ORIGINAL ARTICLE
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Correlation between prostate-specific antigen and histopathological difference of prostate carcinoma

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ABSTRACT

BACKGROUND: *Adenocarcinoma of prostate (ACP) is one of the most frequent tumors in men older than 50. Prostate specific antigen (PSA) is the most reliable serum marker in the diagnostics and following of prostate carcinoma, and Gleason's system of estimation of tumor differentiation, as well as classical estimation of tumor differentiation from 1 to 3, are generally accepted systems of prostate carcinoma evaluation.*

METHODS: *Forty examined individuals with verified ACP and compared values of PSA and tumor differentiation as well as estimated comparability of these two systems are reported.*

RESULTS: *Highly positive correlation between the values of PSA in serum and the degree of tumor differentiation determined by Gleason's system, as well as the low correlation between PSA and histological differentiation estimated using classical system from 1 to 3 were found.*

CONCLUSION: *It could be concluded that Gleason's system for tumor differentiation determination is more superior system of histological grade determination than the other systems.*

KEY WORDS: *Prostatic Neoplasms; Adenocarcinoma; Prostate-Specific Antigen; Neoplasm Staging; Cytodiagnosis; Sensistivity and Specificity*

INTRODUCTION

Prostate-specific antigen (PSA) is the most useful tumor marker in the diagnostics of prostate carcinoma (1). PSA is serin protease produced by ductal and acinal epithelial cells of normal, hyperplastic, and malignant tissue of the prostate. By the influence of pathological processes the cell integrity is destroyed leading to release of PSA into circulation, i.e. the processes inside prostate, such as hyperplasia, inflammation, tumors, lead to the increase of serum PSA value the most frequently (2-4). The investigations have revealed that every gram of cancer prostate tissue increases the value of serum PSA for 2.3 ng/ml in average, while every gram of hyperplastic tissue increases the same parameter 10 times less compared to cancer tissue (5,6). The PSA value increase is determined by histological characteristics of epithelial cells. In neoplastic processes the increase of serum PSA depends on differentiation of tumor cells. The less differentiated prostate tumors can cause lower PSA concentrations in comparison to those well differentiated (7). In prostate carcinoma (PC) evaluation there are few systems used for estimation of tumor cells differentiation i.e. histological grade of tumor. In literature the grade systems suggested by Mostofi, Broders, and Gleason are the most cited. Classical determination of histological grade according to Mostofi is based on criteria of nuclear anaplasia and formation of gland structures. According to this system prostate carcinoma could exert three histological grades: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated) (8).

Meanwhile, Gleason's system (GGS) is nowadays one of the most used grade systems in PC (9). The base of GGS is represented by five histological figures, which, using small microscopic magnification, encompass analysis of gland architectonics, the degree of glandular differentiation as well as stromal invasion, but not the degree of nuclear anaplasia (10,11). The aim of the work is to determine the relation between serum PSA and differentiation of prostate carcinoma using Gleason's system and classical determination of histological grade from 1 to 3, as well as to estimate comparability of these two systems.

MATERIALS AND METHODS

The investigation included 40 individuals in age from 60 to 79 years (average age, 69.9 years), who had the clinical symptoms of prostatism at digitorectal examination (DRE), established enlargement of prostate suspected to malignant process or benign prostate enlargement accompanied with PSA values above 4ng/ml. The investigation was carried out at Urology Section and Section for Pathology at the Military Hospital in Niš, at the Clinic for Urology and Institute for Pathology of Clinical Center Niš, and in the radioisotopic laboratory "Pharmacia Diagnostica" in Niö in the period from January 2002 to January 2003. Beside the basic disease the examined individuals didn't have any other health disorder which could significantly influence the function of urinary tract. All patients have been taken a standard urological examination according to modified protocol in keeping with diagnostic protocol for prostate carcinoma (12) (Table 1).

Table 1. Modified diagnostic protocol for prostate carcinoma

PSA (ng/ml)	DRE	Diagnostic protocol
≤ 4 ng/ml	Negative	Following by PSA and DRE
> 4 ng/ml	Negative	Ultrasonography and biopsy of suspected lesions
>10 ng/ml or any other values	Positive	Biopsy of palpable and ultrasonographycally suspected lesions

DRE – digitorectal examination

Using this protocol the standard diagnostic methods have been applied: DRE, transabdominal ultrasonography of prostate, determination of serum PSA, biopsy of prostate.

Indications for biopsy

The biopsy was performed with "Tru-cut" needle using transrectal or transperineal approach with previous preparing of patient (purgation and antibiotic protection). Also, the material obtained by transurethral resection (TUR) of prostate, used in diagnostic and therapeutic purposes, was analyzed. The indications for biopsy were: changes of prostate clinically assigned as adenoma with a presence of areas suspected to malignant process, suspected malignant changes on DRE, clinically clear malignant changes, chronic indurative inflammation changes refractory to antibiotic therapy, intermediary or high serum PSA values.

PSA determination

In all investigated individuals the level of PSA was determined in identical way. PSA was estimated in venous blood using two position and fluoroimmunometric method based on direct "sandwich" technique. There was no immediate manipulation on prostate (DRE, prostate massage, endoscopic examination) before taking a blood sample for PSA.

DELFIA PSA equipment manufactured and distributed by WALLAC was used for PSA determination. The range of PSA determination using this equipment is 0.1-500ng/ml.

Histological verification

Micromorphometric analysis of obtained material was done on standard HE preparations. Fixation of tissue samples has been done in 10% formaldehyde solution for 24 hours. The tissue was prepared routinely, put in paraffin, cut on microtom to the thickness of 4 microns, and then the sections were colored by hemotoxyllin-eosin (HE) method. Determination of differentiation of tumor was performed using classical determination of histological grade from 1 to 3, as well as histological grade according to Gleason.

The grade determination according to Gleason means establishment of primary (dominant) and secondary (the second frequent) histological feature, as well as estimation of Gleason's score. The values of Gleason's score range from 1-5 and the total score is obtained as the sum of the values of primary and secondary Gleason's grades. The lowest value of Gleason's score is 2, and the highest is 10. The patients were divided into three groups according to the value of Gleason's score: group I (Gleason's score 2-4), group II (Gleason's score 5-7), and group III (Gleason's score 8-10).

The analysis of planned parameters was done inside the groups and according to Gleason's grades. The following statistical tests were performed: Student t test for two big and two small independent samples, Kruskal-Wallis, χ^2-test , Pearson's coefficient of linear correlation (r_{xy}).

RESULTS

PSA values in individuals with prostate carcinoma ranged from 2.20 to 210.00 ng/ml. In one examined person PSA concentration was at the level of referent values, while in 11/40 (27.5%) it was in the range of intermediary values 4.01 - 10.00 ng/ml. On the other side, 28/40 (70%) of examined persons had high values of PSA (above 10.00 ng/ml) (Table 2).

Table 2. Distribution of examined persons according to obtained PSA values (ng/ml)

PSA(ng/ml)	Carcinoma of prostate Number		%
0.01- 4.00	1		2.50
4.01-10.00	11		27.50
10.01-20.00	7		17.50
> 20.00	21		52.50
Total	40		100.00
X ± SD	min-max	Me	Interquartile difference
34.09 ± 37.94	2.20 - 210.00	22.0	8.85 - 46.825

The highest number of patients with prostate carcinoma, 21/40 (52.5%) had intermediary Gleason's score (5-7). In this group serum PSA values ranged from 5.00 - 60.00 ng/ml with Me - 22.0 ng/ml. One third of tested persons - 12/40 (30.0%) had a high Gleason's score (8-10). These persons had PSA value in the range 5.00 - 210.00 ng/ml with Me - 41.50 ng/ml. The smallest number of persons had a low Gleason's score (<5), i.e. 7/40 or 17.5%. PSA concentration was the lowest in this group with Me - 7.50 ng/ml (Table 3).

Table 3. Gleason's score and PSA level in serum of examined persons with

Gleason's score	PSA (ng/ml) Number (%)	X ± SD	min - max	Me	Interquartile difference	p
2 - 4	7 (17.5%)	10.47 ± 6.99	2.20 - 22.00	7.50	6.70 - 18.00	
5 - 7	21 (52.5%)	28.05 ± 17.25	5.30 - 63.00	22.00	13.25 - 39.45	p = 0.0188
8 - 10	12 (30.0%)	58.45 ± 58.80	5.00 - 210.00	41.50	11.13 - 90.05	p < 0.05
Total	40 (100.0%)	34.09 ± 37.94	2.20 - 210.00	22.00	8.85 - 46.825	

PSA values in serum of patients with prostate carcinoma were statistically significantly different between the three groups of examined persons, where the leading criteria was the value of Gleason's score (low, intermediary, high).

Kruskal-Wallis test was used and its value was χ^2=7.9522, and the statistical significance was p<0.05. Looking at data in Table 3 it could be noticed that the average values (arithmetic mean and median) of serum PSA in patients with prostate carcinoma are higher in groups with higher Gleason's score. To investigate possible relations between Gleason's score and PSA concentration, we calculated the coefficient of linear correlation and constructed the regression line (Figure 1).

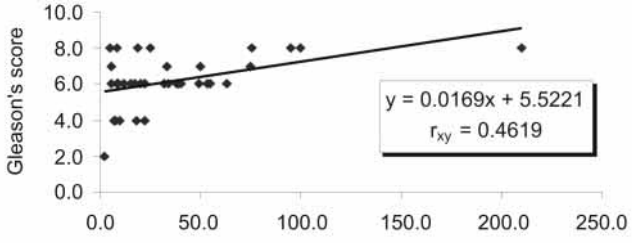

Figure 1. Regression line and a coefficient of linear correlation between PSA (ng/ml) and Gleason's score

It is documented that there is statistically highly significant positive correlation between PSA and Gleason's score in prostate carcinoma (r_{xy}=0.4619; p=0.003; p<0.01) (Figure 1). Determination coefficient (r_{xy2}=0.213) points out the fact that Gleason's score is one of the factors that influence serum PSA concentration in patients and that its part is 21.3%. Beside Gleason's score, the classical determination of tumor histological grade (1-3) was used for the estimation of tumor cell differentiation. The most patients had tumor grade 2 and 3 (35/40 or 87.5%). Only 5 persons with prostate carcinoma had grade 1. In the group of patients with well-differentiated adenocarcinoma of prostate (G1) the values of PSA were the lowest. PSA concentration in serum of patients with prostate carcinoma with differentiation grade- grade 1, ranges from 2.20-22.0 ng/ml with Me=7.50 ng/ml. In the group of patients with tumor grade - 2, the value of Me for PSA was higher (Me=22.0 ng/ml), as well as the variation interval (min-max) and interquartile difference (9.60-42.27 ng/ml). The individuals, whose tumor cell differentiation grade was estimated as 3, had the highest values of serum PSA (Me=33.00) (Table 4).

Table 4. Tumor grade and the level of serum PSA in patients with carcinoma

Grade	PSA (ng/ml) Number (%)	Xm ± SD	min - max	Me	Interquartile difference	p
1	5 (12.5%)	11.28 ± 8.33	2.20 - 22.00	7.50	4.45 - 20.00	
2	26 (65.0%)	28.33 ± 19.91	5.30 - 75.00	22.00	9.60 - 42.27	p = 0.0572
3	9 (22.5%)	63.41 ± 65.92	5.00 - 210.00	33.00	13.75 - 97.50	p > 0.05
Total	40 (100.0%)	34.09 ± 37.94	2.20 - 210.00	22.00	8.85 - 46.825	

Using Kruskal-Wallis χ^2 test it was established that the differences in PSA values between these three groups are at the border of statistical significance (χ^2=5.7234; p=0.0572; p<0.05). Table 4 clearly shows that the increase of PSA in serum of patients with prostate carcinoma is followed by less differentiation of tumor. To establish whether this relation is accidental or not, we had used regression and correlation analysis. It was proved that there was statistically significant positive correlation between prostate carcinoma cell differentiation grade expressed through grade and the concentration of PSA in serum of examined persons (r_{xy} = 0.4325; p = 0.005; p < 0.001) (Figure 2).

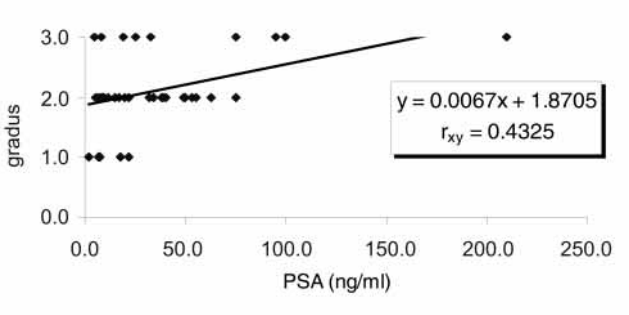

Figure 2. Regression line and linear correlation coefficient of PSA level and prostate carcinoma histological grade

Determination coefficient is low (r_{xy2} = 0.187) pointing out the fact that PSA level in men with prostate carcinoma is determined in 18.7% by tumor cell differentiation histological grade (histological grade), while 81.3% represent other factors (age, etc.).

DISCUSSION

PSA is tumor marker, which serum levels are under the influence of physiological and pathological processes, meaning that PSA is not highly specific for prostate carcinoma. Clinically applicable referent values for this marker are from 0 - 4.0 ng/ml, but they don't point out the absence of carcinoma always. Intermediary PSA values, i.e., value interval from 4.0 - 10.0 ng/ml, could be present in patients with benign hyperplasia of prostate, prostatitis, intraepithelial neoplasia as well as prostate carcinoma (3,13).

The results of our investigation show that PSA values in patients with prostate carcinoma ranged widely, i.e. in the interval of referent, intermediary and high values. Approximately one third of examined persons had serum PSA levels in the interval of intermediary values, where it was necessary to distinguish whether it was prostate carcinoma or benign disease, which was only possible to determine by biopsy of prostate. This is one of examples of limited use of PSA test.

Our choice of standard clinically changeable PSA intervals with cut-off value of 4 ng/ml and not age-specific referent values had been based on studies of authors who proved that PSA didn't correlate with age. There are also numerous studies in which the usage of different levels of age-specific referent values has been reported (14-16). In the last years, the attention was paid on lowered cut-off value for PSA, i.e. 2.5 ng/ml, where inside the value interval of 2.6-4.0 ng/ml (20% to 25%) of biopsied patients had prostate carcinoma (17,18). Our results show that serum PSA level is in positive correlation with Gleason's score, as well as that two thirds of our patients have intermediary Gleason's score which is in accordance with other authors' studies (19-21).

Literature data point out that the highest number of patients with prostate carcinoma has intermediary value of Gleason's score (5-7) (22). For example, in a big study of Roehel et al., related to 241 patients with prostate carcinoma confirmed by biopsy, more than half of patients had clinically localized carcinoma and moderate differentiation with predominant intermediary Gleason's grade 6 in the interval of PSA values from 2.5-4.0 ng/ml (23).

Determination coefficient r_{xy2}=0.213 points out the fact that Gleason's score is one of the factors determining serum PSA concentration of our patients with prostate carcinoma and its part is 21.3%. Meanwhile, certain studies report the fact that serum PSA is not in high correlation with Gleason's score, which could be explained by the fact that less differentiated tumors sometimes produce less PSA. This could be explained by the loss of phenotype expression of PSA, which follows dedifferentiation of tumor cells (7,17,18,24).

The results of study of correlation between PSA and tumor histological differentiation noted as 1-3, point out also positive but not highly significant correlation, which is in correlation with other authors' investigations (16). Determination coefficient is low r_{xy2} = 0.187 pointing out the fact that PSA is determined with 18.7%, while the rest represents the influence of other factors.

It could be concluded that Gleason's system of tumor differentiation determination is more superior system of differentiation determination in relation to other systems. Vis and Epstein suggest that application of PSA cut-off value lower than 4 ng/ml contributes to finding of higher number of tumors limited to prostate, i.e. clinically unmanifested tumors, which frequently have Gleason's score value less than 7 and volume smaller than 0.5cc (25,26).

CONCLUSION

This study showed that there was high positive correlation between serum PSA value and carcinoma differentiation grade determined by Gleason's system, as well as low correlation between PSA and tumor differentiation grade determined by classical determination of histological grade from 1 -3. Dominant histopathological finding during revealing of prostate carcinoma is the presence of carcinoma of high Gleason's grade and score.

REFERENCES

1. Radić S. Prostate cancer molecular staging. State of - the - Art in prostate and breast cancer treatment. European school of oncology. Advanced course. September, 2002; Education boo. 2000. p. 101-4.
2. Tchetgen MB, Oesterling JE. The role of prostate specific antigen in the evaluation of benign prostatic hyperplasia. Urol Clin North Am 1995;22(2):333-44.
3. Živković S. Comparation of prostate specific antigen and density of prostate specific antigen in patients with benign hyperplasia of prostate and prostate carcinoma, dissertation. Niš: Medical Faculty; 1998. p. 109-10.
4. Veličković Lj, Katić V, Tasić D, Kutlešić Č, Dimov D, Đorđević B et al. Prostate specific antigen (PSA) in neoplastic and hyperplastic prostate tissue. Arch Oncol 2001;9(1):100-1.
5. Stamey TA, Yang N, Hay AR, McNeal JE, Frina FS, and Redwine E. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987;317:909-16.
6. Walsh PC. Why make an early diagnosis of prostate cancer. J Urol 1990;147:853-4.
7. Gleave ME, Hseih J, Wu H, Echenbach AC von, Chung LWK. Serum prostate specific antigen levels in mice bearing human prostate LNCaP. Tumors are determinated by tumor volume and endocrine and growth factors. Cancer Res1992;52:1598-605.
8. Petersen R. Prostate and Seminal Vesicles. In: Petersen R, editor. Urologic Pathology. Philadelphia: Lippincott Company; 1992. p. 586-648.
9. Gleason DF. Histologic grading of prostate cancer: a perspective. Hum Path 1992;23:273-9.
10. Poel HG, Schalken JA, Debruyne FMJ. Image analisys and grading of prostate adenocarcinoma. W J Urol 1991;9:86-94.
11. Epstein JA. Grading of prostatic adenocarcinoma. In: Epstein JA, editor. Prostate biopsy interpretation. Biopsy Interpretation series. New York: Raven Press; 1989. p. 129-51.
12. Oesterling JE, Jacobson SJ, Chute CG, Gues HA, Girman GJ, Panser LA et al. Serum prostate-specific antigen in a community-based population of healthy man: Establishment of age-specific reference ranges. JAMA 1993;270:860-4.
13. Oesterling EJ, Jacobsen JS, Klee GG, Pettersson K, Piironen T, Abrahamsson PA et al. Free complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. J Urol 1995;154:1090-5.
14. Thon FW, Gadban MC, Truss M, Kuszyk M, Hartmenn U, Tomas U. Prostate specific antigen density a reliable parameter for the detection of prostate cancer. World J Urol 1996;14(1):53-8.
15. Kuriyama M, Uno H, Watanabe H, Yamanaka H, Saito J, Shida K. Determination of reference values for total PSA F/T and PSAD according to prostatic volume in Japanese prostate cancer patients with slighty elevated seru PSA levels. Jpn J Clin Oncol 1999;29(12):617-22.
16. Karazanashvili G, Abrahamsson AP. Prostate specific antigen and human grandular kallikrein in early detection of prostate cancer. J Urol 2003;169:445-57.
17. Schroder FH, Van-Der-Crvijsen, Koeter I, De Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate-specific antigen. J Urol 2000;163(3):806-12.
18. Horninger W, Reissigl A, Rogatsch H, Volgger H, Studen M, Klocker H. Prostate cancer screening; in the Tyrol Austria; experience and results. Eur J Cancer 2000;36(10);1322-35.
19. Catalona WJ, Stein AJ, Fair. Grading errors in prostatic needle biopsies: relation to the accuracy of tumor grade in predieting pelvic lymph node metastases. J Urol 1982;127;919-22.
20. Bostwick DG. Gleason grading of prostatic needle biopsies: correlation with grade in 316 matched proseatectomies. Am J Surg Pathol 1994;18:796-803.
21. Veličković Lj. Micromorphological, hystochemical and immunohystochemical characteristics of prostate carcinoma and in surrandins premalignant lesions, dissertation. Niš: Medical Faculty; 2000 p. 110-2.
22. Low W, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Radical prostate cancer: Inflence of conlomita nt pathological variabiles. J Urol 2002;167:117-22.
23. Roehl AK, Antenor AJ, Catalona JW. Robustness of free prostate specific antigen measurements to reduce unnecessary biopsies in the 2,6 to 4,0 ng/ml range. J Urol 2002;168:922-5.
24. Basso D, Fogar P, Piva MG, Novaglica F, Mazza S, Brayer-Galen T et al. Total PSA, free PSA/total PSA ratio and molecular PSA detection in prostate cancer; which is clinically effective and when? Urology 2000;55(5):710-5.

25. Vis AN, Hoedemaeker RF, Roobol M, van der Kwast TH, Shroder FH. Tumor characteristics in screening for prostate cancer with and without rectal examination as an initial creening test at low PSA (0,0-3,9 ng/ml). Prostate 2001;47(4):252-61.

26. Epstein JI, Chan DW, Sokoll IJ, Walsh PC, Cox JL, Rittenhaus H et al. Non palpabile stage. T1c prostate cancer, prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. J Urol 1998;160(6Pt2):2407-11.

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Predictive ECG coding using linear time-invariant models

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ABSTRACT

Electrocardiogram (ECG) signal compression suffers of lack of standards for analogue-digital conversion. Results of this study have shown that 8 bits/sample, although frequently in use, does not satisfy quality criteria for medical doctors. This paper also presents predictive technique for lossless ECG compression using linear time-invariant models. Tests on clinically measured ECG signals confirm a very good performance in terms of compression ratio.

KEY WORDS: *Electrocardiography; Signal Processing, Computer Assisted; Analog-Digital Conversion; Linear Models*

INTRODUCTION

A typical ECG signal requires less storage capacity than for medical images. However, ECG monitor devices are used frequently, even on a regular medical exams, while the medical images are recorded only when is necessary. Nowadays, electrocardiograph represents a necessary diagnostic device. Consequently, large amounts of data have to be stored. A need for efficient coding of ECG signals is continually increasing with modern use of long-term monitoring and telemedicine. Modern medical telemetry systems with low bit-rate channels require signal compression for efficient functioning.

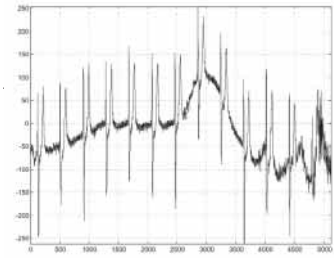

Figure 1. ECG signal

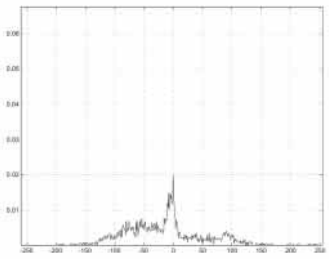

Figure 2. Probability distribution of ECG signal

For example, high-resolution electrocardiogram monitoring device, records 12-chanells ECG with 11-bit resolution and sampling rate of 1000 samples per second, and therefore it generates over 56 MB per hour (about 1360 MB per day), or charges the network with constant flow of 132 kb/s. Thus, the ECG signal compression is not only desirable and useful, but also necessary.

Signal compression methods fall into two common categories: lossy and lossless. Lossless ECG compression is essential for storage and transmission of electrocardiographs. The purpose of ECG compression should not be only to transmit or store the signal with fewer bits, but also to preserve the clinically significant information. According to the law regulations in many countries, medical signals after lossy compression cannot be used in diagnostics.

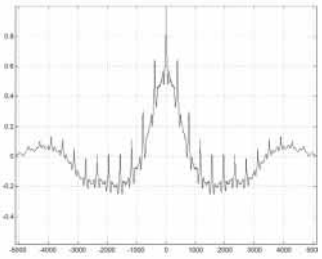

Figure 3. Covariance of ECG signal

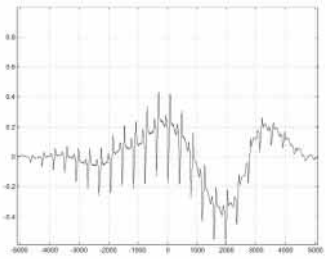

Figure 4. Cross-covariance of ECG signals

Predictive methods are a subclass of the lossless techniques. These methods exploit redundancy between samples, beats and leads of ECG signal, so that only new information has to be coded. Correlation of ECG samples is significant, and it is illustrated in Figures 3. and 4. In this paper, predictive techniques for lossless ECG compression are introduced. In combination with entropy coding, they achieve very good results.

The Massachusetts Institute of Technology and Beth Israel Hospital (MIT-BIH) ECG Compression Test Database and the MIT-BIH Arrhythmia Database were used for testing the different compression methods. The MIT-BIH ECG Compression Test Database contains 168 short ECG two-lead recordings (20.48 seconds each). The recordings were digitized at 250 samples per second per lead with 12-bit resolution over a 10 mV range. The MIT-BIH Arrhythmia Database contains 48 half-hour excerpts of two-lead ambulatory ECG recordings. The recordings were digitized at 360 samples per second per lead with 11-bit resolution over a 10 mV range.

The amount of compression is often expressed with the compression ratio (CR)

$$CR = \frac{b_{orig.}}{b_{comp.}}$$

that is defined as the ratio between the bit rate of the original ECG signal and the bit rate of the compressed one. In this way, compression ratio shows how much the ECG data is being compressed compared to the original.