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Original

Normative values of ^{99m}Tc-MIBI distribution in myocardium in males and females, as a basis for quantitative planar scintigraphic method for detection of coronary artery disease in patients of both sexes

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Abstract

BACKGROUND: Radionuclide perfusion studies of myocardium are being performed using planar and tomographic (SPECT) procedures. The latter method enables better detection as well as assessment of localisation and severity of scintigraphically visualised perfusion defects. On the other hand, lower cost of planar procedures using ^{99m}Tc-MIBI as the tracer and their much wider availability in countries of Central and Eastern Europe could significantly increase the diagnostic potential of nuclear cardiology in this region.

The aim of the study was an assessment of normal distribution of ^{99m}Tc-MIBI in the myocardium and generation of normative basis for quantitative planar scintigraphic procedure, aiming at detection of CAD in patients of both sexes.

MATERIAL AND METHODS: The study was based on 250 patients. The reference (control) group consisted of 53 individuals (29 men, 24 women) with the low (< 10%) initial probability of CAD as estimated on basis of Diamond's tables. The second group included 197 patients (132 men, 65 women) with diagnosed CAD or with substantiated suspicion of its presence. In all patients of the latter group coronary angiography was performed and was used as the reference method for assessment of diagnostic efficacy of the scintigraphic procedure.

RESULTS: The original own method of acquired data evaluation was based on creation of circumferential profiles of activity and on using the procedure of trend-fitting for obtaining average curves and their dispersion around the mean values. The mean profile curves were obtained for three projections (anterior, LAO 45° and LAO 70°). These mean curves differed significantly between both sexes. In LAO 45° projection the differences affected mostly the region of the septum and postero-lateral wall of the left ventricle (LV). In LAO 70° projection differences were most pronounced in the antero-septal wall of the LV.

CONCLUSION: Sensitivity, specificity and accuracy of CAD detection using the elaborated method, taking into account inter-sex differences, amounted to 86, 87 and 86% respectively in males, and correspondingly 81, 84 and 83% in females. The differences between corresponding indices for two sexes were statistically insignificant. For the whole group of patients the sensitivity, specificity and accuracy was 85, 86 and 85%, respectively.

Key words: myocardial perfusion scintigraphy, planar study, ^{99m}Tc-MIBI, quantification, normal data base, gender differences, coronary artery disease

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Introduction

Myocardial perfusion scintigraphy forms the basic asset of nuclear medicine in detection of coronary artery disease. Indications for perfusion scintigraphy or stress echocardiography arise when initial diagnosis does not provide data for high probability of CAD diagnosis or its exclusion. In such a situation the above-mentioned non-invasive specialised methods may facilitate appropriate pre-selection of patients for the invasive and expensive coronary angiography.

In spite of the enormous development and sophistication of echocardiography, the degree of subjective judgement in this method is still higher than in scintigraphic assessment of perfusion. Moreover, for various reasons, 10–15 per cent of the results of conventional echocardiographic studies cannot permit reasonable evaluation of all segments of the LV.

Scintigraphic evaluation of left-ventricular perfusion is conducted either by means of the planar method, or using the procedure of single photon emission tomography (SPECT). Evaluation of the results can be either visual (semi-quantitative or qualitative) or quantitative. Better contrast of images and analysis of consecutive slices of left ventricle while using the SPECT technique makes this procedure a method of choice when very detailed localisation and severity of perfusion defects is the main objective of the study. However, clinically significant perfusion abnormalities can easily be detected in a planar study using three projections (anterior, LAO 45° and LAO 70°). Moreover, the cost of a planar scintillation camera is much lower than that of a rotational one. The degree of complication of the SPECT study is higher when compared with the planar one, particularly when all requirements of quality assurance are rigorously observed. These requirements also increase significantly the cost of SPECT procedure v. planar scintigraphy. On top of all these considerations there is still a large number of planar cameras, which sometimes constitute the only scintigraphic equipment available that could be used for perfusion studies. Such a situation obtains inter alia in countries of Central and Eastern Europe where planar cameras still account for about 2/3 of the total number of the imaging instruments in nuclear medicine units [1].

Therefore, elaboration of a suitable, quantitative method for detection of coronary perfusion impairment by means of planar scintigraphy, using ^{99m}Tc-MIBI as a radiopharmaceutical, seemed to be an essential element of effective use of the nuclear medicine potential in creating a widely accessible procedure for detection of CAD in diagnostically uncertain cases of the disease.

The aim of the study was therefore to develop a procedure for possibly objective assessment of ^{99m}Tc-MIBI in normal myocardium, separately for males and females, that could be used for quantitative evaluation of planar scintigraphic images for detection of CAD in individuals of both sexes. It should be mentioned at this stage that normative values for analysis of planar scintigrams, obtained after administration of ^{99m}Tc-MIBI in humans and presented in scientific literature on the subject were either sex-averaged data (usually with overwhelming excess of males), or had been derived only for males.

Material and methods

Two hundred and fifty patients comprised the study group. In neither of them was there any history or electrocardiographic signs of myocardial infarction. Valvular heart disease, cardiomyopathy or myocardial hypertrophy were also excluded.

The reference group consisted of 53 individuals (29 males and 24 females) aged between 21 and 53, mean value 32 years, with atypical complaints in the chest, who were referred to the myocardial perfusion scintigraphy for possible exclusion of CAD. The initial probability of the disease, as estimated according to Diamond [2, 3] on the basis of clinical investigations (age, sex, symptom classification and exercise-induced ECG ST segment depression) was low, i.e. below 10%.

The second group included 197 patients (132 males and 65 females) aged between 31 and 73, with the mean value of 49 years, with diagnosed or suspected CAD. The mean probability of the disease, acc. to Diamond, amounted to 56 $\pm$ 34 (SD) per cent. In all patients of this group coronary angiography was performed; results of this procedure were taken as the reference for evaluation of the efficacy of myocardial perfusion scintigraphy. The CAD was diagnosed on basis of the angiography when at least one of the three main coronary arteries demonstrated presence of critical stenosis ($\geq$ 70% of the cross section area).

The perfusion scintigraphy was conducted on the basis of a two-day protocol. On the first day a stress test was performed after intravenous administration of 555 MBq of ^{99m}Tc-MIBI at the peak of monitored physical effort. On the next day a rest study was made after administration of the same activity of the radiopharmaceutical. The acquisitions were made in a planar mode, in three projections: anterior, LAO 45° and LAO 70°, using a Picker DDC camera coupled to the SIEMENS MaxDelta computer system.

Quantitative evaluation of the results was based upon analysis of ^{99m}Tc-MIBI distribution in the myocardium of left ventricle, in the form of circumferential profiles. Analysis of profile curves of a given patient depended on comparison of their course with the reference, normal shape of the corresponding average curves, as derived for patients of the reference group.

The original own method for obtaining average, normal trends of profile curves in the reference patients was based on fitting the sequential individual curves, by means of the least square method, to the already averaged profile curves, separately for men and women (Fig. 1). This method leads to distribution of errors resulting from the fitting procedure over the entire length of the average profile curve. The method of obtaining an optimal criterion for detection of perfusion defects in patients of both sexes, and the verification of the diagnostic criterion accepted for efficacious detection of CAD on basis of the planar perfusion scintigraphy, was presented in earlier publications [4–9].

Significance of differences between average profile curves for males and females of the reference group was evaluated by analysis of corresponding points from analogous curves, applying Student's t-test of equality of the means for normally distributed points and the Mann-Whitney test for points with non-normal distribution.

A comparison of sensitivity, specificity and accuracy of the method for CAD detection in males and females was based on the tests for comparison of two frequencies among two binomial distributions, for independent variables.

Results

Mean normal trends of the profile curves, together with confidence intervals $\pm$2 SD, obtained from the stress scintigrams, in three

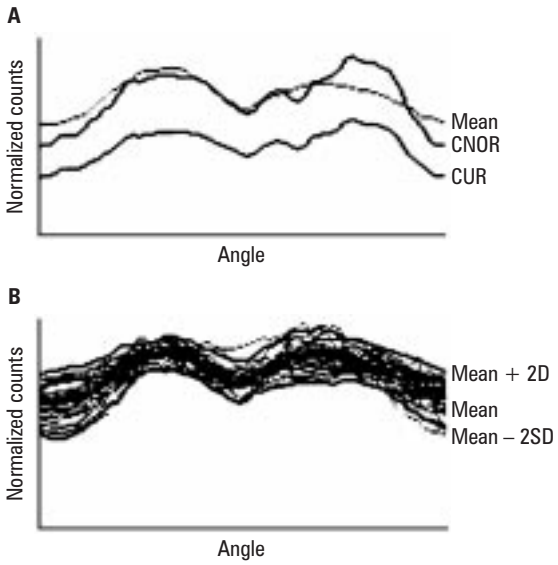

Figure 1. A method for obtaining a normal trend of the profile curves. **A.** A profile curve before (CUR) and after (CNOR) fitting into a normal average trend (MEAN), obtained from earlier fitting of the curves (from the reference group). **B.** A normal trend (mean values ±2 standard deviations), obtained from fitting of the profile curves of individuals (grey shaded area) from the reference group.

projections, separately for males (n = 29) and females (n = 24) from the group 1, are presented in Figure 2. Corresponding mean trends for rest scintigrams are very similar to the stress curves, and have been omitted from presentation.

In anterior projection the curves, both in males and in females, display two maxima corresponding to accumulation of ^{99m}Tc-MIBI in the inferior and antero-lateral wall of the LV. The lower activity in the profile curve corresponds to the apical and basal parts of the ventricle. In males, the two-peak course of the profile curve described above depicts also the distribution of the radiopharmaceutical in the two remaining projections (LAO 45° and LAO 70°). In contrast, in females in the LAO 45° projection there appears a peak in the apical part of the septum and in the postero-lateral wall. The infero-apical part of the curve displays a mild depression of the profile and a pronounced decline, more abrupt than in males, is seen toward the basis of the LV. In LAO 70° projection in females there is only one mild peak visible in the profile curve, corresponding to the postero-inferior wall; there is no apical depression of the curve, which in the whole antero-septal part shows a trend of a uniform decline towards the basis of the heart.

In Figure 3 segments of normal trends significantly differing between two sexes ($p < 0.05$) have been marked. In the anterior projection this difference affects only a small segment of the curve, corresponding to the periapical (distal) part of the antero-lateral wall. In females, this part of the curve is significantly depressed relative to the trend in males. In LAO 45° projection the differences between the mean curves for two sexes affect most segments of profile curves. A significantly lower course of the profile in females relates both to the septal and the postero-inferior part of the LV (together with basal parts). The antero-septal segment of the postero-inferior part of the profile curve is significantly elevated, relative to males.

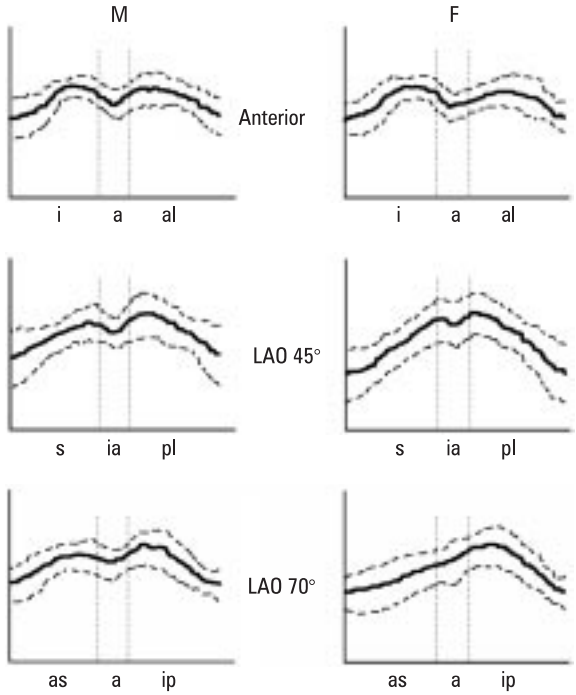

Figure 2. Normal trends (mean values ±2 standard deviations), obtained from the profile curves of individuals with normal perfusion (reference group). The trends are calculated separately for males (M) and females (F); i — inferior wall, a — apex, al — antero-lateral wall, s — septum, ia — infero-apical wall, pl — postero-lateral wall, as — antero-septal wall, ip — infero-posterior wall

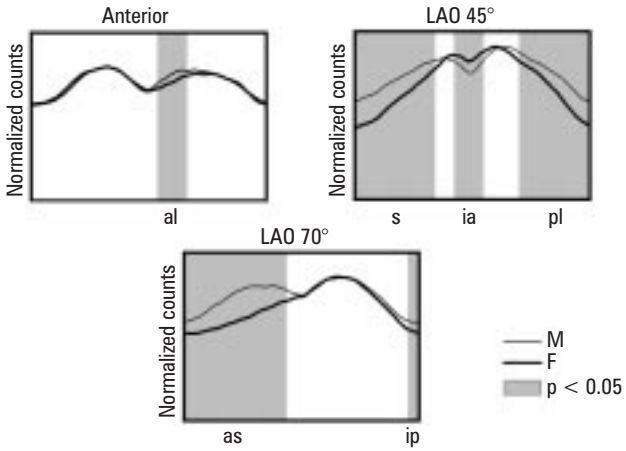

Figure 3. Differences between average normal profile curves for males (M) and females (F). Shaded areas show parts of profile curves differing significantly ($p < 0.05$); al — antero-lateral wall, s — septum, ia — infero-apical wall, pl — postero-lateral wall, as — antero-septal wall, ip — infero-posterior wall.

Sensitivity, specificity and accuracy of CAD detection, based upon the normative values of the profile curves described above, separately for both sexes, amount to correspondingly for men (n = 132) to: 86, 87 and 86%, and for women (n = 65) to: 81, 84 and 83%. All these values do not differ significantly between two sexes. For the whole group of 197 patients the indices of sensitivity, specificity and accuracy reach values of 85, 86 and 85%, respectively.

Discussion

A quantitative, normative analysis of perfusion scintigrams of myocardium requires knowledge about normal distribution of the radioactivity in the LV images. The range of normal values may be obtained from examination of individuals with a low initial probability of CAD, without perfusion defects. The method, used for the first time in this study, leads to distribution of fitting errors, resulting from individual differences between profile curves, upon the whole course of the profiles. Therefore, the obtained variation interval is approximately uniform over the whole range.

Other authors [10–12] have adopted a different concept for obtaining the average course of the profile curves. They had normalised maxima of consecutive curves of individuals from the reference group to 100% with subsequent calculation of mean values for each point. The confidence intervals of normative mean profiles obtained by applying such an algorithm are very wide, particularly in the fragments remote from the maximum. This makes detection of reduced uptake of the radiopharmaceutical in corresponding regions of LV very difficult. Moreover, such a way of quantitative evaluation of the tracer uptake may lead to incorrect results in cases where existing defect of the perfusion is being depicted by that part of the curve, at which in normal conditions the maximum uptake should occur. In this situation the whole curve is artificially "pushed up" and a quantitative measure of a perfusion defect is minimised or not detected at all.

The analysis of the data obtained in this study demonstrated clearly that the reference group should be treated separately for both sexes. This results from the different shape of the mean curves for males and females, particularly in LAO 45° and LAO 70° projections. Significantly lower values in some parts of average profile curves in females as presented above, may be related to the increased absorption of gamma photons by the female breast and perhaps also by the lateral wall of the thorax. On the other hand, lower values recorded in males in the infero-apical region in LAO 45° projection, could perhaps be attributed to the more pronounced photon absorption by the diaphragm, more developed and of larger muscular mass than in women. This paper demonstrates for the first time significant differences between normal profile curves generated from planar ^{99m}Tc-MIBI studies for males and females. In the literature on quantitative, normative analysis of similar ^{99m}Tc-MIBI perfusion scintigrams, published by other authors [10–13], the shape of profile curves is close to that demonstrated by us for males. This resulted from the composition of the reference groups which included either mostly, or exclusively, men [10–15]. It is obvious that if such curves are being used for perfusion evaluation in females the result may be misleading.

Differences between normal profile curves, generated from planar scintigrams by means of circumferential profiles for several radiopharmaceuticals, such as ^{201}TlCl, ^{99m}Tc-MIBI, ^{99m}Tc tetrofosmin and ^{99m}Tc furifosmin were demonstrated by Naruse and coworkers [11]. However, sex related differences were not investigated. The differences in profile curves have been attributed by those authors to differences in kinetics and biodistribution of individual radiopharmaceuticals (that resulted inter alia in different extracardiac distribution in the body), and also to the difference between photon energy for ^{201}Tl and ^{99m}Tc. Photons emitted by ^{201}Tl, due to their lower energy, are more efficiently absorbed by surrounding tissues and organs.

Substantial differences between normative values for males and females were demonstrated by SPECT perfusion studies [16–19]. Quantitative analysis of heart tomograms, obtained after administration of ^{201}Tl, ^{99m}Tc-MIBI and ^{99m}Tc tetrofosmin should be performed utilising separate bases of normative distribution values for men and women (they are usually presented in the form of polar-maps) [19–21].

In summary the presented method of normative evaluation of heart perfusion planar scintigrams, taking into account inter-sex differences, is characterised by satisfactory good indices of diagnostic efficacy for patients of either sex.

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