Diagnosis of Coronary Artery Disease by Radionuclide Angiography: Effect of Combining Indices of Left Ventricular Function

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The aim of this study was to determine whether the diagnostic capability of radionuclide angiography (RNA) in detecting coronary artery disease (CAD) might be improved by using several indices of left ventricular (LV) function in concert. Three different models (rest data, exercise data, and rest plus exercise data) were derived by stepwise multivariate discriminant analysis of RNA data in 65 normal volunteers and 111 patients with CAD and normal ejection fraction (EF) at rest. The model with only resting indices yielded a diagnostic capability comparable to the simple measure of EF response to exercise (area under receiver operating characteristic curve = 89% and 91%, respectively). Both the exercise and rest plus exercise models gave better results (area = 94% and 97%, respectively), but only the rest plus the exercise model was better than the EF response alone ($p < 0.001$). Thus (a) if resting studies alone are performed, the diagnostic potential of RNA may be improved by combining several indices of resting function; and (b) combined rest and exercise data may improve the sensitivity of RNA in detecting CAD over what could be obtained with the EF response to exercise alone.

J Nucl Med 30:1966–1971, 1989

Radionuclide angiography (RNA) has proven to be useful in the diagnosis of coronary artery disease (CAD) (*1–3*). Among the quantitative measurements of left ventricular (LV) function derived from RNA, the exercise ejection fraction (EF) and the change in EF from rest to exercise have been considered the most important indicators for detecting CAD (*3–6*). In the last few years several other quantitative indices of LV function derived from the LV volume curve at rest have been shown to differ between normal and CAD subjects (*7–11*). These parameters have usually been considered of marginal clinical utility because when taken alone they frequently possess poor sensitivity and/or specificity. In addition, many of them are correlated with each other (*7,8*), or with such factors as heart rate and age (*12, 13*). However, while not possessing a very high sensitivity and/or specificity when taken alone, these indices might be used in concert with the EF response to exercise (that is, the change in EF from rest to exercise) to increase the overall ability of RNA to distinguish normal subjects from those with CAD. In addition, some subjects cannot be studied during exercise.

We hypothesized that combining several resting indices might improve the diagnostic capabilities of RNA. To test this hypothesis, we used the technique of multiple regression analysis. While this technique has been used before (*5, 6, 14*), it has not been applied to the situation studied here, namely the addition of new indices of LV function, particularly descriptors of diastolic function, in order to determine whether the diagnostic capability of RNA might be enhanced.

Received Jan. 20, 1989; revision accepted July 24, 1989.

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METHODS

Study Population

We studied 111 patients with proven CAD documented by coronary arteriography, and 65 normal volunteers. The 65 normal volunteers were completely asymptomatic and had normal physical examinations (including blood pressure), rest electrocardiograms, and echocardiograms. All subjects over age 60 yr also underwent exercise electrocardiography; all had normal ST segment responses. There were 40 men and 25 women, ranging in age from 21 to 77 yr (mean 43 ± 16). The patients with CAD had no evidence of previous myocardial infarction by history or electrocardiography, no other associated cardiac disease (including hypertension), and normal EF at rest by RNA. The lower limit of normal for resting EF is 45% in our laboratory (*1,2*). Cardiac drugs are routinely discontinued for RNA in our laboratory; only those patients in whom such drugs were withdrawn before evaluation were included in the study. There were 88 men and 23 women, ranging in age from 31 to 70 yr (mean 54 ± 9).

Coronary Arteriography

All the patients with CAD underwent coronary arteriography in multiple left and right anterior oblique projections, according to the percutaneous femoral technique. Coronary artery stenosis was defined as ≥ 50% reduction in luminal diameter. Of the 111 CAD patients, 49 (44%) had stenosis of one major coronary artery, 28 (25%) had stenosis of two coronary arteries, 28 (25%) had stenosis of all three major coronary arteries, and six (5%) had left main CAD.

Radionuclide Angiography

RNA was performed at rest and during maximum symptom limited exercise in the supine position (*1,2*). Before imaging, red blood cells were labeled in vivo with technetium-99m (^{99m}Tc) (*15*). The radionuclide data were acquired using a conventional Anger camera equipped with a high sensitivity, parallel hole collimator oriented in a modified left anterior oblique (LAO) projection. High temporal resolution (10–20 ms/frame) cardiac image sequences were constructed by computer-based electrocardiographic gating, with the use of list mode data acquisition, exclusion of extrasystolic and postextrasystolic cycles and combined forward and reverse gating from the R wave (*1,2,16–18*). LV time-activity curves, representing relative changes in LV volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction using a fixed LV region of interest (ROI). The image sequence and time-activity curves were constructed without the use of temporal smoothing processes. A total of 10 to 12.5 million counts were acquired for each rest study. For exercise studies, imaging was begun shortly after onset of exercise, but only that portion of the data series that occurred during maximum exercise, encompassing the final 2 to 2.5 min of exercise, was selected for analysis.

LV-EF at rest and during exercise was determined by computer analysis of the time-activity curve (*1,2,17*), and the EF response to exercise was defined as exercise EF minus rest EF. Other indices of LV function measured at rest were the peak ejection rate, peak filling rate, time-to-peak ejection rate, time to peak filling rate, and time to end systole. Peak ejection rate and peak filling rate were calculated by fitting a third order polynomial function to the limited portion of the LV volume curve representing the ejection and rapid filling phase of the cycle using a least square method (*18*). Both were expressed relative to end diastolic counts (end diastolic volumes per second) (*7,19*). The time-to-peak filling rate was measured from end systole to the time of occurrence of peak filling rate (*7,19*). The reproducibility of these measurements of LV function in patients with CAD with normal LVEF at rest has been reported previously (*20*).

Discriminant Analysis

Discriminant analysis (*21,22*) was applied to the parameters of LV function listed in Table 1. Using these parameters, three different models were developed. In the first model only the rest variables were allowed to enter the discriminant function (rest model). This model might be applied in practice to patients who are unable to exercise. In the second model (exercise model) only variables obtained during exercise, including the change in EF from rest to exercise, were included. In the third model (rest plus exercise model) all rest and exercise variables were included. In each of these three models,

TABLE 1
Indices of Left Ventricular Function in Normal Subjects and in Patients with Coronary Artery Disease*

Variable	Normal volunteers	Coronary artery disease patients	p Value
Age	43 ± 16	54 ± 9	<0.0001
Rest			
EF at rest (%)	56 ± 6	56 ± 7	n.s.
PER (EDV/sec)	−2.7 ± .4	−2.9 ± .6	<0.05
TPER (ms)	195 ± 19	185 ± 21	<0.01
TES (ms)	367 ± 26	348 ± 37	<0.001
PFR (EDV/ec)	3.3 ± .7	2.4 ± .7	<0.001
TPFR (ms)	149 ± 27	169 ± 31	<0.001
rest R-R (ms)	922 ± 162	863 ± 145	<0.001
Exercise			
Exercise EF Response (%)	11 ± 7	−4 ± 10	<0.001
Exercise R-R (ms)	436 ± 53	536 ± 75	<0.001

*EDV = end diastolic volume; EF = ejection fraction; exercise EF response = exercise EF minus rest EF; PER = peak ejection rate; PFR = peak filling rate; TES = time to end systole; TPER = time to peak ejection rate; TPFR = time to peak filling rate.

the patients' age was also among the variables investigated. A fourth model was also chosen for comparison purposes, namely the magnitude of the change in EF occurring from rest to exercise. In each model, the R-R interval data were obtained from the gated equilibrium data rather than from an ECG rhythm strip. Thus, the exercise R-R intervals represent the average heart rate during the last 2 to 2.5 min of peak exercise rather than the peak heart rate itself. The gated mean R-R intervals were chosen as they correspond exactly to the cardiac cycles from which the other gated indices of LF function were computed.

Statistical Analysis

Values are expressed as mean ± 1 s.d. Differences between the two groups were assessed for significance with the unpaired t-test. Discriminant functions (*21, 22*) were obtained applying the stepwise analysis (*23*) to RNA measurements of LV function against a discrete end point (normal = 0, disease = 1). The stepwise procedure automatically adds or removes variables on the basis of the F values (*23*). A partial F-test (*23*) was used to assess the usefulness of new predictors. The relative contribution of each variable to each of the three models was determined by comparing the standardized coefficients (*24*). The larger the magnitude of the standardized coefficient of a variable, the greater the contribution of that variable to the equation describing the model.

After the stepwise procedure had selected the variables in each model, the diagnostic value of the discriminant functions were assessed. To accomplish this, the patients with CAD and the normal volunteers were randomly divided into subgroups in which the relative frequencies of normal subjects and patients with 1, 2, and 3 vessel and left main disease were the same as in the total group. Each subgroup omitted from the analysis resulted in recomputing the coefficients of the discriminant functions, which were then used to classify the subjects of the omitted subgroup. In this way, the equations used to group any subject did not include the results of that subject. For each model and for the EF response to exercise a receiver operating characteristic curve was constructed (*25, 26*). A difference in area under these curves defined the difference in diagnostic capability between different models (*25, 26*). Statistical comparisons of these areas were performed using the method of Hanley and McNeil (*27*).

RESULTS

In examining the results which follow, it should be emphasized that the purpose of this study was not to characterize the absolute diagnostic capability for the various models. Instead, our primary concern was to compare the relative ability of the models to each other and to assess the improvement (if any) obtained by combining several resting indices of LV function or by adding them to the usual EF response to exercise.

Patients with CAD

All the variables considered were significantly different between normal volunteers and patients with CAD (Table 1), except rest EF (the latter finding being expected on the basis of the selection criteria). Increased peak ejection rate and reduced time to peak ejection rate and time to end systole in the patients with CAD compared to the normal volunteers might reflect the significant difference in resting heart rate between these subjects, since these three variables are influenced by heart rate. However, the significant different values obtained between the two populations in the diastolic filling variables, with reduced peak filling rate and prolonged time to peak filling rate in the patients with CAD, were opposite to the directional changes that might be anticipated on the basis of heart rate differences alone.

Discriminant Analysis

The variables automatically selected by the stepwise procedure for each the three discriminant models are shown in Table 2; in each instance, the variables shown were only those chosen automatically by the stepwise procedure. Table 2 also shows the standardized coefficients of each of the variables, in order to compare the relative contribution of each to the three models. Although age was one of the variables considered in the analysis, the stepwise procedure did not itself select age in any of the models. Despite very similar EF at rest between the two groups of subjects (Table 1), resting

TABLE 2
Discriminant Functions*

Rest model		Exercise model		Rest plus exercise model	
Variables	S.C.	Variables	S.C.	Variables	S.C.
PFR	0.42	Exercise EF	0.56	Exercise EF	0.48
TPER	0.35	R-R during exercise	0.33	PFR	0.45
TPFR	0.25			R-R during exercise	0.22
EF at rest	0.20			R-R at rest	0.16
R		0.65 (0.65)		0.73 (0.73)	0.78 (0.78)
R square		0.42 (0.43)		0.53 (0.53)	0.61 (0.61)
SEE		0.372 (0.371)		0.366 (0.366)	0.306 (0.307)

*S.E.E. = standard error of the estimate; S.C. = standardized coefficients. Other abbreviations as in Table 1.
Values in parentheses indicate results obtained by forcing age into the models.

EF was selected as a significant variable in the first model in which only resting data were considered (Table 2). This may reflect differences in the frequency distribution of the EF data between the two groups. In the CAD patients, the EF distribution showed positive skewness (coefficient of skewness = 0.69, $p < 0.01$), whereas in the normal subjects the frequency distribution of EF showed no significant skewness (coefficient of skewness = 0.22, p = N.S.). Rest EF had the least relative contribution of the four variables chosen for the rest model (Table 2) and did not contribute to either the exercise or the rest plus exercise model.

In the case of the rest plus exercise model, the stepwise procedure was employed to determine which resting indices were most valuable to include with the exercise data in order to optimally distinguish normal volunteers from patients with CAD. The resulting parameters, as chosen automatically by this procedure, were rest R-R interval and rest peak filling rate. The value of adding these two variables to the previously selected stress variables in the exercise model (exercise R-R interval and EF response to exercise) to form the rest plus exercise model was assessed by a partial F-test, which suggested an improvement of the rest plus exercise model over the exercise model alone ($p < 0.001$ for each rest variable after all the others had been included in the model). Previous data indicate that many indices of LV function obtained from RNA are influenced by age (*12, 13, 28*); in addition there was a significant age difference between the patients with CAD and the normal subjects (Table 1). For these reasons we wished to examine further the effect of including age in the models. However, when age was forced to enter the discriminant functions, the partial F-test did not show any usefulness in adding age to each of the three models. It should also be noted that forcing age into each of the equations did not significantly alter the results (Table 2).

Receiver Operating Characteristic Curves

The three models proved to be helpful in separating patients with CAD from normal subjects. Each subject was classified using the equations that were developed after omitting that subject from the computation of the coefficients of each model. The receiver operating characteristic (ROC) curves for the three models and for the EF response to exercise are shown in Figure 1. The area under the receiver operating characteristic curve for the rest model (89% ± 3%) was not significantly different from that of the EF response to exercise alone (91% ± 2%) and from that of the exercise model (94% ± 2%) (Fig. 2). The area under the receiver operating characteristic curve for the rest plus exercise model (97% ± 1%) was significantly larger than that of the EF response to exercise ($p < 0.001$) and that of the rest model ($p < 0.005$), but not than the area of the exercise model ($p = 0.08$) (Fig. 2).

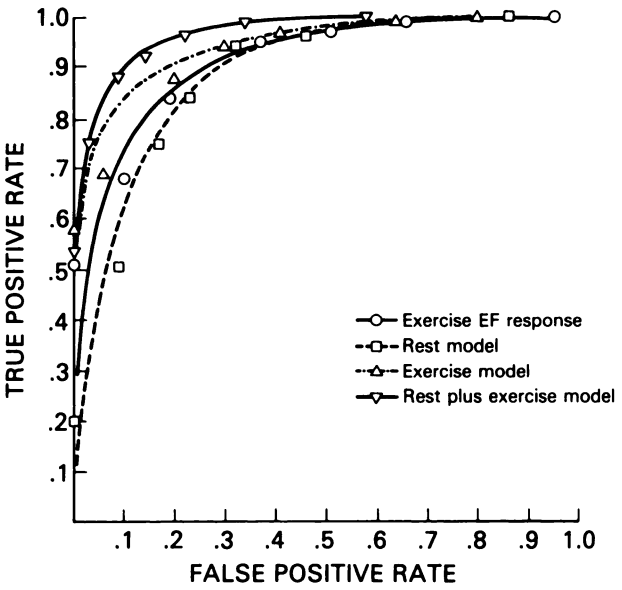

FIGURE 1
ROC curves for patients with CAD and normal subjects. From the lowest to the highest, these curves represent the rest model, the exercise EF response (exercise EF minus rest EF) alone, the exercise model, and the rest plus exercise model.

DISCUSSION

The exercise EF, the change in EF with exercise and the detection of wall motion abnormalities are the most widely used indicators for the detection of CAD with RNA. We did not use the presence of wall motion abnormalities during exercise as an additional criterion in this study, despite its known diagnostic value (*1–6*), since our purpose was not to determine the absolute diagnostic capability, but rather to compare the relative improvement to be gained by taking not one but several

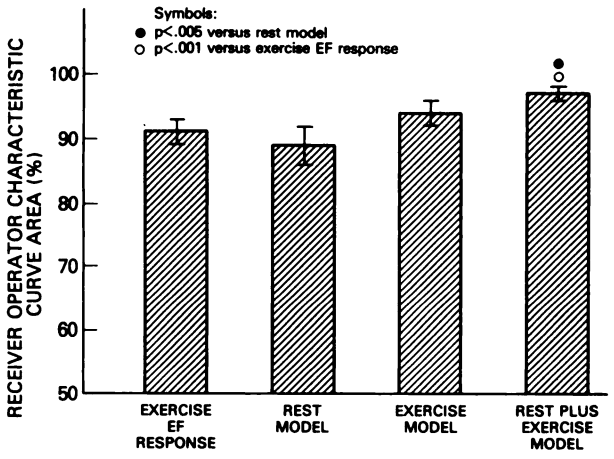

FIGURE 2
ROC curve areas for patients with CAD and normal subjects. Each bar represents a mean value and its standard deviation. An area of 50% is equivalent to an information content of 0.

quantitative indices of LV function by RNA in distinguishing patients with CAD from normal subjects.

The sensitivity we observed using the EF response to exercise alone was lower than previously reported values (*2, 3*). This discordance could be due to patient selection differences (as we excluded patients with evidence of prior myocardial infarction and abnormal EF at rest) or to different criteria to define the significance of coronary stenosis by arteriography.

The result for the rest model suggests that rest variables used in concert might help distinguish CAD patients from normal subject, as least as well as an exercise test in which only the change in EF with exercise was evaluated. However, it must be emphasized that abnormalities in LV diastolic filling at rest are not specific and are present in many diseases other than CAD (*29, 30*). This would limit the usefulness of this model in patients with hypertension. When indices of LV function at rest were added to the exercise model, i.e., the rest plus exercise model, the best result in terms of area under the receiver operating characteristic curve was obtained.

Since age is correlated with certain RNA measurements (*12, 13, 28*), particularly those included in the discriminant function, it was not surprising to find that age was not one of the parameters selected by the stepwise procedure. The apparent contrast of this finding with previous reports (*12, 13, 28*) of an age correlation presumably arises because the age dependance was already taken into account by the inclusion of several parameters known to be correlated with age. In fact, when age was forced as a variable into each of the three models, it did not alter the results (Table 2). These results show that, although there is an age dependance of many indices of LV function, age alone does not explain the significant difference observed between normal volunteers and the patients with CAD once the other variables are included in each model (as shown by the partial F-test).

The addition of rest variables (in this case peak filling rate and R-R interval at rest) to the exercise data appears to improve the differentiation of CAD patients from normal subjects. These results are different from previous data obtained by Austin and Jones (*9*). This difference could be due to methodological differences, since we used equilibrium RNA while the previous data were obtained using the first pass technique (*9*). Of even greater importance, however, are patient selection factors. We studied normal volunteers as a control group, whereas the previous report compared patients with three vessel disease to a control group consisting of subjects with chest pain and angiographically normal coronary arteries. Cannon et al. (*31, 32*) have shown that many patients with chest pain and normal coronary arteriograms have dynamic abnormalities of coronary vasodilator reserve, and that such abnormalities, when present, are often associated with both abnormal diastolic function at rest and systolic dysfunction with exercise. These data (*32*) show that the subjects with chest pain and normal coronary arteriograms are not a homogeneous population. Moreover, Rozansky et al. (*33*) and Leighton and Fraker (*34*) have pointed out that normal volunteers and subjects with chest pain but normal coronary arteriograms are not equivalent standards for cardiac normality, often because selection of patients with chest pain and normal coronary arteries involves a post-test referral bias (in which patients undergo coronary ateriography because of a previously abnormal RNA) (*35*). Because of the heterogeneity of patients with chest pain and normal coronary arteriograms and the inability to exclude a post test referral bias in such patients, we chose normal volunteers as control group. Although this particular asymptomatic control group prevented us from evaluating the diagnostic efficacy of these models if applied to a population with chest pain, this was not our goal. Rather, our goal was to compare the three models with each other and with the standard clinical method of measuring only exercise/rest EF response. While the use of these models derived from RNA yields excellent results when applied to distinguish patients with proven CAD from normal volunteers, this method should be tested in an unselected population of subjects with chest pain and suspected CAD to determine the true clinical potential of these models in identifying patients with CAD.

CONCLUSIONS

In the subjects we studied, a combination of indices of LV function obtained only at rest by RNA gave a diagnostic capability comparable to that of the EF response to exercise. Moreover, the addition of some of the resting indices (i.e., peak filling rate and R-R interval at rest) to the exercise variables improved the ability of RNA to distinguish patients with CAD from normal subjects. We have not determined the sensitivity or specificity of these methods in an unselected patient population with chest pain. However, our data do show that discriminant analysis yields better separation of CAD patients from normal subjects than does the change in EF during exercise. Thus, we speculate that this analysis may also yield greater diagnostic accuracy in identifying patients with CAD in the population at large.

ACKNOWLEDGMENTS

The authors thank Edward Lakatos, PhD, and Robert F. Wagner, PhD, for their valuable suggestions.

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