Resting electrocardiogram and stress myocardial perfusion imaging in the determination of left ventricular systolic function: an assessment enhancing the performance of gated SPET

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Abstract

This study *aimed* to determine systolic dysfunction and estimate resting left ventricular ejection fraction (LVEF) from information collected during routine evaluation of patients with suspected or known coronary heart disease. This approach was then compared to gated single photon emission tomography (SPET). *Patients having* undergone stress ^{201}Tl myocardial perfusion imaging followed by equilibrium radionuclide angiography (ERNA) were separated into derivation (n=954) and validation (n=309) groups. Logistic regression analysis was used to develop scoring systems, containing clinical, electrocardiographic (ECG) and scintigraphic data, for the discrimination of an ERNA-LVEF<0.50. Linear regression analysis provided equations predicting ERNA-LVEF from those scores. In 373 patients LVEF was also assessed with ^{201}Tl gated SPET. *Our results* showed that an ECG-Scinigraphic scoring system was the best simple predictor of an ERNA-LVEF<0.50 in comparison to other models including ECG, clinical and scintigraphic variables in both the derivation and validation subpopulations. A simple linear equation was derived also for the assessment of resting LVEF from the ECG-Scintigraphic model. Equilibrium radionuclide angiography-LVEF had a good correlation with the ECG-Scintigraphic model LVEF (r=0.716, P=0.000), ^{201}Tl gated SPET LVEF (r=0.711, P=0.000) and the average LVEF from those assessments (r=0.796, P=0.000). The Bland-Altman statistic (mean±2SD) provided values of 0.001±0.176, 0.071±0.196 and 0.040±0.152, respectively. The average LVEF was a better discriminator of systolic dysfunction than gated SPET-LVEF in receiver operating characteristic (ROC) analysis and identified more patients (89%) with a ≤10% difference from ERNA-LVEF than gated SPET (65%, P=0.000). *In conclusion,* resting left ventricular systolic dysfunction can be determined effectively from simple resting ECG and stress myocardial perfusion imaging variables. This model provides reliable LVEF estimations, comparable to those from ^{201}Tl gated SPET, and can enhance the clinical performance of the latter.

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Introduction

Early detection of left ventricular systolic dysfunction, with or without symptoms, is of great importance as medical treatment can improve the outcome and the quality of life [1-3]. Coronary heart disease (CHD) is by far the most common cause of left ventricular systolic function impairment [4] and is frequently accompanied by electrocardiographic (ECG) abnormalities

Previous studies supported a normal ECG to virtually exclude resting left ventricular systolic dysfunction and the 12-lead ECG is advocated by international guidelines as first line investigation in patients suspected of having the disorder [5-10]. However, the clinical value of a resting ECG has been disputed [11-14], whereas clinical and radiographic criteria were found to offer limited predictive information in situations other than the acute or primary care setting [15-17]. More recently, left ventricular ejection fraction (LVEF) derived from gated single photon emission tomography (SPET) myocardial perfusion scanning, with either ^{201}Tl or ^{99m}Tc compounds, has been validated successfully against other accepted techniques [18-20]. However, various limitations with this type of assessment also have been recognized [21-25], while the clinical relevance of non-gated myocardial perfusion images in predicting the level of left ventricular function has not been determined.

Based on earlier observations and the pathophysiology that underlies depression of left ventricular systolic function, we hypothesized that it is possible to predict reliably resting systolic function impairment in patients with suspected or known CHD from simple and readily available demographic, clinical, resting ECG and stress myocardial perfusion imaging data. Moreover, an estimation of resting LVEF would be feasible with a high degree of certainty. There-

fore, the aim of this study was twofold: a) to investigate the above hypothesis and develop an optimal scoring system for the assessment of left ventricular systolic function, and b) to determine the clinical value of this approach in relation to gated SPET, using equilibrium radionuclide angiography (ERNA) as the reference standard.

Patients and methods

Patient's recruitment

From our database, among all patients with suspected or known coronary artery disease referred for routine SPET myocardial perfusion imaging over a 2-year period, those having undergone the following examinations were identified: a stress-redistribution ^{201}Tl myocardial perfusion study followed by a resting ERNA assessment. During the period of collection of those data we were performing this combination of studies in patients referred for risk assessment and myocardial viability evaluation. Among patients referred for diagnostic purposes, left ventricular function was assessed in those with a higher perceived clinical probability of CHD [26] or manifestations suspicious of heart failure (breathlessness, fatigue). In a subgroup of those patients, assessed in a predefined day of the week, ^{201}Tl SPET acquisition was triggered to the ECG signal for the simultaneous assessment of left ventricular function from myocardial perfusion data.

In order to minimize the bias introduced by not enrolling consecutive patients, participants were separated into two groups. The derivation group consisted of patients presenting during the first 18 months of the study and was used to determine independent predictors of systolic dysfunction and develop scoring systems. These findings were then tested in the validation cohort including patients presenting during the last 6 months of the study period. Duplicate nuclear examinations were removed and only one assessment per patient, at the earliest available date, was entered in the study database.Demographic characteristics, medical history, symptoms, medication and the reason for testing were recorded by the physician supervising the stress. Exclusion criteria for entry in the study were a history of an acute myocardial infarction or percutaneous coronary intervention in the last month, coronary artery bypass grafting in the last six months, significant valve disease, congenital heart disease, paced rhythm, hypertrophic cardiomyopathy, digitalis therapy and atrial fibrillation or flutter. The duration of disease was estimated from the time point of the index event in the following order: a) coronary intervention, b) acute coronary syndrome, c) symptoms, d) first presentation to medical office.

Electrocardiography

All patients had a standard resting 12-lead ECG obtained before stress testing. Electrocardiograms were interpreted prospectively by the physician performing the stress without knowledge of imaging data. The observer described ECG findings and categorized them as normal or abnormal according to his best judgment, in a way similar to that employed in routine clinical practice. Patients having borderline abnormalities (minor ST-segment and T-wave changes, left ventricular hypertrophy and so forth) were placed in the abnormal category. The ECG from 100 consecutive patients was interpreted independently by two physicians (E.M. and V.S.) to assess inter-observer agreement.

Stress testing

Participants were submitted to dynamic exercise, dipyridamole or dobutamine stressing and an activity of 90-130MBq ^{201}Tl, depending on body weight, was intravenously administered prior to cessation of stress [23]. The discontinuation of cardio-active medication was left at the discretion of treating physicians, but it was ensured that nitrates were withheld for at least 12h and all patients were instructed to abstain from caffeine containing beverages and smoking for 24h.

^{201}Tl SPET acquisition, processing and analysis

Post-stress SPET acquisition was performed with a single-headed, large field of view γ-camera (APEX-SPX4, Elscint, Haifa, Israel), using an acquisition methodology that has been described previously in detail [23]. Imaging was repeated 3-4h later to assess redistribution. In a random sample of patients with no more than 6 extrasystolic beats per minute, delayed ^{201}Tl SPET acquisition was triggered to the ECG signal for the assessment of LVEF using a commercially available software (QGS, Cedars-Sinai) [18].

From the reconstructed slices the myocardium was divided into 20 segments, tracer accumulation in each segment was graded using a 5-point scale, and the sum of the stress scores (SSS) and rest scores (SRS) were calculated [27]. Fixed defects in at least two contiguous segments with moderately or severely reduced or absent tracer accumulation were considered myocardial infarction. Left ventricular dilatation was assessed semi quantitatively from both the raw data and the reconstructed mid-ventricular slices. Two different 3-point scales were used to grade the relative size of the ventricle in the thoracic cage (1, normal; 2, equivocal; 3, definite enlargement) and the relative width of the ventricular cavity to the thickest adjacent normal wall (1, cavity smaller; 2, equal size; 3, cavity wider than the wall). When both criteria were scored with 3, dilatation was classified as present and otherwise as absent.

Myocardial images were independently assessed by two experienced observers (E.M., T.S.), unaware of patients' data; discrepancies were resolved by consensus. Scan interpretation was performed prospectively to provide a report. Left ventricular ejection fraction from gated SPET myocardial imaging was calculated twice, separately by two observers, and the mean value was entered in analysis.

Equilibrium radionuclide angiography

Resting ERNA was performed immediately after the completion of myocardial perfusion imaging with 740MBq ^{99m}Tc labeled red blood cells, in the best septal view, using the same imaging system and a previously described methodology [23]. Left ventricular ejection fraction was calculated in duplicate, separately by two observers (E.M., T.S.), in the standard manner; the mean value of these measurements was incorporated in patients' report and entered in analysis. The lower limit of normality in our site is 0.50.

Statistical analysis

Continuous variables are expressed as mean ±1 standard deviation (SD) and categorical variables as numbers or proportions. Mann-Whitney statistic was used for the comparison of two independent samples of patients. The chi-square statistic, including Yates' continuity correction, and Fischer's exact test were used for categorical data comparisons. Inter-observer agreement of ECG interpretations was evaluated by Cohen's kappa statistic (κ); both the standard error of the estimate (SEE) and the percentage of recordings with identical classification are also reported.

In each category of data sets, logistic regression analysis was used to identify independent predictors of a resting ERNA LVEF<0.50 among variables with a P value<0.10 in univariate analysis. In variables from each category considered to be significant (P<0.05) were then added those of the next category to create a new model, which contained only the variables that continued to remain independent predictors and so forth. A final model was created after the addition of all significant variables from all categories in a hierarchical order (demographic characteristics, prior cardiac history, risk factors, symptoms, resting electrocardiogram, myocardial perfusion results). Since logistic regression formulas take the form of exponentials and require complex calculations, a simple linear score was created by the analysis. To accomplish this, before entered in logistic regression analysis all continuous variables were coded in a binary fashion using a cut-off point defined at the level below which the number of false positive responses exceeded the number of true positive responses in the determination of a resting LVEF<0.50 [28]. The interval with the largest values was assigned a value of one and that with the lowest values was given zero. Nominal variables were coded also with zero if absent and one if present. The coefficients of all variables provided by the regression equation were divided by the smallest coefficient and adjusted to their proportional whole integer weights. This resulted in a simple linear equation in which each variable code (zero or one) was associated with the probability of systolic dysfunction and was multiplied by its respective weight and summed to produce a composite score.

Receiver operating characteristic (ROC) analysis was used to compare the discriminatory performance of various models in the prediction of a resting ERNA LVEF<0.50 [29]. Both the area under the curve (AUC) and the SEE are reported. Linear regression analysis was used to provide equations for the prediction of the ERNA derived LVEF from the scoring systems and also to estimate the correlation between various methods of LVEF calculation. Pearson's coefficient of correlation (r) is quoted together with the 95% limits of agreement according to Bland-Altman statistic [30]. Statistical significance was accepted for P values<0.05.

Results

Patients' details

One thousand two hundred and sixty-three patients fulfilled the entry criteria. Among them 514(41%) were referred for diagnostic purposes, 536(42%) for risk assessment, 186(15%) for evaluation after a coronary intervention and 27(2%) for myocardial viability determination. At the time-point of the examination, 86(7%) patients had angiographically documented CHD and were treated medically, whereas 58(5%) patients had been submitted to percutaneous coronary interventions and 152(12%) to coronary artery bypass grafting on the grounds of chronic CHD. Among 454 patients having suffered a myocardial infarction, 82(7%) had a subsequent angioplasty and 75(6%) had undergone bypass surgery. The characteristics of the 954(76%) patients in the derivation group and 309(24%) patients in the validation cohort are listed in Table 1, allocated in subgroups according to resting ERNA LVEF.

Left ventricular ejection fraction at rest was calculated by ^{201}Tl gated SPET myocardial perfusion imaging in 373 patients (319 male and 54 female, and 286 versus 87 in the derivation and validation subsets, respectively). Among them, 209(56%) had suspected CHD, 21(6%) had angiographically documented CHD and were on medical treatment and 105(28%) gave a history of myocardial infarction in the past. Eighteen patients (5%) had undergone percutaneous coronary interventions and 45(12%) bypass surgery. An ERNA LVEF<0.50 was found in 77(21%) of these patients.

Electrocardiography and nuclear testing

All resting ECG interpretations and stress data are presented in Table 1. In 100 ECG recordings the inter-observer agreement of an entirely normal versus abnormal interpretation was very good (κ=0.949, SEE 0.035; absolute agreement in 98% of cases). In identifying particular resting ECG changes (with the priority left bundle branch block > Q wave > poor R wave progression in precordial leads > inverted T waves > ST-segment deviation > other minor abnormalities > normal) inter-observer agreement was good (κ=0.715, SEE 0.051; absolute agreement in 77% of cases).

Scintigraphic results are summarized in Table 1. Myocardial perfusion images were judged normal or near normal (SSS 0-4) in 479(38%) patients (359 in the derivation group and 120 in the validation cohort). Measurements LVEF with ERNA are also presented in Table 1. A resting LVEF<0.40 was found in 152 (12%) patients and a LVEF<0.30 in 71 (6%) patients.

Models in the determination of systolic function

Acording to the criterion used in logistic regression analysis, the dichotomous points of continuous variables were set as follows: age >60 yrs, history time >8 months, resting heart rate >70bpm, systolic blood pressure >135mmHg, SSS>10 and SRS>3. The independent variables of the models provided by logistic regression analysis and their coefficients in the determination of a resting ERNA LVEF<0.50, presented as scoring systems, are listed in Table 2. A model comprising resting ECG readings alone and a different scoring system combining ECG and scintigraphic variables are also included in that Table. These data are more readily available and reliable than clinical information.

Receiver operating characteristics analysis showed no significant difference between the Clinical-ECG-Scintigraphic and the ECG-Scintigraphic scoring systems in both the derivation (AUC 0.914, SEE 0.011 versus AUC 0.910, SEE 0.001, respectively, P=0.803) and validation subpopulation (AUC 0.866, SEE 0.028 versus AUC 0.870, SEE 0.028, respectively, P=0.920) in the discrimination of resting left ventricular dysfunction. Therefore, only the latter was entered in further analyses, as it contains fewer categories of data. In the derivation group, the ECG-Scintigraphic model was a better predictor of a resting ERNA LVEF<0.50 than both the Clinical-ECG scoring (AUC 0.847, SEE 0.014, P=0.000)

Table 1. *Characteristics of all study participants allocated in subgroups according to ERNA LVEF*

	Derivation group		
	LVEF≥0.50 (n=702)	LVEF<0.50 (n=252)	P
Age (yrs)	59.2±10.2	62.5±9.5	0.000
Male	561 (80%)	215 (85%)	0.060
Diabetes mellitus	117 (17%)	66 (26%)	0.001
Dyslipidemia	197 (28%)	89 (35%)	0.038
Hypertension	374 (53%)	113 (45%)	0.023
Smoking	220 (31%)	64 (25%)	0.078
Family history of CHD	78 (11%)	20 (8%)	0.183
Dyspnoea on exertion	72 (10%)	52 (21%)	0.000
Angina	125 (18%)	39 (16%)	0.437
Atypical chest pain	286 (41%)	72 (29%)	0.001
Asymptomatic	219 (31%)	89 (35%)	0.262
Suspected CHD	325 (46%)	63 (25%)	0.000
Angiographic CHD	48 (7%)	16 (6%)	0.905
MI	192 (27%)	145 (58%)	0.000
PCI	82 (12%)	13 (5%)	0.002
CABG	118 (17%)	63 (25%)	0.006
History time (mo)	24.8±38.1	42.0±48.2	0.000
Antiplatelet	494 (70%)	203 (81%)	0.002
Long acting nitrate	363 (52%)	135 (54%)	0.659
Beta-blocker	374 (53%)	152 (60%)	0.055
CC inhibitor	133 (19%)	53 (21%)	0.532
Diuretic	143 (20%)	62 (25%)	0.189
ACE-i / ARB	325 (46%)	147 (58%)	0.001
Entirely normal ECG	359 (51%)	21 (8%)	0.000
Fascicular block	83 (12%)	44 (18%)	0.031
ST-segment changes	86 (12%)	44 (18%)	0.050
Inverted T wave	94 (13%)	70 (28%)	0.000
Poor R progression	71 (10%)	53 (21%)	0.000
Any Q wave	68 (10%)	109 (43%)	0.000
Anterior Q wave	32 (5%)	74 (29%)	0.000
Inferior Q wave	36 (5%)	36 (14%)	0.000
Lateral Q wave	4 (0.5%)	18 (7%)	0.000
LBBB	21 (3%)	32 (13%)	0.000
Dynamic exercise	446 (64%)	125 (50%)	0.000
Dipyridamole stress	250 (36%)	123 (49%)	0.000
Dobutamine stress	6 (1%)	4 (2%)	0.303
Resting HR (bpm)	72.6±13.9	75.7±14.6	0.001
Resting SBP (mmHg)	141.5±22.9	138.0±22.0	0.060
Resting DBP (mmHg)	88.0±9.9	87.3±9.9	0.558
Summed Stress Score	6.5±6.3	17.9±10.1	0.000
Summed Rest Score	2.4±4.0	10.8±9.1	0.000
Anteroseptal MI	25 (4%)	102 (41%)	0.000
Inferior MI	55 (8%)	91 (36%)	0.000
Lateral MI	11 (2%)	40 (16%)	0.000
Dilated left ventricle	8 (1%)	59 (23%)	0.000
ERNA LVEF	0.62±0.07	0.38± 0.10	0.000

Table 1. (Continued)

	Validation group		
	LVEF≥0.50 (n= 228)	LVEF<0.50 (n=81)	P
Age (yrs)	59.9±9.9	60.3±11.7	0.824
Male	173 (76%)	67 (83%)	0.219
Diabetes mellitus	42 (18%)	19 (24%)	0.415
Dyslipidemia	77 (34%)	28 (35%)	1.000
Hypertension	114 (50%)	41 (51%)	1.000
Smoking	72 (32%)	17 (21%)	0.086
Family history of CHD	17 (8%)	9 (11%)	0.433
Dyspnoea on exertion	27 (12%)	13 (16%)	0.438
Angina	54 (24%)	14 (17%)	0.276
Atypical chest pain	86 (38%)	21 (26%)	0.058
Asymptomatic	61 (27%)	33 (41%)	0.027
Suspected CHD	104 (46%)	21 (26%)	0.002
Angiographic CHD	15 (7%)	7 (9%)	0.712
MI	73 (32%)	44 (54%)	0.001
PCI	37 (16%)	8 (10%)	0.201
CABG	31 (14%)	15 (19%)	0.375
History time (mo)	26.7±38.6	39.1±52.0	0.163
Antiplatelet	169 (74%)	66 (82%)	0.225
Long acting nitrate	107 (47%)	49 (61%)	0.039
Beta-blocker	124 (54%)	54 (67%)	0.067
CC inhibitor	54 (24%)	12 (15%)	0.115
Diuretic	47 (21%)	25 (31%)	0.085
ACE-i / ARB	108 (47%)	47 (58%)	0.121
Entirely normal ECG	103 (45%)	6 (7%)	0.000
Fascicular block	36 (16%)	19 (24%)	0.167
ST-segment changes	36 (16%)	11 (14%)	0.721
Inverted T wave	27 (12%)	22 (27%)	0.002
Poor R progression	34 (15%)	12 (15%)	1.000
Any Q wave	23 (10%)	29 (36%)	0.000
Anterior Q wave	8 (4%)	21 (26%)	0.000
Inferior Q wave	13 (6%)	8 (10%)	0.305
Lateral Q wave	4 (2%)	8 (10%)	0.003
LBBB	4 (2%)	14 (17%)	0.000
Dynamic exercise	134 (59%)	43 (53%)	0.449
Dipyridamole stress	90 (40%)	36 (44%)	0.515
Dobutamine stress	4 (2%)	2 (3%)	0.621
Resting HR (bpm)	73.3±12.7	74.2±12.8	0.600
Resting SBP (mmHg)	141.5±22.3	138.2±23.8	0.356
Resting DBP (mmHg)	88.2±9.8	87.7±10.3	0.842
Summed Stress Score	6.9±6.1	15.6±10.4	0.000
Summed Rest Score	2.5±3.5	9.7±9.3	0.000
Anteroseptal MI	9 (4%)	30 (37%)	0.000
Inferior MI	24 (11%)	24 (30%)	0.000
Lateral MI	0 (0%)	13 (16%)	0.000
Dilated left ventricle	0 (0%)	20 (25%)	0.000
ERNA LVEF	0.61±0.06	0.38±0.10	0.000

MI,myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CC, calcium channel; ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LBBB, left bundle branch block; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Rest of abbreviations as in the text.

and ECG scoring (AUC 0.816, SEE 0.016, P=0.000) (Fig. 1a). Similarly, in the validation sample the ECG-Scintigraphic scoring system had a better discriminatory probability for systolic function impairment than both the clinical-ECG model (AUC 0.789, SEE 0.030, P=0.001) and the ECG score (AUC 0.795, SEE 0.029, P=0.003) (Fig. 1b). The Clinical-ECG model was a better discriminator of resting left ventricular dysfunction than ECG scoring in the derivation cohort (P=0.001), but not in the validation sample (P=0.757).

Regression analysis provided the following equation for the prediction of resting ERNA LVEF from the ECG-Scintigraphic scoring system:

"ERNA LVEF = 66 - 3 x ECG-Scintigraphic score" (r=0.731, P=0.000) (1).

Table 2. *Models for the prediction of a resting ERNA LVEF<0.50.*

Variables	Models and scoring if the particular feature is present*			
	Clinical-ECG	Clinical-ECG-Scintigraphic	ECG	ECG-Scintigraphic
Age > 60	1	1	-	-
Dyspnoea on exertion	1	2	-	-
History of myocardial infarction	2	-	-	-
Resting heart rate >70bpm	2	2	-	1
Abnormal ECG	2	3	1	2
ST-changes	1	-	1	-
Inverted T wave	1	-	1	-
Poor R wave progression	1	-	1	-
Any Q-wave	2	-	2	-
Anterior Q-wave	2	2	1	1
Lateral Q-wave	-	-	2	2
LBBB	4	3	3	2
Dilated left ventricle	-	7	-	4
SSS >10	-	2	-	1
Anteroseptal MI	-	5	-	3
Lateral MI	-	4	-	2
Inferior MI	-	3	-	2
Sum	0 - 19	0 - 34	0 – 12	0 - 20

*For example: "ECG-scintigraphic score = 1 (if resting HR>70) + 2 (if ECG is abnormal) + 1 (if anterior Q-wave present) + 2 (if lateral Q-wave present) + 2 (if LBBB present) + 4 (if left ventricle is dilated) + 1 (if SSS>10) + 3 (if anteroseptal MI present in scan) + 2 (if lateral MI present in scan) + 2 (if inferior MI present in scan)". If the particular characteristic is not present the respective value is 0

Apparently, LVEF values with equation (1) are provided in 3-point increments.

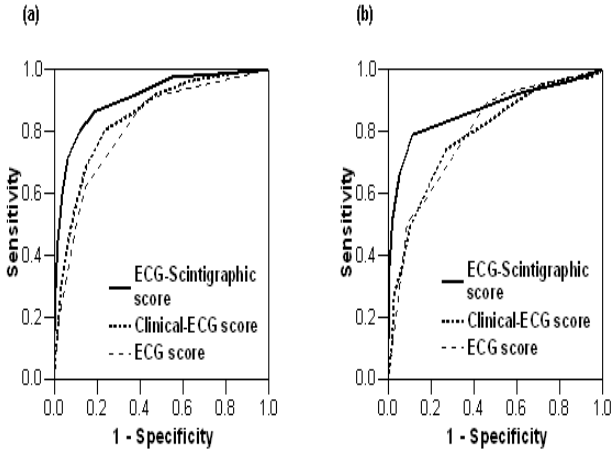

Figure 1. Receiver operating characteristic curves of scoring systems in the prediction of a resting ERNA LVEF<0.50 in the derivation (a) and validation (b) groups.

Scoring systems and gated SPET

In 373 patients who had undergone gated SPET, ROC analysis showed a similar diagnostic efficacy between the ECG-Scintigraphic scoring system predicted LVEF (AUC 0.912, SEE 0.020) and the LVEF calculated by ^{201}Tl gated SPET myocardial imaging (AUC 0.920, SEE 0.022, P=0.7642) in the discrimination of a resting ERNA LVEF<0.50 (Fig. 2). Moreover, the average of LVEF values from that scoring system and gated SPET (AUC 0.961, SEE 0.016) had a significantly better discriminatory performance than either calculation of LVEF alone (P=0.004 and P=0.001, respectively) (Fig. 2).

The associations between ERNA LVEF versus gated SPET LVEF, the ECG-Scintigraphic model LVEF and the average LVEF by both these approaches are plotted in Figure 3. The corresponding 95% limits of agreement ranged 0.071±0.196 versus 0.001±0.176 versus 0.040±0.152, respectively. Although as opposed to Bland-Altman statistic, linear regression analysis does not express agreement between tests, for reasons of consistency and for facilitating comparison with previous studies, we have also performed such analysis in the current study. An ERNA LVEF<0.50 was predicted correctly in 63/77 patients (82%) with gated SPET (adjusted for the systematic underestimation of 7.1% in Bland-Altman analysis) and in 71/77 patients (92%, P=0.000) with the average LVEF.

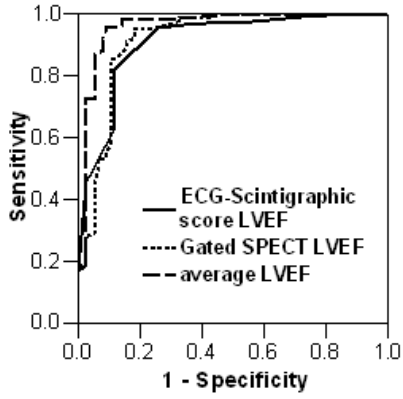

Figure 2. Receiver operating charateristic curves of the ECG-scintigraphic scoring system LVEF, ^{201}Tl Gated SPET LVEF and average LVEF, derived from both those assessments, in the discrimination of a resting ERNA LVEF<0.50.

In the 191 patients with an ERNA LVEF ≤60%, a ≤10% difference between ERNA LVEF and gated SPET LVEF (adjusted for the underestimation) was found in 125(65%) cases. In using the average LVEF of the ECG-Scintigraphic model and gated SPET, 170 patients (89%, P=0.000) were found with no more than 10% difference from the ERNA LVEF.

Discussion

Left ventricular ejection fraction has the attraction of being a simple numerical parameter that characterizes systolic function and is an established determinant of prognosis in patients with suspected or known CHD [31, 32]. This study developed models, based on readily available variables collected during routine clinical evaluation of those patients, for the discrimination of

resting left ventricular systolic impairment and also for the estimation of LVEF. It was demonstrated that this is best achieved by a simple algebraic summation of coded and weighted ECG and scintigraphic data, which offers information comparable to that provided by ^{201}Tl gated SPET and can enhance the clinical performance of the latter.

Gated SPET has been a major achievement and has become standard practice in nuclear cardiology. Numerous studies showed a high degree of correlation between gated SPET and other accepted modalities in the assessment of left ventricular function [18]. However, in clinical practice individual values, rather than average group tendencies need to be determined. Thus, in an individual patient the variability of the predicted value (e.g. ERNA LVEF) from a given independent value (e.g. gated SPET LVEF) can be assessed with the 95% prediction intervals of the regression equation. These are different from the commonly quoted 95% confidence intervals of the regression line, which provide the error of the comparisons between groups [33]. The Bland-Altman statistic can also be used as an indicator of the agreement of paired measurements. In using similar imaging techniques, we have reported previously on wide 95% prediction intervals and 95% limits of agreement in comparing ^{201}Tl gated SPET with ERNA LVEF and we have found a ≥10% absolute difference in LVEF in no less than 25% of cases [23]. Our figures were essentially replicated when we extracted and re-analyzed data from other published series administering higher ^{201}Tl doses at rest [24, 34]. Similar findings with ^{201}Tl gated SPET have been reported by other investigators [35], whereas a comparable degree of inaccuracy between ^{99m}Tc gated SPET LVEF and ERNA LVEF has also been observed previously by our team and other authors [21, 36]. Moreover, meta-analyses also concurred in that a substantial disparity exists in LVEF between ^{99m}Tc gated SPET and cardiac magnetic resonance or contrast ventriculography on a per-patient basis [22, 25]. Tools for improving precision of LVEF measurement and agreement amongst different imaging techniques are therefore desirable.

It should be emphasized that international bodies recommend reliance on echocardiography, ERNA or cardiac magnetic resonance for the assessment of systolic function in clinical decision making [10, 37], whereas no clinical guideline endorses the use of gated SPET for this purpose. Thus, in this study ^{201}Tl gated SPET and the developed scoring systems were treated as modalities identifying patients with presumed left ventricular dysfunction. It is also important to emphasise that although patients were enrolled retrospectively, left ventricular systolic function related estimates were performed prospectively.

In keeping with previous data [7], a high inter-observer agreement in ECG interpretations was found in our study. We have also reported earlier an excellent inter-observer agreement in the calculation of LVEF by both ERNA and ^{201}Tl gated SPET [23]. In our internal control we have found a good and consistent over time agreement between experienced observers in the evaluation of both myocardial ischaemia and left ventricular dilatation by the above set criteria. Although inter-institutional differences may exist in grading myocardial perfusion, imaging systems usually offer the option of perfusion quantification in a polar map format, thus minimizing interpretative discrepancies. Similarly, many ECG recorders identify abnormal patterns automatically.

Prediction of left ventricular dysfunction

This study shows that left ventricular systolic dysfunction at rest is highly unlikely if the ECG is entirely normal (Table 1), which is in substantial agreement with earlier series [5-9]. However, many patients with an abnormal ECG would also have normal systolic function. Clinical variables seemed to add no or limited predictive information over ECG readings in the discrimination of a resting ERNA LVEF<0.50 (Fig. 1). Other authors have reported conflicting results on the usefulness of clinical features alone or in combination with ECG and radiographic information in the determination of impaired left ventricular function [15, 16, 38, 38]. Extending previous observations, in a large cohort of patients we demonstrated that the prediction of a resting ERNA LVEF<0.50 by the ECG is significantly improved with the assimilation of myocardial perfusion data (Fig. 1). In this setting the ECG-scintigraphic scoring system estimated LVEF had a discriminatory performance comparable to that of ^{201}Tl gated SPET LVEF (Fig. 2). More importantly, by averaging LVEF values from the proposed model and gated SPET the discriminatory probability was further increased (Fig. 2) and significantly more cases with an ERNA LVEF<0.50 were correctly identified (92%) compared to gated SPET (82%).

Estimation of left ventricular ejection fraction

The assessment of LVEF from coded and weighted ECG and scintigraphic information with equation (1) provided a proportion of unexplained variability to ERNA LVEF measurements and 95% limits of agreement comparable to those of the association between ^{201}Tl gated SPET and ERNA LVEF (Fig. 3).

In this setting, average LVEF values from the proposed scoring system and gated SPET provided a decreased proportion of unexplained variability and narrower 95% predictions intervals (Fig. 3). Furthermore, the 95% limits of agreement to ERNA LVEF ranged ±19.6% with gated SPET versus ±15.2% with the average LVEF. This improvement was reflected in patients with an ERNA LVEF≤60%, in which an accurate LVEF assessment is particularly important in clinical decision making. In that subpopulation average LVEF values predicted significantly more cases (89%) with no more than 10% deviation from the ERNA LVEF, compared to gated SPET LVEF alone (65%).

In studies of head-to-head comparisons of ^{201}Tl and ^{99m}Tc gated SPET in the assessment of LVEF, a similar coefficient of correlation and 95% limits of agreement between those methods and either first-pass angiography or magnetic resonance imaging has been reported [19, 20]. However, ^{201}Tl is considered somewhat inferior to ^{99m}Tc-compounds in terms of image quality, study repeatability and interpretive reproducibility [40, 41]. Despite the fact that our gated myocardial data were of suboptimal count statistics, the association between ^{201}Tl gated SPET and ERNA LVEF measurements in our population is in agreement with previous works [18, 23, 25, 34, 35]. Moreover, the uncertainty in the prediction of ERNA LVEF from ^{201}Tl gated SPET in our study is comparable with the disparity found between ERNA, contrast ventriculography or MRI measured and ^{99m}Tc gated SPET calculated LVEF values [21, 22, 25, 36].

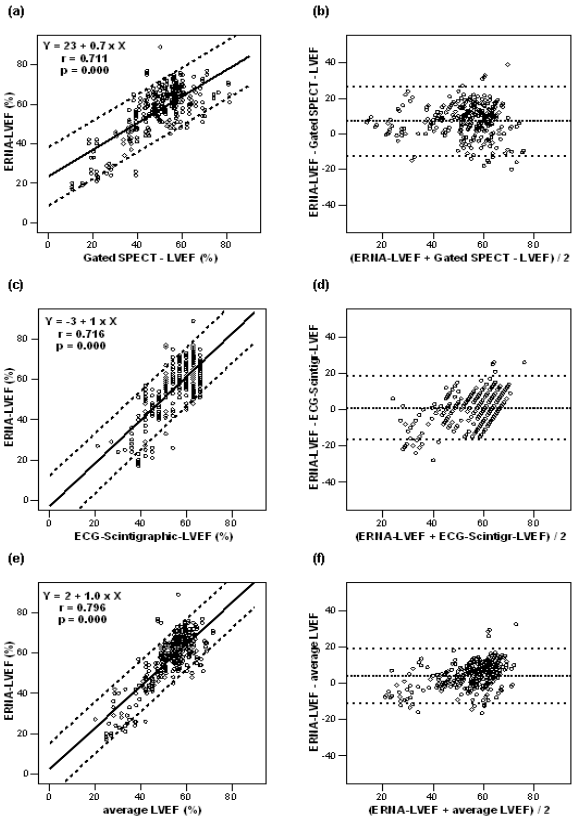

Figure 3. Linear regression analysis, with the regression line (solid line) and the 95% prediction intervals (dotted lines) illustrated, and the Bland-Altman statistic between ERNA LVEF and ^{201}Tl gated SPET LVEF (a, b), the ECG-scintigraphic score LVEF (c, d) and the average LVEF from the ECG-Scintrigraphic score and gated SPET (e,f).

Thus, it would be expected that our results would not have been significantly affected if ^{99m}Tc gated SPET was used instead, although firm conclusions on this issue require a direct evaluation.

Clinical relevance

The ECG-scintigraphic scoring LVEF offers information equivalent to that of gated SPET LVEF in the determination of systolic function. This can be explained by the uncertainty in the prediction of ERNA LVEF with gated SPET on a per-patient basis [21-25, 35, 36] and the independent estimation of LVEF from the EGC-Scintigraphic scoring system. As this model contains no stress ECG variables, it is applicable with either exercise of pharmacologic myocardial scintigraphy. Thus, the proposed scoring system can serve as a control tool of resting LVEF assessments with gated SPET, as in averaging LVEF values from those approaches leads to a more accurate prediction of ERNA LVEF. Moreover, in sites in which gated SPET is not performed or in situations it cannot be applied for various reasons (e.g. tachyarrhythmia), the proposed scoring system would offer a competent alternative.

Limitations of the study

It is possible that selection bias skews our patients. In an effort to minimize this, the results of a derivation group were verified in a second cohort. Moreover, since study participants were evaluated with myocardial perfusion imaging, referral bias is also a problem. It should be added, however, that in a less selected population, patients with suspected or less severe disease would be represented in larger proportions. In that subpopulation, LVEF would very likely be well above the threshold of abnormality. Hence deviations in LVEF with gated SPET would not be important from the clinical standpoint, because predicted values would fall almost invariably within the normal range.

Patients with atrial fibrillation or flutter were excluded. Apart from the effect of the rhythm on systolic function, however, other ECG and scintigraphic features probably would also be important in this subpopulation.

Regarding medication, no clinically significant changes in resting LVEF have been noted with heart rate limiting drugs [42], whereas more recent evidence showed that beta-blockers can increase left ventricular systolic function in patients with heart failure [43]. In addition, heart rate limiting medication would not have masked extensive ischemia.

In conclusion, in patients with suspected or known CHD left ventricular systolic dysfunction at rest can be determined effectively from a simple model containing resting ECG and stress myocardial perfusion imaging variables. This scoring system can provide an estimation of resting LVEF with a reliability which is comparable to that of ^{201}Tl gated SPET calculations and can enhance the clinical performance of the latter.

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