	0.62 $\pm$ 0.23	0.56 $\pm$ 0.28	0.58 $\pm$ 0.22	0.68 $\pm$ 0.32	1.26 $\pm$ 0.54*	0.72 $\pm$ 0.48
f/tPSA (%)	0.41 $\pm$ 0.22	0.38 $\pm$ 0.18	0.37 $\pm$ 0.16	0.42 $\pm$ 0.18	0.38 $\pm$ 0.25	0.41 $\pm$ 0.21

\**p* < 0.01, compared with baseline

## Discussion

Prostate cancer is one of the most common neoplasms in men. Prostate biopsy is used to confirm the diagnosis and the most common indication of prostate biopsy is an elevated serum PSA level [1]. The prevalence of both prostatic and cardiovascular disorders rise with age. More recently, several studies have evaluated the relationship between elevated PSA levels and cardiovascular conditions [4, 12]. As coronary artery stenting is one of the most frequently performed procedures for the male population suffering from coronary artery disease, the results of the previous studies led the authors to investigate the impact of coronary stent implantation on serum PSA levels. However, to the authors knowledge the effect of coronary stent implantation on serum tPSA and fPSA has not been reported previously.

In the present study, the men who had undergone coronary stent implantation showed rises in serum tPSA and fPSA 24 hours after stent implantation. Although, the authors demonstrated that serum tPSA and fPSA values decreased to baseline 30 days after the procedure. In contrast, it was found that the f/tPSA ratio did not change after coronary stent implantation and coronary angiography did not affect the values of tPSA, fPSA and f/tPSA ratio. As the effect of coronary angiography and stent implantation on serum PSA levels has not been described previously, we did not perform a closer follow-up by monitoring PSA levels at several time points in the period between 24 hours after the procedure and 30 days postprocedure. With regard to a certain time of PSA testing, the authors think that further studies will be needed to evaluate the levels of PSA in the early postoperative period after stent implantation.

Massive prostatic infarction during aorto-coronary bypass surgery was first described by Taussig et al. [13]. This problem has also been linked with pelvic ischemia, that is presumed to occur after cross-clamping of the aorta for coronary or aortic surgery [14, 15]. This mechanism has been supported by several studies that have documented PSA elevations after cardiovascular events. Koller-Strametz et al. found that mean PSA values increased rapidly after 12 to 24 hours, and gradually decreased to near baseline values 7 days after cardiopulmonary resuscitation [5]. They concluded that prolonged cardiopulmonary resuscitation induced pelvic ischemia, leading to epithelial cell damage of the prostate gland and PSA elevation. Parlaktas et al. reported elevations of the PSA values in the first and fifth postoperative days after conventional coronary artery bypass and off-pump or beating-heart coronary artery bypass [10]. They emphasized that coronary revascularization can cause a rise in serum PSA levels. However, the effect of coronary stent implantation on serum tPSA and fPSA has not been reported previously.

In recent decades, several biomarkers have become accepted tools in cardiovascular conditions [16]. However, the exact mechanism of PSA elevation related to cardiovascular conditions is not clearly understood. Pelvic ischemia due to cross clamping of the aorta during coronary artery bypass grafting, aortic and iliac arterial surgery, hypotensive shock and acute myocardial infarction is presumed to be the reason for prostatic ischemia and/or infarction, leading to elevation of serum PSA levels. Recently, a case of diminution of PSA has been reported in a patient with coronary spasm and without significant coronary stenosis [17]. Moreover, it has also been concluded that when elevation of PSA occurs during acute myocardial infarction, coronary lesions are frequent and often more severe than when diminution of PSA occur. Compared with baseline, the current study did not have the finding of diminished PSA levels after the procedures.

In general, PSA can bind to natural substrates like alpha-1-antichymotrypsin or circulate in unbound (free) forms (fPSA). Percent fPSA has been used to help distinguish benign prostatic hyperplasia from prostate cancer and it was approved by the FDA in 1998 as an aid to prostate cancer detection in men with tPSA levels of 4–10 ng/mL [2]. Although previous studies demonstrated tPSA elevation related to cardiovascular conditions, most of them did not evaluate fPSA levels and f/tPSA ratio [6–11]. In the present study, it was observed that neither coronary artery stent implantation nor coronary angiography affected f/tPSA ratio.

PSA elevation after cardiovascular events might not be explained only by prostatic ischemia. However, PSA has been identified as a member of the human kallikrein family of serine proteases, and kallikrein kinin system is related to inflammation. Patané and Marte have reported elevation of both tPSA and fPSA during acute myocardial infarction [12]. They concluded that the inactive precursor form of PSA, proPSA, is converted rapidly to active PSA by human kallikrein 2 (hK2), suggesting an important *in vivo* regulatory function by hK2 on PSA activity. On the other hand, the formation of irreversible PSA complexes has a significant correlation with high-sensitivity C-reactive protein and that seems to play a crucial role [12]. It has been reported that hK2 alone might not be able to activate proPSA *in vivo* and hK2 has been found to cleave high molecular weight kininogen producing bradykinin [18]. Unlike PSA, hK2 has also been found to activate single-chain urokinase type plasminogen activator [19].

In conclusion, the current results demonstrate that coronary artery stenting is associated with a rise in serum tPSA and fPSA levels 24 hours after the intervention. It was also found that

the increased tPSA and fPSA levels had returned to baseline levels by 30 days after coronary stent implantation. The authors suggest that serum PSA levels should not be used as marker for prostate malignancy during the first 30 days after coronary artery stenting, rendering invasive urological examinations inappropriate during that time. Although only follow-up measurements and continuous increases of PSA are valuable for cancer diagnostics, we think that coronary stent implantation may be added to list of the events in which PSA measurements must be interpreted with caution.

*Correspondence:*

*Murat Bozlu, M.D.*

*Professor of Urology*

*Department of Urology*

*University of Mersin School of Medicine*

*Zeytinlibabce Caddesi*

*TR-33079-Mersin*

*muratbozlu@yahoo.com*

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