Bayesian analysis of data from radionuclide angiocardiograms for diagnosis of coronary artery disease

THOMAS D. CHRISTOPHER, M.D., GEORGE KONSTANTINOW, PH.D., AND ROBERT H. JONES, M.D.

ABSTRACT A continuous Bayesian model was developed by fitting a β-function to the frequency distributions of resting ejection fraction, exercise ejection fraction, and change in end-systolic volume during exercise measured by radionuclide angiocardiography in a group of 249 men with coronary artery disease (CAD) and in a group of 56 men without disease. This model, then prospectively applied to 250 men with chest pain, did not increase the overall accuracy of the test but did increase the diagnostic content for individual patients. The diagnostic efficacy of the continuous Bayesian model was compared with previously determined optimal discrete criteria of a positive or negative test. Patients with CAD showed a maximum and mean increase in probability of disease of +0.58 and +0.11, respectively, by the continuous Bayesian model and +0.14 and +0.05, respectively, by discrete criteria. Men without significant disease showed a maximum and mean decrease in probability of disease of −0.73 and −0.38, respectively, by Bayesian analysis and −0.36 and −0.27, respectively, by optimal discrete criteria. Moreover, all 29 patients who died during a 35 month interval after study had a probability of CAD of 0.95 or greater by the continuous Bayesian model. These findings indicate that Bayesian analysis of radionuclide angiocardiographic test results with continuous distributions of left ventricular function measurement enhances the diagnostic and prognostic information for individual patients with symptoms suggestive of CAD.


MYOCARDIAL ISCHEMIA induced by exercise impairs ventricular function in patients with coronary artery disease (CAD). Exercise-induced abnormalities of left ventricular function detected by radionuclide ventriculography have been used to diagnose CAD in patients with chest pain. Previous studies evaluating radionuclide angiocardiography (RNA) for the diagnosis of CAD have used discrete end points of each left ventricular functional parameter measured to define a positive or negative test result. However, variables describing cardiac function are continuous. A patient with severe exercise-induced left ventricular dysfunction, for example, would appear more likely to have CAD than a patient with only mild exercise-induced dysfunction. Diamond and Forrester suggested that Bayes' theorem is applicable to continuous variables derived from nuclear cardiologic studies for predicting the likelihood of CAD for individual patients. They did not, however, have adequate data to test this hypothesis prospectively.

Quantitative RNA in patients at rest and during exercise has been used at Duke University Medical Center since 1977 to evaluate cardiac function in patients with chest pain. We have used data from RNA studies to develop and test prospectively a model based on Bayesian analysis. This model defines the individual probability of CAD in men with chest pain in terms of left ventricular functional descriptors.

Methods

Clinical material. Between 1970 and 1980, 5042 men with chest pain underwent cardiac catheterization and coronary arteriography at Duke University Medical Center. The patient population from the computerized cardiology data base at Duke University Medical Center was used to define prevalence of CAD, probability of test results from RNA in a population with CAD, and probability of test results from RNA in a population without CAD. At least 75% narrowing of the luminal diameter of at least one major coronary artery was required for the diagnosis of significant CAD. Patients with stenoses less than 75% were considered to be "normal." The prevalence of CAD as a function of age and character of chest pain was determined from this population of 5042 men.
Typical angina was defined as: (1) crushing or squeezing in character, (2) substernal in location (with or without arm or neck radiation), (3) stress-evoked, and (4) promptly relieved by rest or nitrates. Pain exhibiting one to three of these characteristics was considered atypical angina, and pain exhibiting none of the characteristics was defined as nonanginal. The prevalence of CAD was determined in each subgroup with chest pain over five age ranges: less than 40 years old, 41 to 50 years old, 51 to 60 years old, 61 to 70 years old, and greater than 70 years old. A linear fit to these prevalence data provided a function for each subgroup with pain describing pretest probability of disease.

Between January 1, 1977, and December 31, 1979, 305 men with chest pain underwent rest and exercise RNA within 3 months of catheterization and angiography; 249 of these men had CAD and 56 had either normal coronary arteries or insignificant coronary arterial narrowing. These 305 patients had no history of valvular, congenital, or cardiomyopathic heart disease and no history of cardiac surgery. None had taken β-blocking medications for at least 24 hr before study. Patients with evidence of prior myocardial infarction determined by electrocardiography were included in the study population. All patients achieved an adequate exercise end point.

The protocol for an initial transit rest and exercise radionuclide angiography has been described previously. Subjects were seated in the erect position on a bicycle ergometer, and a resting blood pressure and an eight-lead electrocardiogram were recorded. Fifteen millicuries of technetium-99m pertechnetate was injected as a bolus into a peripheral vein to acquire the radionuclide angiogram in a patient at rest. Exercise was then started at a workload of 200 kpm/min and was increased by 100 kpm/min every minute. Blood pressure and the electrocardiogram were monitored, and exercise was continued until the subject experienced pain suggestive of myocardial ischemia, showed electrocardiographic evidence of ischemia, felt severe fatigue or shortness of breath, or reached 85% of predicted maximal heart rate, at which point the exercise radionuclide angiogram was obtained. Background-corrected data were used to calculate left ventricular ejection fraction (EF) by subtracting end-systolic counts from end-diastolic counts and dividing the difference by end-diastolic counts. Left ventricular end-diastolic volume (EDV) in patients at rest and during exercise was calculated by the area-length method of Dodge et al. All other hemodynamic measurements were derived from the EF and EDV by accepted relationships. We have previously documented these measurements as accurate and reproducible.

Development of diagnostic model. Results of studies on the 305 men who underwent RNA before January 1, 1980, were used to define discrete and continuous parameters of left ventricular function in the normal groups and groups with CAD. Previous work from this laboratory has defined the abnormalities of measurement of left ventricular function (discrete parameters) that are optimal for diagnosis of CAD in patients undergoing cardiac catheterization for chest pain. These abnormalities are: (1) a resting EF less than 50%, (2) an exercise EF at least 6% less than predicted (expected increase in EF with exercise was defined by sex, age, and rest-to-exercise change in the EDV index), (3) an exercise-induced decrease of greater than 20 ml in end-systolic volume (Δ ESV), or (4) the appearance or exacerbation of a wall motion abnormality during exercise. These criteria were used as discrete end points to define results of studies by RNA as positive or negative.

For the continuous model, resting EF, exercise EF, and Δ ESV were considered as continuous random variables with a range of zero to one. Means and standard deviations were calculated to define a β-distribution, β (n, r), for each of the three variables in the two patient populations. The β-distribution describes the probability of any given test result by RNA occurring in the specified population:

\[ \beta(n, r) = \frac{\Gamma(n)}{\Gamma(r) \Gamma(n - r)} (1 - x)^{r - 1} \cdot (1 - x)^{n - r - 1} \]

The variable x can represent any of the three variables of interest: resting EF, exercise EF, or Δ ESV. The n and r parameters for the population are defined from the mean (\( \bar{x} \)) and standard deviation (SD) by

\[ n = [\bar{x}(1 - \bar{x})] \cdot \text{SD}^2 \] \[ r = n \cdot \bar{x} \]

Finally, the gamma function, Β(y), is defined by

\[ \Gamma(y) = \int_{0}^{\infty} e^{-x} x^{y-1} \, dx \]

For integer values of y > 0, \( \Gamma(y) = (y - 1)! \)

The probability of an individual patient having disease was calculated by applying Bayes’ theorem of conditional probability to data obtained by RNA:

\[ P(D|RNA) = \frac{P(D) \cdot P(RNA|D)}{P(D) \cdot P(RNA|D) + P(\overline{D}) \cdot P(RNA|\overline{D})} \]

In this formula, RNA is a given test result, P(D|RNA) is the posttest probability of disease given the test result, P(D) is the prior probability of disease (or prevalence), and P(RNA|D) and P(RNA|\overline{D}) are the probabilities of the test result in the diseased and normal populations, respectively.

Prospective testing of diagnostic model. The derived model was tested prospectively with a separate population of 250 men with chest pain who underwent cardiac catheterization and RNA between January 1, 1980, and September 15, 1981. For each patient the probability of CAD calculated was compared with probability defined by discrete test criteria. The continuous Bayesian model was validated with the chi-square statistic to compare the average posttest probability of disease in each of three subgroups (less than 0.60, 0.60 to 0.90, and greater than 0.90), with the actual incidence of disease in the subgroup identified by catheterization.

Follow-up after cardiac catheterization. Information on life-death status was available for 412 (90%) of the 456 total patients with significant CAD in both the retrospective and prospective groups studied by RNA an average of 35 months after cardiac catheterization. Death from any cause occurred in 29 patients an average of 15 months after cardiac catheterization. Five men had left main CAD, 15 had triple-vessel CAD, six had double-vessel CAD, and three had single-vessel CAD. The incidence of death was then analyzed as a function of pretest and posttest probability of disease.

Results

Prevalence of CAD related to age and type of chest pain. In the population of 5042 men, 3422 (68%) had typical angina, 1278 (25%) had atypical angina, and 342 (7%) had nonanginal chest pain. There was a sufficient number of patients with typical angina to permit separation into five groups according to age. The number of patients with atypical angina and nonanginal chest pain, however, was adequate to provide data for only four age subgroups in each category of pain. In each pain classification, the fraction of patients in each subgroup of age was plotted at the average age for the subgroup (figure 1). A linear fit to these data gave correlation...
coefficients of .99, .96, and .99 for typical angina, atypical angina, and nonanginal chest pain, respectively. Equations derived from these data that permit calculation of the pretest probability of disease, P(D), as a function of age and type of chest pain were:

Typical angina: \( P(D) = 0.0031 \cdot A + 0.772(3) \)
Atypical angina: \( P(D) = 0.0109 \cdot A + 0.098(4) \)
Nonanginal chest pain: \( P(D) = 0.0161 \cdot A - 0.398(5) \)
in which \( A \) equals age in years.

**Derivation of continuous Bayesian model.** CAD was present in 249 of 305 men catheterized for diagnosis of chest pain. In this group the mean and standard deviation of resting EF were 0.54 ± 0.16; exercise EF, 0.51 ± 0.16; and \( \Delta ESV \), 21 ± 30 ml. Cardiac catheterization showed normal coronary arteries or insignificant CAD in 56 of the 305 patients. In this group, the mean and standard deviation of resting EF were 0.63 ± 0.12; exercise EF, 0.71 ± 0.13; and \( \Delta ESV \), −1 ± 19 ml. These values of mean and standard deviation were used to establish parameters for the 6-distribution (table 1). Curves defined by these parameters depict the degree to which populations of patients with normal coronary arteries differ from those with CAD (figure 2). The exercise EF was the single variable that best separated patients with and without disease, but all three variables contributed diagnostic information. Algebraic manipulation of equations 1 and 2 for all three variables taken simultaneously resulted in the following equation for defining the posttest probability of disease:

\[
P(D|RNA) = \frac{P(D) \cdot (1 - ExEF)^{1.4}}{1 + \{1 - P(D)\}(3.14 \times 10^7)(Rest EF)^5 (1 - Rest EF)^{1.5}}\]

(6)

where \( P(D|RNA) \) = posttest probability of CAD, \( P(D) \) = prior probability of CAD, \( Rest EF \) = resting EF, \( ExEF \) = exercise EF, and \( \Delta ESV_{sc} \) = scaled rest-to-exercise change in ESV. \( \Delta ESV_{sc} \) is calculated by:

\[
\Delta ESV_{sc} = \frac{\Delta ESV - \Delta ESV_{min}}{\Delta ESV_{max} - \Delta ESV_{min}}
\]

(7)

where \( \Delta ESV_{min} \) is the greatest decrease in ESV and \( \Delta ESV_{max} \) is the greatest increase in ESV observed during exercise. In our population, \( \Delta ESV_{min} = -98 \text{ ml} \) and \( \Delta ESV_{max} = 113 \text{ ml} \). Thus, equation 7 becomes:

\[
\Delta ESV_{sc} = \frac{\Delta ESV + 98}{211}
\]

(8)

**Validation of model.** Posttest probabilities of disease were calculated in the prospective study with the continuous Bayesian model for the 250 patients who underwent both coronary arteriography and RNA after January 1, 1980. Catheterization showed that 207 men had significant CAD. This group comprised 52 patients with single-vessel stenosis, 63 with double-vessel stenosis, 83 with triple-vessel stenosis, and nine with left main coronary artery stenosis. The group of 43 men without significant CAD consisted of 28 with normal coronary arteries and 15 with coronary lesions less than 75%. For each patient, prior probability of CAD was calculated from equation 3, 4, or 5, and the posttest probability of disease after RNA was calculated from equation 6.

In this group of 250 men, individual posttest probabilities of CAD provided by the continuous Bayesian

**TABLE 1**

<table>
<thead>
<tr>
<th>Parameters describing the ( \beta )-distributions in the populations with and without CAD</th>
<th>CAD</th>
<th>No CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting EF</td>
<td>Exercise EF</td>
</tr>
<tr>
<td>Mean</td>
<td>0.54</td>
<td>0.51</td>
</tr>
<tr>
<td>SD</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>( n )</td>
<td>9.7</td>
<td>9.8</td>
</tr>
<tr>
<td>( r )</td>
<td>5.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>
model were compared over three probability ranges, with the percentage of these patients with CAD proved by angiography (table 2). The mean posttest probability of disease, which ideally should equal the percentage of patients with CAD in any range, was greater than the percentage of patients with CAD in the low and middle probability ranges. However, in no group was the difference statistically significant.

**Prospective application of model to 250 patients with chest pain.** The posttest probability of CAD was calculated for each patient with optimal discrete radionuclide angiographic criteria and continuous distributions of resting EF, exercise EF, and ΔESV. The continuous Bayesian model was more effective than the application of optimal discrete criteria in showing a decreased probability of disease in the normal population. Application of optimal discrete radionuclide angiographic criteria in the retrospective study of 305 men resulted in a test sensitivity of 89% and a specificity of 51%. Discrete test end points correctly showed decreased probability of disease from pretest values in 22 of 43 (51.2%) men without CAD (table 3). Application of Bayes’ theorem to these 43 men in whom the radionuclide angiogram was categorized as positive or negative, showed a maximum and mean decrease in probability of disease of −0.36 and −0.27 and an appropriate decrease in probability for 36 of 43 (84%) normal men (figure 3). For 24 of these 36 men, the probability of disease was lowered to a greater extent than that attainable with discrete criteria (maximum and mean decrease: −0.73 and −0.38). The continuous Bayesian model yielded inappropriate increases in probability up to 20% in three, between 21% and 30% in three, and by 45% in one normal man.

In the population of 207 men with significant CAD, application of optimal discrete radionuclide angiographic criteria resulted in 184 of 207 (88.9%) for whom probability of disease correctly increased (table 3). The continuous Bayesian model yielded an appropriate probability increase for 149 of these 207 patients (72%) (figure 4). Maximum and mean increase in probability were +0.14 and +0.05 by optimal discrete criteria and +0.58 and +0.11 by the continuous Bayesian model.

The net diagnostic gain for each approach can be determined from the magnitude and number of correct and incorrect changes in probability (table 3). In the 43 men with normal coronary arteries and insignificant CAD, the average diagnostic gain was 0.09 for the discrete model and 0.28 for the continuous Bayesian model. In the 207 men with CAD, the net diagnostic gain was 0.02 for the discrete model and 0.01 for the continuous model. Therefore, for the entire population of 250 patients, the continuous Bayesian model resulted in an average 0.02 more correct change in probability of disease than did the discrete test end points. This slight diagnostic advantage resulted from the greater decrease in probability of disease with the continuous model in patients without CAD. Fifty-eight patients exhibited a large increase in diagnostic gain by use of the continuous model vs 15 patients by use of the discrete model.

Decreases in probability resulting from the continuous Bayesian model occurred more frequently in the group of patients with anatomic less extensive CAD. None of the men with left main CAD showed lower probability of disease; whereas for 18%, 33%, and 46% of patients with triple-, double-, and single-vessel disease, respectively, the probability of CAD was lower.

**TABLE 2**

**Validation of continuous Bayesian model**

<table>
<thead>
<tr>
<th>Posttest probability range</th>
<th>&lt; 0.60</th>
<th>0.60 to 0.90</th>
<th>&gt; 0.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean posttest probability of CAD for continuous model</td>
<td>0.28</td>
<td>0.79</td>
<td>0.98</td>
</tr>
<tr>
<td>Fraction of patients with CAD demonstrated by catheterization</td>
<td>0.46 (25/54)</td>
<td>0.83 (38/46)</td>
<td>0.96 (144/150)</td>
</tr>
<tr>
<td>Chi-square statistic</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Follow-up after cardiac catheterization on 412 men with significant CAD. Twenty-nine patients in the study population have died. Cause of death, results from RNA, and pretest and posttest probabilities of disease in the 29 patients who died an average of 15 months after study are summarized in table 4. For all these 29 patients, the posttest probability of disease calculated by the continuous Bayesian model increased to 0.95 or greater. Comparison of pretest and posttest probabilities of CAD as a function of the cumulative incidence of death documents that results from RNA provide both diagnostic and prognostic information (figure 5). The rightward shift of the pretest to posttest curve reflects the prognostic information added by the radionuclide angiographic test beyond that information reflected by age and character of pain.

Discussion

Thomas Bayes, an eighteenth century clergyman, developed a theorem of conditional probability that has become popular recently in medical diagnostic testing. Bayes' theorem is usually applied to tests that exhibit discrete outcomes. The goal of this study was to use a continuous Bayesian model regarding presence or absence of CAD to quantify the degree of normality or abnormality of test results by RNA for individual patients with chest pain. This idea was first suggested by Diamond and Forrester, who pooled radionuclide data from numerous institutions in developing continuous frequency distributions. Our investigation is the first in which a model has been developed and tested in a homogeneous population of patients from a single institution.

Development of the continuous Bayesian model required several assumptions. We assumed that the β-distribution accurately describes the distribution of resting and exercise EF in normal populations and in those with CAD. The β-distribution appears to be a reasonable choice because it is naturally constrained by the values zero and one, as is EF, and because it is similar to a Gaussian distribution in that each is fully defined by the mean and standard deviation. Moreover, we assumed that the β-distribution accurately describes ΔESV as well once values for ΔESV are scaled to values between zero and one (by identifying the minimum and maximum changes in ESV during exercise in both normal populations and patients with CAD). If the populations used to create the continuous distributions were to change, it would be necessary to reidentify the minimum and maximum values of ΔESV and to rescale individual measurements. Finally, we assumed implicitly in our model that the parameters used are mutually independent. The variables used here are, most likely, highly dependent. The use of such dependent variables can erroneously alter the

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td><strong>Comparison of effectiveness of continuous and discrete approaches</strong></td>
</tr>
<tr>
<td>Normal subjects and those with insignificant disease (n = 43)</td>
</tr>
<tr>
<td><strong>Discrete</strong></td>
</tr>
<tr>
<td>True negative</td>
</tr>
<tr>
<td>Mean ΔP</td>
</tr>
<tr>
<td>Maximum ΔP</td>
</tr>
<tr>
<td>False positive</td>
</tr>
<tr>
<td>Mean ΔP</td>
</tr>
<tr>
<td>Maximum ΔP</td>
</tr>
<tr>
<td>Net ΔP all patients</td>
</tr>
</tbody>
</table>

ΔP = change in probability of disease observed in population.
were therefore used through Bayesian parameters. The model derived through Bayesian continuous linear probability. Posttest probability. For example, if one variable results in a probability change in one direction, adding a second (dependent variable) will change the probability further in that direction. Resting EF, exercise EF, and ΔESV have been demonstrated as the most effective parameters in identifying patients with CAD and were therefore used to obtain probability estimates through Bayesian analysis.9

The model was derived and applied only for men because the sample size of women evaluated for CAD was inadequate. Cardiac catheterization performed on 5042 men with chest pain at Duke University Medical Center provided the data base to derive pretest probabilities (prevalence) of disease in our model. Linear functions described the prevalence of disease as a function of age and type of pain to permit use of this simple relationship to estimate pretest probabilities of disease in our population. A nonlinear model encompassing more variables would probably enhance the accuracy of this estimate somewhat. However, our data correlate closely with data on prevalence that are similarly based on sex, age, and type of chest pain reported for 5347 male patients from the Coronary Artery Surgery Study10 and for 17,013 male patients reported by Diamond and Forrester.12 The major difference of the data from Duke from the other data was a higher prevalence

Posttest Probability of CAD (%)

FIGURE 4. Pretest and posttest probability of CAD in 207 men with chest pain and CAD. Patients with both pretest and posttest probabilities of disease greater than 90% (n = 117) are represented at right. The curved line represents the expected increase in probability of CAD resulting from a positive test with optimal discrete radionuclide angiocardiographic criteria. All patients with significant stenosis of the left main coronary artery had both pretest and posttest probabilities greater than 90%.

Probability of CAD

Pre-test Probability of CAD

Post-test Probability of CAD

FIGURE 5. Probability of death as a function of both pretest and posttest probability of disease by the continuous Bayesian model. All patients who have died thus far had a posttest probability of CAD of 0.95 or greater.
of disease among male patients with nonanginal pain at all ages. This difference may be due to a relatively smaller number of patients with nonanginal pain or to different criteria used to identify these patients, who often present confusing clinical pictures.

Approximately one-third of the patients in this study had evidence of prior myocardial infarction on their electrocardiograms. The prevalence of CAD in this subgroup is sufficiently high (94%) that noninvasive testing does not add further useful information. If these patients had been excluded from our study, the diagnostic power of the left ventricular functional variables, particularly resting EF, would have been diminished by 0.07. However, these patients were not excluded from the study for two reasons. First, any diagnostic model used in clinical practice should be tested with this population to be certain that the model does not inappropriately lower recognition of disease in this subgroup. More important, many of the patients who died during the time of follow-up had prior myocardial infarction. Data describing the prognostic importance of measurements of ventricular function are important for patients with prior myocardial infarction. In fact, the radionuclide angiocardiogram was usually obtained in these patients for prognostic and not diagnostic information.

A relatively simple expression incorporating the pretest likelihood of disease and test results by RNA yielded the posttest probability of significant CAD in individual patients. The fact that only 22% of the men studied had a posttest probability of disease less than 0.60 limits evaluation of the accuracy of the continuous Bayesian model for patients with a low likelihood of CAD. These are the patients for whom noninvasive testing might provide the most important clinical information. Even for the entire population, the sensitivity
and specificity of the radionuclide angiogram was not enhanced by the continuous Bayesian model. The resting and exercise radionuclide angiogram contributed little diagnostic information beyond that available from clinical information in the entire patient group. However, the continuous model of data obtained by RNA provided additional diagnostic information for individual patients. In the prospective analysis, the continuous Bayesian approach showed a greater decrease in probability of disease for patients with no significant CAD but a lesser increase in probability of disease for patients with significant CAD. The observation that in both approaches the probability of disease increased little for men with CAD reflects the fact that most patients with CAD had a high probability of disease before values were determined.

Calculation of posttest probabilities of disease by continuous Bayesian analysis may aid in making clinical decisions about individual patients. For example, from our prospective study of 250 men, the criterion that no patient who has a posttest probability equal to or less than 0.10 be sent for cardiac catheterization would miss one of the 207 patients in our study with significant CAD but would spare 12 of the remaining 43 men (28%) with normal coronary arteries or insignificant disease the risk and discomfort of the procedure.

Of the group of 207 studied, the 29 patients who died at an average of 15 months after initial study all had a posttest probability of disease equal to or greater than 0.95 by the continuous Bayesian model. When age and character of pain are used to define probability of disease, only 12 of these 29 had a probability of disease equal to or greater than 0.95. The fact that prognostic information is added by resting and exercise EF and ΔESV in this population suggests that the same parameters that detect the presence of CAD also index the severity of disease. Moreover, the fact that no patient died who had a posttest probability of disease less than 0.95 diminishes the clinical importance of an incorrect decrease in probability of disease for men with CAD. If further experience confirms these observations, the most important use of RNA will be to obtain prognostic rather than diagnostic information.

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