



Proposal of a Modified Bayesian Model to Improve the Clinical Utility of Treadmill Stress Testing

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Abstract

Bayes' theorem has been an integral part of traditional treadmill stress testing for many years. However, several issues have been raised regarding this approach: imperfect identification of important coronary obstruction, limited usefulness in certain patients, inconsistent results and interpretations, and confusion regarding the outcomes of various studies. This has led to disenchantment with basic stress testing in favor of more expensive methods, and difficulties for the clinician in managing patients. The proposal presented in this paper modifies the traditional Bayes approach so as to provide greater clinical utility for physicians performing treadmill stress tests.

Keywords: Bayes' theorem; Treadmill; Stress testing

Introduction

In the traditional usage of Bayes' theorem, the clinician assigns an individual suspected of having coronary artery disease (CAD) a pretest probability of disease. This probability comes from several studies [1,2] in which patients are characterized by age, sex, and symptoms (asymptomatic, atypical chest pain, typical angina). In addition to these three, today's clinician uses much more data in trying to determine this pretest probability.

These include the resting ECG, the physical exam (presence of carotid, aortic, or peripheral vascular disease), major risk factors (hypertension, hyperlipidemia, smoking, family history), other risk factors (lipoprotein profile [3], homocysteine metabolism [4], iron studies [5], postmenopausal estrogen use [6], fibrinogen and coagulation profiles [7], and perhaps other techniques (computerized tomography coronary calcification and angiography [8], carotid intima-media measurements [9]. Although there are some coronary risk algorithms which incorporate some of these factors [10,11], it can be seen that it is difficult if not impossible for the clinician to integrate all of these and compute an exact number for a patient's pretest probability of CAD.

Studies using Bayes' theorem divide the stress test result into either negative or positive, usually defined as 1 mm or greater ST-segment depression. Many studies have shown that the degree of ST depression and the results of other stress test variables (changes in systolic blood pressure, peak heart rate, time to onset of angina, arrhythmias, repolarization abnormalities, and others) are related to the extent of CAD and prognosis [12-16]. Thus a simple positive/negative classification leaves out important data useful to the clinician.

Additionally, many studies using Bayes' theorem define CAD as the

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Citation: Robert M Peters. Proposal of a Modified Bayesian Model to Improve the Clinical Utility of Treadmill Stress Testing. Archives of Clinical and Biomedical Research. 9 (2025): 67-73.

Received: February 16, 2025

Accepted: February 25, 2025

Published: March 15, 2025

presence of a 50% stenosis in any coronary artery. Besides not considering the extent of CAD, this simple presence/absence classification ignores the importance of lesions less than 50%, often called luminal disease. It is now known from thrombolysis studies that such lesions can become unstable and cause clinical coronary syndromes [17], even though they may not have been evident on the exercise stress test.

Given the above considerations, it is not surprising that studies based on the traditional Bayes' model have produced inconsistent results, imperfect detection of important CAD, difficulty in interpreting individual stress tests, limited usefulness in certain patients, and often abandonment of the routine EST in favor of more expensive procedures [18,19].

In this study, modifications are made in the way Bayes' theorem is used, to incorporate many of the above considerations and hopefully improve the utility of the EST for clinicians.

Methods and Results

Pretest probability profiles t1 through t9 were constructed (Table 1). Within each t profile the probability of five degrees of CAD (C1 normal coronaries, C2 any lesion less than 50% diameter including coronary plaques, mural abnormalities, or abnormalities seen on coronary ultrasound, C3 single vessel disease, C4 double vessel disease, C5 triple vessel or left main disease) were assigned. This was done to enable the clinician to assign a patient a CAD pretest probability profile rather than try to compute an exact number for a pretest probability. Thus the clinician has greater freedom to integrate clinical data and clinical judgement in picking a t profile for an individual patient, rather than simply characterize the patient as low, intermediate, or high probability as traditionally done, or use a complicated algorithm to compute an exact number. The clinician may be helped in assigning a pretest probability by using approaches such as the Framingham Risk Prediction Score [31] which incorporates age, cholesterol profile, blood pressure, diabetes, and smoking, or various equations using multivariable analysis [32] which usually include age, cholesterol measurement, symptoms, and history of diabetes. Unfortunately, these approaches may leave out many of the risk factors noted above, and were not developed as extent of disease predictors.

Rather than classify stress tests as either positive or negative, they were divided into four classifications: normal (no ischemic response), mildly abnormal, intermediate or moderately abnormal, and severely abnormal. Severely abnormal tests were characterized by abnormalities such as very prominent ST changes (ST elevations) or greater than 2 mm downsloping ST-segment depressions, hypotension or failure to increase blood pressure with exercise, early onset angina and short treadmill times, serious arrhythmias such

as ventricular tachycardia, and prolonged repolarization abnormalities in the recovery period [20-22]. Mildly abnormal stress tests were characterized by long treadmill times with good exercise tolerance, absence of angina or brief angina at peak exercise, normal blood pressure response to exercise, short duration of repolarization abnormalities, and mild ST changes (1 mm upsloping or horizontal ST-segment depressions). Intermediate stress tests fall between these two extremes, and may be assigned as such according to the judgement of the clinician.

This type of approach, using several variables in addition to ST depression and dividing abnormal stress tests into three groups according to the degree of abnormality has been used in other studies including the Duke treadmill score [30], the VA clinical-exercise test score [33], and Fuzzy Cluster Analysis [16].

Table 1: Pre-test probability profiles.

	t1	t2	t3	t4	t5	t6	t7	t8	t9
C1	.88	.72	.67	.53	.46	.30	.17	.04	.01
C2	.10	.17	.15	.13	.11	.08	.07	.04	.02
C3	.02	.08	.14	.17	.22	.33	.28	.20	.16
C4	.001	.02	.04	.07	.12	.16	.25	.33	.31
C5	.005	.01	.02	.04	.09	.13	.23	.39	.50

For each t profile, calculations for the change in pretest probability for each C were done using the Bayesian formula for positive predictive value:

$$\frac{\text{Sensitivity X Prevalence}}{(\text{Sensitivity X Prevalence}) + (1 - \text{Specificity}) X (1 - \text{Prevalence})}$$

However, the following modifications were used:

The values for Prevalence (prevalence of pretest likelihood) are the values for C in any given pretest profile t-- the probability of normal coronaries (C1) in pretest profile t1 is .88 [Table 1]. Sensitivity was defined as the probability of a given stress test result (normal, mild, intermediate, severely abnormal) for any given C [Table 2].

Specificity was defined as the probability of not having a particular stress test result in a patient who does not have a given C. Thus the probability of having a normal stress test in a patient with C5 is 0.04 (Sensitivity), while the probability of not having a normal stress test in a patient who does not have C1 is 0.75 (Specificity). These values were derived from general literature review [20,23,24], and studies relating a treadmill score, such as the Hollenberg [34] treadmill score, or three-part stress test classifications such as the Duke [36] treadmill score (low, moderate, high risk), or Fuzzy Cluster

Analysis [16] classifications of mild, moderate, and severely abnormal, to angiographically determined extent of coronary disease.

Table 2: Sensitivities and specificities of normal, mildly, moderately, and severely abnormal stress tests for different degrees of coronary artery disease.

	Normal	Mild	Moderate	Severe
C1	.80 (.75)	.15 (.63)	.04 (.67)	.01 (.70)
C2	.70 (.72)	.22 (.64)	.06 (.70)	.02 (.75)
C3	.27 (.68)	.43 (.76)	.20 (.73)	.05 (.80)
C4	.08 (.67)	.20 (.70)	.37 (.76)	.35 (.85)
C5	.04 (.65)	.17 (.60)	.40 (.80)	.39 (.90)
Sensitivities--no parentheses			Specificities--listed in parentheses	

The results of these calculations are given in Table 3. In any pretest profile t, the probability of each C is changed (either up or down) by the result of the stress test. Because of different values for C, Sensitivity, and Specificity in each calculation, the post-test probabilities in each t do not add up to 1.0--thus the post-stress values are more a reflection of the magnitude of the change of each C value.

Table 3: Pre and post-test probability values for normal, mildly, moderately, and severely abnormal stress tests.

t1	Pre-test	Normal	Mild	Moderate	Severe
C1	0.88	0.96	0.75	0.47	0.2
C2	0.1	0.22	0.06	0.02	0.01
C3	0.02	0.01	0.04	0.02	0.01
C4	0.001	0.002	0.007	0.002	0.002
C5	0.0005	0.0001	0.0002	0.001	0.002
t2					
C1	0.72	0.89	0.51	0.24	0.08
C2	0.17	0.34	0.11	0.04	0.02
C3	0.08	0.07	0.13	0.06	0.02
C4	0.02	0.005	0.013	0.03	0.05
C5	0.01	0.001	0.004	0.02	0.04
t3					
C1	0.67	0.87	0.45	0.2	0.06
C2	0.15	0.31	0.1	0.03	0.01
C3	0.14	0.12	0.23	0.11	0.04
C4	0.04	0.01	0.03	0.06	0.09
C5	0.02	0.002	0.009	0.04	0.07
t4					
C1	0.58	0.81	0.36	0.14	0.04
C2	0.13	0.27	0.08	0.03	0.01
C3	0.17	0.15	0.08	0.13	0.05
C4	0.07	0.02	0.05	0.1	0.15

C5	0.04	0.005	0.02	0.08	0.14
t5					
C1	0.46	0.73	0.26	0.09	0.02
C2	0.11	0.24	0.07	0.02	0.01
C3	0.22	0.19	0.34	0.17	0.07
C4	0.12	0.03	0.08	0.17	0.24
C5	0.09	0.01	0.04	0.17	0.28
t6					
C1	0.3	0.58	0.15	0.05	0.01
C2	0.08	0.18	0.05	0.02	0.007
C3	0.33	0.29	0.47	0.27	0.11
C4	0.16	0.04	0.11	0.23	0.31
C5	0.13	0.02	0.06	0.23	0.37
t7					
C1	0.17	0.4	0.08	0.02	0.007
C2	0.07	0.16	0.04	0.01	0.006
C3	0.28	0.25	0.41	0.22	0.09
C4	0.25	0.07	0.18	0.34	0.44
C5	0.23	0.03	0.11	0.37	0.54
t8					
C1	0.04	0.12	0.02	0.005	0.001
C2	0.04	0.09	0.02	0.008	0.003
C3	0.2	0.17	0.31	0.16	0.06
C4	0.33	0.11	0.25	0.43	0.53
C5	0.39	0.07	0.21	0.56	0.71
t9					
C1	0.01	0.03	0.004	0.001	0.003
C2	0.02	0.05	0.01	0.004	0.002
C3	0.16	0.14	0.25	0.12	0.05
C4	0.31	0.1	0.23	0.41	0.51
C5	0.5	0.1	0.3	0.67	0.8

If the result of the stress is normal, the probability of normal coronaries (C1) is increased in any t profile. This increase is greatest in the t3 through t7 profiles. The chance of luminal disease (C2) is also increased with a normal stress test, especially in the low and intermediate pretest profiles t1 through t6. The possibility of obstructive CAD (either C3, C4, or C5) is decreased across all t profiles. However, the decrease is less for C3, and there is still a small chance of C3 even with a normal stress test in profiles t5 through t9.

The increased chance of luminal disease and the small chance of C3, is consistent with the phenomenon of a patient having a myocardial infarction after a normal stress test. Although the possibilities of C4 and C5 are very low after a normal stress test, there is still a small possibility of these after a normal stress test in the t8 and t9 profiles.

For mildly abnormal stress tests, the possibility of C1 decreases especially from t2 through t6. C2 decreases for all t profiles. C3 increases for all t profiles, especially for t4 through t8. C4 and C5 show decreased probability across all t profiles, however, with a mildly abnormal stress test, there is still a fairly significant possibility of C4 and C5 in profiles t7 through t9.

For intermediate (moderately abnormal stress tests), the possibility of C1 decreases especially from t1 through t6. C2 decreases for all t profiles. The probability of C3 decreases very slightly across all t profiles. The probability of C4 and C5 increase for all t profiles, especially t5 through t9.

For severely abnormal stress tests, the probability of C1 decreases greatly for all t profiles, however, there is still a small possibility of C1 for the t1 profile. C2 is likewise greatly reduced across all t profiles. The possibility of C3 is also reduced especially in t4 through t9. C4 and C5 are significantly increased, especially from T5 through t9.

The following examples contrast this new method with the traditional usage of Bayes' theorem. These examples are for illustrative purposes only, and are not in any way obtained from actual patient charts or patient data.

Example 1. A 40-year-old asymptomatic woman developed 1 mm ST-segment depression during a standard Bruce protocol treadmill stress test. Given the prevalence of CAD of 0.01 in this population, and a sensitivity of 0.70 and a specificity of 0.90 for the stress test, the post-test likelihood of CAD given a "positive" stress test only rises to 0.07. Thus the test has little impact on predicting the presence, absence, or extent of CAD, may well represent a false positive, and is of somewhat limited use to the clinician [25]. Using the new method, the clinician feels the patient most closely fits the t2 pretest profile because she is obese, had been mildly hypertensive for the last 3 years, and has a mildly elevated triglyceride level. During the stress test, the patient exercise for 8 minutes, stopped due to fatigue, had a normal blood pressure response, no arrhythmias, attained 90% of predicted maximum heart rate for age, and had 1 mm upsloping ST-depression which resolved 2 minutes into the recovery period. The clinician classified this test as mildly abnormal. Although the probability of C1 is reduced (from 0.72 to 0.51), there is still a good chance that the patient is normal and that this is a false positive test. The patient may still have only luminal disease (C2) as this possibility is reduced only slightly (0.17 to 0.11). The possibility of C3 increases (from 0.08 to 0.13) but is still relatively low given the low pretest probability. The probabilities of C4 and C5, decrease slightly from their pretest probability, consistent with the fact that the stress test was only mildly abnormal. Thus although this patient has a small chance of having CAD, if present it is probably C2 or C3.

Example 2. A 50-year-old man relates a 2 month history of intermittent, sharp, anterior, chest discomfort lasting 1 to 60 minutes, that once occurred with exertion. Atypical chest pain in a male this age would be associated with a prevalence or pre-test likelihood of CAD of 0.40. Using traditional Bayes', a positive stress test (1 mm ST depression) would raise the post-test probability of CAD to 0.82. It is in this intermediate middle range of pre-test likelihood that traditional Bayes' has its greatest diagnostic impact and the largest change in probability is seen [25]. A positive test may be useful in alerting the clinician that CAD is probably present, but adds no information related to extent of CAD.

Because the patient has a positive family history of several relatives with CAD, and because he has a mildly low HDL cholesterol level on several occasions, the clinician feels that the patient most closely fits a t5 pretest profile. The clinician used the Framingham Risk Score [31] to help assign a pretest probability profile in this patient.

The patient exercised for 2 minutes and 30 seconds, he had slight chest discomfort at peak exercise, he developed 3 mm downsloping ST-segment depressions at peak, with T wave inversions that lasted 15 minutes into recovery, his blood pressure response was flat, he reached 70% of predicted maximum heart rate for age, and he had some occasional PVCs during the recovery period. The clinician classified this stress test as severely abnormal.

Using the new method, the post-test probabilities of C1 and C2 are reduced to very small values, consistent with the severity of the stress test. The probability of C3 decreases, while the probability of C4 doubles (from 0.12 to 0.24), and the probability of C5 triples (from 0.09 to 0.28). These values alert the clinician to the possibility of high-grade CAD, and thus are helpful in further management.

Example 3. A 60-year-old man has a 3 month history of exertional anterior chest pressure relieved by nitroglycerin. For a positive stress test in a male this age with typical angina, traditional Bayes' increases the pre-test likelihood of 0.95 to a post-test likelihood of 0.99. This small change has little diagnostic impact and is therefore not much help to the clinician [25].

The clinician also takes into consideration the fact that the patient has mild diabetes for 6 years on an oral agent, and he has a left carotid bruit on physical examination. The clinician used the equation published by Morise et al. [35] that incorporates gender, age, symptoms, cholesterol measurement, and history of diabetes, as an aid to assigning a t8 profile to this patient. The patient exercises on the treadmill for 6 minutes and 30 seconds, he develops his typical anginal symptom after 5 minutes and 30 seconds, he has 1 mm horizontal ST-segment depressions at peak which

last for 10 minutes into the recovery period, he attains 78% predicted maximum heart rate for age, his blood pressure rises 10 mm Hg with exercise, and one couplet is noted during recovery. The clinician classifies this stress test as moderately abnormal.

Using the new method, the post-test probabilities of C1 and C2 become very, very small. The probability of C3 decreases slightly, while the probability of C4 increases (from 0.33 to 0.43) as does the probability of C5 (from 0.39 to 0.56). Thus the method alerts the clinician to the possibility of high-grade CAD in this patient. If the stress test had been normal (no ST depression, no angina, normal blood pressure response, duration of 10 minutes reaching 90% of predicted maximum heart rate for age), the probability of C1 would triple, while that of C2 would double. However, although the probabilities of C4 and C5 would be greatly reduced, the probability of C3 would be reduced only slightly. Thus despite the normal stress test, there is still a possibility of CAD in this high-risk profile patient, alerting the clinician to a possible false negative stress test [37].

Discussion

Bayes' theorem is most directly applicable clinically when an exact pretest probability can be easily defined, when the subsequent test is clearly either positive or negative with no gradation of abnormality between these two, when the sensitivity and specificity of the test are clearly defined and agreed on, and when the disease in question is either present or absent, rather than a spectrum of disease severity ranging from normal to very severe [2,26]. When these conditions are not met, the theorem is less conceptually appealing, more difficult to use, and may produce varying results, a combination sometimes called the "haze of Bayes" [27].

Coronary artery disease is an example of this latter situation [38,39]. There is no standardized method of combining clinical evaluation with an expanding list of risk factors and calculating an exact pre-test probability of CAD for an individual patient. even among the three traditional Bayesian pretest probability groups (low, intermediate, high), there can be considerable heterogeneity [40]--the clinician may have a stronger suspicion of CAD, especially high-grade CAD, in a high intermediate than a low intermediate patient. Limiting the pre-test probability assessment to only three variables (age, sex, type of chest pain) ignores other important data [3-9].

Defining a stress as either positive or negative based solely on a 1 mm ST depression criteria likewise ignores data from other stress test variables having an important bearing on the extent of CAD and prognosis [12-15]. New methods of stress test analysis also try to capture the gradation of abnormality of the stress test from normal to severely abnormal rather than

use a sharp cutoff point based on ST depression alone [16,28]. Although 1 mm ST depression has been traditionally used for sensitivity and specificity, some studies have changed the criteria (especially for different populations) in an attempt to increase either sensitivity or specificity [2].

Given what we have learned about CAD, especially acute coronary syndromes [17], it no longer seems reasonable as was done in many earlier studies to ignore lesions of less than 50% diameter and label such patients as not having CAD. In addition, CAD is not a disease that is either present or absent. Extent of disease is an important factor in a patient's prognosis and management [29].

Given all these considerations, it is not surprising that studies using Bayes' theorem as traditionally applied have produced varying results, may not detect important CAD, may not be useful for certain populations, and have led to disenchantment with the method in favor of other approaches [13,18,19]. Some clinicians feel that the theorem is only useful in patients with intermediate range pre-test probability as in this setting a positive or negative test has the greatest impact on the predictive value [25].

Despite its limitations, clinicians do go through the Bayesian process in the evaluation of a patient--a pre-test probability assessment, new information (the stress test), revision of the pre-test assessment to a new post-test probability as a result of the new information [13]. The method presented in this paper attempts to preserve this basic process while improving on the utility of Bayes' theorem. It allows the clinician to choose a pre-test probability profile for an individual patient, a profile that includes the wide spectrum of CAD. It incorporates into the analysis the degree of abnormality of the stress test, plus allowing the clinician to use stress test variables in addition to ST depression. The clinician may use treadmill scores or other methods of analysis [16,28,30] to classify the stress test. In addition, by incorporating extent of CAD into the analysis, the method alerts the clinician to possible high-grade CAD, allows for the fact that a stress test may be negative even in the presence of CAD, allows for the fact that a false positive stress test may be seen in certain populations, can be applied over a wide range of patients rather than only be useful in the intermediate range group, and changes the clinician's pre-test probability profile in such a way that is more useful than previously, given the considerations discussed above.

However, this modified Bayesian method does have certain limitations at present. It has never been tested in a clinical trial. It is not known how actual clinicians would use clinical data to classify patients into these nine defined pre-test probability profiles. The sensitivities and specificities of the various levels of CAD may not be universally agree upon. There is no standard way of classifying stress tests

into mildly, moderately, and severely abnormal, and using different methods may produce varying results. The method only alerts the clinician to the change in the probability of particular types of CAD--how useful this would be in the further management of patients has not been tested. The incorporation of computer software, including artificial intelligence (AI) and machine learning (ML), could be useful to clinicians using such a method, and may in time actually improve the method and its results [41]. Further studies may be of great interest.

Conclusion

Despite its limitations, the modified version of Bayes' theorem as applied to basic treadmill stress testing is an interesting method which may improve clinical utility compared to its traditional usage. Further studies are needed.

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