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Assessment of ventricular function with first-pass radionuclide angiography using technetium 99m hexakis-2-methoxyisobutylisonitrile: a European multicentre study

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Abstract. In the context of a multicentre study on the use of technetium 99m hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-Sestamibi), we evaluated the accuracy of the ventricular function assessed at rest by means of first-pass radionuclide angiocardiography acquired during the injection of the tracer for myocardial perfusion scintigraphy. The results were compared with first-pass studies performed using reference tracers sodium pertechnetate Tc 99m or technetium 99m diethylene triamine penta-acetic acid or with gated radionuclide angiocardiography. A total of 66 patients of the 105 enrolled in the study could be evaluated. The comparison of the first-pass studies was possible in 33 subjects with regard to the left ventricular ejection fraction, yielding $r=0.909$ ($P<10^{-6}$), and in 22 cases with regard to the right ventricular ejection fraction, yielding $r=0.712$ ($P<0.001$). The comparison between the first-pass study using ^{99m}Tc-Sestamibi and the equilibrium gated radionuclide angiocardiography was possible for the left ventricular ejection fraction in 26 cases, with $r=0.937$ ($P<10^{-6}$), and for the right ventricular ejection fraction in 15 subjects, with $r=0.783$ ($P<0.001$). In conclusion, the assessment of ventricular function performed by acquiring a first-pass radionuclide angiocardiograph during the injection of ^{99m}Tc-Sestamibi for perfusion myocardial scintigraphy can be considered reliable and accurate, when compared with the usually employed techniques. This result confirms the feasibility of a combined evaluation of perfusion and function at rest and during stress testing, which represents one of the most interesting advantages offered by the use of ^{99m}Tc-Sestamibi.

Key words: Technetium 99m hexakis – 2-Methoxyisobutylisonitrile – First-pass radionuclide angiocardiography – Ventricular function

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Introduction

Perfusion studies using myocardial scintigraphy are among the most employed and probably the most accurate non-invasive tests for the diagnosis and assessment of coronary artery disease (Okada et al. 1980; Melin et al. 1981, 1985; Uhl et al. 1981; Leppo et al. 1982; Gerson 1987). On the other hand, the evaluation of left ventricular function by means of non-invasive methods, such as 2-dimensional echocardiography or radionuclide angiocardiography, has gained increasing importance in the past few years, owing to the high relevance of this variable in the management choices and in the prognostic stratification (Borer et al. 1980, 1987; Sanz et al.

1982; Corbett et al. 1983; De Pace et al. 1983; Iskandrian et al. 1985; Grodzinski et al. 1985; Multicenter Postinfarction Research Group 1986; Jones 1987). Up to now the two kinds of studies could not be performed simultaneously, since the characteristics of the perfusion tracer usually employed, thallium 201, are not suitable for the acquisition of a first-pass radionuclide angiocardiography during its injection (Jansholt Anderson 1988). The availability of the isonitrile derivatives, a new class of myocardial perfusion tracers labelled with technetium 99m (McKusick et al. 1986; Maddahi et al. 1987; Okada et al. 1988; Kiat et al. 1989), opens a new perspective, making possible the evaluation of function during perfusion studies (Schelbert 1987). The necessary prerequisite for this combined assessment is that the quality of radionuclide angiocardiography performed with the ^{99m}Tc-labelled isonitrile compound, injected at the required dosage for myocardial scintigraphy, has to be comparable with that obtained using a traditional radiopharmaceutical such as sodium pertechnetate Tc 99m or technetium 99m diethylene triamine penta-acetic acid (^{99m}Tc-DTPA).

In this paper we present the results of left ventricular function evaluation with first-pass radionuclide angiocardiography performed in the context of a multicentre study concerning the use of technetium 99m hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-Sestamibi) in the evaluation of patients with coronary artery disease.

Methods

The study involved nine centres in four different countries. In each country the use of ^{99m}Tc-Sestamibi (Cardiolite, Du Pont) was authorized according to local laws regarding the experimental evaluation of new radiopharmaceuticals, and the study protocol was approved by the local ethical committees. Informed consent was obtained from each patient.

Patient population. The study protocol included the execution of first-pass radionuclide angiocardiography at rest with ^{99m}Tc-Sestamibi and of a comparative evaluation technique, possibly first-pass radionuclide angiocardiography employing another established tracer or, alternatively, either equilibrium gated radionuclide angiocardiography or contrast ventriculography. Of the 105 patients recruited from 9 centres, 35 did not undergo any comparative assessment of ventricular function and were therefore excluded from any further evaluation. Four more subjects were also excluded because the interval between the ^{99m}Tc-Sestamibi study and the comparative one exceeded 3 months. Therefore, a total of 66 patients (58 males and 8 females, mean age 55 ± 9 years, range 37–74 years) could be evaluated with regard to the comparison of ventricular function. Coronary artery disease was diagnosed in 63 subjects, 2 of whom also had valvular disease; one patient suffered from a dilated cardiomyopathy, one was considered normal, and finally the clinical data of one case were missing. Treatment for the underlying disease was administered to 48 patients, including nitrates in 31, calcium channel blockers in 30 and β-blocking agents in 12. No changes in drug regimen were introduced during the study, and the clinical condition of the patients remained stable.

First-pass radionuclide angiography with ^{99m}Tc-Sestamibi. Two different types of ^{99m}Tc-Sestamibi kits were employed, the first (RP30), which was administered to 9 patients, was frozen and needed to be stored at $-20°$ C whereas the second (RP30A), which was used with the remaining 57 subjects, was lyophilized and could be stored at room temperature. After labelling with ^{99m}Tc both kits form the same complex without any demonstrable difference in chemistry or animal tests; the radiochemical purity assessed by chromatographic techniques was $>90\%$ in all except one case ($>95\%$ in 81.8% of the reconstituted kits); therefore, the type of kit employed was not further considered in the evaluation of the results.

The administered dose of ^{99}Tc-Sestamibi ranged between 370 and 1480 MBq (10–40 mCi) and the injected volume, between 0.35 and 3 ml. None of the patients experienced any adverse effect; after injection some subjects perceived a transient metallic taste.

The projection employed for the study was anterior in 10 patients, left anterior oblique in 18 and right anterior oblique in 38. Acquisition was performed in either list or frame mode using a small field-of-view gamma-camera (either multicrystal or digital single crystal), equipped with a high sensitivity collimator and a 20% window centred on the 140 keV photopeak of ^{99m}Tc and interfaced with a computer. The study was elaborated according to the different software packages employed in the centres involved. At least three repeat determinations of the right and left ventricle ejection fraction were required and had to be recorded in the case report form.

Comparative methods for ventricular function evaluation. According to the protocol the recommended comparative method was first-pass radionuclide angiocardiography with either sodium pertechnetate Tc 99m or ^{99m}Tc-DTPA. This was actually performed with 33 patients, in each case using the same projection and procedure employed when ^{99m}Tc-Sestamibi was administered; the time interval between the two studies was never shorter than 24 h, with a mean of 3.95 ± 3.47 days. The injected tracer activity was not significantly different from the ^{99m}Tc-Sestamibi dose. The left ventricular ejection fraction was measured in all cases and the right ventricular ejection fraction, in 22.

In 44 patients, equilibrium gated radionuclide angiocardiography could be used as a comparative method. In 32 of them, a comparison with the first-pass studies was also possible, whereas in 12 the equilibrium study was the sole comparative radioisotopic method available. The time interval between the two studies was never shorter than 24 h, with a mean of 4.34 ± 2.94 days. The equilibrium gated radionuclide angiocardiography was performed in each centre using a small field-of-view cardiological gamma-camera, equipped with a low-energy all-purpose collimator and a 20% window centred on the 140 keV photopeak of ^{99m}Tc and interfaced with a computer. The acquired data were processed according to the different routine procedures. In all patients the left ventricular ejection fraction was determined, while in 32 the right ventricular one was also measured.

In 40 patients, left contrast ventriculography was performed as the comparative method, and it was the sole one available in 20. The time interval between the ^{99m}Tc-Sestamibi first-pass angiocardiography and the contrast ventriculography ranged from 1 to 66 days (mean 18.4 ± 17.3 days). The left ventricular ejection fraction was calculated from the volumetric measurements of end-diastolic and end-systolic images, using either the monoplane or the biplane area-length method.

Statistical analysis. The ejection fraction values obtained by the different methods were compared using the Student *t*-test for paired

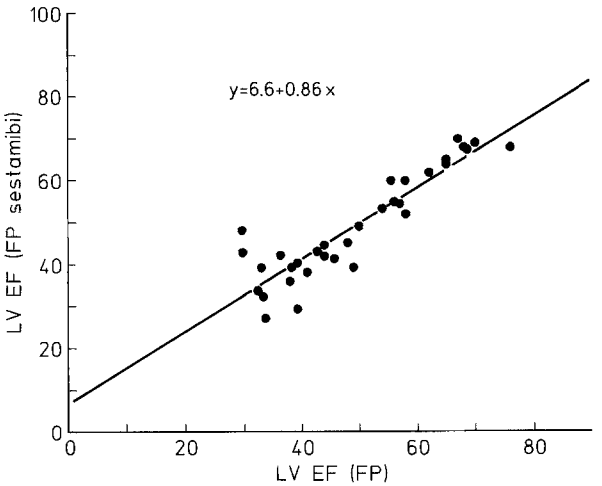

Fig. 1. Comparison of left ventricular ejection fraction (*LVEF*) measured using first-pass radionuclide angiocardiography performed with a reference tracer (*FP*) and with technetium 99m hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-Sestamibi): $n=33$, $r=0.909$

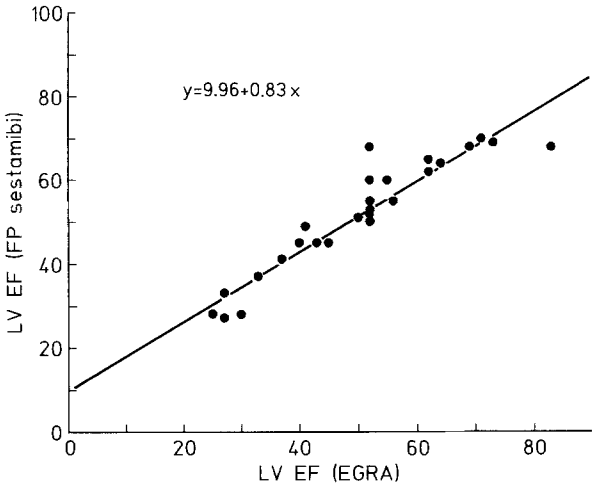

Fig. 2. Comparison of left ventricular ejection fraction (*LVEF*) measured using gated equilibrium radionuclide angiocardiography (*EGRA*) and first-pass radionuclide angiocardiography with ^{99m}Tc-Sestamibi: $n=26$, $r=0.937$

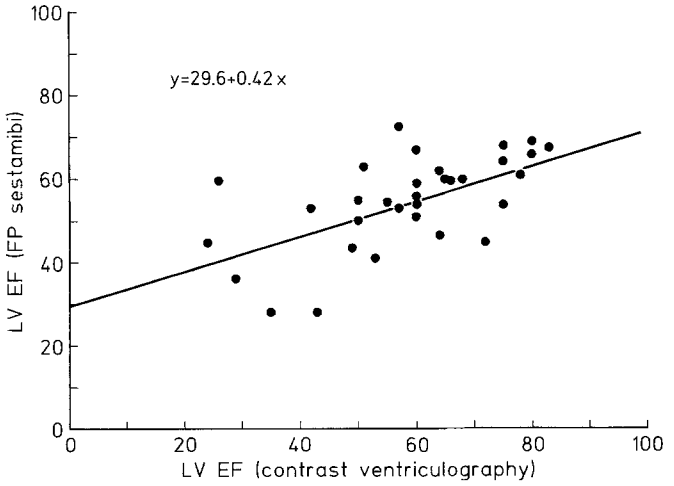

Fig. 3. Comparison of left ventricular ejection fraction (*LVEF*) measured using contrast ventriculography and first-pass radionuclide angiocardiography with ^{99m}Tc-Sestamibi: $n=33$, $r=0.60$

data, linear regression and Pearson's correlation coefficient. The probability level was fixed at $P<0.05$. All data are expressed as the mean $\pm$SD.

Results

Left ventricular ejection fraction

The left ventricular ejection fraction calculated with first-pass radionuclide angiocardiography using ^{99m}Tc-Sestamibi was not significantly different from the reference first-pass study performed using either sodium pertechnetate Tc 99m or ^{99m}Tc-DTPA: 49.1% $\pm$12.7% (^{99m}Tc-Sestamibi) vs 49.3% $\pm$ 13.4%. A satisfactory correlation between the two values could be demonstrated: $r=0.909$ ($P<10^{-6}$), irrespective of the projection employed, which was always the same in each subject (Fig. 1).

For the comparison of the results from equilibrium radionuclide angiocardiography and from contrast ventriculography, only data from first-pass ^{99m}Tc-Sestamibi studies performed using right anterior oblique or anterior views (26 cases) were considered. The left ventricular ejection fraction calculated with the two methods was not significantly different: 51.8% $\pm$ 13.5% (^{99m}Tc-Sestamibi) vs 50.2% $\pm$ 15.2%. The correlation with the equilibrium technique was very good with $r=0.937$ ($P<10^{-6}$) (Fig. 2). On the contrary, only a relatively low correlation with the results of contrast ventriculography could be achieved, with $r=0.60$ ($P<0.001$) (Fig. 3). However, also in this case no significant difference between the value obtained by the two techniques could be found: 54.6% $\pm$ 11% (^{99m}Tc-Sestamibi) vs 58.3% $\pm$ 15.5%.

Right ventricular ejection fraction

Comparison of the right ventricular ejection fraction calculated with first-pass radionuclide angiocardiography using ^{99m}Tc-Sestamibi and a reference tracer showed an acceptable correlation: $r=0.712$ ($P<0.001$) (Fig. 4), and the two sets of values were not significantly different: 42.6% $\pm$ 7.7% (^{99m}Tc-Sestamibi) vs 41.7% $\pm$ 7.2%. For comparison of the ^{99m}Tc-Sestamibi first-pass studies with the results of equilibrium angiocardiography, once again only the data obtained using right anterior oblique or anterior projection were considered (15 cases). The calculated values were not significantly different: 45.5% $\pm$ 7.6% (^{99m}Tc-Sestamibi) vs 44.4% $\pm$ 5.9%, and showed a satisfactory correlation: $r=0.783$ ($P<0.001$) (Fig. 5).

Discussion

Radionuclide angiocardiography, performed using either the first-pass or gated equilibrium technique, allows

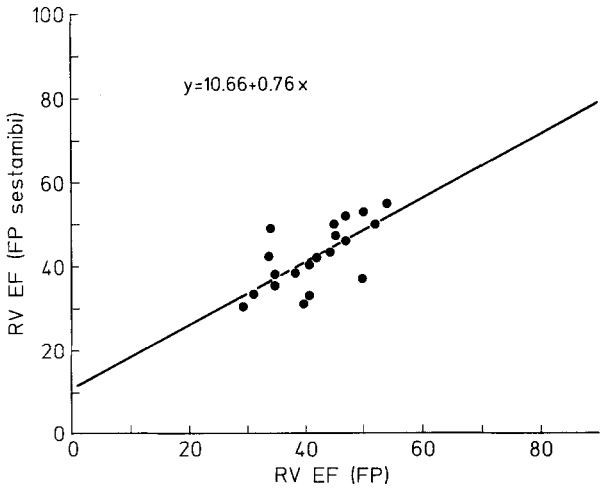

Fig. 4. Comparison of right ventricular ejection fraction (*RVEF*) measured using first-pass radionuclide angiocardiography performed with a reference tracer (*FP*) and with ^{99m}Tc-Sestamibi: $n=22$, $r=0.712$

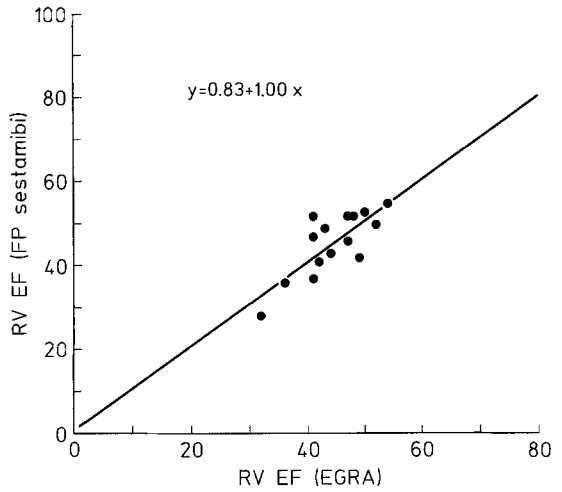

Fig. 5. Comparison of right ventricular ejection fraction (*RVEF*) measured using gated equilibrium radionuclide angiocardiography (*EGRA*) and first-pass radionuclide angiocardiography with ^{99m}Tc-Sestamibi: $n=15$, $r=0.783$

an accurate and reproducible evaluation of both left and right ventricular function, by means of various quantitative parameters, chiefly the ejection fraction, and of the visualization of the ventricular wall motion pattern (Folland et al. 1977; Wackers et al. 1979; Jones et al. 1981). Several reports stress the value of a functional evaluation of the cardiac performance, in particular with prognostic stratification (Borer et al. 1980, 1987; Sanz et al. 1982; Corbett et al. 1983; De Pace et al. 1983; Grodzinski et al. 1985; Iskandrian et al. 1985; Multicenter Postinfarction Research Group 1986; Jones 1987). Since the strict relation between perfusion and function abnormalities has been demonstrated, the assessment of both of them would be highly desirable (Bodenheimer et al. 1978; Massie et al. 1978; Rozanski et al. 1981) and would naturally be more accurate if simultaneously performed (Mena et al. 1984), as well as having the further advantage of reducing the radiation burden to the patient. Using ^{201}Tl as a perfusion tracer, functional assessment was possible only by performing a radionuclide angiocardiography during a separate study. The availability of Sestamibi, an isonitrile derivative labelled with ^{99m}Tc, which allows good quality perfusion imaging (McKusick et al. 1986; Maddahi et al. 1987; Okada et al. 1988; Kiat et al. 1989), opened the way to a combined assessment of perfusion and function by taking a first-pass radionuclide angiocardiography as the perfusion tracer is injected (Schelbert 1987). However, an evaluation of the study quality possible with ^{99m}Tc-Sestamibi was necessary, since the influence of lung and myocardial uptake on background activity has been observed (Baillet et al. 1989). A comparison of results obtained with ^{99m}Tc-Sestamibi with those using the established tracers, such as sodium pertechnetate Tc 99m or ^{99m}Tc-DTPA, and with other accepted non-invasive reference techniques, particularly equilibrium radionuclide angiocardiography, was therefore mandatory. This was the aim of the present study, planned as part of a more extensive and complete evaluation of the reliability of ^{99m}Tc-Sestamibi for perfusion myocardial scintigraphy.

According to our results, the left ventricular ejection fraction values obtained with first-pass radionuclide angiocardiography using ^{99m}Tc-Sestamibi were comparable with those from the established tracers, as reported by Baillet et al. (1989). This is true independent of the examination technique used. On the other hand, the comparison with equilibrium radionuclide angiocardiography also yields good results, which are comparable with those obtained using the traditional tracers (Folland et al. 1977; Wackers et al. 1979; Kaul et al. 1984; Knesewitsch et al. 1986). For this comparison it is naturally necessary to take into account only the first-pass studies performed using a correct projection, such as right anterior oblique or anterior (Wackers 1987; De Puey 1988; Holman 1988), since the absolute value of a left ventricular ejection fraction calculated starting from a left anterior oblique projection is unreliable. The same is true when the first-pass ejection fraction has to be compared with another reference method such as contrast ventriculography. In this regard, our results were less satisfying when compared with already published data (Jengo et al. 1978; Iskandrian et al. 1981; Gal et al. 1986). This can be partly explained by the longer time interval which elapsed between the first-pass and this particular comparison method in our study group (Cohn et al. 1974; McAnulty et al. 1974), by the fact that the quantitative assessment of contrast ventriculography was not performed according to a specific protocol but as part of the routine left heart catheterization procedure (Rogers et al. 1979) and by the presence in the study group of patients with poor left ventricular function (Iskandrian et al. 1982). The absence of any significant difference between the values calculated with

the two methods, however, allows one to exclude a systematic error in the results of ^{99m}Tc-Sestamibi first-pass angiocardiography.

Also, the right ventricular ejection fraction which was obtained using ^{99m}-Sestamibi correlates with both the data attained using first-pass with other tracers and those of equilibrium radionuclide angiocardiography. Again, only the ^{99m}Tc-Sestamibi first-pass studies performed in a correct projection were considered. The anatomical shape of the right ventricle makes the ejection fraction calculation more difficult and justifies a lower level of correlation among measures performed in different studies or with other methods (Maddahi et al. 1979; Manno et al. 1984).

We may conclude that the evaluation of cardiac function with first-pass radionuclide angiocardiography performed during the injection of ^{99m}Tc-Sestamibi seems reliable and accurate. The execution of combined studies of perfusion and function coupled with an appropriate stress test is the logical consequence of these preliminary experiences. This approach is certainly more demanding than a simple perfusion scintigraphy, for instance because the gamma-camera is occupied during the entire exercise test. Moreover, the use of a single-day protocol is no longer possible. Further studies are therefore necessary in order to identify in which patients the use of a combined evaluation is worthwhile. The simultaneous assessment of perfusion and function, even if performed in selected cases only, appears to be a noteworthy advantage offered by ^{99m}Tc-Sestamibi over ^{201}Tl.

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