Clinical Chemistry 42:5
691–695 (1996)

Physical activity releases prostate-specific antigen (PSA) from the prostate gland into blood and increases serum PSA concentrations

GERHARD M. OREMEK and ULRICH B. SEIFFERT*

Determination of prostate-specific antigen (PSA) is an established tool in detecting prostate cancer. However, the effect of physical activity on the PSA concentration in serum is controversial. We measured serum concentrations of PSA and prostatic acid phosphatase (PAP) in 301 healthy outpatients before and after they performed standardized exercise. Immediately after 15 min of exercise on a bicycle ergometer, their serum PSA concentrations increased by as much as threefold. The increase was age dependent and correlated to the PSA concentration before exercise. This increase was evident in both the free and complexed fractions of PSA. The amount of PSA secreted into blood depends on the volume of the prostate, whereas productivity of the prostate epithelium remains constant or increases slightly with age. We present cutoff values for clinical use. PAP was also increased, but to a lesser extent. The PSA and PAP secretion mechanisms differ. Our data suggest that extensive physical activity should be avoided before blood sampling for diagnostic purposes and, in case of an increase, the PSA concentration should be controlled after an exercise test.

INDEXING TERMS: prostatic acid phosphatase • prostate cancer • exercise, effects of

Testing blood for prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP; EC 3.1.3.2) is used to detect prostate cancer.[1] Assays with high sensitivity and specificity should facilitate early detection of curable and localized tumors as well as clinically significant malignancy *[1–3]*. Because the normal concentration of PSA in serum depends on several biological factors, not every increase is a cancer signal. Thus, conditions involved in the liberation of PSA into the serum should be elucidated. The normal function of PSA, produced by the epithelial cells of the prostate gland, is its secretion into the ejaculate and not into the body tissue or blood—although in tissue PSA acts as a biological factor *[3–7]*. Here we report important findings concerning the efficacy of PSA estimation in detecting prostate cancer.

There is some controversy concerning alterations of the prostate gland and the PSA concentration by physical events. The concentration of PSA might be increased as a consequence of digital rectal examination, transrectal ultrasound, or any kind of biopsy. This is why the collection of blood for PSA assay is not recommended after such manipulations *[2, 8, 9]*. Stamey et al. found that serum PSA concentration decreases by a mean of 18% 24 h after hospitalization *[9]*. The reason for differences in PSA concentrations between in- and outpatients is unknown *[10]*. Even the influence of ejaculation on PSA concentrations is not clear *[11, 12]*. To date, physical activity has not been regarded as an important factor affecting PSA or PAP concentrations *[13]*. Obviously, several variables contribute to the serum PSA concentration. The variability of intensity and kind of manipulation or exercise as well as the time of sample drawing and analysis may contribute to contradictory results. This study was designed to investigate the role of physical activity on PSA concentrations, to allow further definition of applicable cutoff values.

Materials and Methods

PATIENTS AND METHODS

Included in the study were 301 male outpatients, presumably free of prostate illness and clinically healthy, with results for the following routine clinical chemical serum analytes within the normal range: sodium, potassium, calcium, chloride, carbon dioxide, phosphate, iron, urea, creatinine, albumin, total protein, glucose, bilirubin, uric acid, cholesterol, triglyceride, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, γ-glutamyltransferase, alkaline phosphatase, amylase, and lipase. No urological check was undertaken in persons younger than 40 years.

Samples from these subjects taken during the study were

Clinical Chemistry Laboratories, Klinikum der Goethe-Universität, Theodor Stern Kai 7, 60590 Frankfurt am Main, Germany.
*Author for correspondence. Fax 49 069 6301 7202.

[1] Nonstandard abbreviations: PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; ACT, α_1-antichymotrypsin; and PSA_m, change in PSA concentration after exercise.

Received December 6, 1995; accepted January 29, 1996.

analyzed immediately, without any preservation procedure. Total PSA was estimated by a solid-phase two-site immunoenzymometric assay with a monoclonal antibody (Tandem-E PSA; Hybritech, San Diego, CA). PAP was estimated by a solid-phase two-site immunoenzymometric assay with an enzyme-labeled monoclonal antibody (Tandem-E PAP; Hybritech). Free PSA was estimated by a solid-phase IRMA (Immunocorp., Montreal, Canada) with a monoclonal antibody against human PSA and iodinated polyclonal antibodies recognizing different epitopes of PSA. PSA and α_1-antichymotrypsin (ACT) in complexed PSA were estimated by a sandwich ELISA with solid-phase and two monoclonal antibodies against total PSA and ACT (Dianova, Hamburg, Germany). Values were calculated from total PSA and from PSA bound by ACT *[14]*. Statistics and boxplots were calculated and drawn by SPSS for Windows (SPSS, Chicago, IL).

PHYSICAL ACTIVITY AND EXERCISE

From the following considerations, we designed a preliminary standardized exercise test. In cardiologic examination, the usual exercise tests are climbing one or more flights of stairs or walking on a treadmill *[15]*, techniques that allow calibration of the duration of exercise and workload. In a PSA stimulating test, the object is not to test the oxygen intake, cardiac function, or energy expenditure but rather to induce movement of the muscles in the pelvic area, so that the exercising muscles squeeze the prostate gland and the plexus to yield a hemodynamic response. High work loads may exhaust the subject, such that he fails to perform sufficient movement of his pelvic muscles. Walking is inappropriate because virtually the entire body weight is supported by exercising legs. However, a subject seated on a bicycle ergometer develops more muscle movement that squeezes the blood plexus and the prostate gland. Therefore, we chose to use exercise on a bicycle ergometer for 15 min, with at least 100 W as a suitable technique to stimulate PSA secretion into the bloodstream. The patient or subject must be cooperative and properly motivated to perform on the bicycle ergometer; generally, they are easily convinced to do so, although some patients are not accustomed to bicycling. Patients who have been confined to a bed or chair for some time exhibit cardiovascular deconditioning and are not motivated to continue even moderate exertion. Patients with cardiovascular disease are less motivated to attain sufficient movement. We emphasize that this test should be performed with able and willing subjects only.

Results

In men without prostate illness, we compared the concentration of PSA in blood after the exercise test with the concentrations in the morning after rest. We found an increase in all subjects, from 2 to 3.3 times the value before exercise. Preliminary exercise tests indicated that changes in the workload between 75 and 225 W did not alter the observed increase of prostatic constituents in serum. Routine clinical chemical analytes before and after exercise remained unchanged. The PSA concentration and its increase were related to age (Fig. 1), the baseline values increasing by ~0.45 g/L per decade. PAP in serum shows the same behavior, but to a lesser extent.

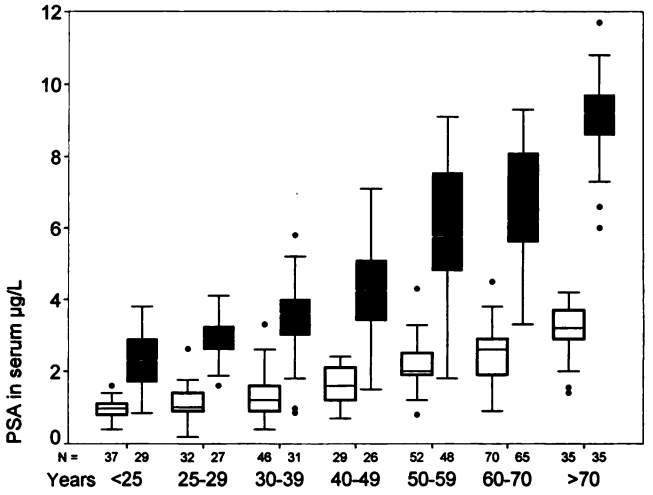

Fig. 1. PSA µg/L in serum measured before (*white*) and immediately after (*black*) exercise.

Exercise was performed on a bicycle ergometer for 15 min at 75–100 W. Subjects were men without prostate illness, divided into age groups, in numbers as indicated in each group. Boxplots show mean and 25th and 75th percentiles; single extreme values are listed by dots (SPSS).

To demonstrate the amount of PSA released after exercise (PSA_m), we subtracted the resting PSA value from the value measured after exercise. The value determined for PSA_m increases with age (Fig. 2), presumably in correlation to the volume of the prostate gland, assuming that the concentration of PSA before exercise is also related to this volume *[10, 16–19]*. PSA_m highly correlates to PSA concentration before exercise (r = 0.860, P = <0.001, n = 260). Thus, the amount of PSA liberated by exercise depends on the volume of the prostate gland, which enlarges with age *[16]*. However, the amount of PAP released by exercise remains constant with age (Fig. 2).

For practical use in clinical management, we express cutoff values as the 95th percentiles for PSA in serum before exercise and for PSA_m released by exercise. For comparison, Table 1 lists the age-related reference values for PSA *[2]*.

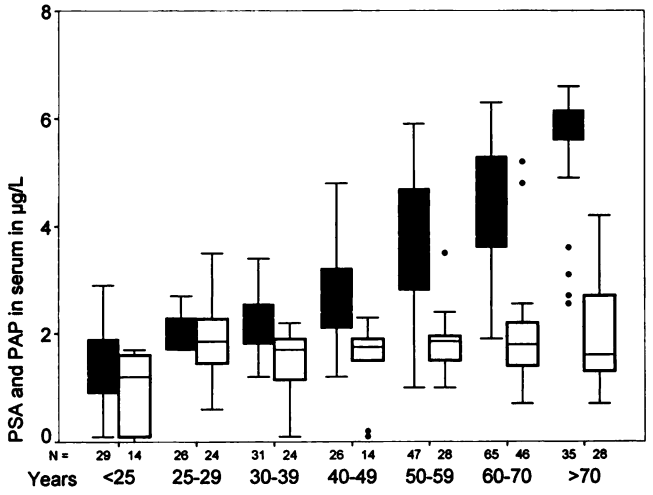

Fig. 2. Amount of PSA (*black*) and PAP (*white*) delivered into blood by exercise.

Other conditions as described in text and in legend of Fig. 1.

Table 1. Effects of exercise on PSA concentrations in serum.

Age, years	PSA at rest	PSA after exercise	PSA_m released by exercise	PSA at rest (from ref. 2)
<25	1.4	3.7	2.7	
25–29	1.7	4.1	2.7	
30–39	2.2	5.4	3.6	
40–49	2.4	7.1	4.7	2.5
50–59	3.2	8.8	5.8	3.5
60–70	3.7	9.0	6.0	4.5
>70	4.7	12.6	8.0	6.5

95th percentiles of PSA in serum before and after exercise, and PSA_m released by exercise in men without prostate illness. Last column compares age-related percentiles from literature.

To find out whether the amount of PSA_m is related to the increased volume of the prostate and (or) to increased leakage of PSA or production *[16]*, we calculated PSA production per prostate gland volume, comparable with PSA density *[20, 21]*. However, because the subjects' gland volume was not measured by transrectal ultrasound, we used the primary PSA value as a measure of volume *[10, 16–19]*. According to this calculation, the productivity of the prostate cells might slightly increase with age under normal conditions. As a result, PSA_m was again shown to be closely related to the volume of the gland (Fig. 3). Free and complexed subfractions of PSA are age-related and increased by equal amounts after exercise (Fig. 4). There was no indication that the free fraction might predominate.

In contrast PAP exhibits a relatively low measurable signal. Its output increases with age, but PAP production per volume of the prostate gland decreases by ~50% in elderly men. The expression of PAP in the blood differs from that of PSA (Figs. 2 and 3).

Discussion

PSA in serum is a product of epithelial cells of the prostate gland *[5]*, which is why the concentration of PSA in serum depends on the number of parenchymal cells. The preoperative serum concentration of PSA has been found to be a highly significant predictor of prostate volume *[1]*. As the volume of the gland enlarges with age, the PSA concentration increases concomitantly (Fig. 1). These findings on PSA concentrations agree with those reported in the literature *[1, 16, 20]*.

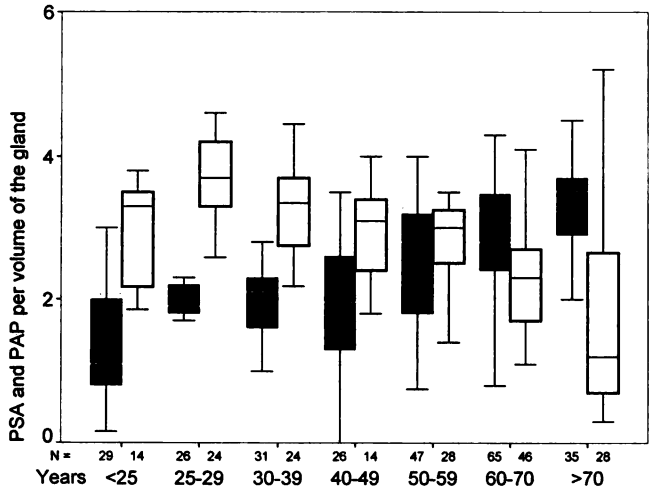

Fig. 3. Calculated productivity (no dimension) of prostatic epithelial cell: PSA (*black*) and PAP (*white*) secreted per volume of the prostate.
Other conditions as described in text and in legend of Fig. 1.

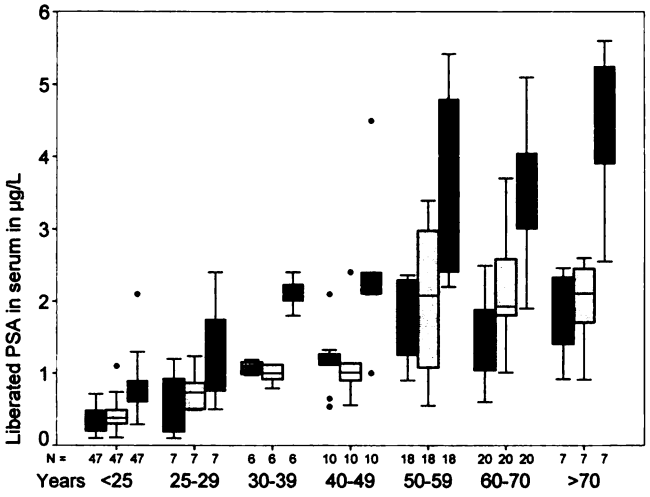

Fig. 4. Amount of PSA secreted into the blood: free (not ACT-complexed; *gray checked*), ACT-complexed (*gray dotted*), and total PSA (*black*).
Other conditions as described in text and in legend of Fig. 1.

The observed PSA changes after exercise depend on the type and intensity of the exercise. Slow walking does not produce a measurable PSA increase in all cases. This is why we developed a preliminary standardized exercise test, acceptable to most patients, that yielded comparable results among subjects to measure the influence of physical activity on the PSA concentration. The amount of PSA liberated by exercise (PSA_m) corresponds to the volume of the prostate gland and to the number of functional prostatic parenchymal cells. PSA_m is the better measure for prostate volume than PSA at rest, which sometimes may be influenced by several uncontrollable events. In our experiments, PSA production resembled PSA density (a measure of the ability of the prostate gland to secrete PSA *[10, 16, 20]*) in demonstrating a slight age-dependent increase (see Fig. 3). However, although testicular dysfunction as a result of aging may reduce cellular PSA production *[20]*, PSA density has been found not to change with age *[16]*.

The pathophysiology of the delivery of PSA from tissue into blood is not yet understood. The concentration of PSA in serum depends on several factors. Because PSA is normally secreted into the ejaculate, its appearance in serum indicates leakage *[3, 20]*. However, its enzymatic activity in serum may exhibit a certain growth-factor-like effect; i.e., PSA in serum should be considered a biologically active factor. The enzyme activity of PSA in blood possesses mitogenic activity *[4, 6]*, may be involved in growth regulation *[3]*, and in high concentrations might favor the growth of cells, especially the formation of metastases *[5, 7]*.

The concept of measuring PSA in serum is based on the premise that under normal conditions each epithelial cell synthesizes a certain amount of PSA, which maintains the serum

concentration. PSA must pass the basement membrane of acini cells, the prostatic stroma, capillary endothelial basement membrane, and capillary endothelial cells to be released into tissue and thus into circulation *[16]*. Or, it may reach the bloodstream by way of the lymph stream, with blood bringing PSA from the glandular tissue to the circulation. The PSA concentration in blood will be influenced by the variability of blood perfusion, which may be low in the plexus. Physical activity will increase blood flow, similar to that in the vein plexus of the legs. The release from tissue to circulation can be enhanced by manipulation. Physical alterations of the gland for diagnostic purposes or therapy might influence the PSA concentrations *[8, 9]*. Physical activity is an important factor, potentially increasing the PSA concentration in serum as much as threefold. Probably, the blood flow increases and washes the PSA into the circulation.

PSA in serum is bound to several acute-phase proteins, predominantly ACT, a proteinase inhibitor *[3, 5, 22, 23]*. In all tissues the complexed form predominates. Free PSA without proteinase inhibitors also exists, but in much lower concentrations, and a certain amount of PSA adheres to the tissue close to the prostate gland *[14, 24]*. This feature of binding to different proteins might be another explanation for the increased output of PSA under certain conditions. Given that the composition of PSA fractions in PSA_m remains unchanged, we assume that PSA is washed out rather than newly secreted.

Elimination of PSA from the circulation has been investigated in patients after prostatectomy. The time to decrease to one-half its original concentration has been established as 2–3 days, but the mechanism of elimination is unknown *[9, 10]*. Investigation of the decrease only hours after prostatectomy has revealed a rapid elimination in the first 6 h, and these authors estimated the time to loss of half of the PSA as only 12–19 h *[9]*. We have found serum PSA to be increased immediately after ejaculation (unpublished data), but 12 h later no increase in PSA could be established *[11, 12]*, probably because of the biphasic elimination rate from the plasma *[9]*. This feature may explain contradictory reports showing no increase of PSA after exercise *[13]*.

Our procedure differs from others in three ways: (*a*) The exercise involved riding on a bicycle ergometer for 15 min at ~100 W instead of walking on a treadmill; (*b*) blood for assay was drawn immediately after exercise to avoid a possible loss of PSA by fast decay; (*c*) the subjects were agile, healthy men, not patients suffering from coronary heart disease and its treatment. The increase in PSA resulting from activity may explain the differences described in in- and outpatients *[10, 13]*. In general, exercise status should be considered when interpreting PSA concentrations.

In clinical investigation for early detection of cancer, any PSA value in the gray area or higher should be assessed by reassaying before and after an exercise test. Some high false-positive rates for detecting prostate cancer are caused by an uncertain amount of PSA washed out by blood flow in addition to the high volume of benign prostatic hyperplastic tissue within the gland. Measuring PSA_m may improve assay specificity while maintaining its sensitivity. This will allow the classification of some patients as having a low risk of prostate cancer. Introducing appropriate specific reference ranges for age and for PSA_m liberated by physical activity as a measure of functional prostate volume should enhance the clinical usefulness of PSA for early detection of cancer and thus minimize the number of biopsies.

Our findings may make PSA an even more important and useful marker for prostate carcinoma. The sensitivity of the PSA assay alone is too low for use in mass, nonselective screening. However, PSA_m may become a useful marker for early detection of prostate cancer, given its close relation to prostate volume. The aim of further investigation is to develop an easily performed, standardized test for PSA release, after exercise, as a measure for the functional volume of the prostate gland *[25]*.

We are indebted to Karen Nelson for help in preparing the manuscript.

References

1. Humphrey PA, Baty J, Keetch D. Relationship between serum prostate specific antigen, needle biopsy findings, and histopathologic features of prostatic carcinoma in radical prostatectomy tissues. Cancer 1995;75(Suppl):1842–9.
2. Partin AW, Oesterling JE. The clinical usefulness of prostate specific antigen: update 1994. J Urol 1994;152:1358–68.
3. Benson MC. Prostate specific antigen [Editorial]. J Urol 1994;152: 2046–8.
4. Diamandis EP. New diagnostic applications and physiological functions of prostatic specific antigen. Scand J Clin Lab Invest 1995;55(Suppl 221):105–12.
5. Diamandis EP, Yu H. New biological functions of prostate-specific antigen [Editorial]? J Clin Endocrinol Metab 1995;80:1515–7.
6. Peehl DM. Prostate specific antigen role and function. Cancer 1995;75(Suppl):2021–6.
7. Graves HCB. Nonprostatic sources of prostate-specific antigen: a hormone-dependent phenomenon [Editorial]? Clin Chem 1995; 41:7–9.
8. Chybowski FM, Bergstralh EJ, Oesterling JE. The effect of digital rectal examination on the serum prostate specific antigen concentration: results of a randomized study. J Urol 1992;148:83–6.
9. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909–16.
10. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate [Review]. J Urol 1991;145:907–23.
11. Simak R, Madersbacher S, Zhang ZF, Maier U. The impact of ejaculation on serum prostate specific antigen. J Urol 1993;150: 895–7.
12. Kirkali Z, Kirkali G, Esen A. Effect of ejaculation on prostate specific antigen levels in normal men. Eur Urol 1995;27:292–4.
13. Leventhal EK, Rosanski TA, Morey AF, Rholl V. The effects of exercise and activity on serum prostate specific antigen levels. J Urol 1993;150:893–4.
14. Stamey TA, Prestigiacomo AF, Chen Z. Standardization of immunoassays for prostate specific antigen. A different view based on experimental observations. Cancer 1994;74:1662–4.
15. Bruce RA, Blackmon JR, Jones JW, Strait G. Exercising testing in adult normal subjects and cardiac patients. Pediatrics 1963; 32(Suppl II):742–56.
16. Oesterling JE. Prostate specific antigen: its role in the diagnosis and staging of prostate cancer. Cancer 1995;75:1795–804.
17. Lepor H, Wang B, Shapiro E. Relationship between prostatic

epithelial volume and serum prostate specific antigen levels. Urology 1994;44:199–205.

18. Clements R, Etherington RJ, Griffiths GJ, Peeling WB, Hughes H, Penney MD. Inter-relation between measurement of serum prostatic specific antigen and transrectal ultrasound in the diagnosis of benign prostatic hyperplasia and prostatic cancer. Br J Urol 1992;70:183–7.
19. Collins GN, Lee RJ, McKelvie GB, Rogers ACN, Hehir M. Relationship between prostate specific antigen, prostate volume and age in the benign prostate. Br J Urol 1993;71:445–50.
20. Benson MC, Olsson CA. Prostate specific antigen and prostate specific antigen density. Roles in patient evaluation and management. Cancer 1994;74:1667–73.
21. Benson MC, Wang IS, Pantuk A, Ring K, Kaplan SA, Cooner WH. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992; 147:815–6.
22. Stenman UH, Leionen J, Alfthan H, Rannikko S, Tukahnen K, Alfthan O. A complex between prostate-specific antigen and α_1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res 1991;51: 222–6.
23. Christenson A, Laurell CB, Lilja H. Enzymatic activity of prostate specific antigen and its reaction with extracellular serine proteinase inhibitors. Eur J Biochem 1990;194:755–63.
24. Jung K, Lein M, Schnorr D, Henke W, Brux B, Loening S. Prostate specific antigen: influence of its free and complexed form on the clinical validity as tumour marker. Lab Med 1995;19:210–7.
25. Hammerer PG, McNeal JE, Stamey TA. Correlation between prostate specific antigen levels and the volume of the individual glandular zones of the human prostate. J Urol 1995;153: 111–4.