Evaluation of the Incremental Diagnostic Value and Impact on Patient Treatment of Thallium Scintigraphy

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The incremental diagnostic yield of exercise ^{201}Tl scintigraphy with visual and quantitative analysis was determined in 191 patients with known or suspected coronary artery disease (CAD). The coronary arteriogram was used as the gold standard. After pre-test clinical and exercise electrocardiographic data were taken into consideration, scintigraphy was found to have additional diagnostic value both in the diagnosis of CAD and of multivessel disease, with quantitative analysis being superior to visual analysis. The impact of ^{201}Tl scintigraphy on the patient's treatment—conservative treatment versus revascularization—was also evaluated. The impact was relatively low, as the decision for revascularization was based primarily on the angiographic result and the severity of the anginal pain. This result reflects only the decision making process used in our clinic and permits no conclusion to be made concerning the possible value of ^{201}Tl scintigraphy in this type of medical decision making process.

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In clinical cardiology, daily practice requires the making of decisions concerning the treatment of patients suffering from coronary artery disease (CAD). Optimal use of all patient data, including noninvasive and invasive test results, is of crucial importance in the diagnosis of CAD. Furthermore, each test should add diagnostic value. Much clinical data and the results from investigations have influenced the decision making process. Detailed decision analyses have been published, based on objective criteria concerning complications and survival (*1*). Exact knowledge of the influence of these factors in clinical practice is, however, scarce. A description of the impact of these factors could reveal the exact decision making process which can then be tested against accepted standards.

The purpose of this study was two-fold. First, the evaluation of the additional diagnostic yield of ^{201}Tl myocardial scintigraphy in predicting the presence and extent of CAD after clinical and exercise electrocardiographic variables are considered. Second, we report on the impact that ^{201}Tl scintigraphy has had on the decision making process in cardiac patients at our institution.

METHODS

Patient Population

The patient series was comprised of 160 males and 31 females with a mean age (s.d.) of 54 (9) yr referred to our cardionuclear department for detection and evaluation of CAD. After clinical examination, rest and exercise electrocardiography in conjunction with stress and redistribution ^{201}Tl myocardial scintigraphy and coronary arteriography tests were performed. Those patients with a disease history of the following categories were excluded from the study: coronary bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA); valvular, congenital or cardiomyopathic heart disease; inadequate exercise ergometry (less than 85% of the age-predicted maximal heart rate) in the absence of angina or ischemic ST-depression.

Coronary Angiography

The coronary arteriogram utilized by Sones et al. (*2*) was used as the gold standard to determine the presence or absence of CAD. The arteriograms were visually interpreted by two cardiologists unaware of the other's findings. Disagreement between the two was resolved by a third independent interpreter. Obstruction of at least 50% of the luminal diameter of one or more of the major coronary branches was classified as positive for CAD or multivessel disease (MVD), respectively.

Exercise Electrocardiography

Exercise electrocardiography was performed on a bicycle ergometer. For all patients, drugs, such as beta-blocking agents and calcium antagonists, were discontinued 24 hr before the test. An ischemic ST response was indicated by: (a) 1 ml or greater ST-

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depression within 80 msec of the J point and (b) in the presence of ST-segment abnormalities, an additional ST-depression of 0.2 mV or more. An exercise ECG was equivocal when resting ST-segment abnormalities were present, with the exclusion of (b), or conduction disturbances such as a bundle branch block or accelerated conduction (Wolff-Parkinson-White syndrome).

Exercise ^{201}Tl Scintigraphy

An intravenous bolus of 74 MBq (2 mCi) of ^{201}Tl was injected at maximal exercise, which was continued for 1 min after injection. Imaging was performed in the anterior, 30° and 70° left anterior oblique views at approximately 5 min and 4 hr after injection with a minimum of 300,000 counts per image.

Visual Analysis

Exercise and re-perfusion images were interpreted by means of semiquantitative analysis (*3,4*). Each image was divided into five roughly equal segments for a total of 15 segments. The ^{201}Tl scintigrams of the initial uptake and the delayed interval or redistribution phase were inspected without smoothing or background subtraction. Thallium-201 activity in each segment was graded from 1 to 3 (1 = no defect, 2 = possible defect, 3 = definite defect). The total score for the three views was between 15 and 45. The scintigram was considered abnormal when the total score was higher than 18 (*5*).

Computer Processing and Analysis

The technique used for computer processing and quantitative analysis of ^{201}Tl images has been described elsewhere (*5*). Briefly, the computer algorithm involved the following steps: each image was compensated for tissue crosstalk (*6*); an ellipse was centered around the left ventricle; radiating vectors (120) spaced at three-degree intervals were constructed from the center of the left ventricle; the maximal ^{201}Tl activity point was plotted along each vector radius. The combination of all 120 points resulted in a circumferential profile (*7*). In addition to this, washout circumferential profiles were also generated by calculating the percentage washout for each point from the time of stress to the time of delayed imaging. The circumferential profiles were interpreted by a computer program which compared each curve to a reference curve. The scintigram was considered abnormal when an arc consisting of at least 28 consecutive sample points fell below the normal limit, as determined by the combination of the uptake scintigram and washout curve (*5*).

Statistical Analysis

Two analyses were performed. In the first, a logistic regression function was estimated for the prediction of the presence of CAD based on clinical, exercise and scintigraphic data. Due to the high prevalence of CAD in patients with a previous myocardial infarction, these patients (n = 58) were excluded from the first analysis. All variables presented in Table 1 were included in the analysis.

In the second analysis, a logistic regression function was estimated for the prediction of MVD in all patients (n = 191). Based on the coronary arteriogram, patients were classified as having no MVD (no CAD or single-vessel disease), or as having MVD (two or three vessels with 50% or more occlusion).

Both analyses were performed in a stepwise fashion, taking first the variable that gave the largest contribution to the difference between the two groups. Successive variables were then added to the regression equation in order of the magnitude of their effects upon the final result. Each time a new variable was entered into the analysis, its influence, together with the parameters already entered, was calculated.

The incremental diagnostic value of the ^{201}Tl scintigraphic

TABLE 1
Variables Used in the Multivariate Analysis Together with the Odds Ratios to Indicate the Possible Presence of CAD and the 95% Confidence Intervals

Variable	Reference group	(n)	% CAD	Study group	(n)	% CAD	Odds ratio	95% CI
Age (yr)	<55	(63)	52%	55–65	(56)	86%	5.5	2.2–13.4
				≥65	(14)	64%	1.6	0.5–5.4
Gender	F	(27)	33%	M	(106)	76%	6.5	2.6–16.2
Obesity index	≤27	(106)	65%	>27	(27)	78%	1.9	0.7–5.1
Anginal pain NYHA	I	(51)	27%	II	(49)	92%	29.7	9.0–98.1
				III	(22)	95%	55.5	6.8–452
				IV	(11)	91%	26.5	3.1–226
Angina during test	no	(93)	54%	yes	(40)	100%	∞	—
Ischemic ST	neg	(51)	43%	equi.	(16)	56%	1.7	0.5–5.3
				pos	(66)	89%	11.1	4.3–29.0
Other exercise data								
% Max. pred. HR ≥95	yes	(76)	54%	no	(57)	86%	5.2	2.2–12.5
peak SBP ≥175	yes	(74)	64%	no	(59)	73%	1.5	0.7–3.2
RPP ≥25	yes	(78)	55%	no	(55)	85%	4.8	2.0–11.4
Scintigraphic findings								
VA	neg	(62)	42%	pos	(71)	90%	12.7	5.0–32.1
QA	neg	(70)	41%	pos	(63)	97%	43.1	9.8–191

CI = confidence interval; HR = heart rate (bpm); equi. = equivocal; pos = positive; % Max. pred. HR = % maximal age-predicted heart rate (bpm); SBP = systolic blood pressure (mm/Hg); RPP = Rate-pressure product (heart rate × blood pressure/1000); Obesity index = weight (kg)/length^2(m^2); VA = visual analysis; and QA = quantitative analysis.

results was assessed when they were added sequentially into the model. The analysis was performed for the diagnosis of both CAD and MVD. The improvement of the diagnostic value after the inclusion of scintigraphic data was tested statistically using the likelihood-ratio test.

Impact on Patient Treatment

A logistic regression function was estimated for the prediction of the patient treatment (revascularization versus conservative treatment), based on clinical, exercise and scintigraphic data. All variables presented in Table 3 were included in the analysis. The treatment of each separate coronary vessel (573 vessels in 191 patients) was related to scintigraphic and angiographic findings from the corresponding vascular area.

This logistic regression function, however, included a random component for each patient in order to cope with the fact that the observations of the coronary arteries of a single patient were correlated. The variance of the random component was estimated jointly with the regression parameters of the logistic function.

RESULTS

Patients' Characteristics

The clinical, electrocardiographic and scintigraphic characteristics of the patients analyzed for CAD (n = 133) are summarized in Table 1. As was previously mentioned, patients with previous Q-wave myocardial infarction (n = 58) were not included in this analysis. The prevalence of CAD was 68% (90/133). Test termination due to anginal pain was a definite diagnostic sign of CAD, resulting in an indefinite high odds ratio.

Multivariate Analysis in the Diagnosis of CAD

Forty of 133 patients had anginal pain during the test and were excluded from the multivariate analysis, since all had CAD on catheterization. Anginal pain was a definite sign for the presence of CAD, and the scintigram results will not add to the diagnosis of CAD in these patients. Three variables from Table 1 were selected in the multivariate analysis, which added significant diagnostic value. These variables were: severity of anginal pain, gender and classification of the ST-segment during exercise. Other variables did not have additional diagnostic value. These three variables are listed in Table 2, Analysis 1. The additional diagnostic value of ^{201}Tl scintigraphy (visual analysis) to the diagnosis of CAD was nearly significant (Analysis 2: odds ratio 3.9, $p = 0.065$). The additional diagnostic value of ^{201}Tl scintigraphy (quantitative analysis) to the diagnosis of CAD was significant (Analysis 3: odds ratio 42.1, $p < 0.01$).

Pre-scintigraphic and post-scintigraphic probabilities for the presence of CAD were estimated using the logistic regression function reported in Table 2. According to this model, 34% (32/93) of the patients had a high pre-scintigraphic probability ($p > 0.80$) for CAD. Twenty-nine of 32 patients had CAD at angiography. The percentage of false-negative scintigraphic results in this group was 34% (10/29 for visual analysis) and 45% (13/29 for quantitative analysis). Furthermore, in the group of patients with anginal pain during the test (n = 40), all those with a positive coronary angiogram, 20% (8/40 for visual analysis) or 23% (9/40 for quantitative analysis), had negative scintigrams. When added together, in the group with a high probability for CAD, 26% (18/69) had a false-negative scintigraphic test result at visual analysis and 32% (22/69) at quantitative analysis.

Multivariate Analysis in the Diagnosis of MVD

The analysis outlined above was also applied in the diagnosis of MVD. The prevalence of MVD was 53% (102/191). Five variables were selected in the logistic

TABLE 2
The Incremental Diagnostic Value of ^{201}Tl Scintigraphy

Variable	Analysis 1		Analysis 2		Analysis 3	
	Odds ratio	(95% CI)	Odds ratio	(95% CI)	Odds ratio	(95% CI)
Angina (NYHA classification)						
II	37.8	(6.3–228)	24.4	(4.2–142)	23.7	(3.9–142)
III	10.7	(0.9–124)	10.6	(0.8–141)	4.8	(0.3–70.3)
IV	145	(4.9–4363)	174	(5.2–5832)	881	(4.5–1.7 10^5)
Gender (male)	21.7	(3.5–136)	14.9	(2.3–94.2)	33.8	(1.8–619)
Ischemic ST						
Equivocal	0.3	(0.04–2.9)	0.2	(0.03–2.5)	0.4	(0.002–1.1)
Positive	10.3	(2.1–50.1)	7.1	(1.4–36.5)	6.1	(0.9–41.0)
Constant	0.014	(0.002–0.10)	0.014	(0.002–0.11)	0.006	(0.0002–0.13)
Scintigraphy VA		—	3.9	(0.9–16.3)		—
Scintigraphy QA		—		—	42.1	(3.5–505)

Logistic regression function of the probability for CAD (with odds ratios and 95% confidence intervals). Analysis 1: based on clinical and exercise data only. Analysis 2: addition of scintigraphic data with visual analysis. Analysis 3: addition of scintigraphic data with quantitative analysis.

VA = visual analysis and QA = quantitative analysis.

regression function: angina during the test, previous MI, classification of ST-segment depression during exercise, gender and the severity of anginal pain. The additional diagnostic value of ^{201}Tl scintigraphy (visual analysis) to the diagnosis of MVD was significant (odds ratio 3.6, $p < 0.001$). The additional diagnostic value of ^{201}Tl scintigraphy (quantitative analysis) to the diagnosis of CAD was also significant (odds ratio 4.9, $p < 0.001$).

Impact of ^{201}Tl Scintigraphy on Patient Treatment

Of all patients, 43% (83/191) underwent revascularization within one year after coronary angiography and ^{201}Tl scintigraphy. Eighteen patients (9.4%) had had PTCA; 65 patients (34%) had had CABG. One hundred and eight patients (57%) were treated conservatively. As the outcome of treatment was evaluated per coronary vessel, a correction was made for the fact that the treatment of the three coronary vessels per patient is highly correlated. A total of 573 vessels in 191 patients were analyzed. Clinical, electrocardiographic and scintigraphic characteristics are summarized in Table 3. The endpoints were: conservative treatment versus revascularization (CABG or PTCA).

The highest odds ratios were related to coronary angiography and to the severity of anginal pain. All variables presented in Table 3 were entered into a multivariate analysis model. The parameters that significantly predicted the outcome of patient treatment were: angiographic result, gender, severity of anginal pain, percentage of maximal age-predicted heart rate, ischemic ST response and age (Table 4). Thallium-201 scintigraphic results had no additional value in the decision making process. Stratification of the scintigraphic findings in fixed and reversible defects did not alter this.

TABLE 4
Results of Multivariate Analysis with the Variables Significantly Predictive for the Treatment per Vessel (Conservative Treatment Versus Revascularization)

Variable	Odds ratio	95% CI
Angiography	159.7	24.1–1057
Gender (male)	14.5	1.8–120
Angina (NYHA)		
II	7.2	1.3–38.5
III	63.9	5.2–779
IV	91.8	3.1–2690
% Max. pred. HR <140 bpm	14.2	2.1–98.4
Ischemic ST response		
Equivocal	2.0	0.3–13.3
Positive	7.1	1.2–42.4
Age		
55–65 yr	3.1	0.8–12.3
>65	1.1	0.1–9.1
Constant	9.3E–6	0.1E-6–0.8E-3

CI = confidence interval and % Max. pred. HR = % maximal age-predicted heart rate.

DISCUSSION

The results of this study show an additional diagnostic value of ^{201}Tl scintigraphy in the diagnosis of both CAD and MVD in our study group. A positive ^{201}Tl scintigram alone was related with an odds ratio for CAD of 12.7

TABLE 3
Variables Used in the Multivariate Analysis Together with the Odds Ratios and 95% Confidence Interval for Revascularization (CABG or PTCA) per Coronary Vessel

Variable	Reference group	(n)	% Revascularization	Study group	(n)	% Revascularization	Odds ratio	95% CI
Age (yr)	<55	(282)	27%	55–65	(225)	54%	24.7	5.7–107
				≥65	(66)	39%	3.0	0.3–31.7
Gender	F	(93)	13%	M	(480)	44%	57.3	4.7–706
Anginal pain (NYHA)	I	(189)	12%	II	(234)	42%	32.0	5.2–199
				III	(117)	66%	231	35.2–1508
				IV	(33)	76%	676	5.7–7793
Angina during test	no	(393)	28%	yes	(180)	64%	78.2	10.9–561
Ischemic ST	neg	(186)	17%	equi	(102)	36%	4.7	0.7–32.8
				pos	(285)	55%	38.0	9.6–150
History of MI	neg	(399)	35%	pos	(174)	48%	6.7	1.7–26.2
Other exercise data								
% Max. pred. HR	≥95	(306)	20%	<95	(267)	61%	43.4	12.7–148
peak SBP	≥175	(291)	30%	<175	(282)	48%	11.0	3.1–39.4
RPP	≥25	(306)	22%	<25	(267)	59%	46.0	12.4–171
Obesity index	≤27	(456)	41%	>27	(117)	33%	0.3	0.06–1.4
Angiography	Norm	(283)	9%	Abn	(290)	68%	359	69.3–1856
LV function	Norm	(333)	31%	Abn	(210)	58%	33.1	6.6–165
Scintigraphy	Norm	(333)	23%	Abn	(240)	61%	7.8	3.7–16.5

See Table 1 for definitions.

(visual analysis) and of 43.1 (quantitative analysis) (Table 1). These findings suggest a high diagnostic value of ^{201}Tl scintigraphy, with better results when quantitative analysis is applied (*8*). When evaluating a diagnostic test, however, the pre-test probabilities and prevalences need to be taken into consideration. The additional diagnostic yield can be determined using multivariate analysis. Only a few studies address the additional yield of ^{201}Tl scintigraphy after exercise electrocardiography in the diagnosis of presence and extent of CAD (*9,10*).

In the diagnosis of the presence of CAD, only patients without previous Q-wave myocardial infarction were studied, since in these patients significant CAD is almost invariably present. Additionally, patients with anginal pain during the test all had CAD at coronary angiography. These patients were also excluded from further analysis. The remainder of the patients ($n = 93$) had less definite signs and symptoms of CAD. By taking clinical and exercise data into consideration, ^{201}Tl scintigraphy with quantitative analysis contributed significantly to the diagnosis of CAD.

In the diagnosis of MVD, no patients were excluded from the analysis since there were no definite signs indicating MVD. After clinical and exercise data were taken into consideration, ^{201}Tl scintigraphy, both after visual analysis and after quantitative analysis, had significant diagnostic value.

In the present study group, 77% (72/93) had a high pre-scintigraphic probability for CAD ($p > 0.80$). This high probability corresponded with a positive angiogram in 96% (69/72) of the cases. In these patients, a high proportion of false-negative ^{201}Tl scintigrams were found: 26% (18/69) with visual analysis and 32% (22/69) with quantitative analysis. This illustrates the general Bayesian rule for all diagnostic tests, in that the highest diagnostic yield is to be expected in cases with an equivocal, not a high or a low, pre-test probability for a particular outcome.

In determining the impact of ^{201}Tl scintigraphy on the decision of whether to treat a patient with angina invasively or conservatively, our data show that the impact was low. In multivariate analysis, no significant attribution to the decision making process could be demonstrated.

In many studies, the value of ^{201}Tl scintigraphy for the detection of CAD was evaluated using coronary angiography as a gold standard. More recently, however, ^{201}Tl scintigraphy has been regarded as giving additional diagnostic value to angiography. When angiography shows stenoses, ^{201}Tl shows the relative impairment of coronary flow. Thallium-201 scintigraphy is used to assess myocardial viability prior to revascularization (*11*). Patients with chronic ischemia show regional dysfunction despite having viable myocardium (*12*). Thallium-201 imaging can be useful in determining the degree of viability in these cases. In many studies, it has been shown that if a revascularization procedure has been successful, ^{201}Tl imaging abnormalities should reverse (*11*). Based on these studies, one could argue that the ^{201}Tl result should have more influence on the decision making process. Thallium-201 scintigraphy is part of the preoperative workup in most cases in our clinic. However, the present results show that the decision to operate on a patient in our clinic is based predominantly on the angiographic result and the degree of anginal pain. The recent introduction of the ^{201}Tl reinjection study (*13*) will most likely change this negative outcome. Through the use of this technique, myocardial segmental viability is investigated prior to treatment. In this way, revascularization can be performed more selectively with a higher predictive outcome for myocardial function.

In conclusion, ^{201}Tl scintigraphy has additional diagnostic value after consideration of clinical and exercise parameters in the diagnosis of both CAD and MVD. Thallium-201 scintigraphic results do not greatly influence the decision to treat a patient conservatively or invasively in our clinic.

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