Single-day combined evaluation of regional myocardial perfusion and function at rest and peak exercise with ^{99m}Tc -MIBI in patients with coronary artery disease

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Abstract

^{99m}Tc -labeled methoxy-isobutyl-isonitrile (MIBI) allows a simultaneous radionuclide assessment of regional heart function and perfusion. In this study the effectiveness of functional and perfusional images obtained with ^{99m}Tc -MIBI in the detection of coronary stenoses was compared with that of their combination.

We studied 197 patients who underwent coronary angiography and a single-day radionuclide protocol including first pass angiography (multicrystal gamma camera) and single photon emission computed tomography, by means of 2 injections of ^{99m}Tc -MIBI at rest and at peak exercise. Fifteen patients had < 50% stenoses, 50 had 1-vessel, 69 2-vessel and 63 3-vessel disease, for a total of 377 pathological major coronary vessels; 129 patients had previous myocardial infarction. Functional images, perfusional tomograms and their combination showed the same sensitivity (98%) and specificity (80%) in detecting coronary patients. Regional sensitivity and specificity of the combined analysis achieved 87% and 82%, respectively, vs. 94% ($p < 0.005$) and 60% ($p < 0.001$) of functional images, and 88% ($p = \text{N.S.}$) and 74% ($p < 0.05$) of perfusional tomograms.

Thus, the combined analysis of regional functional and perfusional abnormalities increased significantly the specificity in the detection of coronary stenoses, in comparison with the separate evaluation of function and perfusion, achieving also a slightly higher diagnostic accuracy (85%, vs. 81% and 83%, respectively). The results confirm that a single-day protocol simultaneously assessing regional myocardial function and perfusion with ^{99m}Tc -MIBI represents a rapid and effective diagnostic method, that allows the physician to assess the presence and functional importance of coronary stenoses in less than 4 hours.

Abbreviations: CAD – coronary artery disease, FPRNA – first pass radionuclide angiography, LAD – left anterior descending artery, LCx – left circumflex artery, MIBI – methoxy-isobutyl-isonitrile, RCA – right coronary artery, SPECT – single photon emission computed tomography

Introduction

Myocardial scintigraphy and radionuclide angiography currently represent very sensitive non invasive methods to assess the presence of coronary artery disease (CAD) [1]. The suboptimal imaging properties of ^{201}Tl prevent from simultaneously carrying out the 2 procedures, as the radiation exposure to the patient would be unacceptably high. Conversely, among the recently developed $^{99\text{m}}\text{Tc}$ -labeled cardiac imaging agents, 2-methoxy-isobutyl-isonitrile (MIBI) provides such capabilities [2].

In fact, the favourable imaging characteristics of $^{99\text{m}}\text{Tc}$ allow to perform radionuclide angiography with low radiation exposure to the patient. At the same time, perfusional studies can be carried out, as the isotope is coupled with a molecule that is 65% taken up on first pass by myocytes, mainly by simple diffusion, and does not redistribute significantly over time [3–6].

Moreover, myocardial distribution of $^{99\text{m}}\text{Tc}$ -MIBI is closely related to that of ^{201}Tl , and its uptake shows a linear relation with myocardial blood flow over a wide range of flows, reflecting blood distribution in normal and ischemic myocardium [3, 5, 7].

Only a few investigations simultaneously assessed ventricular function and myocardial perfusion with $^{99\text{m}}\text{Tc}$ -MIBI, either evaluating heart function only at rest [8] or performing rest and stress studies on subsequent days [9, 10], or using gated scintigraphy [11], which provides regional wall motion analysis, but is limited to the study of heart function at rest or >1 hour after exercise.

It is known from previous studies [12, 13] that a second injection performed in the same day with a 3-fold higher activity dose does not affect the reliability of the second study, even if it increases the radiation dose to the patient. The latter limitation can be overcome by using a multicrystal gamma camera, that achieves high count rates with very small amounts of $^{99\text{m}}\text{Tc}$ [14, 15].

Aim of the study was to compare the diagnostic effectiveness of regional functional images, of perfusional tomograms, and of their combination, in a large series of patients with angiographically-assessed CAD, undergoing a rest/exercise single-day protocol with $^{99\text{m}}\text{Tc}$ -MIBI.

Methods

Patients

Of 207 consecutive patients who had undergone coronary angiography at our Institution for either suspected or already ascertained CAD and presented neither significant associated heart disease, nor previous revascularization procedures, 202 patients provided written informed consent and entered the study.

All patients, within 4 months of coronary angiography, underwent first pass radionuclide angiography (FPRNA) and single photon emission computed tomography (SPECT) at rest and at peak exercise in the same day by means of 2 injections of $^{99\text{m}}\text{Tc}$ -MIBI; 5 patients were subsequently excluded from the analysis because of bad isotope boluses during FPRNA.

Of the remaining 197 patients (168 men and 29 women, mean age: 56 ± 8 years), 129 patients had a history consistent with previous (> 6 months old) myocardial infarction (7 patients had 2 infarctions), documented by ST-T wave changes ($n = 26$) or new Q waves ($n = 110$) at ECG, associated with a pathological increase in serum MB-creatine kinase levels. At heart catheterization the ECG location of the infarction was confirmed by the presence of a narrowed artery supplying an abnormally contracting ventricular wall.

Patients were instructed to discontinue beta-blockers and calcium-channel blockers 48 hours before and nitrates 24 hours before the execution of the study.

Heart catheterization

Left ventriculography was performed in right and left anterior oblique views by Seldinger's approach. Selective coronary arteriography was performed by Judkins' technique in multiple views, including sagittal obliques. Coronary angiograms were visually and blindly graded by 2 experienced investigators. The regions supplied by the 3 major coronary arteries were taken into account separately.

Coronary stenoses graded as $\geq 50\%$ were found in 182 patients; 50 had 1-vessel, 69 2-vessel and 63 3-vessel disease. A total of 377 stenoses were identified: 158 on left anterior descending artery (LAD), 107 on left circumflex artery (LCx), and 112 on right coronary artery (RCA) territory. Seventy-five coronary stenoses were graded as 50–70%, 160 as 71–90%, and 142 as $> 90\%$ (Table 1).

Data acquisition

Tracer preparation

In a vial containing 1 mg of lyophilized MIBI salt 5500 MBq of ^{99m}Tc in 1–2 ml was added; labeling

was performed by placing the vial in a water bath at 100°C for 10 min, allowing it then to cool for 15 min. Labeling efficacy was checked by thin layer chromatography and exceeded 95% in all preparations.

Rest study

FPRNA was performed in upright position in 30° right anterior oblique view with a multicrystal gamma camera (Scinticor, USA), set over 140 KeV photopeak and equipped with a high sensitivity parallel hole collimator 0.5 inch thick. A bolus of 350–450 MBq of ^{99m}Tc -MIBI in 0.5 ml was injected into an antecubital vein through a 17–18 Gauge polyethylene catheter and automatically flushed with 20 ml of saline in 2 s. The gamma camera, during the first pass of the radioactive bolus through heart chambers, acquired 1200 R-wave gated frames at a rate of 25 frames/s. The patient was then encouraged to drink 200 ml of milk, to speed up hepatobiliary clearance of ^{99m}Tc -MIBI. At least 90 min after injection, in order to increase heart/background activity ratio, SPECT was performed with a single crystal tomographic camera (Starcam 400AT, G.E., USA), equipped with a general purpose parallel hole collimator; 32 projections of 30s each from 45° right anterior oblique to 45° left posterior oblique view were acquired.

Exercise study

A bicycle exercise test was then performed with the patient and the detector of the multicrystal camera in the same position, during continuous ECG monitoring. The small size of the detector (about 8 squared inches), and the presence of a foam wedge, allowed the patient to keep this position throughout the test. Exercise test was carried out with an initial work load of 25 W, increased stepwise by 25 W every 2 min, and terminated because of excessive fatigue, weakness or shortness of breath, severe angina, hypotension or dizziness, life-threatening arrhythmias, attainment of maximal age-predicted heart rate (220 minus age) or ischemic ECG response (horizontal or downsloping ST depression ≥ 1 mm or upsloping depression ≥ 1.5 mm 80 ms after J point). At peak exercise, a bolus of 1050–1350 MBq of ^{99m}Tc -MIBI in 0.5 ml of

Table 1. Summary of study population data.

Patients	Normal	Ischemic	Infarcted
<i>Demographics</i>			
Number	15	53	129
Age (years)	53 ± 8	55 ± 8	56 ± 9
Sex (M/F)	10/5	44/9	114/15
<i>Major vessels with $\geq 50\%$ stenoses</i>			
1	–	19 (36%)	31 (24%)
2	–	12 (23%)	57 (44%)
3	–	22 (41%)	41 (32%)
<i>% Amount of vessel stenoses</i>			
50%–70%	–	29 (26%)	46 (17%)
71%–90%	–	53 (49%)	107 (40%)
$> 90\%$	–	27 (25%)	115 (43%)
<i>Distribution of vessel stenoses</i>			
LAD	–	44 (40%)	114 (43%)
LCx	–	34 (31%)	73 (27%)
RCA	–	31 (29%)	81 (30%)

saline was automatically injected intravenously and flushed. The gamma camera acquired 1200 R wave-gated frames at a rate of 50 frames/s. Counting was started 5 heart cycles before isotope injection, to allow subtraction of background activity during study processing. At least 1 hour later, SPECT was repeated, using the same procedure as above described for rest study.

Data processing

First pass radionuclide angiography

Data processing procedures were described in detail elsewhere [14, 16, 17]. Briefly, a representative cycle was created by adding up 6–9 R wave-gated heart cycles obtained from left ventricular time-activity curve during the wash-out phase. Left ventricular border was then defined by processing 2 spatial gradient images which reflect bidimensional count changes on the end-diastolic representative image. Measurement and subtraction of non-homogeneous background was achieved by semiautomatically determining a precise mask of lung perfusion within left ventricular limits. Time-activity curves were then processed for each pixel of the images composing the representative cycle. Activity (i.e. volume) changes in each pixel during preselected time intervals of heart cycle were visualized on numerical matrices, subsequently color-coded for easier interpretation to form parametric or so-called functional images [18].

The most useful images from a clinical point of view were previously demonstrated to be the regional ejection fraction image, the regional ejection rate image and the regional rapid filling rate image [19, 20]. Normal rate images present regional temporal activity gradients in form of symmetric bands of equal range of value along the longitudinal axis of the ventricle, where the maximum (white, referring to a 10 color-coded number scale) is crescent-shaped and lies just inside the contour of the chamber. Interruption or loss of part of the normally crescent-shaped high rate band results in a net contrast between the zones with high and low rates, allowing the delineation of abnormal coronary regions with very high diagnostic sensitivity [19, 20].

Computed tomography

Raw data sets were checked in order to detect patient motion and transaxial tomographic sections were reconstructed from the original 32 planar views, using standard Ramp-Hanning filtering and bidimensional spatial smoothing. Standard correction procedures for nonuniformity as well as for center-of-rotation were used; neither attenuation nor scatter correction was used.

Three sets of 0.6 cm thick orthogonal sections were generated, producing short axis, vertical long axis and horizontal long axis slices. Five pairs of rest and stress representative slices on each axis were simultaneously displayed in order to compare rest and stress tomograms in the same view. Maximal counts per pixel of respectively rest and stress slices were then normalized to a value of 100%.

Data analysis

Two experienced investigators, unaware of clinical and angiographic findings, analyzed blindly and separately regional functional images of left ventricular ejection fraction, ejection rate and rapid filling rate, and, on a separate occasion, the 5 rest and stress pairs of perfusional tomograms on the 3 orthogonal axes.

According to previous investigations [9, 20–22], left ventricular segments on functional images, as well as on perfusional tomograms, were related to coronary regions as follows: LAD region included the whole anterior wall, the interventricular septum and the apex; LCx region included the lateral wall, and RCA region (when preponderant) included the inferior and posterobasal wall. Inferolateral and inferoapical wall assignment was modified depending on the vessel corresponding to the neighboring abnormality present.

Although an overlapping of coronary regions is present in functional images obtained in right anterior oblique view, the morphology and location of functional abnormalities is peculiar of each region and allows the experienced investigator to correctly identify the vessel supplying the ventricular wall showing motion abnormalities [19–21]. Regional accuracy in the attribution of wall motion abnor-

malities to the 3 main coronary regions previously obtained in our laboratory was over 90%.

Functional images obtained at rest were analyzed through a qualitative regional score (3 = normal, 2 = mild hypokinesis, 1 = severe hypokinesis, 0 = akinesis or dyskinesis). A score ≤ 1 was considered pathological; it always corresponded to a $\geq 30\%$ reduction in regional function in comparison with normal reference images obtained in our laboratory. Functional images obtained at peak exercise were defined as pathological whenever a $\geq 10\%$ regional reduction in the percentual level of the considered parameter in comparison with rest study was found. The same coronary region had to be abnormal on at least 2 functional images in order to consider it as pathological [17, 19].

Perfusion was considered to be significantly decreased if the color scale showed a $> 30\%$ reduction in myocardial activity in at least 2 contiguous slices [21, 23]. Regional abnormalities at exercise only were defined as reversible, whereas regional abnormalities both at rest and exercise were defined as persistent.

A combined abnormality was considered to be present whenever both ventricular function and myocardial perfusion were pathological in the same coronary region, according to the definitions described above. As a consequence, abnormal findings occurring at only one of the 2 radionuclide techniques were not taken into account by this method of analysis.

Interobserver variability was assessed by randomly selecting 40 patient studies and comparing

the interpretation of both FPRNA and SPECT images by the second observer. Intraobserver variability was assessed by having the same investigator to reanalyze 40 randomly selected patient studies on a separate occasion. The agreement between the 2 interpretations was then assessed.

Quantitative data are reported as mean values ± 1 standard deviation. Sensitivity, specificity, diagnostic accuracy, positive and negative predictive values of radionuclide results in comparison with coronary angiography were calculated both for patients and coronary regions. Mean differences for continuous variables were compared with Student's unpaired t-test. Qualitative data were compared with χ^2 -test. A p value < 0.05 was considered significant.

Results

Exercise test (Table 2)

Both ischemic and infarcted patients achieved significantly lower mean values of exercise duration, percentage of maximal heart rate and double product at peak exercise, in comparison with normal subjects.

In 106 patients and 15 normal subjects exercise test was interrupted because of excessive fatigue, in absence of ECG abnormalities. A heart rate $> 80\%$ of maximal age-predicted one was achieved by 68 patients and 14 normal subjects, whereas $71.8 \pm 6.7\%$ of maximal heart rate was achieved by the remainders.

Exercise test was terminated because of ST depression in 53 patients, and because of ST depression and angina of increasing severity in 23 patients. Of the total of 76 patients with pathological stress test, 27 (31%) achieved a heart rate $> 80\%$ of maximal age-predicted one, whereas in the remaining 49 patients the test was interrupted at $71.6 \pm 5.6\%$ of maximal heart rate.

Table 2. Results of exercise testing.

	Normal	Ischemic	Infarcted
Number	15	53	129
Duration (seconds)	558 ± 97	$332 \pm 176\#$	$374 \pm 149\#$
% of maximal heart rate	88 ± 11	$80 \pm 9\#$	$79 \pm 8\#$
Double product (mmHg*bpm/100)	29.1 ± 3.1	$24.8 \pm 5.7\#$	$23.3 \pm 4.5\#$
Pathological tests	0	28 (53%)	48 (37%)
Normal tests	14 (93%)	17 (32%)	51 (40%)
Nondiagnostic tests	1 (7%)	8 (15%)	30 (23%)

#: p < 0.05 in comparison with normal subjects.

Fig. 1. Example of parametric images of left ventricular function obtained at rest (*above*) and at peak exercise (*below*) in right anterior oblique view in a patient with exercise-induced ischemia on the antero-septal wall and the apex, due to a > 90% proximal LAD stenosis. Regional functional images of ejection rate (SYS DEC) and rapid filling rate (DIA INC) are presented. The adopted color-scale is composed of 10 steps, ranging from 0 to 100%. SYS DEC image shows already at rest a thinner yellow band on the anteroapical wall, and the substitution of red coded rates with lower blue coded ones (*arrow*). At peak exercise the loss of functional symmetry along the left ventricular long axis is visible, with shifting of the yellow and red high rates away from the abnormally contracting anteroapical wall (*arrows*). In this area the lost high rates are substituted by lower ones (blue coded). DIA INC image shows at rest more irregular filling flows, with a certain degree of asymmetry, on the anteroapical wall, where the yellow and red high rates are interrupted by a shell of lower rates (*arrows*). At peak exercise a further deviation of high filling rates away from the anteroapical wall is visible, with the complete loss of symmetrical inflow rates, and the substitution of yellow and red-coded high rates with blue and darker coded lower filling ones (*arrows*).

Fig. 2. Perfusional tomograms at rest (*above*) and at peak exercise (*below*) of the same patient presented in Fig. 1. As an example, 0.6 cm thick slices were selected on the short axis (*left*) and the horizontal long axis (*right*) at the level where abnormal findings were better detectable. To allow comparison, the same slice for rest and stress study is presented. Rest images show normal tracer uptake in all segments, apart of the inferior wall, where a slightly reduced uptake represents a common finding at this section level also in normal subjects. At peak exercise, the anteroseptal and apical walls show a severe reduction in tracer uptake (*arrows*), localized on the same myocardial walls presenting abnormal wall motion.

Radionuclide findings (Tables 3 and 4)

Normal subjects

Functional images, perfusional tomograms and the combined analysis of the 2 methods showed normal findings in 12/15 individuals (80% specificity) at rest and under stress. Three subjects showed abnormal functional and perfusional findings only at peak exercise on 1 ($n = 2$) and 2 ($n = 1$) coronary regions.

CAD patients

Of 182 patients presenting significant CAD (Figs 1, 2), abnormal findings were detected at peak exercise in 178 by functional images, vs. 179 by perfusional tomograms, and 178 by the combined analysis; the resulting sensitivity was 98% for each method.

Of 53 non-infarcted patients, 51 (96%) were correctly identified as abnormal by the 3 methods of analysis. The 2 false negative patients presented a

single 50% stenosis on the first obtuse marginal branch and on distal LCx, respectively.

Of 129 infarcted patients, abnormal findings at rest were detected in 127 (98% sensitivity) by both functional images and the combined analysis, vs. 128 (99% sensitivity) by perfusional tomograms ($p = \text{N.S.}$). False negative results were obtained in 1 patient with previous non-Q wave infarction and residual 60% LAD stenosis, that presented abnormal findings only at SPECT, whereas ventricular function improved significantly at peak exercise, and in 1 patient with previous inferior infarction and residual 75% RCA stenosis, who had normal findings at both techniques at rest as well as at peak exercise.

Normal regions

Of a total of 214 normal coronary regions (45 belonging to normal subjects, 169 to CAD patients), 176 were correctly identified by the combined analysis, vs. 128 by functional images ($p < 0.0001$), and 158 by perfusional tomograms ($p < 0.05$), achieving 82%, 60%, and 74% specificity, respectively. Also

Table 3. Effectiveness of ^{99m}Tc -MIBI radionuclide evaluation of heart function and perfusion in the detection of coronary patients and coronary stenoses.

	SENS	SPEC	PPV	NPV	ACC
Patients					
Total ($n = 197$)					
Functional images	98%	80%	98%	75%	96%
Perfusional tomograms	98%	80%	98%	80%	97%
Combined analysis	98%	80%	98%	75%	96%
No infarction ($n = 68$)					
Functional images	96%	80%	94%	86%	93%
Perfusional tomograms	96%	80%	94%	86%	93%
Combined analysis	96%	80%	94%	86%	93%
Regions					
Total ($n = 591$)					
Functional images	94%	60%	80%	84%	81%
Perfusional tomograms	88% #	74% #	86%	77%	83%
Combined analysis	87% #	82% #§	90% #	78%	85%
No infarction ($n = 455$)					
Functional images	91%	60%	72%	85%	76%
Perfusional tomograms	82% #	74% #	78%	78%	78%
Combined analysis	80% #	82% #§	84% #	79%	81%

SENS: sensitivity; SPEC: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: diagnostic accuracy. #: $p < 0.05$ in comparison with functional images; §: $p < 0.05$ in comparison with perfusional tomograms.

Table 4. Sensitivity of ^{99m}Tc -MIBI functional and perfusional results in the detection of coronary stenoses in relation to the amount of luminal narrowing and to individual main coronary regions.

% Stenosis	50-70		71-90		> 90		Total	
	N	%	N	%	N	%	N	%
LAD								
Functional images	35	95	60	97	59	100	154	97
Perfusional tomograms	31	84	55	89	59	100	145	92#
Combined analysis	30	81	55	89	59	100	144	91#
LCx								
Functional images	10	77	52	87	33	97	95	89
Perfusional tomograms	5	38#	46	77	34	100	85	79#
Combined analysis	5	38#	46	77	33	97	84	79#
RCA								
Functional images	20	80	35	92	49	100	104	93
Perfusional tomograms	18	72	34	89	49	100	101	90
Combined analysis	17	68	33	87	49	100	99	88
Total								
Functional images	65	87	147	92	141	99	353	94
Perfusional tomograms	54	72#	135	84	142	100	331	88#
Combined analysis	52	69#	134	84#	141	99	327	87#

#: $p < 0.05$ in comparison with functional images.

perfusional tomogram specificity was significantly higher ($p < 0.005$) than that of functional images.

More in detail, in the subgroup of coronary regions belonging to normal subjects, false positive results were obtained at peak exercise in 3 regions by the combined analysis (1 LAD and 2 LCx), vs. 4 regions by functional images (1 LAD, 2 LCx, 1 RCA) and perfusional tomograms (2 LAD and 2 LCx), achieving 93%, 91%, and 91% specificity, respectively ($p = \text{N.S.}$).

In the subgroup of normal regions belonging to CAD patients, false positive results were obtained at peak exercise in 35 coronary regions by the combined analysis, vs. 82 by functional images ($p < 0.0001$), and 52 by perfusional tomograms ($p < 0.05$), achieving 79%, 51%, and 69% specificity, respectively. Also perfusional tomogram specificity was significantly higher ($p < 0.001$) than that of functional images.

Pathological regions

Of a total of 377 coronary regions (136 infarcted and 241 non-infarcted) supplied by stenotic vessels, 353 were correctly identified by functional images, vs. 327 by the combined analysis ($p < 0.005$), and 331 by perfusional tomograms ($p < 0.01$), achieving 94%, 87%, and 88% sensitivity, respectively. No significant difference was found between perfusional tomograms and the combined analysis.

In the subgroup of non-infarcted regions, sensitivity of functional images was 91%, vs. 82% of perfusional tomograms ($p < 0.005$) and 80% of the combined analysis ($p < 0.005$). No significant difference was found between perfusional tomograms and the combined analysis.

Ten coronary regions without clinical or ECG evidence of previous infarction presented already at rest severe hypokinesia, as well as significantly decreased tracer uptake, compatible with the presence of a previous unrecognized infarction. Since only radionuclide results showed signs of myocardial scar, these regions were not considered as infarcted, though they were included in the true positive group for $^{99\text{m}}\text{Tc}$ -MIBI identification of CAD.

Of coronary stenoses on vessels supplying non-infarcted regions, 65 were graded as $> 90\%$: in this subgroup the sensitivity of functional images

achieved 98%, vs. 100% of perfusional tomograms, and 98% of the combined analysis, respectively ($p = \text{N.S.}$). Coronary stenoses were found on 102, 86, and 53 non-infarcted LAD, LCx, and RCA regions, respectively. In LAD region, sensitivity achieved 97% for functional images, vs. 92% for perfusional tomograms ($p < 0.01$), and 91% for the combined analysis ($p < 0.01$); in LCx region it was 89% for functional images, and 79% for perfusional tomograms and the combined analysis ($p < 0.05$); in RCA region it was 93%, 90%, and 88%, respectively ($p = \text{N.S.}$).

Interobserver and intraobserver agreement

Both interobserver and intraobserver agreement for the evaluation of radionuclide images were good, achieving an r-value of 0.94 ($p < 0.0001$) for functional images, and of 0.95 ($p < 0.0001$) for perfusional tomograms.

An abnormal region was correctly attributed to the involved coronary vessel in 90% of cases for functional images, and in 94% of cases for perfusional tomograms.

Discussion

In the past the assessment of heart function and perfusion had to be accomplished in 2 separate days, using ^{201}Tl scintigraphy and $^{99\text{m}}\text{Tc}$ ventriculography, for an overall absorbed radiation dose exceeding 10 mGy/900–1200 MBq [24]. Such approach was time-consuming, 2 exercise tests were needed, with all the risks entailed, and ischemic threshold could change unpredictably in between [25]. In addition, patients to be studied off-medications were forced to stop them twice.

The concept of simultaneously assessing heart function and perfusion originated a decade ago with Mena and coworkers, who obtained interesting results with the combined use of ^{201}Tl and $^{195\text{m}}\text{Au}$ [26]. However, it was only with the development of $^{99\text{m}}\text{Tc}$ -labeled isonitriles that this issue was addressed again, as these compounds allow to overcome the above mentioned drawbacks, decreasing

at the same time the radiation dose to the patient to 8–9 mGy/2200 MBq [2, 27], and to less than 7 mGy/1500 MBq, if a multicrystal gamma camera is used.

Among the additional advantages of the single-day protocol is that it is at lower risk and more easily accepted by the patient, allowing more often to perform the whole procedure totally off-medications. Second, the physician can detect coronary stenoses and assess their importance in a shorter time, than by using one test at a time. Finally, it warrants economical and social advantages, both for in-patients, whose hospitalization time is decreased, and for out-patients, who generally have to be on leave from their job in order to undergo the examination.

Functional images

In our study group, functional images confirmed the results obtained in previous investigations [19, 20, 23, 28], proving to be very sensitive in the detection of both CAD patients (98%) and pathological coronary regions (94%). As expected, specificity was lower, as false positive results were found in 20% of normal subjects and in 40% of normal coronary regions.

Previous investigations reporting functional findings obtained with ^{99m}Tc-MIBI evaluated mainly left ventricular volumes [15] and regional wall motion [9, 10]. Though their prognostic importance for CAD patients is accepted [29], the diagnostic effectiveness of functional images for CAD detection is known to be much higher [18, 19].

However, processing reliable parametric images of systolic and early diastolic regional function requires a high count-rate [17], as routinely achieved by a multicrystal gamma camera (300,000 cps, even injecting 350 MBq of ^{99m}Tc) [14]. As a consequence, high counts as well as reliable volume curves can be obtained for each pixel, and parametric images of regional rates can be processed on very short time intervals, thus increasing diagnostic sensitivity [19, 20].

According to previous experience [19, 21], the presence of wall motion abnormalities in at least 2

functional images was requested to define a myocardial region as pathological. Such a criterion proved to be the most effective also in this study, achieving a higher diagnostic accuracy in the detection of coronary stenoses, in comparison with other combinations of images (Table 5).

Perfusional tomograms

Among the great deal of studies carried out with MIBI as a perfusional tracer, the few of them which used SPECT obtained results similar to ours, achieving 82–95% sensitivity in the detection of CAD patients [14, 32, 40], 79–89% regional sensitivity and 72–86% regional specificity [9, 22, 27].

A > 30% reduction in myocardial activity was chosen in this study as a cut-off point to define abnormal perfusion, based on previous experience acquired in our laboratory. In fact, when comparing diagnostic accuracy of > 30% with that of > 40% activity reduction, as chosen by others [8, 30], no significant difference for CAD detection was found. Nevertheless, we cannot exclude that such a 10% activity difference could, at least partially, account for the higher sensitivity, and conversely the slightly lower specificity, of our perfusional results, in comparison with previous studies [22, 27].

Table 5. Compared effectiveness of different combinations of parametric images of regional heart function in the detection of coronary stenoses.

Criteria	SENS	SPEC	PPV	NPV	ACC
– EF	70%	70%	80%	57%	70%
– ER	81%	59%	78%	64%	73%
– RFR	89%	48%	75%	71%	74%
– EF or ER or RFR	99%	26%	70%	95%	73%
– EF + ER	56%	83%	85%	52%	66%
– EF + RFR	61%	81%	85%	54%	68%
– ER + RFR	72%	78%	85%	61%	74%
– EF + ER or EF + RFR or ER + RFR	94%	60%	80%	84%	81%
– EF + ER + RFR	47%	91%	90%	50%	63%

EF: ejection fraction image; ER: ejection rate image; RFR: rapid filling rate image. Other abbreviations same as in Table 3.

Combined analysis of function and perfusion

The combined analysis showed the same sensitivity and specificity as functional and perfusional images alone in the detection of patients and normal subjects, respectively. Conversely, from a regional point of view, it achieved a significantly higher specificity and a slightly lower sensitivity. Since diagnostic accuracy of functional and perfusional images alone was already relatively high, it was very difficult to prove a statistically significant additional value of one method on the other.

However, the lower regional sensitivity of the combined analysis did not affect the capability of detecting situations in which the impending risk and the amount of jeopardized myocardium are particularly high [31, 32], such as severe (> 70%) coronary stenoses as well as stenoses involving LAD region (94% and 91% sensitivity, respectively).

Limitations of the study

Our study population was composed by consecutive patients recruited from catheterization laboratory, where the prevalence of CAD and pathological coronary regions is much higher than in the general population. Surely this bias overestimated the sensitivity of radionuclide methods, providing limited informations about their specificity in the general population. However, such referral bias probably affected to a lesser degree the localization of disease, as the prevalence of normal coronary regions was relevant (> 36%).

The prevalence of patients with previous infarction (64%) was higher in our study than in other investigations [9, 15, 27]. However, the number of non-infarcted patients included in the study was relevant ($n = 53$), and 96% of them were correctly identified by the 3 methods of analysis. In addition, the combined analysis confirmed its superiority even after the exclusion of infarcted regions (Table 3).

Although the visual method still represents the most widely used technique for assessing coronary stenosis severity [8, 9, 20, 22, 23, 27], it introduces

an additional level of subjectivity in data analysis, and represents a source of bias, as the use of a rough percent diameter narrowing ignores the full geometric impact of a stenosis on coronary blood flow [33]. Therefore, the true significance of these results needs be confirmed by studies using computer-assisted quantitation of luminal narrowings.

Further implications

In the 39 exercise tests interrupted at a heart rate < 80% of maximal age-predicted in absence of ischemic ECG abnormalities (i.e. non diagnostic tests), regional sensitivity and specificity of functional images achieved 94% and 59% vs. 82% and 75% of perfusional tomograms, and 81% and 78% of the combined analysis, although the prevalence and severity of coronary stenoses was the same as in the whole study group. Therefore, > 80% regional diagnostic accuracy was obtained even in sub-maximal (i.e. at lower risk) exercise tests, confirming that ^{99m}Tc -MIBI results are not affected by the exercise level very much, in comparison with ^{201}Tl [34], probably because of the different characteristics of the 2 tracers [4, 5, 7].

Furthermore, a simultaneous assessment of function and perfusion can provide additional, but at times complementary informations, about the impact of an unbalance in blood flow during exercise on the resulting wall motion, thus determining both the ischemic importance of coronary narrowings and the pathophysiologic significance of underperfused areas.

Interestingly, functional and perfusional abnormalities developed at peak exercise also in some coronary regions supplied by visually normal vessels. In addition, abnormal wall motion and perfusion at rest, suggestive of myocardial scar, were found in some regions without clinical and ECG evidence of previous infarction. These controversial results deserve further studies, specifically designed to differentiate false findings due to diagnostic inaccuracy of the methods from either hibernating myocardium or peculiar pathophysiological situations, different from atherosclerotic coronary disease.

Future investigations should take advantage of the combined evaluation of rest and stress heart function and perfusion with ^{99m}Tc -MIBI in the same day, in order to assess tissue viability after myocardial infarction and to better define the true impact of coronary stenoses on blood supply and myocardial performance.

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