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Kinetics of Prostate-specific Antigen After Manipulation of the Prostate

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Kinetics of prostate-specific antigen (PSA) were investigated after manipulation of the prostate in two groups of patients: those treated with digital rectal examination (DRE), and those with needle biopsy. 8 patients had serial PSA measurements to study the effect of DRE (group 1). 7 of 8 patients had PSA baseline values <10 ng/ml. Blood samples were taken at 1 min, 30 min, 1, 3, 6, 12 and 24 h after DRE. Some patients were further monitored for 5 days with one blood sample taken at the same time each day. Statistically significant increased PSA levels were found after DRE ($P < 0.001$). Maximal increase was 70%. In most patients, peak levels were found between 30 and 60 min after DRE. Based on the results, it is concluded that after DRE it is prudent to wait 3 days before PSA is determined. 7 patients had serial PSA measurements after transrectal prostate needle biopsy (group 2). PSA sampling was similar as in the previous group. All patients had increased PSA levels after biopsy (range 1.3–9.5-fold). After 5 days, only 2 of 7 patients had returned to baseline levels. We conclude that biopsies of the prostate induce an important and long-lasting PSA elevation.

Key words: prostate-specific antigen, serial measurements, digital rectal examination, needle biopsy
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INTRODUCTION

IN 1979, WANG [1] isolated and purified a glycoprotein specific for prostatic epithelial cells. It was called prostate-specific antigen (PSA) and has a molecular weight of 34 000 Dalton. Elevations of serum PSA levels are found in benign prostatic hyperplasia (BPH) and adenocarcinoma of the prostate. Transiently increased levels are also found after manipulation of the prostate (cyctoscopy, needle biopsy, transurethral prostatectomy), acute prostatitis and acute urinary retention [2]. PSA is clinically used for screening, diagnosis, staging, prognosis, assessment of response to treatment, and prediction of relapse in adenocarcinoma of the prostate [3]. Serum PSA measurements fluctuate unpredictably over the course of a day in patients with and without prostatic disease [4]. Prostatic acid phosphatase (PAP) is a less sensitive tumour marker for prostatic disease than PSA, and nowadays PSA has replaced PAP measurements [3].

Because PSA is produced by all types of prostatic tissue (normal, hyperplastic and malignant), the use of PSA for screening and early detection was thought to have a limited value. The establishment of a reference range for normal PSA concentrations (<4.0 ng/ml) has resulted in both high false-positive rates, generated by BPH, and false-negative rates in men with early stage, organ-confined cancer [5]. New analytic techniques that may refine the use of PSA as a screening test for prostate cancer have been proposed. PSA density, PSA velocity and age-specific PSA reference ranges are new concepts that may facilitate the important transition from prostate cancer screening to the early detection of malignant disease. PSA density (PSAD) is defined as the serum PSA concentration divided by the volume of the prostate gland. The analysis of PSAD has been explored especially in the "grey zone" of PSA values between 4.0 and 10.0 ng/ml. In this range occurs the greatest overlap between diagnoses of BPH and of prostate cancer, contributing to unacceptably low specificity rates for PSA screening. Another technique for enhancing the clinical usefulness of serum PSA is to monitor the change in serum PSA over a defined unit of time. Termed "PSA velocity", this technique may provide useful information as more and more patients are returning on an annual basis for a serum PSA determination and digital rectal examination (DRE). The rate of change in serum PSA proved to be more useful than the actual serum PSA value for detecting prostate cancer. Using a cut-point of 0.75 ng/ml per year, the specificity was 90% compared with 60% for the cut-point of 4.0 ng/ml. In addition, the specificity of PSA velocity in cancer detection was maintained when PSA was less than 4.0 ng/ml and when it was between 4.0 and 10.0 ng/ml [5]. Age-specific PSA reference ranges have been determined recently by Oesterling [6] to make PSA a more sensitive and specific tumour marker: 50–59 years, 0–3.5 ng/ml; 60–69 years, 0–4.5 ng/ml; 70–79 years, 0–6.5 ng/ml.

There is still controversy concerning the effect of DRE or prostate massage on PSA levels. Several studies have been

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published, and while some authors have found no effect, others have reported an increase as high as 4.7-fold [4, 7–14]. In most of these studies, a single PSA measurement was done after manipulation of the prostate, and the time of that blood sample varied between one study to another from 1 min to 30 h. The exact time at which peak levels are found after DRE is not known. To find an answer to this question, serial PSA measurements were performed in the present study. We found statistically significant increased PSA levels after DRE and the time at which peak levels are reached was determined.

Falsely elevated PSA levels after DRE can be misleading when PSA is used for cancer screening, even in patients with baseline levels between 4.0 and 10.0 ng/ml where new analytical techniques can be used (PSAD, PSA velocity and age-specific PSA reference ranges) for early detection of malignant disease.

PATIENTS AND METHODS

Digital rectal examination

The effect of DRE was monitored in a group of 8 patients, 2 of whom had a normal prostate (PSA < 1 ng/ml), 4 had BPH (PSA > 4 and <10 ng/ml) and 2 had adenocarcinoma (PSA < 20 ng/ml). Diagnosis was assessed with DRE and transrectal ultrasound (TRUS) in all patients and with biopsy in 3 patients. We excluded patients who had undergone prostate needle biopsy or prostatectomy 6 months or DRE 3 weeks prior to this intervention. One blood sample was taken 15 min before DRE as a baseline value. 5 patients were examined by a urologist and 3 patients were examined by a resident. Blood samples were taken at 1 min, 30 min, 1, 3, 6, 12 and 24 h after DRE. 5 patients were further monitored for 5 days with one blood sample taken each day at the same time of the day. The blood samples of the first 24 h were obtained by using an indwelling heparin-locked plastic intravenous catheter. Venous congestion was avoided during blood sampling. Samples were separated and immediately frozen for subsequent PSA analysis by the Tandem R-E kit from Hybritech (Hybritech Inc., San Diego, California, U.S.A). All samples from each patient were measured within the same assay run. The normal PSA range for this assay is 0–4 ng/ml [3].

Needle biopsy

7 patients were monitored for the effect of prostate biopsy on PSA levels. Biopsies were performed transrectally with an 18-G needle and a biopsy gun under ultrasonic guidance. Four to six biopsies were taken from each patient. Pathological diagnosis was as follows: 2 patients had BPH (PSA 5 and 5.8 ng/ml), 2 had granulomatous prostatitis (PSA 1.2 and 12.9 ng/ml) and 3 had adenocarcinoma of the prostate (PSA 3.1, 28 and 65 ng/ml). PSA sampling was similar as in the previous group. The first sample after the procedure was taken 1 min after the last biopsy. All patients were monitored for 5 days.

RESULTS

The intra-assay and inter-assay coefficients of variation of the assay were 6.4% and 6.1%, respectively, at the level of twice normal.

Digital rectal examination

Figures 1a and b show the progression of PSA levels after DRE. The upper five curves are from patients examined by the urologist. Statistically significant increased PSA levels were found after DRE ($P < 0.001$). Data were analysed using a Fisher *t*-test. The maximal increase was 1.7-fold. In general, increase was more pronounced in patients examined by a urologist. These patients also had the highest initial values (>5 ng/ml). PSA values immediately after DRE (within 1 min) were never increased. Peak levels were reached between 30 and 60 min in 6 of 8 patients. The other patients had peak levels after 3 and 12 h. Return to baseline levels varied between 24 and 72 h after DRE. There was no difference in PSA increase and time to reach baseline related to diagnosis (BPH, prostatitis or adenocarcinoma).

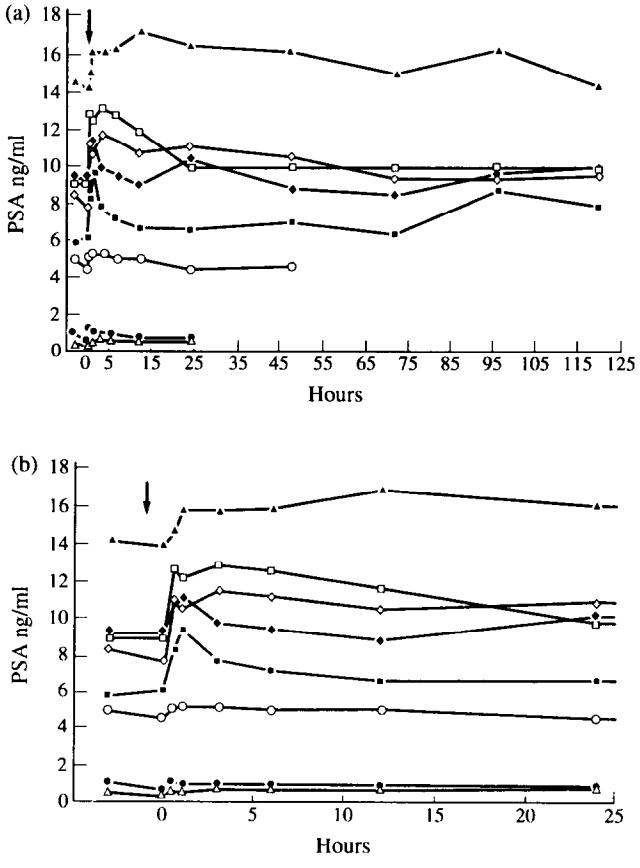

Figure 1. (a) Effect of digital rectal examination on prostate-specific antigen (PSA) levels of 8 patients. Arrow = digital rectal examination. (b) Detail of (a): first 24 h after digital rectal examination.

Needle biopsy

Important fluctuations of PSA concentrations were observed after needle biopsy. All patients had an increase in PSA levels after biopsy (Figure 2a and b). The mean increase was 3-fold (range 1.3–9.5). The highest increase (9.5-fold) was found in a patient with a baseline level <4 ng/ml. Peak levels were reached between 1 min and 6 h after biopsy in 6 of 7 patients; 1 patient reached peak levels after 2 days. Only 2 patients had returned to baseline levels at the latest sample after 5 days. The remaining 5 still had increased PSA levels (1.3–2.4-fold). There was no correlation between the amount of increase or time to reach baseline level and the pathological diagnosis of the prostate.

DISCUSSION

Digital rectal examination

Many studies have been reported on the effect of DRE, prostate massage or TRUS on PSA levels with contradictory results. They are summarised in Table 1. Some authors found no effect at all [8, 12, 13], others reported increased levels as high as 4.7-fold [7]. These different results can partially be

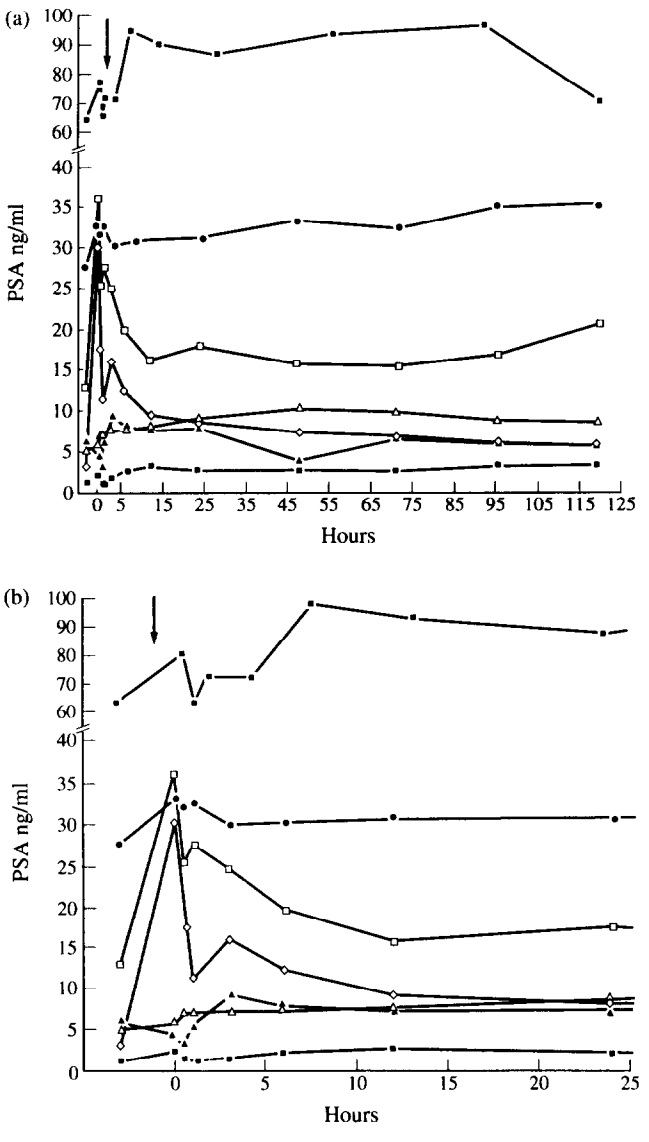

Figure 2. (a) Effect of prostate needle biopsy on prostate-specific antigen (PSA) levels. Patient nos 1 to 6. Arrow = needle biopsy. (b) Detail of (a): first 24 h after biopsy.

explained by the time of blood sampling. The present study of the kinetics of PSA after DRE has demonstrated that the highest levels are usually reached between 30 and 60 min after manipulation. In previous reports only a single blood sample was generally taken instead of serial measurements, and the time of blood sampling showed much variation between the reports, ranging from 1 min [2] to 30 h [11].

Other factors can influence the effect of rectal examination on PSA values including the intensity of the rectal examination, the initial PSA value and the disease status of the prostate gland. Adjiman [7] and Yuan [4] also mentioned the role of the intensity of the DRE. Adjiman [7] only found an increase if DRE was performed by a urologist (mean increase 4.7-fold in 11 subjects on 13). Comparable to our study, maximum levels were found 1 h after DRE. No increase was found if DRE was done by a resident, probably because it was less vigorous. In Yuan's report [4] increase was more pronounced after prostate massage compared to DRE (15 versus 9% of the patients). In our study, increase was also more pronounced when DRE was performed by a urologist. The baseline PSA value can also be important for the ultimate outcome after prostate manipulation. In the present study a less significant increase was found in patients with baseline values <1 ng/ml. Crawford [9] reported, in a study of 2754 men, that statistically significant increases were only found in patients with baseline values >20 ng/ml.

The role of the pathological status of the prostate and the effect of manipulation for PSA levels is unclear. In the present study, no correlation was found between the amount of increase of PSA after DRE and the pathological status of the prostate, but the patient population was very small. Hughes [14] examined the effect of TRUS on PSA levels in three groups of patients: adenocarcinoma of the prostate, BPH and chronic prostatitis. Increase was only found in the latter group. These men had the lowest PSA baseline values (mean 1.58 ng/ml). These findings contrast with those of Crawford [9] and the present results, where an increase was more obvious in patients with the highest baseline values. Stamey [2] found the highest increase (nearly 2-fold) in patients with BPH. Blood sampling was performed 1 min after prostate massage. In the present study, no increase was found at that time of blood sampling. Stamey was one of the few to use the polyclonal Yang assay, which possibly can explain his results. Differences in sensitivity between the Yang and Hybritech assays have been reported [9].

Table 1. *Summary of previous reports on the effect of digital rectal examination, prostate massage or transrectal ultrasound (TRUS) on prostate-specific antigen (PSA) values*

Author [ref.]	No. of patients	Manipulation	Time of blood sampling	Effect on PSA levels
Stamey [2]	16	Massage	1 min	Increase (mean 2-fold)
Brawer [13]	24	DRE	5–30 min	No effect
Hughes [14]	85	TRUS	30 min	Increase (mean 1.3-fold) if low baseline level
Adjiman [7]	27	DRE by non-urologist	1, 12, 24, 72 h	No effect
	13	DRE by urologist	1, 12, 24, 72 h	Mostly increase (mean 4.7-fold)
El-Shirbiny [8]	13	Massage	1 h	No effect
Crawford [9]	2754	DRE	5–20 min	Small increase when baseline level >20 ng/ml
Yuan [4]	43	DRE	5 or 90 min	Increase in 9% of patients
	23	Massage	5 or 90 min	Increase in 15% of patients
Chybowski [11]	143	DRE	2–30 h	Increase (median 0.4 ng/ml)
Walz [12]	11	Massage	10, 30, 60 min, 2, 3, 5, 10, 24 h	No effect

DRE, digital rectal examination.

Table 2. Summary of previous reports on the effect of prostate needle biopsy on prostate-specific antigen (PSA) values

Author [ref.]	No. of patients	Manipulation	Time of blood sampling	Effect on PSA levels
Stamey [2]	7	Perineal true-cut biopsy	Immediately after biopsy	Increase (mean 57-fold)
Charrie [15]	14	Perineal true-cut biopsy	20 min after biopsy	Increase (mean 2.4-fold)
Yuan [4]	100	Transrectal ultrasound guided biopsy	5 min after biopsy	Increase (mean 5.91-fold)
Oesterling [10]	19	Transrectal ultrasound guided biopsy	4–24 h after biopsy	Increase (median 7.9 ng/ml)

Chybowski [11] was one of the first to make a prospective randomised controlled trial on the effect of DRE on serum PSA concentrations. The study group consisted of 71 men, all of whom had a serum PSA determination followed by a DRE and then a second PSA determination. The control cohort consisted of 72 men, all of whom had two serum PSA determinations without an intervening DRE. A statistically significant effect was found with a median increase of 0.4 ng/ml.

Brawer, El-Shirbiny and Walz [8, 12, 13] found no effect at all of prostate manipulation on PSA values. Brawer [13] found no increase in 24 patients after DRE performed by a urologist, but blood samples were taken after 5–30 minutes, which could be too early to detect any effect. In addition to this observation, 73% of the patients had low baseline PSA values (mean 1.29). El-Shirbiny [8] could not find any effect of prostate massage on PSA levels, but again most of the patients had low baseline levels <1.5 ng/ml. Walz [12] could not find a clear effect of prostate massage on PSA levels in 11 patients. After massage, PSA showed non-significant variations, at no time was a uniform alteration detectable.

Needle biopsy

Biopsy causes higher increases of PSA levels compared to DRE. In our small series, there was no correlation between the baseline PSA level or anatomopathological findings and the amount of increase. Peak levels were found between 1 min and 6 h in most of the patients, this time range is larger than observed after DRE. Only 2 of the 7 patients returned to baseline levels after 5 days. This half-life is longer than seen after radical prostatectomy [2]. It could be the effect of a continuous "leak" of PSA in blood circulation caused by the trauma of the puncture.

Table 2 shows results of previous reports. Stamey [2] found a mean increase of 57-fold in 7 patients immediately after perineal biopsy. This higher increase may be the effect of the thicker true-cut needle used. Charrie [15] measured PSA levels 20 min after transperineal true-cut biopsy in 14 patients. There was an increase in all patients, mean 2.4-fold (range 2–25 times). Yuan [4] measured the effect of transrectal ultrasound guided biopsy (mean 4.8 cores) in 100 patients. Blood sampling was performed 5 min after biopsy and then at weekly intervals until PSA levels had returned to baseline levels. In 92% of the patients, PSA levels were elevated immediately following biopsy. The immediate increase of serum PSA varied from zero to 52-fold, with a mean of 5.91 times the baseline levels. Only 35 men of 100 had returned to baseline after 1 week, similarly to our findings. Oesterling [10] studied the effect of transrectal ultrasound guided biopsy of the prostate in 19 patients. A median increase of 7.9 ng/ml was found after biopsy, and the median time required for the serum PSA value to return to a stable level after biopsy was 15–17 days.

Based on the present results, we conclude that DRE can induce falsely elevated PSA levels. Maximal increase was 70%. Increase is more pronounced after an intense rectal examination. Peak levels are usually found 30–60 min after the digital manipulation and return to baseline levels can last 72 h. Therefore, it is safe to wait 3 days after DRE before PSA is determined. However, PSA levels can be determined safely immediately after rectal examination (within 1 min), since we found no increase at that time of blood sampling.

One should be very careful in interpreting PSA values after prostate needle biopsy. It causes an important and long-lasting elevation of PSA levels. Increased levels are found even 5 days after the procedure, and there is no correlation between the initial PSA level and the level of increase.

1. Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human specific antigen. *Invest Urol* 1979, **17**, 159–163.
2. 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**, 909–916.
3. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991, **145**, 907–923.
4. Yuan JJ, Coplen DE, Petros JA, *et al.* Effects of rectal examination, prostatic massage, ultrasonography and needle biopsy on serum prostate specific antigen levels. *J Urol* 1992, **147**, 810–814.
5. Crawford ED, De Antoni EP. PSA as a screening test for prostate cancer. *Urol Clin N Am* 1993, **20**, 637–646.
6. Oesterling JE, Cooner WH, Jacobsen SJ, Guess HA, Lieber MM. Influence of patient age on the serum PSA concentration. *Urol Clin N Am* 1993, **20**, 671–680.
7. Adjiman S, Zerbib M, Brochard M, Dugue MA, Debre B, Steg A. Le toucher rectal modifie-t-il le taux serique de l'antigene prostatique specifique? *Ann Urol* 1989, **23**, 291–293.
8. El-Shirbiny AM, Nilson T, Pawar HN. Serum prostate specific antigen: hourly change/24 hours compared with prostatic acid phosphatase. *Urology* 1990, **35**, 88–92.
9. Crawford ED, Schutz MJ, Clejan S, *et al.* The effect of digital rectal examination on prostate-specific antigen levels. *JAMA* 1992, **267**, 2227–2228.
10. Oesterling JE, Rice DC, Glenski WJ, Bergstralh ES. Effect of cystocopy, prostate biopsy and transurethral resection of prostate on serum prostate-specific antigen concentration. *Urology* 1993, **42**, 276–282.
11. Chybowski FM, Bergstralh E, Oesterling JE. The effect of digital rectal examination on the prostate specific antigen concentration: results of a randomized study. *J Urol* 1992, **148**, 83–86.
12. Walz PH, Shoppmann T, Buscher C, Ennen J, Schriewer H. Influence of prostatic disease and prostatic manipulations on the concentration of prostate specific antigen. *Eur Urol* 1992, **22**, 20–26.
13. Brawer MK, Schifman RB, Ahmann FR, Ahmann ME, Coulis KM. The effect of digital rectal examination on serum levels of prostatic-specific antigen. *Arch Path Lab Med* 1988, **112**, 1110–1112.
14. Hughes HR, Penney MD, Ryan PG, Peeling WG. Serum prostatic specific antigen: *in vitro* stability and the effect of ultrasound rectal examination *in vivo*. *Ann Clin Biochem* 1987, **24**(suppl. 1), 206–207.
15. Charrie A, Fleury-Goyon MC, Dutey P, Perrin P. The effect of prostate aspiration biopsy on serum levels of prostatic acid phosphatase and prostatic-specific antigen. *JAMA* 1986, **474**, 256.