The value of ^{99m}Tc-MIBI myocardial perfusion imaging in differentiation of heart failure conditioned by global left ventricular systolic impairment

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Key words: global left ventricular systolic impairment; idiopathic dilative cardiomyopathy; ischemic heart failure; ^{99m}Tc-MIBI myocardial perfusion imaging; echocardiography; coronary angiography.

Summary. Objective. The global left ventricular systolic impairment with left ventricular dilatation can manifest due to idiopathic dilated cardiomyopathy or ischemic heart disease and can present a similar clinical picture of severe heart failure. The aim of our investigation was to assess a differential diagnostic value of resting ^{99m}Tc-MIBI myocardial perfusion defects in evaluation of the etiology of heart failure.

Material and methods. The data of 2D echocardiography, coronary angiography, and myocardial gated single photon emission computed tomography with ^{99m}Tc-MIBI investigation were evaluated in 43 patients with global left ventricular systolic impairment, characterized by left ventricular end-diastolic diameter of \geq 65 mm and ejection fraction of \leq 40%. The idiopathic dilative cardiomyopathy was diagnosed in 26 patients (Group 1) and ischemic heart failure – in 17 patients (Group 2). The area and the degree (severity) of myocardial perfusion defects (AMPD and DMPD) at rest in regions supplied by three coronary arteries were evaluated in all the patients.

Results. The area of perfusion defects in the left anterior descending (LAD) and right coronary artery (RCA) regions in dilative cardiomyopathy patients was smaller than in ischemic heart failure patients $(1.43\pm0.9 \text{ vs } 2.53\pm0.53, P=0.001, \text{ and } 2.19\pm0.6 \text{ vs } 2.82\pm0.56, P=0.02)$. The degree of perfusion defects was also less severe in the same circulation regions $(1.39\pm0.93 \text{ vs } 2.59\pm0.6, P=0.01, \text{ and } 1.6\pm0.46 \text{ vs } 2.71\pm0.15, P=0.001)$. We have designed a logistic regression model expressed by formula $x=2.52AMPD_{rca}+2.47AMPD_{lad}+2.21DMPD_{rca}$. Idiopathic dilative cardiomyopathy was predicted when x was ≤ 16 and ischemic heart failure when x was > 16. The sensitivity in predicting idiopathic dilative cardiomyopathy was 94.44%, and the specificity was 88.24%.

Conclusion. The difference in the area and degree of ^{99m}Tc-MIBI myocardial perfusion defects at rest in patients with heart failure caused by idiopathic dilative cardiomyopathy or ischemic heart failure is measurable and has a predictive value for differentiation of the etiology of global left ventricular systolic impairment.

Introduction

According to the contemporary definition and classification of the cardiomyopathies suggested by the American Heart Association (AHA) scientific statement, idiopathic dilated cardiomyopathy (IDCM) is characterized by systolic dysfunction and dilatation of the left ventricular (LV) chamber, which lead to progressive heart failure (HF) with subsequent complications (1). IDCM usually is identified in the late stage and is associated with severe symptoms and leads to disability. According to the position statement of the working group on myocardial and pericardial diseases of the European Society of Cardiology (2), IDCM could be defined in the presence of LV dilatation and LV systolic dysfunction and in the absence of ischemic heart disease (IHD), hypertensive heart disease, and

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valvular heart disease. However, all the above-mentioned causes may lead to LV dilatation and severe HF by themselves.

The precise differentiation of the etiology of HF is very important in clinical practice for several reasons. Patients with ischemic heart failure (IHF) have a worse prognosis (3), but they may benefit from interventional or surgical revascularization; prevention of HF progression by lipid-lowering drugs and neurohormone blockade are necessary for these patients (4–6). Conversely, in patients with IDCM, genetic screening of family and exclusion of IHD by noninvasive methods are becoming more important in diagnosis and management of the disease (7). Thus, a precise differential diagnosis allows better selection of optimal conservative or surgical treatment, as well as prognostication of outcomes and selection of preventive measures of disease progression.

However, the differentiation of causes of advanced HF is a complicated clinical task, especially if clinical manifestations of angina pectoris are absent (8). Coronary angiography is helpful in etiological differentiation of HF syndrome (6). In patients without coronary artery stenotic lesions, the diagnosis of IHF is usually excluded. However, such an invasive method as coronary angiography is less accessible in everyday clinical practice for many patients with severe HF; thus, reliable noninvasive methods for differential diagnosis could be preferable.

Therefore, more accurate evaluation of the diagnostic and prognostic value of myocardial perfusion imaging in differentiation of IDCM and IHF is very important. The diagnostic and prognostic value of perfusion defects at rest in patients with IDCM and global left ventricular systolic impairment (GLVSI) is underestimated, and further studies are required (9, 10).

The aim of the study was to assess the diagnostic value of ^{99m}Tc-MIBI regional myocardial perfusion defects at rest in differentiation of HF etiology in patients with IDCM or IHD.

Material and methods

We analyzed the data of 43 patients treated in the Department of Cardiology at the Hospital of Kaunas University of Medicine. All of them had symptoms and signs of moderate to severe HF (New York Heart Association functional classes III–IV). The main inclusion criteria were LV dilatation with LV end-diastolic diameter of \geq 65 mm and LV ejection fraction (EF) of \leq 40%, determined by 2D echocardiography data using Simpson's method (11). All the patients

underwent coronary angiography, and the severity of coronary artery (CA) stenotic lesion was evaluated in points: 0 points, normal CA; 1 point, CA wall irregularity; 2 points, stenosis <50%; 3 points, 50–75% stenosis; 4 points, 75–95% stenosis; and 5 points, a total CA occlusion (100%).

On the basis of coronary angiography findings, all the patients were divided into two study groups: Group 1 comprised 26 patients with normal CA or CA with insignificant (<50%) stenosis, and Group 2 consisted of 17 patients with 50–75% stenosis of three main CA branches or 75–95% stenosis or occlusions of two main CA branches (11, 12).

According to our previously described methodology (13, 14), all the patients underwent a myocardial gated single photon emission computed tomography (SPECT) with ^{99m}Tc-MIBI examination at rest. Degree (severity) of the myocardial perfusion defects (DMPD) was determined in three LV circulatory regions: right coronary artery (DMPD_{rea}), left anterior descending (DMPD_{lad}) and left circumflex (DMPD_{lcx}). The DMPD was graded on a 3-point scale (1 point, a reduction in myocardial perfusion is 20–40%; 2 points, a 40–60% reduction; and 3 points, a significant (>60%) reduction of the perfusion.

The area of myocardial perfusion defects (AMPD) at rest was assessed in all three LV regions as mentioned above: $AMPD_{rea}$, $AMPD_{lad}$, and $AMPD_{lex}$. It was also expressed using a 3-point scale (1 point for one echocardiographic segment, 2 points for 1.2–2.7 segments, and 3 points for 2.7 or more segments) (13, 15).

Statistical analysis. The identification of informative markers allowing differentiate patients with IDCM from those with IHF was performed using the t criterion for independent samples, the U criterion, and the stepwise multiple logistic regression procedure. In order to evaluate the probability of the IDCM taking into account the integrated effect of several attributes, the following multiple logistic regression model was used:

and

logit
$$p \equiv \log\left[\frac{p}{1-p}\right] = b_0 + b_1 x_1 + \dots + b_k x_k$$

 $P(6) = \frac{\exp(b_0 + b_1x_1 + \dots + b_kx_k)}{(1 + \exp(b_0 + b_1x_1 + \dots + b_kx_k))}$

where:

 $x_1, ..., x_k$ – values of the patient's clinical attributes, $b_0, b_1, ..., b_k$ – parameters of the model.

The risk score $B=c_1x_1+...+c_kx_k$ that the patient has

IDCM was defined using b_i coefficients from the multiple logistic regression model and coefficients c_1 , ..., c_k were proportional to odds ratios e^{b1} ... e^{bk} .

Results

The data of 2D echocardiography, myocardial perfusion imaging (MPI), and coronary angiography are presented in Table 1. According to P values of t and U criteria, the patients with IDCM were younger than those with IHF (P=0.001). The significant differences in MPI characteristics between the patients of Groups 1 and 2 were encountered more frequently than in characteristics of echocardiography. Only the echocardiographic LV posterior wall thickness (P=0.03) and anterior wall motion index (P=0.001) were differences in the patient of the provide the provide the patient of the provide the patient of the

ferent between these groups. However, the degree and area of MPI defects in RCA and in the LAD blood supplying regions were significantly different between both patients' groups. Differences in DMPD and AMPD were evidently less expressed in the LCX region (Table 1).

The informative and prognostic value of the MPI characteristics for differentiation of patients with IDCM and IHF was evaluated using the logistic regression method (Table 2).

Using the findings of myocardial perfusion imaging, we designed this multiple logistic regression model:

logit p=16, 16–2.21DMPD_{rca}–2.52AMPD_{rca}– $-2.47AMPD_{lad}(\chi^2=34.4, P<0.001)$

Index	Group 1 (n=26) Patients with IDCM	Group 2 (n=17) Patients with GLVSI	$P ext{ of } t ext{ test}$	P of U test	
Age, years	49.8±11	64.3±7.9	0.001	0.001	
2D echocardiography data					
LVEDD, mm LVEF, % IVS, mm LVPWT, mm LVRWT LVWMI _{rea} LVWMI _{lad} LVWMI _{lax}	$\begin{array}{c} 66.1{\pm}8.1\\ 21.6{\pm}6.8\\ 9.9{\pm}1.0\\ 10.6{\pm}0.97\\ 0.31{\pm}0.07\\ 2.7{\pm}2.1\\ 1.8{\pm}3.6\\ 1.8{\pm}2.3 \end{array}$	$\begin{array}{c} 65.7 \pm 5.3 \\ 22.0 \pm 8.8 \\ 10.04 \pm 1.7 \\ 9.7 \pm 1.42 \\ 0.3 \pm 0.06 \\ 2.72 \pm 2.6 \\ 2.7 \pm 3.4 \\ 1.7 \pm 2.0 \end{array}$	$\begin{array}{c} 0.86 \\ 0.8 \\ 0.9 \\ 0.03 \\ 0.6 \\ 0.9 \\ 0.025 \\ 0.6 \end{array}$	0.56 0.8 0.7 0.03 0.55 0.9 0.001 0.47	
Myocardial perfusion gated SPECT data					
DMPD DMPD _{lad} DMPD _{lcx} AMPD _{rea} AMPD _{lad} AMPD _{lad}	$ \begin{array}{r} 1.6 \pm 0.46 \\ 1.39 \pm 0.93 \\ 0 \pm 0 \\ 2.19 \pm 0.6 \\ 1.43 \pm 0.9 \\ 0 \pm 1.33 \\ \end{array} $	$2.71\pm0.152.59\pm0.60.41\pm1.192.82\pm0.562.53\pm0.530.59\pm1.3$	$\begin{array}{c} 0.001 \\ 0.001 \\ 0.068 \\ 0.02 \\ 0.001 \\ 0.054 \end{array}$	$\begin{array}{c} 0.001 \\ 0.014 \\ 0.25 \\ 0.028 \\ 0.004 \\ 0.25 \end{array}$	
Coronary score of each coronary artery					
RCA LAD LCX	0.08±1.4 0.31±2.1 0.29±3.3	6.59±2.8 9.59±2.7 6.24±2.5	<0.001 <0.001 <0.001	<0.001 <0.001 <0.001	

Table 1. Clinical characteristics of patients' groups

 $AMPD_{rea}$ – area of myocardial perfusion defects in right coronary artery region; $AMPD_{lad}$ – area of myocardial perfusion defects in left anterior descending region; $AMPD_{lex}$ – area of myocardial perfusion defects in left circumflex branch region; $DMPD_{rea}$ – degree of myocardial perfusion defects in right coronary artery region; $DMPD_{lad}$ – degree of myocardial perfusion defects in left anterior descending region; $DMPD_{lex}$ – degree of myocardial perfusion defects in left anterior descending region; $DMPD_{lex}$ – degree of myocardial perfusion defects in left circumflex branch region; GLVSI – global left ventricular systolic impairment; IDCM – idiopathic dilative cardiomyopathy; IVS – interventricular septum; LVEF – left ventricular ejection fraction; LAD – left anterior descending branch; LCX – left circumflex branch; LVEDD – left ventricular end diastolic diameter; LVPWT – left ventricular posterior wall thickness; LVRWT – left ventricular relative wall thickness; $LVWMI_{rea}$ – left ventricular wall motion index in right coronary artery region; $LVWMI_{lad}$ – left ventricular wall motion index in right coronary artery region; $LVWMI_{lag}$ – left ventricular wall motion index in generative wall motion index in left anterior descending region; $LVWMI_{lex}$ – left ventricular wall motion index in right coronary artery region; $LVWMI_{lag}$ – left ventricular wall motion index in region; $LVWMI_{lex}$ – left ventricular wall motion index in region; $LVWMI_{lex}$ – left ventricular wall motion index in region; $LVWMI_{lex}$ – left ventricular wall motion index in right coronary artery region; $LVWMI_{lex}$ – left ventricular wall motion index in region; $LVWMI_{lex}$ – left ventricular wall motion index in left circumflex branch region; RCA – right coronary artery; SPECT – single photon emission computed tomography.

Index	χ^2	Р	b
DMPD	12.36	0.003	-1.92
DMPD	11.9	0.005	-1.75
AMPD	4.95	0.035	-1.61
	10.8	0.006	-1.33

Table 2. The logistic regression analysis of myocardial perfusion scintigraphy defects obtained in patients with dilated cardiomyopathy and patients with global ischemic LV impairment

 $AMPD_{rea}$ – area of myocardial perfusion defects in right coronary artery region; $AMPD_{lad}$ – area of myocardial perfusion defects in left anterior descending region; $DMPD_{rea}$ – degree of the myocardial perfusion defects in right coronary artery region; $DMPD_{lad}$ – degree of the myocardial perfusion defects in left anterior descending region. χ^2 – value χ^2 statistic; P - P value of the test χ^2 ; b – the parameter of the logistic regression model.

Table 3. Reliability of the coefficients of the multiple logistic regression models

Index of the model	$oldsymbol{eta}_1$	Р	e ^β
$\begin{array}{c} \text{DMPD}_{\text{rca}} \\ \text{AMPD}_{\text{rca}} \\ \text{AMPD}_{\text{lad}} \\ \beta \text{o} \end{array}$	-2.21	0.053	0.109
	-2.52	0.073	0.08
	-2.47	0.027	0.085
	16.16	-	-

 $AMPD_{rea}$ – area of myocardial perfusion defects in right coronary artery region; $AMPD_{lad}$ – area of myocardial perfusion defects in left anterior descending region; $DMPD_{rea}$ – degree of the myocardial perfusion defects in right coronary artery region.

 β – parameters of the multiple logistic regression models; P - P value of the test χ^2 .

Table 3 presents the reliability of the coefficients of the multiple logistic regression models. According to the multiple logistic regression models, IDCM was diagnosed when P value exceeded 0.05.

The amount of data was limited; therefore, we used n-fold cross-validation (leave-one-out) to test the model. IDCM was prognosticated in 15 patients (83.3%) and ICM in 16 patients (94.1%).

Instead of the calculation of probability of the DCM, we additionally introduced the total score B, which was calculated using indices of the logistic model multiplied by coefficients expressed in whole numbers and proportional to e^{β} values (β is coefficient in the logistic model). Indices of MPI included into the model acquired values expressed in whole numbers. The total score B was introduced as follows:

Total score B=2AMPD_{rea}+2AMPD_{lad}+3DMPD_{rea}

If the total score B value was ≤ 16 , we diagnosed IDCM, and if the total score B value was $\geq 16 - \text{IHD}$. In prediction of IDCM, the sensitivity was 94.44%, and the specificity was 88.24%.

Discussion

Noninvasive evaluation and differentiation of patients with global left ventricular systolic impairment and moderate to severe HF is difficult but very important clinical task because prognosis and treatment of patients with IDCM and IHF are different (3, 4). Keeping in mind a severe overall condition of HF patients, the invasive investigations of such patients have an additional risk. Therefore, identification of informative and accurate noninvasive methods is still important. The value of stress MPI in identification of patients with myocardial ischemia is adequately evaluated. According to the meta-analysis of numerous pharmacological or echocardiographic studies, the sensitivity of exercise MPI with 99mTc-MIBI in diagnosis of CA stenosis was 83%, and specificity was 78% (16, 17). Such sensitivity and specificity are conditioned by difficulties in selection of similar patients according to the specificity of CA lesion, since the location and degree of CA lesions are very variable. It has also been proved that the MPI with ^{99m}Tc-MIBI is of equal value to contrast echocardiography (17–19). Both contrast echocardiography and cardiac gated SPECT proved to have a similar sensitivity and specificity in diagnosis of CA damage (16).

However, the value of ^{99m}Tc-MIBI gated SPECT at rest is not sufficiently investigated and is underestimated, especially in the evaluation and differentiation of patients with moderate to severe HF of different etiology (20–22).

The diagnostic accuracy of rest MPI is debatable (5, 8, 19, 23, 24). However, the value of different radionuclide techniques in differentiation of patients with IDCM from those with IHD may be very important (6, 20, 21). The MPI is a technique in which radionuclide tracers are used to evaluate myocardial blood flow in order to assess myocardial scarring or fibrosis due to ischemic heart disease. Usually the MPI is performed in conjunction with different stress tests (exercise or pharmacological) in order to induce reversible or irreversible changes (5, 8, 19, 24). Our investigation of diagnostic and prognostic value of myocardial perfusion defects at rest was additionally motivated by the necessity to determine myocardial scarring and fibrosis (20, 25, 26), which usually manifested as fixed perfusion defects and may be interrelated interdependently in patients with IDCM (27).

The study analysis has shown more significant differences between IDCM and IHF groups according to the regional MPI data than the LV global and regional systolic function data assessed by 2D echocardiography (9). Myocardial fibrosis may occur in patients with IDCM as well as in patients with IHF; however, according to our analysis, the myocardial perfusion defects at rest were more expressed in patients with IHF. Other mechanisms, besides myocardial hemodynamic and structural derangements, seems to be important in determining impairment of myocardial blood flow at rest in advanced IDCM (12). The differentiation of HF related to IDCM and IHD using gadolinium-enhanced cardiovascular magnetic resonance imaging has shown that coronary angiography may be flawed in identifying the myocardial substrate for HF as significant CA disease may exist without myocardial infarction, and "normal" CA may be in the presence of myocardial damage coherent with the pattern of subendocardial to transmural enhancement (6).

Other studies, which compared the effectiveness of dobutamine stress echocardiography and cardiac gated SPECT with ^{99m}Tc-MIBI in diagnosis of CA lesions, showed that both techniques have an equal sensitivity and specificity (28).

A number of scientific studies apply various logistic regression models in the diagnosis and prognosis of ischemic heart disease (29). Although, we were not able to find studies describing a logistic regression analysis for the prognostication of IDCM in HF patients according to the data of MPI at rest. There are some studies on prognostication of IDCM according to the comprehensive clinical data (29). In our study, we used the logistic regression method and designed a total score B model that included findings of the MPI data, which allowed the diagnosis of IHF with a sensitivity of 97.4% and specificity of 94.1%, and IDCM – with a sensitivity of 95.2% and specificity of 83.3%

Conclusion

Myocardial gated single photon emission computed tomography with ^{99m}Tc-MIBI performed at rest may be helpful in differentiation of patients with global left ventricular systolic impairment and those with concomitant dilatation manifested by moderate to severe heart failure due to idiopathic dilated cardiomyopathy or ischemic heart disease. Severity and size of myocardial perfusion defects, revealed at rest in anterior and inferior regions of left ventricle defined by multiple logistic regression model, were informative for the diagnosis of idiopathic dilated cardiomyopathy due to its high sensitivity and specificity.

^{99m}Tc-MIBI miokardo perfuzijos tyrimo vertė diferencijuojant kairiojo skilvelio sistolinės visų segmentų disfunkcijos sąlygoto širdies nepakankamumo priežastis

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Raktažodžiai: kairiojo skilvelio sistolinė visų segmentų disfunkcija, idiopatinė dilatacinė kardiomiopatija, išeminės kilmės širdies nepakankamumas, ^{99m}Tc-MIBI miokardo perfuzijos tyrimas, echokardiografija, koronarografija.

Santrauka. *Įvadas.* Kairiojo skilvelio sistolinė visų segmentų disfunkcija gali būti sąlygota idiopatinės dilatacinės kardiomiopatijos ir išeminės kilmės kairiojo skilvelio pažeidimo bei pasireikšti panašia širdies nepakankamumo simptomatika. Šio tyrimo tikslas – nustatyti pradinių ^{99m}Tc-MIBI ramybės būsenos miokardo perfuzijos defektų diagnostinę vertę diferencijuojant šias dvi širdies nepakankamumo priežastis.

Tyrimo medžiaga ir metodai. Išanalizuoti 43 ligonių, kuriems nustatyta kairiojo skilvelio sistolinė visų segmentų disfunkcija (kai kairiojo skilvelio galinis diastolinis diametras buvo \geq 65 mm, išstūmio frakcija (IF) \leq 40 proc.), echokardiografijos, koronarografijos bei miokardo pozitronų emisinės tomografijos, atliktos su ^{99m}Tc-MIBI, duomenys. Idiopatinė dilatacinė kardiomiopatija buvo nustatyta 26 ligoniams (1 grupė), išeminės kilmės širdies nepakankamumas – 17 ligonių (2 grupė). Visiems ligoniams nustatyta miokardo perfuzijos defektų plotas bei laipsnis trijuose vainikinės kraujotakos baseinuose.

Rezultatai. Kairės vainikinės arterijos priekinės tarpskilvelinės šakos ir dešinės vainikinės arterijos zonų perfuzijos defektų plotas sergančiųjų idiopatine dilatacine kardiomiopatija buvo mažesnis nei sergančiųjų išeminės kilmės širdies nepakankamumu: $1,43\pm0,9$ ir $2,53\pm0,53$, p=0,001 bei $2,19\pm0,6$ ir $2,82\pm0,56$, p=0,02. Miokardo perfuzijos defektų laipsnis tose pačiose vainikinės kraujotakos zonose buvo taip pat mažesnis: $1,39\pm0,93$ ir $2,59\pm0,6$, p=0,001 bei $1,6\pm0,46$ ir $2,71\pm0,15$, p=0,001. Miokardo perfuzijos defektų plotas ir laipsnis juosiančiosios šakos zonoje buvo panašūs.

Naudodamiesi logistinės regresijos analize, išvedėme formulę širdies nepakankamumo priežasčiai prognozuoti:

Idiopatinę dilatacinę kardiomiopatiją galima prognozuoti kai $x \le 16$, o IŠN, kai x > 16. Prognozuojant idiopatinę dilatacinę kardiomiopatiją šioje ligonių imtyje, nustatytas 94,44 proc. jautrumas ir 88,24 proc. specifiškumas.

Išvada. Miokardo ^{99m}Tc-MIBI perfuzijos defektų ploto ir laipsnio skirtumas sergantiesiems idiopatine dilatacine kardiomiopatija ir išeminės kilmės širdies nepakankamumu yra akivaizdus ir jis gali turėti prognostinės vertės diferencijuojant šias širdies nepakankamumo priežastis.

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