Med Oncol (2015) 32:156
DOI 10.1007/s12032-015-0602-2

ORIGINAL PAPER

The impact of hypoxemia on serum total and free prostate-specific antigen levels in patients with chronic obstructive pulmonary disease

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Received: 22 April 2014 / Accepted: 12 May 2014

Abstract 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 hypoxic conditions has been described. However, no study has investigated the PSA levels in patients with chronic obstructive pulmonary disease (COPD). The aim of the present study was to investigate the impact of hypoxemia on serum total (tPSA) and free PSA (fPSA) levels in patients with COPD. Between January 2010 and January 2014, 95 male patients who hospitalized for acute exacerbations of COPD and 80 control subjects were enrolled in the study. Serum tPSA and fPSA levels and f/tPSA ratios were determined in all patients on the first day of hospitalization (exacerbation) and 7 days after the treatment (stable state). Statistical analysis included paired *t* test and Mann–Whitney *U* test. No statistically significant differences were found between COPD and control groups with regard to the baseline characteristics, except for smoking status. The levels of serum tPSA and fPSA during exacerbation of COPD were significantly higher than the levels of the stable period ($p < 0.01$), whereas f/tPSA ratio did not change ($p > 0.05$). Hypoxemia during acute exacerbation of COPD can cause a rise in serum tPSA and fPSA levels, but f/tPSA ratio is not affected. Acute exacerbation of COPD may be added to list of the events in which PSA measurements must be interpreted with caution.

Keywords Chronic obstructive pulmonary disease · Hypoxia · Prostate · Prostate-specific antigen

Introduction

Prostate-specific antigen (PSA), a member of the human kallikrein family of serine proteases, is produced exclusively by the epithelial cells of the prostate. It has been used as a biochemical marker in the diagnosis and follow-up of patients with prostate cancer [1, 2]. For practical purposes, it is organ-specific but not cancer-specific, and serum levels may be elevated in the presence of benign prostatic hyperplasia, prostatitis, prostatic trauma, and prostatic infarction [3].

In recent years, several studies have shown elevation of serum PSA levels after the events associated with ischemic conditions, such as prolonged cardiopulmonary resuscitation [4], cardiogenic shock [5], cardiac surgery, and extracorporeal cardiopulmonary bypass [6]. Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible [7]. In COPD populations, severe hypoxemia is not uncommon and no study has investigated the PSA levels in patients with COPD. The aim of the present study was to investigate the impact of hypoxemia on serum total (tPSA) and free PSA (fPSA) levels in patients with COPD.

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Published online: 03 April 2015

Materials and methods

Between January 2010 and January 2014, 95 male patients, diagnosed with acute exacerbations of COPD, in accordance with global initiative for chronic obstructive lung disease (GOLD) guidelines [7], and 80 age-matched subjects with normal pulmonary functions, as control group, were enrolled in the study. The institutional ethics committee approved this study, and all study participants read and signed an informed consent form.

Chest radiographs, respiratory function tests, and arterial blood gas analyses were performed for all patients. All patients received appropriate treatment for acute exacerbation of COPD.[7] Respiratory function tests were performed using a spirometry device (Sensormedics Vmax 22, CA, USA). We calculated the forced expiratory volume in 1 s (FEV_1), the forced vital capacity (FVC), and FEV_1/FVC ratio from maximal expiratory maneuvers. Serum tPSA and fPSA levels and f/tPSA ratios were determined in all patients on the first day of hospitalization (exacerbation) and 7 days after the treatment (stable state). 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).

Patients were excluded from the study if they had a history of prostate biopsy, malignancy of prostate, medical or surgical treatment of benign prostatic hyperplasia, urethral catheterization or instrumentation, prostatitis or a documented urinary tract infection. Patients with malignancy, significant cardiac, renal or hepatic disturbance were excluded.

Statistics

All data are expressed as mean ± standard deviation. Statistical analyses were done using the paired t test and Mann–Whitney U test. A p value less than 0.05 was considered statistically significant.

Table 1 Characteristics of the patients and control groups

	COPD ($n = 95$)	Control ($n = 80$)
Age (years)	67.72 ± 7.25	66.85 ± 6.15
Residual urine volume (ml)	35.54 ± 18.24	34.76 ± 17.19
Prostate volume (ml)	47.22 ± 16.75	48.10 ± 15.17
Transition zone volume (ml)	25.28 ± 11.01	26.12 ± 10.96
Smoking (pack-years)[a]	41.38 ± 3.12	16.28 ± 4.39

Data presented as mean ± standard deviation

[a] $p < 0.05$

Table 2 PSA values of the patients

	Exacerbation	Stable state	Control
tPSA[a] (ng/mL)	7.12 ± 1.08	1.85 ± 0.48	1.79 ± 0.62
fPSA[a] (ng/mL)	2.91 ± 0.42	0.73 ± 0.29	0.69 ± 0.31
f/tPSA (%)	0.41 ± 0.55	0.40 ± 0.71	0.39 ± 0.22

Data presented as mean ± standard deviation

tPSA Total prostate-specific antigen

fPSA Free prostate-specific antigen

[a] $p < 0.01$, compared with exacerbation

Table 3 Respiratory function tests and arterial blood gases of exacerbation and stable periods

	Exacerbation	Stable state
FEV_1^a	36.85 ± 7.95	45.14 ± 8.97
FVC[a]	71.92 ± 5.11	74.08 ± 8.31
FEV_1/FVC[a] (%)	39.92 ± 11.45	47.13 ± 11.81
PaO_2^a (mmHg)	48.94 ± 6.89	76.02 ± 7.22
$PaCO_2^a$ (mmHg)	46.93 ± 10.04	40.38 ± 9.54

Data presented as mean ± standard deviation

FEV_1 forced expiratory volume in 1 s

FVC forced vital capacity

PaO_2 oxygen partial pressure

$PaCO_2$ carbon dioxide partial pressure

[a] $p < 0.01$

Results

Patient characteristics are summarized in Table 1. No statistically significant differences were found between COPD and control groups with regard to the characteristics, except for smoking status. Serum tPSA and fPSA values of exacerbation and stable periods are shown in Table 2. The levels of serum tPSA and fPSA during exacerbation of COPD were significantly higher than the levels of the stable period ($p < 0.01$), whereas f/tPSA ratio did not change ($p > 0.05$). There was a significant difference in respiratory function tests and arterial blood gases of exacerbation and stable periods (Table 3).

Discussion

Our study shows that hypoxemia during acute exacerbation of COPD leads to a significant increase in serum levels of tPSA and fPSA. To our knowledge, this is the first study

that has been described the impact of hypoxemia on serum PSA levels in patients with COPD. On the other hand, we showed that serum tPSA and fPSA values decreased to baseline after the treatment of hypoxemia in patients with COPD. In contrast, it was found that hypoxemia during acute exacerbation of COPD did not affect f/tPSA ratio. Although PSA is not a parameter routinely measured in the patients with COPD, our study implies that any PSA elevation during acute exacerbation of COPD might be re-controlled and prostate biopsy should not be performed based on this only measurement.

Acute exacerbation of COPD is associated with increased alveolar hypoxia and consequent hypoxemia [8, 9]. In recent years, a relationship between PSA levels and ischemic conditions has been described, and evidence suggests that prostatic ischemia damages the epithelial cells of the prostate gland, leading to increased serum PSA [10]. 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 [10, 11]. Although the exact mechanism has not been clearly understood, our study demonstrated that PSA elevation during acute exacerbation of COPD may be related to hypoxia.

An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [7]. Chronic hypoxemia contributes to the development of adverse sequelae of COPD, such as systemic inflammation [12]. In circulation, the majority of PSA is complexed with various protease inhibitors. The proteolytic activity of PSA is inhibited by the formation of irreversible complexes with serum protease inhibitors and other acute-phase proteins. On the other hand, PSA has been identified as a member of the human kallikrein family of serine proteases, and kallikrein kinin system is also related to inflammation.

It has been demonstrated 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 [13]. The formation of irreversible PSA complexes has also significant correlation with other acute-phase proteins [14]. This may be another mechanism of PSA elevation related to acute exacerbation of COPD.

PSA elevation during acute exacerbation of COPD 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. It is generally accepted that proinflammatory mediators, including cytokines, are to a great extent responsible for the metabolic changes associated with tissue injury and inflammation. In common with other chronic disease, patients with acute exacerbation of COPD have increased circulating markers of systemic inflammation and tissue hypoxia likely plays a role in this condition [15].

Patané and Marte [16] have reported elevation of both tPSA and fPSA during acute myocardial infarction. 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. 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 [17]. Unlike PSA, hK2 has also been found to activate single-chain urokinase-type plasminogen activator [18]. However, considerable number of patients who hospitalized for acute exacerbation of COPD have elevated cardiac troponin [19].

In conclusion, our results show that hypoxemia during acute exacerbation of COPD is associated with a rise in serum tPSA and fPSA levels. We also found that the increased tPSA and fPSA levels had returned to baseline levels by 7 days after the treatment. Although only follow-up measurements and continuous increases of PSA are valuable for cancer diagnostics, we think that hypoxemia during acute exacerbation of COPD should be added to the list of events in which PSA measurements must be interpreted with caution.

Conflict of interest None.

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