

Use of early PSA velocity to predict eventual abnormal PSA values in men at risk for prostate cancer[†]

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The purpose of this study was to determine if early PSA velocity (EPSAV), drawn from PSA values within normal ranges, predicts the later occurrence of abnormally high PSA values or positive prostate biopsy early enough to be clinically beneficial.

Early PSAV (ng/ml/y) calculated from two normal PSA readings was tested to predict later PSA exceeding 4 ng/ml (1551 evaluable patients) or 10 ng/ml (1905 evaluable patients) and positive prostate biopsy. The time from EPSAV to develop abnormal PSA was recorded.

A post-EPSAV PSA > 4 ng/ml was reached by 367 patients and >10 by 293. EPSAV was significantly different ($P < 0.001$) between patients whose PSA did or did not reach the PSA cut-off point and also significantly predicted a positive biopsy result ($P < 0.001$). EPSAV predicted abnormal PSA more than 1 y in advance in 68 and 52% of the PSA 4 and 10 ng/ml cut-off point groups, respectively.

Early PSAV from normal PSA readings may allow early detection of men at risk for prostate cancer. This may help identify men for earlier prostate biopsy or for less frequent PSA monitoring.

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Introduction

Although serum PSA level is the most valuable marker for the detection of prostate cancer, its usefulness is limited by a low specificity. Other urologic conditions, specifically prostatitis and benign prostatic hyperplasia, may also result in elevation of serum PSA levels.¹ Thus, most men undergoing prostate biopsy for PSA values in the 4–10 ng/ml range are not found to have prostate cancer.^{1–4} The rate of change in PSA levels over time, or

PSA velocity (PSAV), has been one method investigated to improve the specificity of the standard PSA assay.^{5–7} The specificity of PSAV as a marker for prostate cancer is high because most men without prostate cancer have low PSA velocities. In the original study of PSA velocity using the Baltimore Longitudinal Aging Database, Carter *et al* showed that a PSA velocity of 0.75 ng/ml or greater was present in 72% of men with prostate cancer while it was seen in only 5% of men without prostate cancer.⁵ Significant differences in PSA velocity between men with and without prostate cancer could be detected up to 5 y before the diagnosis of prostate cancer.

Despite the obvious utility of PSAV in improving the specificity of PSA testing, it is not commonly used as an initial screening test for prostate cancer for several reasons. First, it requires that repeat PSA measurements be obtained over time. In men with an initially normal PSA value, repeated tests are required. In addition, because there is significant short-term variability between repeat PSA determinations in a given individual, to be useful in

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prostate cancer detection, it is generally recommended that PSAV be determined using PSA values obtained over 1.5–2 y.^{6–10} Three PSA values obtained over this time interval have been reported to be optimal for calculation of PSAV since several values may 'dampen' the variability between PSA measurements.⁸ The utility of PSAV has generally been investigated in men with PSA values that have reached the 4–10 ng/ml range. Thus, PSAV is most commonly used to increase or decrease the level of suspicion in patients with already abnormal PSA elevations or as a guide in determining the need for repeat biopsy in men with a previously negative prostate biopsy.

On initial screening, many men have PSA levels within the 'normal' range. It is often difficult to predict which of these men with initially normal PSA levels will go on to develop abnormally high PSA values over time. Studies of large screening populations have shown that men with initially low PSA values are unlikely to attain an abnormal PSA level within the next year, suggesting that PSA testing could be less frequent in this subset of men.⁴ However, some of these men will have a higher PSA value the following year. Although an elevated PSAV over a short period of time in men with two normal PSA values might increase the level of suspicion, it might not prompt prostate biopsy at that time. Are these men destined to continue an upward PSA trend, or will they continue to have 'normal' values indefinitely? We wondered if PSAV could be used in men with only two PSA determinations separated by less than the recommended 1.5–2 y while these PSA values were still in the normal range. If so, it may be able to identify men with prostate cancer at an earlier stage of disease and allow institution of potentially more effective therapy.

The objective of this study was to determine if the pattern of change in normal early PSA values, specifically the slope between two consecutive PSA values within normal range (ie below the cut-off point), could predict the later occurrence of abnormally high PSA values far enough in advance to be clinically beneficial. We termed this calculation 'early PSAV' (EPSAV) to differentiate it from the traditionally used method of calculating PSAV. We first explored an abnormal PSA value cut-off point of 4 ng/ml, realizing that even lower thresholds might be considered abnormal in younger men. Since some men with localized prostate cancer and PSA levels between 4 and 10 ng/ml are managed with watchful waiting, we also determined the utility of EPSAV determination in predicting those men who will progress to a PSA greater than 10 ng/ml, since this PSA level might prompt initiation of therapy in some of these cases. Thus, our intention was to determine if PSAV calculated from two PSA values while PSA levels were 'normal' could predict development of abnormally high PSA values that might prompt prostate biopsy (4 ng/ml) or therapeutic intervention in patients being managed by watchful waiting (10 ng/ml).

Methods

The laboratory records of all male patients at the Naval Medical Center, San Diego (CA, USA) were scanned to find those with at least five PSA readings; 2538 such records were found. Since these PSA values were determined by a

retrospective laboratory query, this population of men did not represent an annual prostate cancer screening population and the interval between PSA measurements varied. PSA was measured using the Abbott microparticulate enzyme immunoassay technique (Abbott Laboratories, Chicago, IL, USA). Patients whose first two PSA readings exceeded the PSA cut-off point of interest were deleted because the goal was to predict patients starting below the cut-off point who later rose above it. Patients who began with higher PSA readings and dropped to nearly zero (below PSA = 0.25 ng/ml) were deleted since they were judged to have received therapy and were therefore ineligible for prediction of eventual PSA elevation. A total of 1551 patients were retained for evaluation of the predictability of EPSAV in reaching a PSA cut-off point of 4 ng/ml, and 1905 were available for assessment of the 10 ng/ml cut-off point. The age of these patients ranged from 39 to 99 y, with a mean age of 68 y.

Early PSA velocity (EPSAV) was calculated as change from the first PSA reading to the second, standardized as PSA change per year. A later rise of PSA to abnormal levels, specifically a PSA reading exceeding the PSA cut-off point on at least one of the third, fourth or fifth PSA readings, was determined to be suspicious for prostate cancer. For patients reaching the PSA threshold of interest, the time from the EPSAV calculation (ie the second PSA reading) to the appearance of a PSA above the cut-off point was recorded as the early warning of abnormal PSA that would have been given by calculating the PSAV on the first two readings. The nature of these calculations may be more easily understood by examining the diagram for a sample patient shown in Figure 1.

If EPSAV can predict eventual development of abnormal PSA values, what value of EPSAV is the best trigger value? (The term 'trigger point' will be used for the EPSAV cutting value to differentiate it from the PSA cutting value already termed 'cut-off point'.) Sensitivity, specificity, accuracy, and contingency test *P*-values were calculated for various possible trigger points.

Of patients reaching the PSA = 4 ng/ml threshold, 251 of 367 (68%) underwent biopsy, as did 200 of 293 (68%) reaching the PSA = 10 ng/ml threshold (451 overall). Prostate biopsy results for the 251 patients when the cut-off point of PSA = 4 ng/ml was used (158 negative,

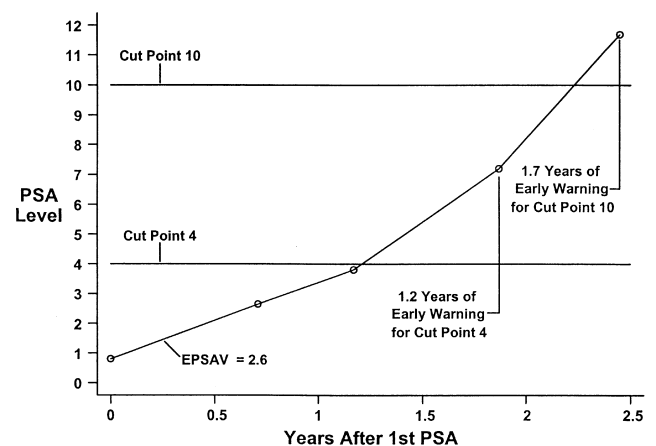


Figure 1 PSA record of a 79-y-old patient to illustrate values used in calculation.

Table 1 Numbers of patients and EPSAV median for patients who did not reach the cut-off point and those who exceeded it for the two cut-off point groups, along with mean and standard deviation of time over which EPSAV was calculated. The cut-off point = 4 and 10 ng/ml groups contained 1551 and 1905 patients, respectively

	PSA cut-off point = 4 ng/ml group		PSA cut-off point = 10 ng/ml group	
	Did not reach	Exceeded	Did not reach	Exceeded
Number of patients	1184	367	1612	293
EPSAV median	0.02	0.13	0.03	0.10
Mean years from first to second PSA readings	0.93	0.93	0.92	0.80
Standard deviation	0.56	0.64	0.59	0.73

93 positive) and 451 for the cut-off point of PSA = 10 ng/ml (236 negative, 215 positive) were available. To assess whether or not the eventual PSA rise truly related to the presence of prostate cancer, EPSAV was examined as a predictor of biopsy result and the association between the eventual PSA rise and biopsy result was assessed.

The consistency of EPSAV after the initial determination was also examined. Is EPSAV, ie the slope from PSA reading 1 to PSA reading 2, a stable phenomenon or will subsequent slopes vary greatly? If they vary, an initial PSAV would be of little use as a predictor of a later rise in PSA. Subsequent PSA readings were utilized as two-value PSAV estimates (ie slope per year) by calculating the change in PSA from reading 1 to reading 3, 4, . . . , 10, divided by the corresponding time period (in years). The number of patients with more than 10 PSA readings was too small to carry the analysis further. The distribution of these slopes was tallied, and the percentage of slopes falling within ± 0.2 PSA levels per year was calculated. If the subsequent slopes are negligibly different from the initial slope, it may be concluded that EPSAV is consistent.

To determine whether or not age was a factor in predicting EPSAV, the association of age with eventual PSA rise and with biopsy results was also tested.

Results

The numbers of patients and EPSAV medians for the groups of patients whose PSA either did or did not reach the cut points of interest (PSA 4 or 10 ng/ml) is shown in Table 1. Rank-sum tests of EPSAV between these patient groups yielded $P < 0.001$ for both cut-off points. (Rank-based tests were used due to the non-normality of the data distributions.) Also shown in Table 1 are the means and standard deviations of times (in years) between PSA readings 1 and 2, ie the length of time over which the EPSAV values were calculated.

Table 2 addresses the amount of early warning of abnormal PSA that would have been available by calculating EPSAV from the patient's first two PSA readings. For the PSA = 4 cut-off point, early warning averaged 20 months, with about seven out of eight cases yielding at least 6 months and two out of three yielding a year of warning. For the PSA = 10 cut-off point, early warning averaged 17 months, with about three out of four cases yielding at least 6 months and half yielding a year of warning. Figure 2 shows the distribution of warning times for an eventual rise above a PSA of 4 ng/ml and Figure 3, warning times for an eventual rise above 10 ng/ml.

Table 2 Range and mean of number of years of early warning of abnormal PSA rise that would have been available by calculating EPSAV, along with the percentage of patients on whom early warning of at least 6 months and 1 y would have been available

Early warning	Cut-off point 4	Cut-off point 10
Range (y)	0–4.76	0–4.88
Mean (y)	1.66	1.42
At least 6 months (%)	86.6%	72.6%
At least 1 y (%)	68.1%	51.8%

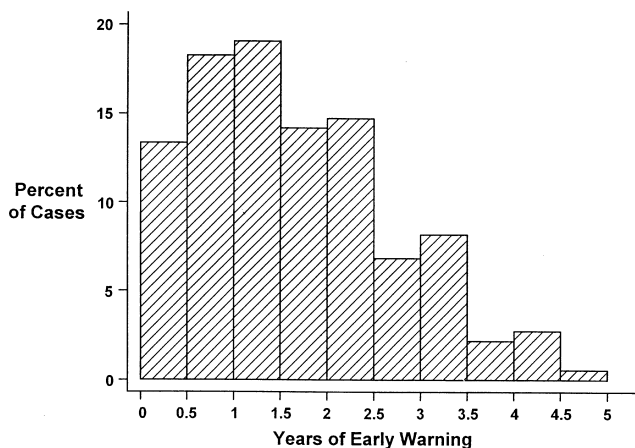


Figure 2 Distribution of early warning times of an eventual rise above PSA = 4.

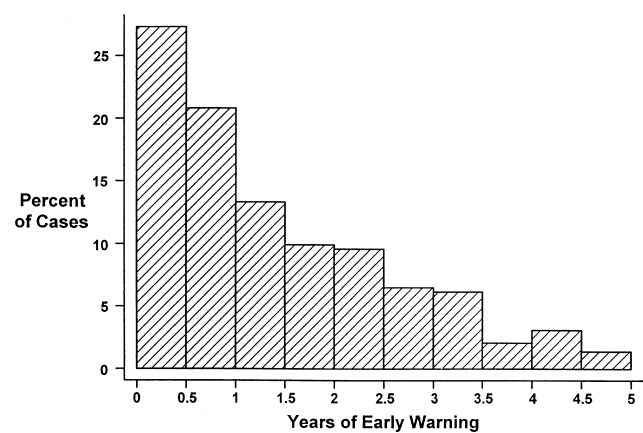


Figure 3 Distribution of early warning times of an eventual rise above PSA = 10.

The value of EPSAV that triggers the assignment of the patient to a high-risk group was compared with resulting abnormal rises or not. Since the median EPSAV values were 0.10–0.13 for abnormal rises, smaller trigger points for EPSAV than the common PSAV triggers of 0.75–1.00 were examined. Table 3 shows a comparison of sensitivity, specificity and accuracy for various PSAV trigger points, *viz.* 0.05–1.00 in various increments. The sensitivity decreases and specificity increases as the trigger point grows larger. At about EPSAV = 0.06, sensitivity and specificity are about equal, and as EPSAV approaches 1.00, the specificity grows quite high and sensitivity low. For both cut-off points, the accuracy (proportion correct, whether true positive or true negative) increases from ~50 to ~70% as the trigger point increases and chi-square tests of contingency are all highly significant. A receiver operating characteristic (ROC) curve shows that sensitivity and specificity are jointly maximized (greatest distance of ROC curve from the line of random prediction) for a trigger point of 0.75.

As noted above, early PSAV can predict a later PSA rise to abnormal levels. To show that early PSAV can predict the presence of prostate cancer, it is necessary to show that the later rise in PSA is associated with the eventual diagnosis of prostate cancer. Prostate biopsy results were available in the records of 251 of the 4 ng/ml cut-off point patients and 457 of the 10 ng/ml cut-off point patients. Biopsy result was lodged in a 2 × 2 contingency table against those groups who did or did not reach these cut-off points, and this contingency was tested by chi-square. Table 4 shows the highly significant *P*-values, along with moderate sensitivity, specificity and accuracy. A ROC curve of biopsy outcome as predicted by EPSAV is maximized at a trigger point of 0.75 ng/ml.

The results of investigating PSAV consistency are given in Table 5. Of all subsequent PSAVs 95–98% fell within the ±0.2 limits, suggesting that our EPSAV calculation was consistent over time.

Another question was whether or not age was a factor in the prediction of later PSA rise by EPSAV. The correlation coefficient of EPSAV with age was 0.004. Thus, age did not interfere with the ability of EPSAV to predict later PSA rises.

All the statistical methods used in this paper may be found in Riffenburgh,¹¹ and most may be found in any thorough statistical methods book.

Table 4 Chi-square *P*-values of a contingency test of association between evidence of disease as defined by EPSAV values and prostate biopsy results, along with sensitivity, specificity and accuracy

	PSA cut-off point = 4	PSA cut-off point = 10
<i>P</i> -value	0.003	<0.001
Sensitivity	0.63	0.45
Specificity	0.56	0.89
Accuracy	0.59	0.68

Table 5 Percentage of patients whose subsequent PSAVs (slopes of change from first PSA level to third, to fourth, ..., to tenth, standardized to change per year) fell within ±0.2 of initial PSAV

Designation of subsequent PSAV	Number of patients in sample	Percentage within ±0.2 of initial PSAV
3	182	98.4
4	182	97.8
5	182	98.4
6	182	98.4
7	116	98.3
8	79	97.5
9	54	96.3
10	43	95.3

Discussion

Our data show that determination of an early PSAV, while men still have normal PSA levels, is helpful in identifying those men who will eventually develop an abnormal PSA level. It also suggests that a high EPSAV value in men with PSA level less than 10 ng/ml might be useful in the early identification of men who will eventually progress to higher PSA levels (>10 ng/ml). Statistical analysis showed that the association between the EPSAV and later PSA rise was highly significant for both PSA cut-off points (PSA of 4 or 10 ng/ml). Using the threshold of PSA = 4 ng/ml, median EPSAV was negligible (0.02 ng/ml/y) for patients not reaching this level, but significantly larger (0.13 ng/ml/y) for those who eventually did. The findings were similar for the PSA = 10 ng/ml threshold.

Table 3 Sensitivity, specificity, accuracy, and *P*-values of χ^2 contingency tests for various EPSAV trigger points, ie EPSAV values above which abnormal rise is predicted

EPSAV trigger	PSA cut-off point = 4				PSA cut-off point = 10			
	Sensitivity	Specificity	Accuracy	<i>P</i>	Sensitivity	Specificity	Accuracy	<i>P</i>
0.05	0.57	0.55	0.56	<0.001	0.55	0.53	0.53	0.018
0.06	0.56	0.56	0.56	<0.001	0.54	0.53	0.53	0.021
0.07	0.55	0.58	0.58	<0.001	0.53	0.55	0.55	0.010
0.08	0.54	0.60	0.58	<0.001	0.53	0.56	0.55	0.007
0.09	0.53	0.61	0.59	<0.001	0.51	0.57	0.56	0.017
0.10	0.53	0.62	0.60	<0.001	0.51	0.58	0.57	0.009
0.25	0.39	0.75	0.66	<0.001	0.41	0.69	0.65	0.001
0.50	0.27	0.85	0.71	<0.001	0.34	0.78	0.72	<0.001
0.75	0.20	0.91	0.74	<0.001	0.30	0.85	0.76	<0.001
1.00	0.15	0.93	0.75	<0.001	0.26	0.88	0.78	<0.001

Thus, early PSAV is an effective discriminator between patients whose later PSA rises, *vs* does not rise, to potentially pathological levels for any reasonable PSA cut-off point.

Most previous investigations suggest that PSAV is accurate only if calculated using at least three PSA measurements obtained over an extended period of time. This recommendation is based primarily on the short-term variability of PSA levels. In men without prostate cancer, Carter *et al* noted significant within-individual PSA variability when sampled at 3 and 6 month intervals.⁸ In men with mean PSA levels of 2.8 ng/ml in that study, repeat PSA measurements varied up or down by 1.3–1.4 ng/ml. In another more recent study, long-term PSA variation was investigated in a large screening population of men without prostate cancer.⁹ The coefficient of variability was significantly higher (18%) if only two *vs* three PSA measurements were done. However, individual variability was not dependent on the interval between PSA measurements. These data suggest that, because of significant within-individual PSA variability, PSAV may be less useful if calculated with fewer PSA values over shorter periods of time.

Since PSA screening is becoming widespread and more accepted, many more men are presenting with a sequence of PSA measurements, usually separated by periods of approximately 1 y. Our EPSAV was calculated based on only two PSA values separated on average by nearly a year. In men with two PSA values in the normal range, can prostate cancer risk be determined from only two PSA readings over this relatively short period of time and, if so, what would be a desirable EPSAV to trigger assignment to a risk category? Our data suggest that a significant rise from one PSA value to the next may be a useful marker of early prostate cancer. The PSAV value, which triggers assignment into risk *vs* non-risk groups, is equivocal because the specificity of this test decreases as the sensitivity increases. At EPSAV = 0.06, sensitivity and specificity are about equal, representing a reasonable trigger point to define increased risk. However, at EPSAV = 0.75, a common trigger point for traditional PSAVs and the best trigger point as defined by a ROC curve for both upward PSA progression and biopsy outcome, the specificity is quite high and sensitivity quite low, representing a value which might be used to identify patients at higher risk.

Although the sample size was much smaller for patients undergoing prostate biopsy, EPSAV was also shown to be significantly associated with a positive biopsy result, with sensitivity, specificity and accuracy of such prediction varying in the middle ranges, 45–89%.

The concern that PSAV may not be a stable enough measure is laid to rest by our data showing that only two or three patients per hundred will have subsequent PSAVs that vary more than negligibly from the EPSAV determination. The predictive value of EPSAV was also unrelated to patient age, suggesting its applicability to all age groups at risk.

Another measure that has found some relation to patients falling or not falling into a risk group is the PSA doubling time, exemplified in a paper by Choo *et al*.¹² For convenience, let us denote PSA doubling time as DbIT. What is the relationship between EPSAV and DbIT? It can be shown by simple analytic geometry (see Appendix) that DbIT is the reciprocal of EPSAV multiplied by

the initial PSA value (P_1), or $\text{DbIT} = P_1/\text{EPSAV}$. Thus, DbIT contains the same information as EPSAV, except weighted by the initial PSA reading, which biases the estimate of allocation to a risk group. The higher is initial PSA, the greater is the frequency of falling into a risk group. This bias would be expected to make DbIT appear to be a better discriminator, but by that very characteristic it fails to accomplish the needed purpose: detecting a pathological change in PSA level while PSA levels are low.

Our data show that most men with low early PSAV fail to progress to abnormal PSA levels. Thus, while identifying men at risk for prostate cancer, early PSAV may be even better in distinguishing those men at low risk in whom less frequent PSA monitoring may be reasonable. For men in this low risk group, other studies have suggested that biannual PSA testing may be adequate. In the study by Smith *et al*,⁴ only 4% of men progressed from a baseline PSA level of less than 2.5 to 4 ng/ml when followed semiannually for 4 y. In contrast, those with PSA levels between 2.6 and 4.0 ng/ml converted to a level above 4 ng/ml in 50% of cases. Using data from the Baltimore Longitudinal Study of Aging, Carter *et al* concluded that curable prostate cancer would be very unlikely to be missed if PSA were measured every other year in men with serum PSA levels of less than 2 ng/ml and a normal digital rectal exam.¹⁰ Our study utilizing EPSAV parallels these findings and suggests that men who do not demonstrate a significant rise in PSA on the initial two measurements may be safely monitored on a less than annual basis.

A useful screening tests should identify men at risk of CaP with a sufficient lead-time to be clinically beneficial. For the patients in our study for whom a pathological rise in PSA was predicted, the average length of time of prediction prior to occurrence was about a year and a half, and was up to 5 y in some cases. About seven out of eight patients would receive more than 6 months of early warning of a PSA rise to over 4, and two out of three, more than a year. Inasmuch as earlier identification of cancer would allow earlier institution of therapy with the potential for a better long-term outcome, this advance marker of potential risk promises to be helpful. A push for earlier identification of men at risk has led some to recommend prostate biopsy at lower PSA thresholds. If prostate biopsy is performed, approximately 20% of men with serum PSA levels in the 2.5–4.0 ng/ml range will be found to have prostate cancer.^{13,14} After radical prostatectomy, these men appear to have a better biochemical (PSA) disease-free outcome than those with preoperative PSAs in the 4.0–10 ng/ml range, despite equally significant disease.¹⁵ Thus, there appears to be an advantage to identifying men at risk for prostate cancer before the PSA reaches 'abnormal' levels. The EPSAV investigated in our study may be an alternative to lower PSA thresholds in selecting patients with 'normal' PSA levels for prostate biopsy.

Conclusion

Many men with prostate cancer in incipient stages will maintain normal PSA readings for a period of time. Our data suggest that early PSAV (EPSAV) calculated from

only two PSA values separated by one year while PSA is within normal levels will provide a significant amount of advance warning of later evidence of disease as manifested by a later rise in PSA to a pathological level and/or a positive biopsy result. Thus, EPSAV can be used to help select patients for earlier prostate biopsy (before PSA reaches abnormal levels) or, alternatively, to identify men who can be safely followed with less frequent PSA monitoring.

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Appendix

We wish to show the relationship between early PSA velocity (EPSAV) and PSA Doubling Time (DbIT). Let us take the equation of a straight line as $y = a + bx$, where x is a position on the horizontal axis representing years, and y is a position on the vertical axis representing PSA values read at the respective x times. Let the first two PSA readings and their respective times be the (x, y) points (t_1, p_1) and (t_2, p_2) . The slope of the line, b , is $\text{EPSAV} = (p_2 - p_1)/(t_2 - t_1)$. Let us denote EPSAV as e to prevent ponderous formulae. Substituting the first point and e leads to the equation for the line through the two points, $y = (p_1 - et_1) + ex$. We can denote the point at which PSA doubling occurs, that is, where y becomes $2p_1$, as $(t_3, 2p_1)$. Substituting this point in the equation and solving for t_3 yields $t_3 = p_1/e + t_1$. The time for PSA to double is $t_3 - t_1$, so that $\text{DbIT} = p_1/e$, the initial PSA reading times the reciprocal of EPSAV.