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CREATINE KINASE IN PERIPROCEDURAL MYOCARDIAL INJURY AFTER PERCUTANEOUS CORONARY INTERVENTION

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Patients with ischemic heart disease undergoing percutaneous coronary intervention are characterized by various degrees of myocardial damage. The purpose of the study is to investigate the dependence of micro-injuries of the myocardium on the nature of the damage to the coronary arteries and the features of the procedure during the interventional treatment in patients with stable angina. Myocardial damage was diagnosed based on the dynamics of cardiospecific biomarkers of creatine kinase-myocardial band isoenzyme before and 24 hours after intervention.

Providing the analysis of the phenomenon in the totality of its characteristics, the use of multivariate statistics (principal component method, stepwise discriminant analysis) allowed not only to differentiate patients with or without periprocedural myocardial damage and to determine the possibility of their differentiation by the impacts of such characteristics as "the total number of inflations" and "total number of affected arteries", but also to point out a level of creatine kinase before intervention as a sign of potential vulnerability/resistance of myocardium.

The latter can be considered as a separate component characterizing the state of cardiomyocytes and the degree of risk of postprocedural myocardial damage. Thus, investigation of nature of the complication is important not only for its prevention but for study the whole cardioprotection issue. Refs 26. Figs 2. Tables 7.

Keywords: stenosis of the coronary arteries, percutaneous coronary intervention, periprocedural myocardial damage, creatine phosphokinase, principal components, stepwise discriminant analysis, cardioprotection.

КРЕАТИНФОСФОКИНАЗА В ОЦЕНКЕ ПОВРЕЖДЕНИЯ МИОКАРДА ПРИ ЧРЕСКОЖНОМ КОРОНАРНОМ ВМЕШАТЕЛЬСТВЕ

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Больным ишемической болезнью сердца, подвергнутым чрескожному коронарному вмешательству свойственен риск возникновения различной выраженности повреждения миокарда. Цель исследования — изучение зависимости микроповреждения миокарда от характера поражения коронарных артерий и особенностей процедуры при данном плановом интервенционном лечении у больных стабильной стенокардией. Повреждение миокарда диагностировалось

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11-1-2017.indd 4 30.05.2017 16:55:53

на основании динамики кардиоспецифического биомаркера креатинфосфокиназы (мобильная фракция) до интервенционного вмешательства и через 24 часа после него.

Использование в исследовании методов многомерной статистики (метод главных компонент, дискриминантный анализ), обеспечивающих анализ изучаемого явления в совокупности его характеристик, позволило не только дифференцировать пациентов с развитием или отсутствием перипроцедурального повреждения миокарда, определить возможность их дифференциации по вкладам таких признаков, как «суммарное число инфляций» и «общее количество пораженных артерий», но и выделить в качестве признака потенциальной ранимости/резистентности миокарда уровень креатинфосфокиназы до выполнения чрезкожного коронарного вмешательства. Полученный признак может рассматриваться как отдельная компонента, характеризующая состояние кардиомиоцитов и степень риска перипроцедурального повреждения миокарда. Исследование природы этого осложнения актуально не только для его профилактики, но и для решения проблемы кардиопротекции в целом. Библиогр. 26. Ил. 2. Табл. 7.

Ключевые слова: стеноз коронарных артерий, чрескожное коронарное вмешательство, перипроцедуральное повреждение миокарда, креатинфосфокиназа (мобильная фракция), главные компоненты, пошаговый дискриминантный анализ, кардиопротекция.

Introduction

Worldwide diffusion of percutaneous coronary intervention (PCI) in everyday cardiological practice is a consequence of its efficacy for myocardial revascularization. According to the many year world experience in up to 50% of patients PCI is complicated by periprocedural myocardial injury (PMI) of different degree including myocardial infarction (MI) — [1–5]. That is why different aspects of PMI problem including its risk factors, methods of identification, clinical evolution and prognosis of postprocedural MI in comparison with spontaneous one continue to be of pathological and clinical interests. At the same time there are out of the mutual concerns studies on individual prognostication of PMI risk while such attempts seem to be real today on the basis of multivariate statistical analysis [6–8] and their results could be promising for improvement of cardioprotection methods [9, 10].

Measurements of troponin (Tn) and creatine phosphokinase myocardial-banding (CK-MB) are preferred for PMI diagnostics among cardiac biomarkers for their high informative value, rapid release for early diagnosis and "diagnostic window" up to the mark of clinical needs [11, 12]. High myocardial specificity together with high sensitivity determine the possibility of Tn evaluation even in rise microzone of myocardial injury. The latter became a cause of definite skepticism associated with risk of hyperdiagnostics based on Tn measurements of acute coronary syndrome (ACS) as well as PMI [12–18]. Simultaneously interest to CK-MB and its place in diagnostics of PMI have been renewed [15, 19, 20].

The objective of the present study was to evaluate the association of coronary artery disease characteristics with the peculiarities of PCI and CK-MB levels in patients with stable angina before and after intervention procedure.

Materials and methods

The study was performed on 114 patients (24 female, 90 male; 32 to 80 years old; mean 56 years) with stable angina of II–IV functional classes (Canadian Cardiovascular Society Classifications) confirmed by a stress test induced myocardial ischemia and hemodynamic significant coronary artery stenosis. Patients with acute myocardial infarction, unstable angina, congestive heart failure, renal failure, pathology of muscles, pericarditis,

11-1-2017.indd 5 30.05.2017 16:55:53

cardioversion, PCI or surgery myocardial revascularization less than six months before the study were not included.

All patients underwent selective coronary angiography according to Judkins. Coronary balloon angioplasty and stenting were performed via femoral approach. Before PCI the patients received double antithrombotic therapy with aspirin (300 mg) and clopidogrel in doses 300 mg and 600 mg. Nonfractional heparin (100 u per kg of b.w.) was infused after location of introducer. Its following dose was calculated accordingly to the activated partial thromboplastin time (APTT) level.

Intraballoon pressure during angioplasty ranged from 11 to 20 atm. There were used drug-eluted stents (CyperSelect — Cordis, CoroflexPlease — B\Braun, Endeuvor — Medtronil, XienceV — Abbott) and holomorphic ones of 10–38 mm length and 2.5–4.0 mm in diameter.

Periprocedural myocardial damage was assessed using CK-MB (mass). Blood samples were taken from the cubital vein and stabilized with EDTA. Then they were centrifuged, plasma was frozen and stored at a temperature –18° C. CK-MB levels were determined using automatic analyzer "AxSYM" (Abbott, USA) with reagents and calibration materials from the same manufacturer, prior to PCI and 24 h after the procedure. The upper reference level was 3.8 ng/ml in accordance with the manufacturer's instructions. The combination of the elevation of biomarker level more than five times over the upper reference level with pain or new ECG changes of ischemic type, or the emergence of new areas of myocardial contractility reduction was regarded as MI associated with PCI [21].

According to recommendations of ACC/AMA [22] there were distinguished three angiographic types — A, B and C. Degree of stenosis was also estimated in points according to Fitzgibbonetal: 25 % — 1, 50 % — 2, 75–80 % — 3, subocclusion — 4 and occlusion — 5 points.

Statistical analysis

The original database consisted of 289 variables, which is more than twice the number of patients. Reducing the quantity of indicators for the application of multivariate statistical methods was carried out taking into account the results of the correlation analysis (correlation Pleiades) and factor analysis (within blocks of the correlation matrix).

All the ordered variables involved in multivariate statistical analysis, were ranked. Some quantitative indicators have been logarithmed with later test for the normality of distribution.

Fisher's exact test and the Wilcoxon test were used to identify the differences between the groups on the studied attributes. To study homogeneity of the groups under investigation and to determine significance of their characteristics in development of myocardial damage the factor analysis (FA) using principal components (PC) and discriminant analysis were used.

All the statistical analysis was performed using "STATISTICA 10" (StatSoft, Inc).

Results and their discussion

Ninety two patients (80.7 %) were free of any sings of PMI in 24 hours after PCI (group A). Group B consisted of 22 patients (19.32 %) with CK-MB level > 3.8 ng/ml. Six of them (5 %) had CK-MB level > 19 ng/ml after PCI.

11-1-2017.indd 6 30.05.2017 16:55:54

Characteristics of patients from both groups are shown in Tables 1–3. The patients did not significantly differ in gender, age, clinical signs and frequency of use of different medications before PCI (Table 1).

Table 1. **Clinical characteristics of patients**

Variables	Group A (n=92)	Group B (n=22)	Significance level, P
Male	74 (80 %)	17 (77 %)	ns
Female	18 (19 %)	5 (22 %)	ns
MI in the past	58 (63 %)	9 (40 %)	ns
Smoking	25 (27 %)	5 (22 %)	ns
Hypertension	81 (88 %)	18 (81 %)	ns
Dyslipidemia (LDL cholesterol >2.5 mmol/l)	53 (57 %)	11 (50 %)	ns
Lack of angina	1 (1 %)	0 (0 %)	ns (Mann—Whitney test)
1 FCHF	1 (1 %)	1 (4 %)	
2 FCHF	37 (40 %)	8 (36 %)	
3 FCHF	42 (45 %)	12 (54 %)	
4 FCHF	0 (0 %)	1 (4 %)	
Spontaneous angina	4 (4 %)	1 (4 %)	ns
Diabetes	18 (19 %)	2 (9 %)	ns
STROKE in the past	5 (5 %)	1 (4 %)	ns
Periph. arteries damage	2 (2 %)	1 (4 %)	ns
Prior PCI	9 (9 %)	2 (9 %)	ns
Prior CABG	4 (4 %)	2 (9 %)	ns
PREVIOUS TREATMENT			
BB	79 (85 %)	17 (77 %)	ns
BPC	39 (42 %)	9 (40 %)	ns
Nitrates	47 (51 %)	12 (54 %)	ns
Therapy with Aceis	59 (64 %)	12 (54 %)	ns
ARBs	15 (16 %)	4 (18 %)	ns
Diuretics	15 (16 %)	5 (22 %)	ns
Statins	89 (96 %)	22 (100 %)	ns
ASA	88 (95 %)	22 (100 %)	ns
Clopidogrel	28 (30 %)	9 (40 %)	ns

LDL cholesterol — cholesterol low density lipoprotein, FCHF — New York Heart Association Functional Classification of heart failure, STROKE — acute violation of cerebral circulation, PCI — percutaneous coronary intervention, CABG — coronary artery bypass grafting, BB — beta-blockers, BPC — blockers slow calcium channels, Aceis — angiotensin converting of enzyme inhibitors, ARBs — angiotensin receptor blockers , ASA — acetyl-salicylic acid, ns — not significant.

11-1-2017.indd 7 30.05.2017 16:55:54

Comparison of angiographic data revealed a significantly more often stenosis of circumflex coronary artery in group B patients (Table 2).

The groups were similar in frequency of single- and multivessel diseases (Table 3).

The group A patients significantly more often needed one stent, while those from group B three or more stents ($p<0.01$). In all, there were used 1.47 and 2.5 stents for a patient in groups A and B correspondingly. There was no difference in use of drug-eluting and bare-metal stents: 1.41 and 1.39 (32/36) correspondingly.

The group B patients were characterized by significantly more often carry out of two and more inflations during predilatation ($p < 0.02$) and of three or more inflations during stent arrangement ($p < 0.05$). They have got more often three or more inflations (73 % of cases) in contrast to 41 % in group A ($p = 0.02$). Both groups were similar in frequency of coronary artery dissections and occlusions of lateral brunches in a zone of stent implantation. A segment of patients with overlapping of stents was higher in group B — 48 % to 19 % in group A.

The method of principle components (PC) was used for complex estimation of the compared groups of patients on the basis of combinations of their characteristics. This

Table 2. **Angiographic characteistics**

Variables	Group A (n = 92)	Group B (n = 22)	P
Number of diseased vessels			
Single	33 (36 %)	6 (27 %)	P = 0.042 (Mann—Whitney test)
Double	32 (35 %)	8 (36 %)	
Three	20 (22 %)	6 (27 %)	
Four	7 (8 %)	2 (9 %)	
Diseased vessels			
Left main	0 (0 %)	1 (5 %)	ns
Left arterior descending	70 (76 %)	18 (82 %)	ns
First diagonal	21 (23 %)	4 (18 %)	ns
Circumflex	29 (32 %)	13 (59 %)	P < 0.05
Right	38 (41 %)	7 (32 %)	ns
Lesion characteristics			
Ostial lesion	22 (24 %)	5 (23 %)	ns
Occlusion	19 (21 %)	4 (18 %)	ns
Bifurcation lesion	31 (34 %)	10 (45 %)	ns
Minor branches	31 (34 %)	9 (41 %)	ns
Severe tortuosity	21 (23 %)	2 (9 %)	ns
Bifurcation angulation 90°	9 (10 %)	0 (0 %)	ns
Restenosis	6 (7 %)	2 (9 %)	ns
Calcified lesion	36 (39 %)	10 (45 %)	ns
Trombus present	10 (11 %)	2 (9 %)	ns
Type of lesion			
A	36 (39 %)	11 (50 %)	ns
B	58 (63 %)	5 (23 %)	ns
C	24 (26 %)	16 (73 %)	ns

11-1-2017.indd 8 30.05.2017 16:55:54

Table 3. **PCI procedure related variables**

Variables	Group A (n = 92)	Group B (n = 22)	P
1-vessel treatment	59 (64 %)	11 (50 %)	ns
2-vessel treatment	31 (34 %)	8 (36 %)	
3-vessel treatment	2 (2 %)	3 (14 %)	
Number of stents: 1	52 (57 %)	7 (32 %)	P < 0.01
2	32 (35 %)	7 (32 %)	
3 and more	8 (9 %)	8 (36 %)	
Left main	0 (0 %)	1 (5 %)	ns
Left anterior descending	64 (70 %)	16 (73 %)	ns
First diagonal	5 (5 %)	3 (14 %)	ns
Circumflex	25 (27 %)	8 (36 %)	ns
Right	23 (25 %)	5 (23 %)	ns
Predilatation	54 (59 %)	16 (73 %)	ns
Postdilatation	17 (18 %)	7 (32 %)	ns
Number of inflations during predilatation: 1	49 (53 %)	8 (36 %)	P < 0.02
2 and more	6 (7 %)	8 (36 %)	
Nuvber of inflations during stent implantation: 1	47 (51 %)	6 (27 %)	P < 0.005
2	38 (41 %)	8 (36 %)	
3 and more	7 (8 %)	8 (36 %)	
Number of inflations during post dilatation: 1	10 (11 %)	2 (9 %)	ns
2	6 (7 %)	5 (23 %)	
Sum of inflations:			
1	20 (22 %)	2 (9 %)	P < 0.02
2	34 (37 %)	4 (18 %)	
3 and more	38 (41 %)	16 (73 %)	
Overlapping stents	11 (48 %)	18 (19 %)	P = 0.04
Maximal intraballoon pressure during predilatation	8–18	8–20	ns
Maximal intraballoon pressure during stent implantation	8–26	10–20	ns
Corornary dissection	4 (4 %)	2 (9 %)	ns
Minor branches occlusion	1 (1 %)	1 (5 %)	ns

step of analysis included 21 of 289 variables from initial database. A process of minimization according to results of analysis of partial correlations and their pleiades supposed a highest possible preservation of mutual information. Finally the following variables were segmented: age, myocardial infarction (MI) in the past, arterial hypertension, smoking, type 2 diabetes, total cholesterol level, numbers of the diseased and of the treated with PCI coronary vessels, of the occluded arteries, arteries with damaged bifurcation, maximally hard type of the dilated stenosis, sum of the types of coronary stenosis exposed to ballooning or stenting (after numbering: A=1, B=2, C=3), maximum in points of dilated and nondilated stenosis, summary damage in points, maximal pressure in balloon

11-1-2017.indd 9 30.05.2017 16:55:54

11-1-2017.indd 10

Table 4. **Factor loadings in groups A and B**

Variables	Group CK-MB < referent level (n = 92)								Group CK-MB > referent level (n = 22)							
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
Age	–0.14	–0.05	0.40	0.53	–0.19	0.35	–0.35	–0.02	–0.17	–0.73	–0.38	0.27	0.02	0.11	–0.06	0.13
IM in the past	0.01	0.19	0.17	–0.27	0.59	0.29	–0.33	0.29	–0.09	–0.09	0.51	–0.22	0.58	–0.20	0.36	0.40
Hypertension	–0.08	0.27	0.46	0.39	0.05	–0.37	0.08	0.33	–0.48	–0.45	–0.27	0.17	–0.28	0.09	0.40	0.02
Smoking	0.32	–0.26	–0.07	–0.40	–0.25	–0.17	0.03	0.55	–0.10	0.31	0.20	–0.46	0.03	–0.23	0.50	–0.35
Diabetes type	–0.03	0.35	0.11	–0.23	0.09	0.65	0.17	0.18	0.37	0.27	–0.15	–0.70	–0.09	0.18	–0.03	0.28
Occlusion	–0.31	0.31	0.46	–0.39	–0.01	–0.03	–0.05	–0.22	–0.39	–0.01	–0.39	–0.59	–0.42	0.07	–0.17	–0.12
Bifurcation	–0.46	0.36	–0.25	0.39	0.36	–0.07	0.17	0.13	–0.32	0.42	0.08	0.28	0.31	0.30	0.01	–0.63
Number of intervened coronary vessels	–0.69	–0.42	0.02	0.12	0.15	–0.07	0.19	0.14	–0.54	–0.45	0.25	0.00	0.42	0.42	–0.13	0.04
Max. type of dilated stenosis	–0.71	0.40	–0.24	0.11	–0.08	–0.13	–0.01	0.08	–0.66	0.51	–0.34	0.07	0.14	–0.01	0.15	0.21
Max. points of dilated stenosis	–0.77	–0.21	–0.01	–0.30	–0.17	–0.15	0.00	0.02	–0.80	–0.26	0.10	0.00	–0.15	–0.07	–0.04	0.02
Cholesterol level	–0.18	–0.05	–0.14	0.25	–0.36	0.28	0.24	–0.33	–0.26	0.50	–0.01	0.23	–0.30	0.52	0.23	0.30
Predilatation max. intraballoon pressure	–0.48	0.51	–0.09	–0.28	–0.06	–0.32	–0.25	–0.15	–0.36	0.59	–0.55	0.18	0.28	0.13	0.13	–0.03
Max. diameter of stent	–0.14	–0.30	0.13	0.18	0.09	–0.13	–0.76	–0.10	–0.37	–0.01	–0.29	0.08	0.34	–0.47	–0.42	0.00
Max. length of stent	–0.44	0.46	0.04	–0.12	–0.43	0.18	–0.12	–0.01	–0.59	0.53	–0.18	0.05	0.06	–0.37	–0.02	0.22
Number of stents	–0.67	–0.48	–0.09	–0.15	–0.09	0.05	–0.12	0.10	–0.75	–0.14	0.52	0.08	–0.14	0.08	–0.07	0.19
Max. intraballoon pressure	–0.33	0.00	0.33	0.14	–0.49	0.14	0.01	0.44	–0.35	0.19	0.17	–0.62	0.23	0.35	–0.32	–0.03
Postdilatation	–0.41	–0.14	–0.48	0.07	0.18	0.38	–0.12	0.11	–0.40	0.26	0.57	0.08	–0.42	–0.19	–0.23	–0.09
Number of inflations	–0.84	–0.06	–0.29	–0.12	–0.09	0.12	–0.14	–0.02	–0.76	0.40	0.37	0.21	–0.13	0.00	–0.09	0.05
Number of stenosed arteries	–0.62	–0.26	0.46	0.02	0.27	0.08	0.31	–0.15	–0.63	–0.56	–0.01	–0.26	0.16	0.08	0.20	–0.17
Sum of points of stenosis	–0.67	–0.17	0.43	–0.23	0.15	–0.01	0.16	–0.16	–0.79	–0.26	–0.08	–0.19	–0.19	–0.27	0.24	–0.14
Sum of types of dilated stenosis	–0.79	0.14	–0.16	0.21	0.12	–0.16	0.05	0.13	–0.82	–0.08	–0.34	–0.17	0.08	0.03	–0.17	0.02
Cumulative explained variance, %	25.6	34.4	42.3	49.4	55.9	62.0	67.8	72.7	27.8	42.7	52.9	62.2	69.5	75.8	81.3	86,4

N o t e. The factors loading with absolute value above 0.5 are shaded in grey, above 0.8 — in black.

30.05.2017 16:55:54

during predilatation and stent implantation, use of postdilatation, total number of inflations, number of stents, their diameter and length.

Eight factors were originated using method of PC — new cumulative independent characteristics ordered accordingly to information of correlations between the variables included into analysis initially. Total information of these factors was 73 % in group A and 86.4 % in group B. As it is shown in Table 4, both groups have similar structure of the first factor (F1) due to their values and sings of loadings. In patients of both groups the explained variances of F1 (25.6 % and 27.7 % correspondingly) were significantly higher than those of the other factors.

In both groups the structure of F1 depended on characteristics of the severity of coronary vessel pathology associated with the extent of intervention. They can be looked at as combination of short-term dynamic obstructions which depends on number of inflations and the treated vessels with the following episodes of reperfusion. The modern conception of evolution of the pathophysiological process permit to propose that the PCI compass and its duration can negatively influence upon endothelial dysfunction native to the patients with the coronary heart disease, development of oxidative stress with the following cascade of the inflammatory defensive reactions as a consequence of PMI [9, 15].

At the same time, the compared groups A and B differed in structure of the F2, F3 and F4. They were more complex for group B patients (with PMI). Their F2 structure was determined by six variables (age, total number of diseased coronary arteries, maximum type of treated with PCI stenosis, maximum intraballoon pressure during predilatation, total cholesterol level, maximum length of stent) while in group A there was only one variable determining F2 (maximum intraballoon pressure). In group B F3 structure included four variables of the greatest loading (MI in the past, maximum intraballoon pressure during predilatation, number of implanted stents, postdilatation) and in group A not one of 21 variables. The structure of F4 was also more complex in group B. It included three characteristics opposite to one (age) in group A. In both groups the structures of F5 were similar (MI in the past). The structures of other same name factors (F6, F7 and F8) did not coincide while the total variances explained by them in both groups were close — 10.7 % and 10.6 % correspondingly.

Thus, the results of the factor analysis with PC method demonstrate identity of variables combinations in structure of F1 in both compared groups and structural nonsimilarity of the other factors. First of all it concerns the difference of F2 and F3 (even taking into account their reordering). This proves possibility to search for combinations of characteristics for discrimination of the patients with a risk of PCI induced by PMI.

For this aim a stepwise discriminant analysis with inclusion of all variables segmented by factor analysis was used. Finally the discriminant function (DF) composed four out of 21 variables which secured a significant difference between the compared groups A and B ($p < 0.0001$; F-test).

To judge from DF factor loadings regulated according to their absolute values one can see that the significant variables defining the difference between groups A and B include characteristics of the PCI intensity (total number of inflations, sum of points of intervened vessels) with "MI in past" and cholesterol level (Table 5).

Comparing the DF histograms of both analyzed groups provides possibility of visual exclusion of eight patients from group A whose DF values are in the range of group B (Figure 1).

11-1-2017.indd 11 30.05.2017 16:55:54

Table 5. **Characteristics of the discriminant function (DF) for groups A and B**

Variables	DF coefficients	DF factor loadings
Number of inflations	1.02	0.66
IM in the past	–0.89	–0.37
Max. points of dilated stenosis	–0.11	0.31
Cholesterol level	–0.38	–0.23
Constant	0.46	–

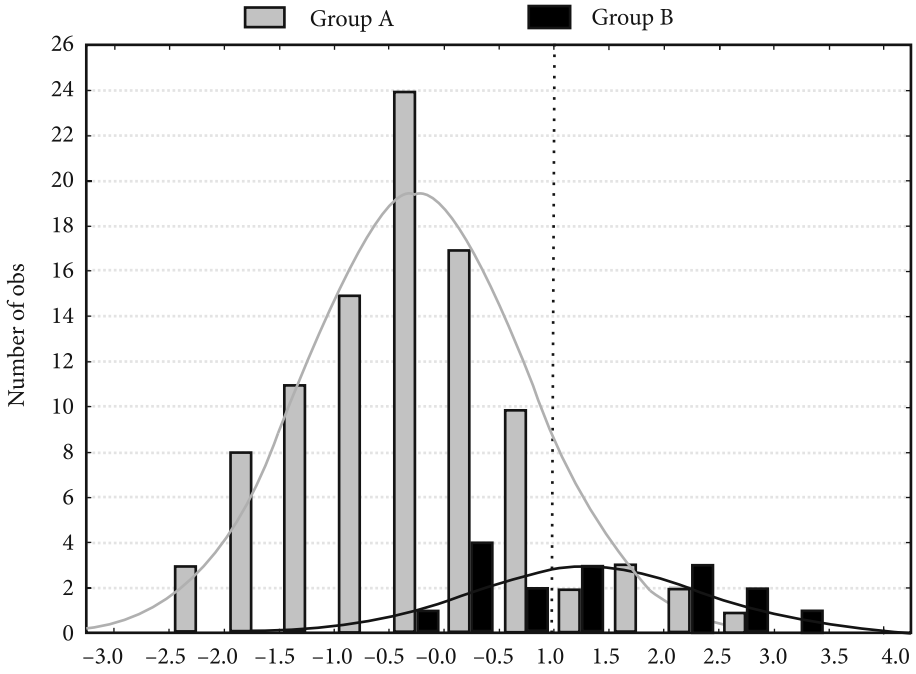

Figure 1. The mutual histogram of DF for groups A and B

According to current mode for estimation of sensitivity and specificity of a diagnostic test, an optimal point (a cut-point) for differentiation of patients must correspond to a dotted line in Figure 1 [23]. Bimodality of the group A histogram is stable with regard to changing of the histogram step ("window closing") that reflects a just of discrimination of the patients [24]. According to the latter, the above-mentioned eight patients (to the right of the dotted line) can be estimated as false positive cases and seven patients of group A (to the left of the line) as false negative. It means that seven patients with PMI initially had a low risk of it during PCI ($p = 7/96 \approx 0.07$) while a risk PMI in eight patients of group A was initially higher ($p = 10/18 \approx 0.56$) but it was not realized.

Odds ratio (OR) for compared groups (to the right and left of the dotted line) is significant with 95 % of confidence difference.

Nevertheless, a presence of a considerable number of patients in the mixed zone of mutual histogram reflects insufficiency of the segmented differentiating characteristics

11-1-2017.indd 12 30.05.2017 16:55:54

for a prognosis of risk of PMI. The reason can be connected with the limitations of patients number in the analyzed groups as well as the absence among the factors included in the study of those defining the mechanisms of CK-MB elevation in conditions of PMI formation [15, 25].

As a rule phenomenon (PMI) examined in this study is analyzed from the point of relation of two components — characteristics of severity of initial coronary affection and intensity of PCI. The post-PCI levels of biomarkers (CK-MB and Tn) are discussed as a result of interaction of these components. However from our point of view in such analysis one misses the factors that can determine a potential myocardial reflection (reaction of cardiomyocyte). In the discussed situation attention could be attracted to effect of reperfusion, formation of oxidative stress phenomenon with its consequence, aggravation of endothelial dysfunction, etc. In this context it would be important to have initially maximum knowledge about a condition of heart depended on the age of patients, myocardial hypertrophy, degree of its fibrosis, previous heart attacks, rhythm and conduction disturbances, severity of systolic and diastolic dysfunction, etc. Above recited variables do not restrict the list of factors which form the third player of PMI formation with a vulnerability of cardiomyocites or their resistance to myocardial injury. As a criterion of the latter in our study a change in CK-MB level was analyzed. So we added to the list of the variables used for factor analysis a new one — pre-PCI level of CK-MB.

According to the data of Table 6 inclusion of this new variable did not reflect on the structures of F1 and F2 in compared groups but CK-MB became determining in structure of F3 in group B and F4 in group A with factor loadings equal to 0.68 and 0.54 correspondingly. In group B this was associated with significant changes of F3 structure: increase in impact of the characteristics reflecting condition of the heart (age, MI in the past, arterial hypertension). They can be considered as the factors regulating myocardial reflection to injury and development of the enzyme elevation reaction. In this case one would discuss peculiarities of its synthesis, elimination from cells, longevity of intravascular circulation, inactivation, etc. [22].

A set of 22 variables (including pre-PCI CK-MB level) was used for the following discriminant analysis. Finally a received DF consisted of five characteristics, including pre-PCI CK-MB level (Table 7). Its factor loading was less than those of characteristics of the intervention aggression (total number of inflations) and close to variables reflecting condition of heart muscle and coronary vessels (MI in the past, stenosed vessels treated with PCI, total cholesterol level). According to F-criterion the difference between groups was significant ($P < 0.0001$).

Simultaneously a strong significant inverse relationship was found between the initial (pre-PCI) CK-MB level and its following 24 hour increment: for group A $r = -0.70$ (Figure 2). By analysis of dynamics of biological characteristics relationship of such kind can be interpreted as reflection of regulation mechanisms (in our case of CR-MB dynamics) independent of other factors [26].

Thus initial CK-MB level can be valued as a prognostic one, actual for estimation of myocardial reaction to intervention affection. Up to now pre-PCI CK-MB level was not included in the list of risk factors of PMI development and was not thought to be of prognostic significance. By analogy, it seems sensible to look for other still unknown risk markers of possible PMI during PCI [15]. They could include not only biomarkers

11-1-2017.indd 13 30.05.2017 16:55:54

11-1-2017.indd 14

Table 6. **Factor loadings in groups A and B with "Pre-PCI CK-MB level"**

Variables	Group CK-MB < referent level (n = 92)								Group CK-MB > referent level (n = 22)							
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
Age	–0.14	–0.06	–0.39	0.34	0.33	0.57	0.05	–0.08	–0.08	0.53	–0.61	–0.20	0.21	–0.06	–0.12	–0.21
IM in the past	0.01	0.12	–0.23	–0.42	0.48	–0.24	0.10	0.17	–0.15	0.22	0.51	0.04	0.37	–0.16	0.62	0.21
Hypertension	–0.07	0.29	–0.43	0.48	0.01	–0.17	0.29	0.27	–0.41	0.31	–0.60	–0.18	–0.09	0.23	0.21	–0.19
Smoking	0.32	–0.27	0.07	–0.26	–0.41	0.00	0.30	0.47	–0.18	–0.11	0.44	0.39	–0.31	0.02	0.36	–0.29
Diabetes type	–0.01	0.32	0.21	–0.21	0.02	0.55	0.21	0.10	0.33	–0.17	–0.43	–0.46	0.23	0.19	–0.23	0.36
Occlusion	–0.31	0.27	–0.52	–0.31	–0.19	–0.09	–0.24	–0.08	–0.40	0.09	–0.17	0.38	–0.47	0.05	–0.41	0.30
Bifurcation	–0.46	0.40	0.24	0.26	0.38	–0.22	–0.07	0.21	–0.33	–0.40	0.22	0.09	0.34	0.33	–0.16	–0.49
Number of intervened coronary vessels	–0.69	–0.43	0.06	0.23	0.04	–0.21	0.12	0.08	–0.53	0.44	0.19	–0.20	0.55	0.21	–0.16	0.11
Max. type of dilated stenosis	–0.71	0.44	0.22	0.10	–0.06	0.03	0.09	0.06	–0.66	–0.55	–0.21	0.21	0.15	–0.01	0.14	0.10
Max. points of dilated stenosis	–0.77	–0.22	0.02	–0.14	–0.33	–0.06	0.18	–0.09	–0.75	0.20	–0.12	–0.29	–0.03	–0.06	–0.01	0.09
Cholesterol level	–0.17	–0.07	0.21	0.34	–0.17	0.30	–0.31	–0.29	–0.29	–0.47	–0.04	–0.09	–0.07	0.61	0.07	0.11
Predilatation max. intraballoon pressure	–0.48	0.53	0.02	–0.27	–0.20	–0.08	0.31	–0.30	–0.34	–0.65	–0.33	0.33	0.32	0.08	–0.03	–0.12
Max. diameter of stent	–0.14	–0.24	–0.18	–0.09	0.38	0.25	0.58	–0.37	–0.34	–0.05	–0.19	0.13	0.35	–0.66	–0.19	–0.16
Max. length of stent	–0.44	0.44	–0.08	–0.12	–0.26	0.40	–0.11	0.04	–0.56	–0.57	–0.14	0.08	–0.02	–0.35	0.16	0.25
Number of stents	–0.67	–0.47	0.11	–0.15	–0.06	0.10	0.13	0.04	–0.72	0.10	0.17	–0.58	–0.01	0.05	0.06	0.22
Max. intraballoon pressure	–0.34	–0.03	–0.31	0.18	–0.22	0.45	0.04	0.47	–0.42	0.00	0.51	0.23	0.10	0.08	–0.43	0.25
Postdilatation	–0.42	–0.13	0.46	–0.15	0.37	0.15	–0.22	0.23	–0.37	–0.21	0.29	–0.53	–0.46	–0.24	–0.11	–0.30
Number of inflations	–0.85	–0.04	0.27	–0.22	0.01	0.17	–0.04	0.00	–0.72	–0.43	0.13	–0.47	–0.08	–0.05	0.00	–0.09
Number of stenosed arteries	–0.62	–0.32	–0.41	0.14	0.10	–0.28	–0.31	–0.02	–0.61	0.64	0.03	0.31	0.02	0.15	0.12	–0.07
Sum of points of stenosis	–0.67	–0.22	–0.41	–0.08	–0.08	–0.26	–0.20	–0.09	–0.68	0.37	–0.11	0.30	–0.31	–0.01	0.27	–0.09
Sum of types of dilated stenosis	–0.78	0.17	0.18	0.23	0.08	–0.15	0.19	0.04	–0.74	0.22	–0.19	0.36	–0.09	–0.07	–0.07	–0.05
Pre-PCI CK-MB level	–0.17	0.08	–0.19	–0.54	0.33	0.29	–0.15	0.17	0.31	–0.32	–0.68	–0.14	0.01	0.08	0.24	0.23
Cumulative explained variance, %	25.7	34.3	42.2	49.5	56.2	62.7	67.9	72.8	25.0	39.5	51.0	60.1	67.3	73.4	79.3	83.9

N o t e. The factors loading with absolute value above 0.5 are shaded in grey, above 0.8 — in black.

30.05.2017 16:55:54

Table 7. **Characteristics of the discriminant function (DF) for groups A and B based on CK MB pre-PCI level**

Variables	DF coefficients	DF factor loadings
Number of inflations	0.97	0.63
IM in the past	–0.91	–0.35
Max. points of dilated stenosis	–0.09	0.33
Pre-PCI CK-MB level	0.85	0.28
Cholesterol level	–0.34	–0.19
Constant	0.34	–

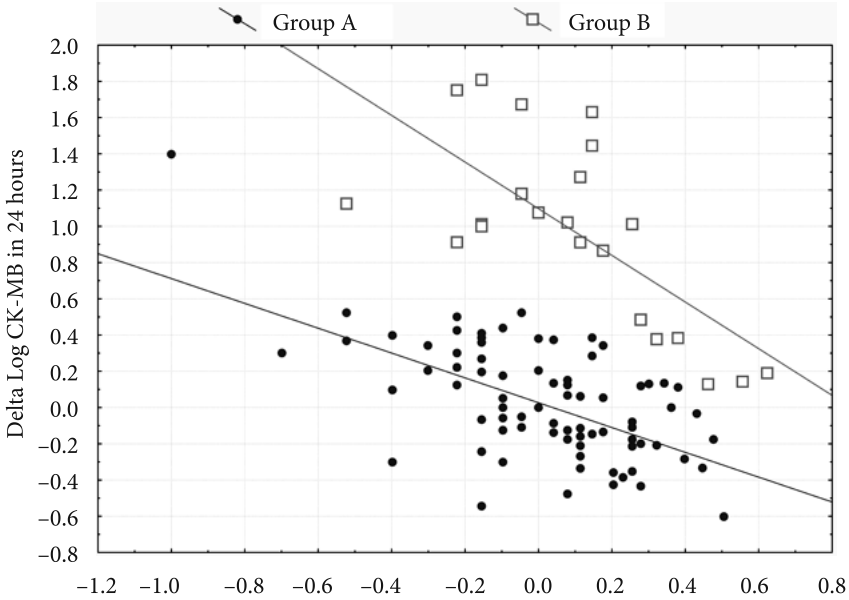

Figure 2. The mutual scatterplot of the initial level of CK-MB and its 24 hour increment in groups A and B

but other factors too, which can obliquely reflect a degree of intervention (surgery) aggressiveness: for instance — a duration of PCI [12].

Conclusion

The results of the study permit to suggest that post-PCI elevation of CK-MB level can be interpreted as a result of three component interaction. Its parts are characteristics of coronary disease, intensity of intervention affection and the factors connected with "enzyme reaction" of cardiomyocyte.

According to modern conception of cardioprotection a realization of such reflection depends on a complex of factors [9]. They include initial structural myocardial affection, sensitivity of myocytes to ischemia, which can be defined as potential vulnerability or

11-1-2017.indd 15 30.05.2017 16:55:54

resistance, degree of aggravation of endothelial dysfunction, pre-PCI measures for myocardial defense, including efficacy of preconditioning, and reaction of cardiomyocytes to injury.

It is suggested that examination of pre-PCI CK-MB level could be useful in estimation of the risk of intervention as well as of the cardiomyocytes state (of potential of their energetic system) taking into account an impact of CK-MB in anaerobic component of myocardial work efficacy and resistance to ischemic load. So one could agree with a view [10] that investigation of PMI nature is important not only for its prevention but for study the whole cardioprotection issue.

References

1. Mironova O. Iu. *Klinicheskoe i prognosticheskoe znachenie infarkta miokarda, razvivshegosia v rezul'tate provedeniia planovoi koronarnoi angioplastiki u patsientov so stabil'noi ishemicheskoi bolezn'iu serdtsa.* Dis. kand. med. nauk [*Clinical and prognostic value of myocardial infarction, developed as a result of planned coronary angioplasty in patients with stable ischemic heart disease.* PhD diss. of medicine]. Moscow, 2015, 114 p. (In Russian)

2. Califf R. M., Abdelmeguid A. E., Kunitz R. E. Myonecrosis after revascularization procedures. *J. Am. Coll. Cardiol.,*1998, vol. 31, no. 2, pp. 241–251.

3. Van Gaal W. J., Banning A. P. Diagnosing peri-procedural myocardial injury following percutaneous coronary intervention: replacing confusion with consensus. *Heart*, 2012, vol. 98, pp. 1473–1475.

4. Lansky A. J., Stone G. W. Periprocedural Myocardial Infarction: Prevalence, Prognosis, and Prevention. *Circ. Cardiovasc. Interv.*, 2010, no. 3, pp. 602–610.

5. White H. D. Defining prognostically important criteria in the periprocedural PCI — Troponin Saga. *Circ. Cardiovasc. Interv.*, 2012, vol. 5, pp. 142–145.

6. Bart A. G. *Analiz mediko-biologicheskikh sistem. Metod chastichno obratnykh funktsii* [*Analysis of Biomedical Systems. The Method of Partially Inverse Functions*]. St. Petersburg, St. Petersburg University Press, 2003, 279 p. (In Russian)

7. Bondarenko B. B., Bart V. A., Demchenko E. A., Bart A. G., Zaslavskii M. L. Aktual'nye aspekty metodologii kliniko-statisticheskogo analiza [Relevant aspects of the methodology of clinico-statistical analysis]. *Klinicheskaia i eksperimental'naia kardiologiia* [*Clinical and experimental cardiology*]. Ed. by E. V. Shlyakhto. St. Petersburg, 2005, pp. 136–148 (In Russian)

8. Vorobyova A. V., Bondarenko B. B., Bart V. A., Dorofeikov V. V., Mashek O. N., Esipovich I. D., Zverev D. A., Kuleshova E. V. O faktorakh povrezhdeniia miokarda pri planovom chreskozhnom koronarnom vmeshatel'stve [On the factors of myocardial damage during elective percutaneous coronary intervention]. *Vestnik of Saint Petersburg University. Series 11. Medicine*, 2014, issue 1, pp. 168–179. (In Russian)

9. Shlyakhto E. V., Petrishchev N. N., Galagudza M. M., Vlasov T. D., Nifontov E. M. *Kardioprotektsiia: fundamental'nye i klinicheskie aspekty* [*Cardioprotection: fundamental and clinical aspects*]. St. Petersburg, 2013, 399 p. (In Russian)

10. Babu G. G., Walker J. M., Yellon D. M., Hausenloy D. J. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur. Heart J.*, 201, vol. 32, no. 1, pp. 23–32.

11. Antman E. M., Morrow D. A. Biomarker release after percutaneous coronary intervention: a message from the heart. *Circ. Cardiovasc. Interv.*, 2008, vol. 1, no. 1, pp. 3–6.

12. Dolci A., Panteghini M. The exciting story of cardiac biomarkers: from retrospective detection to gold diagnostic standard for acute myocardial infarction and more. *Clin. Chim. Acta*, 2006, vol. 369, no. 2, pp. 179–187. DOI: 10.1016/j.cca.2006.02.042

13. Alpert J. S., Thygesen K., Antman E., Bassand J. P. Myocardial infarction redefined — a consensus document of The Joint European Society of Cardiology. *J. Am. Coll. Cardiol.,* 2000, vol. 36, no. 3, pp. 959–169.

14. Arai A. E. False positive or true positive troponin in patients presenting with chest pain but 'normal' coronary arteries: lessons from cardiac MRI. *Eur. Heart J.,* 2007, vol. 28, no. 11, pp. 1175–1177.

15. Lim C. C., van Gaal W. J., Testa L., Cuculi F., Arnold J. R., Karamitsos T., Francis J. M., Petersen S. E., Digby J. E., Westaby S., Antoniades C., Kharbanda R. K., Burrell L. M., Neubauer S., Banning A. P. With the "universal definition," measurement of creatine kinase-myocardial band rather than troponin allows more

11-1-2017.indd 16 30.05.2017 16:55:54

accurate diagnosis of periprocedural necrosis and infarction after coronary intervention. *J. Am. Coll. Cardiol*., 2011, vol. 57, no. 6, pp. 653–661.

16. Grines C. L., Dixon S. A nail in the coffin of troponin measurements after percutaneous coronary intervention. *J. Am. Coll. Cardiol.*, 2011, vol. 57, no. 6, pp. 662–663.

17. Bangalore S., Pursnani S., Kumar S., Bagos P. G. Percutaneous coronary intervention vs. optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart diseas. *Circulation*, 2013, vol. 127, pp. 769–781. DOI: 10.1161/CIRCULATIONAHA.112.131961.

18. Zhang M., He H., Wang Z.-M., Xu Zh., Zhou N., Tao Zh., Chen B., Li Ch., Zhu T., Yang D., Wang L., Yang Zh. Diagnostic and prognostic value of minor elevated cardiac troponin levels for percutaneous coronary intervention-related myocardial injury: a prospective, single-center and double-blind study. *J. Biochem. Res.*, 2014, vol. 28, no. 2, pp. 98–107.

19. Prasad A., Rihal C., Lennon R., Singh M., Jaffe A. S., Holmes D. R. Jr. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: an analysis of preintervention and postintervention troponin T levels in 5487 patients. *Circ. Cardiovasc. Interv.*, 2008, vol. 1, no. 1, pp. 10–19.

20. Prasad A., Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N. Engl. J. Med*., 2011, vol. 364, no. 5, pp. 453–464.

21. Thygesen K., Alpert J. S., Jaffe A. S., Simoons M. L., Chaitman B. R., White H. D. Joint ESC/ACCF/AHA /WHF task force for the universal definition of myocardial infarction. Third universal definition of myocardial infarction. *Eur. Heart. J.,* 2012, vol. 33, no. 20, pp. 2551–2567.

22. Smith S. C., Dove J. T., Jacobs A. K., Kennedy J. W., Kereiakes D., Kern M. J., Kuntz R. E., Popma J. J., Schaff H. V., Williams D. O., Gibbons R. J., Alpert J. P., Eagle K. A., Faxon D. P., Fuster V., Gardner T. J., Gregoratos G., Russell R. O., Smith S. C. Jr. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines) — executive summary: a report of the American College of Cardiology. *J. Am. Coll. Cardiol*., 2001, vol. 37, no. 8, pp. 2215–2239.

23. Lang T. A., Secic M. *How to report statistics in medicine: annotated guidelines for authors, editors, and reviewer*s. Philadelphia, American College of Physicians, 2006, 490 p.

24. Tukey J. W. *Exploratory Data Analysis*. Reading, Mass, Addison Wesley Publishing Company, 1977, pp. XVI + 688.

25. *Wallach's Interpretation of diagnostic tests*. Philadelphia, Lippincott Williams & Wilkins, 2007.

26. Solntsev V. N., Cherkashin D. V. Analiz korreliatsionnoi struktury faktorov serdechno-sosudistogo riska [Analysis of correlation structure of cardiovascular risk factors]. *Bulletin of the Federal Almazov center of heart, blood and endocrinology*, 2010, vol. 2, pp. 217–218. (In Russian).

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11-1-2017.indd 17 30.05.2017 16:55:54