TECHNICAL POINT OF VIEW

The Application of Conditional Probability to Harmonize Nuclear Cardiology Test Results

Timothy F. Christian, MD

Received: October 6, 2022/Revised manuscript received: October 19, 2022/Accepted: November 3, 2022
J-STAGE advance published: November 22, 2022

Abstract

Both exercise single photon emission computed tomography (SPECT) imaging and myocardial perfusion imaging with positron emission tomography produce multiple outcome variables. These include the stress electrocardiogram (ECG), visual perfusion assessment and quantitative myocardial blood flow. Bayes' analysis using conditional probability allows the distillation of multiple test results into a single probability of disease for individual patients. This paper examines the application of conditional probability analysis to two noninvasive modalities that generate multiple outcome results: exercise ECG combined with SPECT imaging and vasodilator RB-82 positron emission tomography perfusion imaging combined with quantitative measure of absolute myocardial blood flow. In this manner, a single probability of disease incorporating all the available data is generated for an individual patient.

Keywords: Coronary artery disease, Positron emission tomography, SPECT, Statistics
Ann Nucl Cardiol 2023; 9 (1): 80–84

The use of multiple noninvasive tests in a patient for a specific question is becoming more common (1). While it is expected that each new piece of noninvasive information will align, the reality is that each test carries strengths and weaknesses that generate a profile of accuracy and associated false positive and false negative results. When two non-gold-standard tests produce non-concordant results, it can be difficult to chart a clinical course. Clinical guidelines for cardiac imaging rely heavily on conditional probability in the form of pre-test clinical risk assessment to maximize the incremental value of the test result. That risk classification is often the main determinant of appropriateness. Bayesian analysis of conditional probability allows the distillation of multiple pieces of information into a single probability of the presence or absence of disease. Probability becomes the common language linking the information.

Conditional probability is a mathematical statement on the probability (P) that an event will occur given prior information on what has already occurred. This is often stated as the probability of A given B. "B" is the pre-test probability, also known as the prior. "A" reflects the post-test probability of interest, such as the likelihood of coronary artery disease following a test result but incorporates all the prior information into the calculation. For nuclear imaging, this has direct impact as all patients have prior information in the form of symptoms, risk factors, physical findings and the stress test variables.

The formulae are straight forward (2):

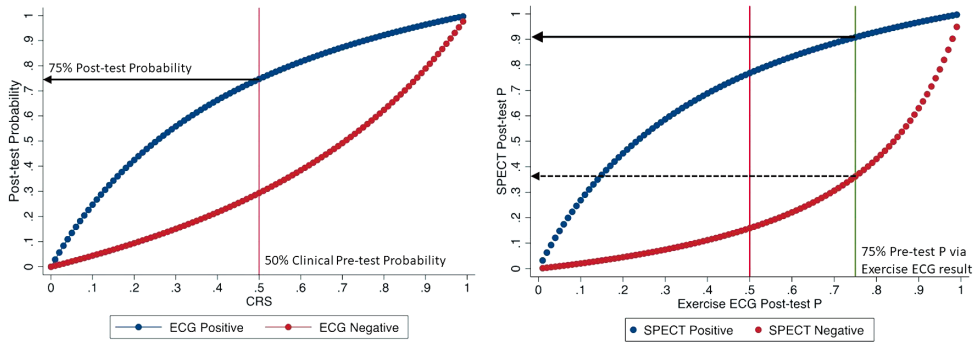
$$P\,(positive\ result) = \frac{(Prev\ CAD * Sensitivity\ test\ A)}{[(Prev\ CAD * Sensitivity\ test\ A) + (False\ positive\ rate)]}$$

$$P\,(negative\ result) = \frac{[(1\text{-}Prev\ CAD) * (Specificity\ test\ A)]}{[(1\text{-}(Prev\ CAD) * Sensitivity\ test\ A) + (False\ negative\ rate)]}$$

To get the prior, a starting point is needed. That starting point is an initial risk score for coronary artery disease (CAD). In the United States, the prevalence of significant CAD is 7% (3). In Japan it is closer to 4% (4). With no other knowledge, an adult patient would have a 4–7/100 chance of having CAD depending on the country they reside in. But it is clear that

DOI: 10.17996/anc.22-00174

Department of Medicine/Division of Cardiology Jacobi Medical Center, Albert Einstein College of Medicine, NY, USA



A B

Figure 1 ECG stress and SPECT conditional probability plots.

A: The pre-test P of CAD in the form of the clinical risk score (CRS, x-axis) plotted against the post-test P for exercise ECG treadmill testing. The upper curve represents a positive test and the lower curve, a negative test (defined as 1 mm exercise-induced ST depression). The two curves are determined by a chosen sensitivity and specificity, in this case, 68% and 77% from a meta-analysis that pooled 24 studies for the detection of significant CAD (9). The space between the two curves reflects the accuracy of the test and is expressed as a percentage of the maximum area (100% of the graph, i.e. two right angle curves creating a square covering the entire x and y axes). In this case the area between the curves is 31.7%.

B: The same analysis for ^{99m}Tc Sestamibi exercise SPECT. This analysis assumes a sensitivity of 86% and specificity of 74%. The area between the curves is higher at 44.4% reflecting its superior accuracy.

The arrows show how the ECG stress results can be incorporated into the final SPECT interpretation. A patient at intermediate pre-test probability (50%) by a clinical risk score undergoes exercise ECG stress. A positive tests increases the post test probability to 75%.

The post-test probability of the ECG stress test (75%), Now becomes the pretest probability of the SPECT result. A positive SPECT result increases the post-test probability to over 90%, whereas a negative SPECT result reduces it to about 35%.

there are risk factors which markedly impact that risk: hypertension, diabetes, lipid status, smoking and family history among others.

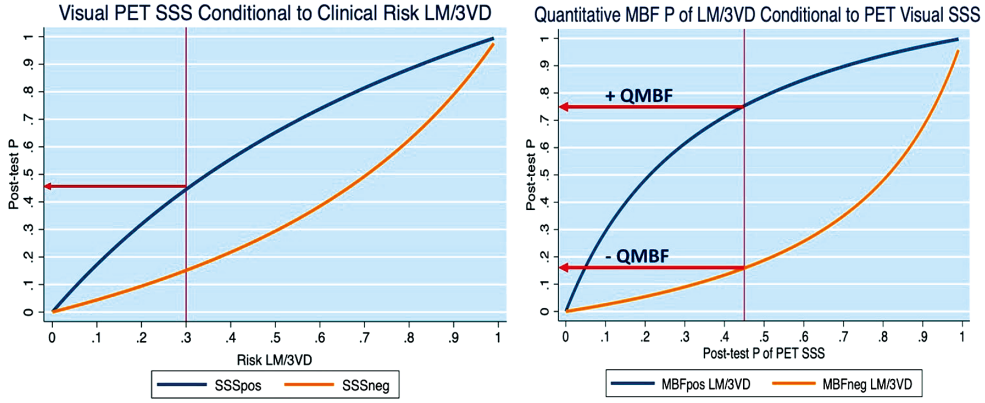
From these variables gathered routinely, a clinical risk score (CRS) for CAD can be calculated using one of a number of scoring models for patients with (5) and for those without (6) chest pain. Each has its own strengths and weaknesses. The key point is that they provide a risk probability for an individual patient.

The case of exercise SPECT myocardial perfusion imaging

The modality of exercise nuclear single photon emission computed tomography (SPECT) imaging has two components that generate separate results: The exercise electrocardiogram (ECG) and the myocardial perfusion images. It is known that SPECT imaging has the higher accuracy in detecting the presence of significant CAD compared to exercise electrocardiography (7). However, it is also known that exercise electrocardiography can provide comprehensive information in some scenarios, limiting the contribution of the SPECT images (8). Consequently, the ECG results cannot simply be dismissed. An alternative approach is to use conditional probability as a means to incorporate both.

Figure 1 is a graphic depiction of conditional probability. It is a display of the accuracy of exercise treadmill testing as a function of the risk of CAD of the individual being tested. The two opposing curves represent the post-test probability of CAD for a positive or negative test result as defined by a dichotomous variable-usually 1 mm ST depression but it could be a Duke treadmill score or an exercise duration threshold. For any prior risk, a post-test probability is calculated. At either extreme of the curves, the pre-test and post-test probability do not change much but there is significant movement in the intermediate risk zone from pre-test to post-test. This is the basis for guidelines being slanted to favor testing of intermediate risk patients. The separation magnitude of the curves is a function of the accuracy of the test. This is reflected in the area circumscribed by the two curves: the greater the area, the more accurate the test. For this particular example, the pooled accuracy of 24 studies of exercise ECG testing was used to derive the accuracy of exercise ECG: sensitivity = 68% and specificity = 77% (9) with an area of 32%. The same curves are shown for the accuracy of myocardial perfusion imaging using SPECT ^{99m}Tc sestamibi imaging (sensitivity = 86%, specificity = 74% area (10). The higher accuracy of SPECT imaging is evident in the wider displacement of the positive and negative curves and consequently the increase in area between the curves, 32% vs 44% (Figure 1B).

But what happens when there are two test results for a single



A　　B

Figure 2　Probability of 3V/LMT disease by PET imaging.

A: The conditional probability curve visual assessment of PET images for the presence of 3V/LMT disease. The area between curves is 25%. A patient with a clinical pre-test probability of severe CAD is 30%. A positive PET SSS result takes them to 45% post-test probability.

B: The conditional probability curve quantitative assessment of PET images by absolute MBF flow reserve for the presence of 3V/LMT disease using the PET SSS result as the prior. The area between the curves is 44%. For the patient with a post-test probability of 3V/LMT disease by SSS PET of 45%, a positive quantitative result increases the probability to 75% whereas a negative result reduces the probability to 15%.

SSS: summed stress score

test such as the stress ECG and the SPECT image interpretation? One approach to handling these two pieces of information is to interpret them as confirmatory when they agree, and favor the one with the greater accuracy when they conflict, perhaps with some adjustment for the clinical risk. An alternative approach is to maintain the clinical risk assessment formally and incorporate one of the tests into the pre-test probability with it when evaluating the second test, particularly when they are acquired in sequence (Figure 1). In this manner, the post-test probability of the first test becomes the pre-test probability of the second test (11).

Consequently, the post-test P of the exercise ECG result becomes the pre-test P for the SPECT analysis. Figure 1 demonstrates the shift in the prior P for SPECT imaging and the impact on the post-test P. The key intervention is that SPECT does not use the clinical risk score as the prior. It uses the CRS combined with the exercise ECG post-test P. The CRS is still present, but it is now a function of the exercise ECG result. This approach has shown to improve the performance of computed tomography (CT) coronary angiography (11).

PET imaging for the identification of three vessel disease

The same approach can be used to better predict which patients that undergo positron emission tomography cardiac stress testing have three vessel disease. Myocardial perfusion imaging is a relative technique in that the reconstruction algorithm identifies the highest count region and sets all the pixels as a percent of this maximal value. Consequently, if all three territories are abnormal, there will be false negative values in identifying hypo-perfused zones at rest or during hyperemia (12). PET perfusion imaging has the potential to provide absolute values of myocardial blood flow (MBF) with the dynamic acquisition of the arterial input function (bolus tracking of radionuclide as it traverses the heart) and modeling of the resultant time activity curves in individual coronary segments. In this manner, quantitative MBF provides incremental information to the visual perfusion assessment (13). But how best to harmonize these two pieces of information into a single probability of severe CAD?

For any analysis of conditional probability, a starting point must be identified. There are several studies which have examined clinical predictors of three vessel/left main disease (3V/LMT) available from the history, physical exam and rest electrocardiogram (14). These risk scores can be used to classify the initial risk of an individual patient before considering the positron emission tomography (PET) results.

Once clinical risk is established, the sensitivity and specificity of visual PET analysis can be applied. For the identification of 3V/LMT this is usually a logistic regression model that identifies independent variables associated the prediction (8). The accuracy of cardiac PET imaging is superior to SPECT for the detection of significant CAD (15). However, the prediction of the presence of 3V/LMT is more difficult. Using the summed stress score (SSS) from the visual interpretation of the perfusion images resulted in a sensitivity and specificity of 75% and 60% (16). Adding absolute MBF measures to the analysis increased the accuracy significantly:

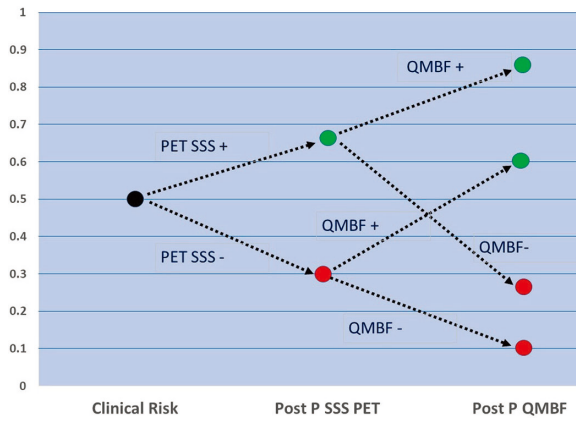


Figure 3

The impact of conditional probability on a single subject with a pre-test probability of having 3V/LMT disease undergoing PET imaging. The results of the PET SSS interpretation generate either a post-test probability of 65% or 28% for a positive or negative test. Now using those values as potential prior P of 3V/LMT disease the post-test P generated from the quantitative coronary flow reserve result produces post-test probabilities ranging from 10–86%.

sensitivity = 82%, specificity＝78%. Consequently, we can use these accuracy values to provide a single probability of the presence of severe CAD in an individual patient using both pieces of information: visual myocardial uptake and absolute MBF.

Figure 2 shows the added synergy of using the PET model which incorporates SSS, visual perfusion score with the quantitative absolute myocardial blood flow (QMBF) data. For any clinical risk of 3V/LMT, a single probability can be generated using both the visual and quantitative PET results. This alleviates the problem of discordant results as a final P can always be obtained for an individual patient.

Concordance and discordance

Figure 3 shows the interplay of sequential test results on probabilities of 3V/LMT disease using this approach. When the two results align: both PET SSS and QMBF are positive or negative, the synergy is strong. For example, a patient with a pretest probability 50% has a post-test probability of 86% with a positive SSS and QMBF result and only about a 10% probability of severe disease with two negative results. However, when there is discord (positive SSS, negative QMBF or the reverse, probabilities remain in the intermediate zone (25–60%-see Figure 3).

It is evident that the utilization of conditional probability (through Bayes' Theorem) allows the synthesis of multiple pieces of information, all of which are clinically relevant, into a single final probability for an individual patient. Using the example of coronary computed angiography and CT coronary flow reserve measures, this methodology was more accurate in identifying patients with significant CAD than either technique alone (11). This needs to be confirmed for PET using angiographic 3V/LMT disease as the end-point.

There are other modalities where multiple results are generated from a single exam (stress echo, stress MRI, and invasive FFR with coronary ultrasound). Consequently, the use of conditional probability to assimilate these dual results will continue to grow and clinicians should begin to familiarize themselves with the simple principles of Bayes' Theorem.

Acknowledgments

This paper is dedicated to Keiichiro Yoshinaga MD, PhD for his help and inspiration.

Sources of funding

None.

Conflicts of interest

None.

Reprint requests and correspondence:
Timothy F. Christian, MD, MPA
Department of Medicine/ Division of Cardiology Jacobi Medical Center, Albert Einstein College of Medicine, 1400 Pelham Parkway, Building one 5-E21, Bronx, New York City, NY, USA
E-mail: christit2@nychhc.org

References

1. Di Carli MF, Geva T, Davidoff R. The future of cardiovascular imaging. Circulation 2016; 133: 2640–61.
2. Diamond GA, Forrester JS, Hirsch M, Staniloff HM, Vas R, Berman DS, et al. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. J Clin Invest 1980; 65: 1210–21.
3. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: A report from the American Heart Association. Circulation 2022; 145: e153–e639.
4. Iso H. Changes in coronary heart disease risk among Japanese. Circulation 2008; 118: 2725–9.
5. Genders TSS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011; 32: 1316–30.
6. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et. al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117: 743–53.
7. Bokhari S, Shahzad A, Bergmann SR. Superiority of exercise myocardial perfusion imaging compared with the exercise ECG in the diagnosis of coronary artery disease. Coron Artery Dis 2008; 19: 399–404.
8. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Exercise

tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms. Ann Intern Med 1994; 121: 825–32.
9. Bourque JM, Beller GA. Value of exercise ECG for risk stratification in suspected or known CAD in the era of advanced imaging technologies. JACC Cardiovasc Imaging 2015; 8: 1309–21.
10. Loong CY, Anagnostopoulo C. Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging. Heart 2004, 90 Suppl 5: v2–9.
11. Christian TF, Marfatia R, Chen LQ, Onuegbu AG, Pollack S, Cao J. Harmonizing multimodality imaging results using Bayesian analysis: the case of CT coronary angiography and CT-derived fractional flow reserve. Int J Cardiovasc Imaging 2022. [Online ahead of print.] doi: 10. 1007/s10554-022-02530-1.
12. Beller GA. Underestimation of coronary artery disease with SPECT perfusion imaging. J Nucl Cardiol 2008; 15: 151–3.
13. Parkash R, deKemp RA, Ruddy TD, Kitsikis A, Hart R, Beauchesne L, et al. Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. J Nucl Cardiol 2004; 11: 440–9.
14. Hubbard BL, Gibbons RJ, Lapeyre AC 3rd, Zinsmeister AR, Clements IP. Identification of severe coronary artery disease using simple clinical parameters. Arch Intern Med 1992; 152: 309–12.
15. Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol 2006; 13: 24–33.
16. Ziadi MC, Dekemp RA, Williams K, Guo A, Renaud JM, Chow BJW, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? J Nucl Cardiol 2012; 19: 670–80.