

Perioperative prostate specific antigen levels among coronary artery bypass grafting patients: Does extracorporeal circulation and body temperature induce prostate specific antigen levels alterations?

Emmanuel Patris, Konstantinos Giakoumidakis¹, Vasileios Patris², Manoj Kuduvalli², Mihalis Argiriou³, Christos Charitos³, Christos Kalaitzis, Stavros Touloupidis

Department of Urology, School of Medicine, Democritus University of Thrace, Dragana, 68100 Alexandroupolis, Greece, Departments of Cardiac Surgery, ¹Cardiac Surgery ICU, "Evangelismos" General Hospital of Athens, Greece, ²Heart and Chest Hospital, Thomas Drive, Liverpool L14 3 PE, United Kingdom, ³"Evangelismos" General Hospital of Athens, 10646 Athens, Greece

Abstract

Purpose: The purpose of this study is to compare the perioperative total prostate specific antigen (tPSA) levels among coronary artery bypass grafting (CABG) patients with and without extracorporeal circulation (ECC), to investigate the changes overtime of tPSA in each group separately and to determine the effect of body core temperature on tPSA levels.

Materials and Methods: A prospective study was conducted. Our sample was allocated to: (a) Seven patients who underwent off pump CABG (Group I) and (b) 16 CABG patients with ECC (Group II). The levels of tPSA were measured preoperatively (baseline), intra-operatively and at the 4th postoperative day. We compared the two groups on their tPSA levels and we investigated the changes of tPSA overtime in each group separately.

Results: Intra-operative serum samples were obtained in significantly lower body temperature in patients of Group II than in those of Group I (31°C vs. 36.9°C, $P < 0.001$). In each group separately, postoperative tPSA levels were increased significantly compared to the baseline values (2.55 ng/ml vs. 0.39 ng/ml for Group I, $P = 0.005$ and 4.36 ng/ml vs. 0.77 for Group II, $P < 0.001$). CABG patients with ECC had significantly lower intra-operative tPSA levels than the baseline values (0.67 ng/ml vs. 0.77 ng/ml, $P = 0.008$). We did not observe significant differences of tPSA levels between the two groups.

Conclusions: CABG surgery affects similarly the perioperative tPSA independently the involvement of ECC. Although all patients had significantly higher early postoperative tPSA levels, only those who underwent CABG with ECC had exceeded normal values and significantly decreased intra-operative tPSA. Hypothermia seems to be the causal factor of tPSA reduction.

Key Words: Cardiopulmonary bypass, coronary artery bypass, hypothermia, off-pump, prostate, prostate-specific antigen

Address for correspondence:

Dr. Konstantinos Giakoumidakis, Cardiac Surgery ICU, "Evangelismos" General Hospital of Athens, 45-47 Ipsilantou Street, 10646, Athens, Greece.
E-mail: kongiakoumidakis@gmail.com

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INTRODUCTION

Prostate specific antigen (PSA) is a kallikrein-like serine protease, which is secreted by the epithelial cells of the prostate gland. Although the serum level of PSA is a widely used tumor marker of prostate cancer,^[1] PSA is not a unique malignant indicator of the prostate gland. PSA may be elevated in some

benign diseases of the prostate gland, such as hyperplasia, infections, prostate abscess and after manipulation, such as biopsy and transurethral resection of the prostate gland.^[2]

In addition, PSA elevation has been associated with cardiac disorders and procedures and many authors have reported increased PSA levels after cardiopulmonary resuscitation,^[3] acute myocardial infarction,^[4-6] coronary artery stent implantation^[7] and coronary artery bypass grafting (CABG) surgery.^[1,8] Indeed, CABG involving extracorporeal circulation (ECC) seems to be strongly associated with increased postoperative PSA levels due to pelvic ischemia, which later is accompanied by prostate ischemia and prostatic epithelial cell damage.^[1,3]

The aim of this study was to compare the perioperative total prostate specific antigen (tPSA) levels among CABG patients with and without ECC, to investigate the overtime changes of tPSA in each group separately and to determine the effect of body core temperature on tPSA levels. Our study seeks to contribute to the limited body of knowledge regarding perioperative tPSA levels among CABG patients with and without ECC. In addition, this was the first study which attempted to examine the effects of core temperature on serum tPSA levels.

MATERIALS AND METHODS

Study design and participants

A prospective cohort study was conducted. A total of 23 consecutive male subjects who underwent CABG in one cardiothoracic center of a tertiary general hospital in Athens – Greece during April 2013 were enrolled in our study. Patients younger than 18 years old and those who had a history of malignancy of prostate or any other organ, previous pelvic and inguinal irradiation, open or transurethral surgery for benign prostatic hyperplasia and preoperative tPSA levels above 4 ng/ml (the upper normal limit) were excluded from the study. In addition, recent genitourinary track infection, acute and chronic prostatitis, any prior urological manipulations within 1 month, urolithiasis, previous cardiac surgery, taking medications affecting tPSA levels and traumatic urinary catheterization were among the other exclusion criteria.

The cohort was divided into two groups: (a) Seven patients who underwent CABG without ECC (Group I) and (b) 16 patients who underwent CABG with ECC (Group II).

Data collection - procedure

For data collection proposes we used a short structured questionnaire on basic demographic and clinical patient data. The questionnaire information included patients' age, a history of chronic obstructive pulmonary disease (COPD), diabetes mellitus, cancer and renal failure, previous cardiac surgery, current medications and an urological history, including

a history of malignancy of prostate and any form of its treatment, previous pelvic and inguinal irradiation, open or transurethral surgery for benign prostatic hyperplasia, recent genitourinary track infection, acute and chronic prostatitis, prior urological manipulations within 1 month and urolithiasis.

In all patients shortly after general anesthesia was induced, an urologist placed a urinary 16 F Foley catheter (Foley two way silicone with thermistor ref 9005IT Kendall Tyco/Healthcare). Serum samples of all patients were obtained preoperatively (baseline), intra-operatively (day 0) and postoperatively (day 4). Specifically, preoperative samples were taken at the morning of surgery, intra-operative samples were taken immediately after receiving the first bypass graft for the patients of the Group I and 15 min after reaching the temperature of 31°C, during the ECC, for the patients of the Group II. Postoperative sample were obtained during the 4th postoperative day after urinary catheter removal. All serum tPSA were assayed at the Department of Biochemistry of our hospital using the chemiluminescent enzyme immunoassay method with reference range of 0-4 ng/ml. Intra-operative body core temperature was measured by the urinary catheter of each patient (urinary bladder temperature). It is well-known that urinary bladder temperature is among the most reliable and accurate methods of body core temperature measurement in critically ill patients.^[9,10]

The literature review reveals that an atraumatic urinary catheterization and general anesthesia are not associated with significant elevation in tPSA levels,^[11,12] so we did not take into consideration these parameters. In addition, as mentioned above, the urinary catheters were removed on the 4th postoperative day and none of the patients developed lower urinary tract symptoms. Aiming to ensure the reliability and validity of the data collection process, the samples were obtained by the same individual each time. In addition, the same individual took the demographic and clinical data based on the medical patient records review.

Statistical analysis

Continuous variables are presented as median (interquartile range [IR]), whereas categorical variables are presented as absolute and relative frequencies. The Chi-square test was used to compare the distribution of categorical variables between CABG patients without and with ECC and the Mann-Whitney test was used to compare continuous variables between the two groups. In addition, we used the Wilcoxon signed ranks test to compare the overtime changes of tPSA levels in each group separately. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS 19.0 for Windows (Armonk, NY: IBM Corporation).

Ethics

The data collection was conducted after written permission from the ethics committee of the hospital. The investigation was carried out in accordance with the ethical standards of the responsible institutional committee for human experimentation and with the Helsinki declaration of 1975, as revised in 2008. Precautions took place to protect the privacy of research subjects and the confidentiality of their personal information, including limiting the amount of personal information to the absolute minimum, assigning an identification number to each subject and attaching the identification number to the actual research information, removing the subject names as soon as data were analyzed and maintaining any identifying information and lists of identification numbers in a safe and locked file.

RESULTS

The median age of patients who were undergone off pump CABG (Group I) and on pump CABG with cardiopulmonary bypass (Group II) was 66 (IR: 60-71) and 66.5 (IR: 59.5-73.75) years old respectively, a difference statistically not significant. As Table I shows, the two groups were similar regarding the baseline patient characteristics (age, history of COPD, renal failure and diabetes mellitus). During obtaining serum samples to measure tPSA levels intra-operatively, core temperature was significantly lower in patients of the Group II compared with those in the Group I (31°C vs. 36.9°C, $P < 0.001$). In addition, hypothermia time for the patients of the Group II was depended on the number of grafts needed to be placed and ranged from 20 to 40 min (median 30 min).

The perioperative tPSA values for both groups are summarized in Table 2. Between the two groups we did not observe statistically significant differences at baseline and on days 0 and 4. Regarding the overtime changes in tPSA values for each group separately, we found a decrease in tPSA values intra-operatively (day 0) compared to preoperative (baseline) levels for patients of both groups, but only for the on pump CABG patients (Group II) this reduction was significant ($P = 0.008$). In addition, for both groups, tPSA levels were significantly higher postoperatively (day 4) compared with preoperative ($P = 0.005$ for Group I and $P < 0.001$ for Group II) and intra-operative levels ($P = 0.005$ for Group I and $P < 0.001$ for Group II). The overtime changes in tPSA levels in each patient group are also depicted at Figure 1.

DISCUSSION

Although we observed no significant differences of tPSA levels between the two groups at baseline and on days 0 and 4, our study indicated a significant increase of postoperative tPSA levels, in both groups, compared with the baseline and

Table 1: Baseline demographic and clinical characteristics in each patient group

Variables	Group I (n=7)	Group II (n=16)	P value
Median (IR) age (years)	66 (60-71)	66.50 (59.50-73.75)	0.815 ^a
COPD (n, %)	2 (28.57)	4 (25)	0.271 ^b
Renal failure (n, %)	1 (14.28)	2 (12.5)	0.255 ^b
Diabetes mellitus (n, %)	2 (28.57)	5 (31.25)	0.671 ^b
Median (IR) intra-operative core temperature (°C)	36.90 (36.80-37)	31 (31-31)	<0.001 ^a

COPD: Chronic obstructive pulmonary disease, IR: Interquartile range. ^aMann-Whitney test, ^bChi-square test

Table 2: Perioperative PSA levels in each patient group and changes of PSA overtime in each patient group separately

Variables	Group I (n=7)	Group II (n=16)	P value
Median (IR) pre-operative PSA (ng/ml)	0.39 (0.27-0.73)	0.77 (0.46-0.90)	0.077 ^a
Median (IR) intra-operative PSA (ng/ml)	0.36 (0.23-0.69)	0.67 (0.33-0.90)	0.144 ^a
Median (IR) post-operative PSA (ng/ml)	2.55 (0.98-5.03)	4.36 (2.70-6.10)	0.144 ^a
P value ^{pre, intra}	0.385 ^b	0.008 ^b	
P value ^{intra, post}	0.005 ^b	<0.001 ^b	
P value ^{pre, post}	0.005 ^b	<0.001 ^b	

IR: Interquartile range, PSA: Prostate specific antigen. ^aMann-Whitney test, ^bWilcoxon signed ranks test

intra-operative levels. In addition, another important finding of the present study was the significantly lower tPSA levels intra-operatively in patients who underwent CABG with ECC compared with baseline values.

As aforementioned, we did not found significant differences on serum tPSA levels pre-, intra- and post-operatively when we compared the two groups. Contrary to our findings Parlaktas *et al.*^[2] and Netto *et al.*^[8] found significantly higher tPSA levels postoperatively in patients who underwent CABG with ECC compared with off pump patients and attributed these finding to the possible more pronounced ischemic damage of prostate tissue during ECC. It is known that CABG without ECC has been associated with a lower incidence of ischemia-reperfusion injury, lower postoperative complications of multiple organ dysfunction and reduced postoperative elevation of markers of systemic inflammatory response.^[2,13-16] The different findings of our study could be explained by its small sample size.

The elevation of tPSA levels was not significantly higher in patients who underwent CABG with ECC when compared to off-pump patients. Nevertheless, we can claim that the higher tPSA levels on day 4 for patients of Group II have significance from a clinical point of view, given the presence of median tPSA levels above 4 ng/dl (the upper normal limit) in these patients. Considering this and in accordance with other authors^[2,3,17] prostate cancer screening should be postponed or avoided in patients who underwent CABG with ECC during the early

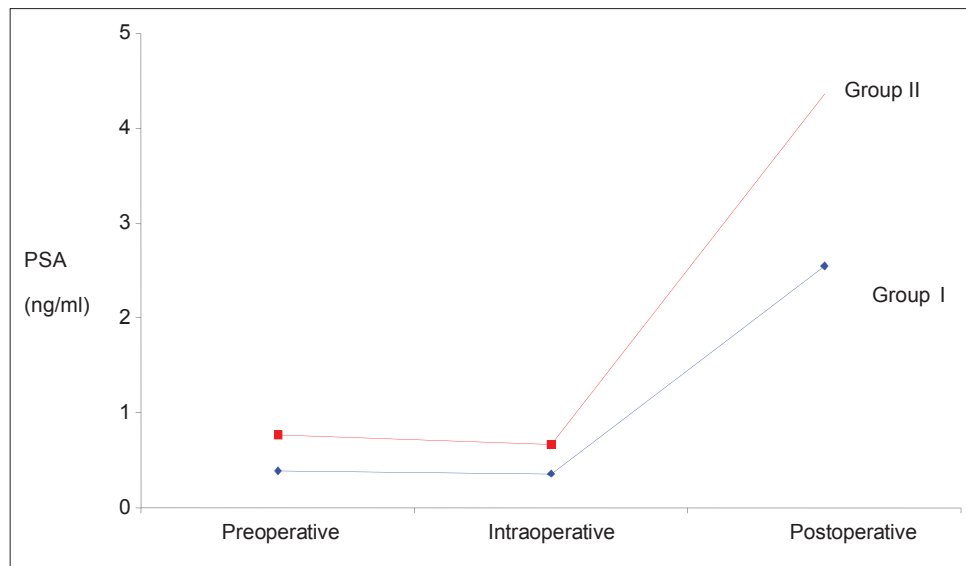


Figure 1: Perioperative prostate specific antigen levels alterations in each patient group. Group I: Patients who underwent coronary artery bypass grafting without extracorporeal circulation, Group II: Patients who underwent coronary artery bypass grafting with extracorporeal circulation, PSA: Prostate specific antigen

postoperative period and tPSA levels should not be as markers of prostate malignancy due to the raised tPSA levels of this period.

Another important finding of this study was the significant elevation of tPSA levels postoperatively in each patient group separately, a result that is in line with the study of Parlaktas *et al.*^[2] In addition, Guvel *et al.*^[17] and Coker *et al.*^[18] investigating patients who underwent CABG with ECC found raised levels of tPSA postoperatively. In contrast, Netto *et al.*^[8] have reported no serum tPSA rise in patients who underwent off pump cardiac surgery. It is well-known from the literature review that prostate ischemia during CABG is the causal factor for the elevated serum tPSA during the postoperative period.^[2,6,18] Nevertheless, it is worth mentioning the significant postoperative increase of tPSA levels among the off pump CABG patients of our study. Although, the effect of ECC on tissue perfusion is arguably detrimental, cardiac surgery without ECC is also accompanied by hypotensive periods with hemodynamic instability, which lead to prostate hypoperfusion. This hypoperfusion may explain the elevated levels of tPSA postoperatively.

As aforementioned, we observed significantly lower levels of tPSA intra-operatively in CABG patients with ECC. This study is the first one which examined intra-operative tPSA levels alterations compared with the preoperative - baseline levels. Patients of Group II had a core temperature of 31°C during the intra-operative measurement of their tPSA levels, a temperature that was significantly lower compared with patients who underwent off pump CABG. It seems that core temperature induced tPSA alterations and hypothermia was associated with decreased levels of tPSA. Hypothermia implies

slowing of cellular metabolism, given that for every 1°C drop in body temperature, cellular metabolism slows by 5-7%^[19] and reduces the harmful effects of ischemia by decreasing the body's need for oxygen.^[20] Consequently we could hypothesize that hypothermia is useful in preventing prostate tissue damage and in prostate cell protection^[21] resulting on tPSA levels reduction during the hypothermic phase of CABG.

Limitations

The present study is the first one which investigated the effect of body core temperature on tPSA levels in men who underwent CABG. In addition, is among the few studies which compared the perioperative tPSA levels in CABG patients with and without application of ECC. However, this study has some limitations. Firstly, the small sample size of our study and its selection by one cardiothoracic center limit the generalizability of the findings and potentially threaten the internal validity of the study. In addition, we did not observe tPSA levels for a longer than the 4th postoperative day period and consequently we were unable to determine when these levels return to normal values postoperatively.

CONCLUSIONS

CABG surgery seems to affect similarly the perioperative tPSA levels independently the application of ECC. Although, the patients of both groups had significantly higher early postoperative tPSA levels compared with the baseline (preoperative) levels, only those who underwent CABG with ECC had exceeded normal values. In addition, these patients had significantly decreased intra-operative tPSA levels. It seems that hypothermia is the causal factor of

this reduction due to the lower metabolic needs of prostate tissue, which prevent the hypoperfusion induced prostate cell damage. Further research, emphasizing in the effect of both hypothermia and ECC on tPSA levels, is needed to address the perioperative alterations of tPSA levels and the role of body core temperature on them.

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