Генетические полиморфизмы матриксной металлопротеиназы-9, тканевого ингибитора матриксной металлопротеиназы-1 и развитие послеоперационной фибрилляции предсердий у пациентов пожилого возраста

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Цель. Оценить ассоциацию между генетическими полиморфизмами матриксной металлопротеиназы-9 (ММП-9), тканевого ингибитора матриксной металлопротеиназы-1 (ТИМП-1) и послеоперационной фибрилляции предсердий (ПОФП) у пациентов пожилого возраста с ишемической болезнью сердца, подвергающихся коронарному шунтированию.

Материал и методы. В исследование включено 80 пациентов, которые подвергались коронарному шунтированию в 2015-2016 годы. У всех пациентов проводились рутинные лабораторные и инструментальные исследования. У пациентов также изучались генетические полиморфизмы ММП-9 A8202G и ТИМП-1 C536T с помощью ПЦР-диагностики. В зависимости от возникновения ПОФП все пациенты были разделены на две группы: в 1 группу включено 56 пациентов без ПОФП (81,8% мужчин, средний возраст 65,9±4,0 лет), во 2 группу — 24 пациента с впервые выявленной фибрилляцией предсердий после операции коронарного шунтирования (87,5% мужчин, средний возраст 67,7±5,4).

Результаты. По данным многофакторного регрессионного анализа отношение шансов развития ПОФП у пациентов со стабильной стенокардией напряжения III функционального класса (ФК) было 1,8 (95% ДИ 0,5-7,5, p=0,4), с хронической сердечной недостаточностью III ФК по NYHA — 0,85 (95% ДИ 0,2-3,5, p=0,55), длительностью ИБС более 20 месяцев — 1,8 (95% ДИ 1,2-8,1, p=0,03), диаметром ЛП менее 39 мм — 4,2 (95% ДИ 1,6-9,5, p<0,0001), аллелем G ММП-9 A8202G — 2,6 (95% ДИ 1,2-7,5, p=0,03).

Заключение. У пожилых пациентов, подвергающихся коронарному шунтированию, диаметр левого предсердия более 39 мм, длительность ишемической болезни сердца более 20 месяцев и наличие G аллеля ММП-9 A820G достоверно ассоциируются с развитием послеоперационной фибрилляции предсердий.

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AF — atrial fibrillation, CABG — coronary artery bypass graft, CAD — coronary artery disease, CI — confidence interval, DNA — Deoxyribonucleic acid, ECG — electrocardiography, LA — left atrium, MMP-9 — matrix metalloproteinase-9, NYHA — New York Heart Association, POAF — postoperative atrial fibrillation, TIMP-1 — tissue inhibitor of matrix metalloproteinase-1.

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Genetic polymorphisms of matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinase-1 and development of postoperative atrial fibrillation in elderly patients

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Aim. The aim of the study was to assess the association of genetic polymorphisms of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) with atrial fibrillation development in elderly patients with coronary artery disease (CAD), undergoing coronary artery bypass graft (CABG) surgery.

Material and methods. Studied were 80 patients who underwent CABG in 2015-2016 years. In all the patients routine laboratory and instrumental tests were performed. Patients also underwent genetic polymorphisms of MMP-9 A8202G and TIMP-1 C536T estimation with polymerase chain reaction. According to occurrence of postoperative atrial fibrillation (POAF) all the patients were divided into two groups: 1 group comprised 56 patients without POAF (81,8% males, mean age 65,9±4,0 years), 2 group — 24 patients with first detected episode of AF after CABG (87,5% males, mean age 67,7±5,4).

Results. According to results of multivariate regression analysis the odds ratio of POAF development in patients with stable angina grade III was 1,8 (95% CI 0,5-7,5, p=0,4), NYHA III — 0,85 (95% CI 0,2-3,5, p=0,55), history of CAD more than 20 months — 1,8 (95% CI 1,2-8,1, p=0,03), LA diameter more than 39 mm — 4,2 (95% CI 1,6-9,5, p<0,0001), allele G MMP-9 A8202G — 2,6 (95% CI 1,2-7,5, p=0,03).

Conclusion. In elderly patients undergoing coronary artery bypass graft surgery left atrial diameter more than 39 mm, history of coronary artery disease more than 20 months and the presence of G allele of MMP-9 A820G are significantly associated with postoperative atrial fibrillation occurrence.

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Key words: elderly patients, atrial fibrillation, coronary artery bypass graft, genetic polymorphisms, matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinase-1.

Conflicts of Interest: nothing to declare.

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Atrial fibrillation (AF) is one of the most common arrhythmia in clinical practice and is accompanied by significantly increased risk of cardioembolic stroke development. AF occurs in 18-40% elderly patients after cardiac surgery and is associated with thromboembolic complications and also with heart failure progression in postoperative period [1, 2].

Usually AF is initiated and sustained by abnormal impulse, which requires structural and electrically active substrate. Atrial fibrosis is a key component in atrial remodeling, thereby playing an important role in AF development [3]. Biomarkers of collagen formation which include matrix metalloproteinases (e.g. MMP-9) and their tissue inhibitors (e.g. TIMP-1) also present in atria may cause AF development [4].

The studies of genomic associations indentified 9 sensitivity regions on 8 gene chromosomes coding transcriptional factors involved in cardiovascular disease development which are responsible for ionic channels expression and also for others signal molecules, which may cause AF development [5].

In spite of epidemiological studies that revealed several genetic factors of AF development, genetic determinants of this arrhythmia remains to some extent unclear, especially in patients undergoing CABG.

Genetic polymorphisms of MMP-9, that lead to increase of concentration and also activity of MMP-9, may model humans perception of atrial fibrillation [6]. Some authors state that elevated levels of MMP-9 are associated with an increasing of AF incidents [4].

Transcription TIMP-1 gene is induced with pro-inflammatory cytokines (interleukin-1, interleukin-6, TNF-α), TGF-β1 and phorbol ethers. Many physiological functions of TIMP-1 are closely tied with functions of matrix metalloproteinases and improper production of MMP-9 and TIMP-1 is associated with severity of cardiovascular diseases [7]. Nevertheless the data from different studies about the role of TIMP-1 and MMP-9 genetic polymorphisms in POAF development in patients undergoing CABG remains uncertain.

Aim. To evaluate the association of genetic polymorphisms of MMP-9 and TIMP-1 with postoperative AF in patients undergoing coronary artery bypass graft surgery.

Material and methods

Studied were 80 patients with coronary artery disease who underwent coronary artery bypass graft (CABG) surgery in 2015 year. Inclusion criteria were age over 60 years, stable angina and signed informed consent. Exclusion criteria were valvular heart disease, renal and liver disorders, oncology diseases, stroke, coagulopathy, history of atrial fibrillation, thyroid diseases.

This study was performed according to the standards of Good Clinical Practice and also the Helsinki Declaration. Study protocol was approved by local ethic committee. All the patients enrolled in the study signed informed consent.

All the patients underwent routine laboratory and instrumental tests. Echocardiography was performed with Logiq-7 (USA) in M-, B- and D- modes. CABG was performed on-pump or off-pump. After median sternotomy, routine unicaval two stage venous cannulation and aortic cannulation was performed for cardiopulmonary bypass. After ante- and retrograde cardioplegia protocol, cross-clamp was placed. The primary study end point was new onset of AF after CABG.

DNA isolation was performed from venous blood with "DNA-express-blood" kit ("LYTECH", Russia). Genotyping of MMP-9 A8202G and TIMP-1 C536T was performed with allele specific amplification with diagnostic kits ("LYTECH", Russia). PCR was performed on thermal cycler C-1000 ("BIORAD", USA) with electrophoresis in 2% agarose gel. The results of electrophoresis were evaluated with transilluminator "GelDoc" ("BIORAD", USA).

Genotype AA of MMP-9 A8202G matches "wild type" genotype, AG — heterozygous genotype and GG — homozygous genotype. Genotype CC of TIMP-1 C536T matches "wild type" genotype, CT — heterozygous genotype and TT — homozygous genotype.

All the patients were divided into two groups according to POAF development after CABG surgery: 1 group comprised 56 patients without POAF (81,8% males, mean age 65,9±4,0 years), 2 group — 24 patients with first detected episode of AF after CABG (87,5% males, mean age 67,7±5,4). AF registration was performed with 12 channel ECG Monitor in intensive care unit.

Statistical analysis was performed in Statistica 6.1 software (StatSoft inc., USA). Quantitative variables are shown as mean ± standard deviation. In order to compare two independent groups we used Mann-Whitney U test. We used logistic regression analysis for odds ratio calculation. We also performed ROC-analysis in order to calculate sensitivity and specificity. Differences were considered significant at p value less than 0,05.

Results

Patients characteristics are shown in table 1.

AF occurred at mean on 4,6±3,4 days after CABG. In the 1 group the II grade of stable angina was significantly more frequent than in patients of the 2 group (32,1% vs 12,5%, p=0,009). Patients of the 2 group had significantly longer history of CAD (87,2±72,4 months vs 46,9±31,4 months, p=0,03), more often — NYHA III (45,8% vs 12,5%, p=0,01) and larger LA diameter (43,8±3,5 mm vs 37,5±3,9 mm, p<0,001) than patients of the 1 group. On the other hand patients of the 1 group more often had NYHA II than patients of the 2 group (87,5% vs 54,2%; p=0,01). Left coronary artery stenosis more often was found in patients of the 2 group (25,0% vs 16,1%, p=0,04). Off-pump CABG was performed more often in patients of the 1 group (17,9% vs 8,3%, p=0,04).

Genotypes distribution fulfilled expectations of Hardy-Weinberg equilibrium. Genotype AA MMP-9

Table 1

Clinical and instrumental indicators of patients enrolled in the study

		Group 1 (n=56)	Group 2 (n=24)	p
Males, n (%)		45 (81,8%)	21 (87,5%)	0,13
Age, years		65,9±4,0	67,7±5,4	0,13
Smokers, n (%)		23 (41,1%)	9 (37,5%)	0,24
Body mass index		29,7±4,8	29,5±4,2	0,65
Stable angina	I	0 (0%)	0 (0%)	1,0
	II	18 (32,1%)	3 (12,5%)	0,009
	III	30 (53,6%)	19 (75,0%)	0,28
	IV	0 (0%)	0 (0%)	1,0
History of myocardial infarction, n (%)		37 (66,1%)	17 (70,8%)	0,46
History of CAD, months		46,9±31,4	87,2±72,4	0,03
Hypertension, n (%)		57 (98,3%)	24 (100,0%)	0,52
Diabetes mellitus, n (%)		10 (18,0%)	7 (29,2%)	0,37
NYHA	I	0 (0%)	0 (0%)	1,0
	II	49 (87,5%)	13 (54,2%)	0,01
	III	7 (12,5%)	11 (45,8%)	0,01
	IV	0 (0%)	0 (0%)	1,0
Transient ischemic attack/stroke, n (%)		7 (12,5%)	5 (20,8%)	0,08
Chronic obstructive pulmonary disease, n (%)		6 (10,7%)	3 (12,5%)	0,66
Medical treatment before surgery	β blockers, n (%)	44 (78,6%)	21 (87,5%)	0,29
	ACE inhibitors /ARBs, n (%)	42 (75,0%)	20 (83,3%)	0,63
	calcium channel blockers, n (%)	12 (21,4%)	9 (37,5%)	0,71
	nitrates, n (%)	33 (59,0%)	17 (70,8%)	0,22
	diuretics, n (%)	29 (51,8%)	12 (50,0%)	0,58
	statins, n (%)	41 (73,2%)	14 (58,3%)	0,09
	aspirin, n (%)	49 (87,5%)	22 (91,7%)	0,36
	clopidogrel, n (%)	26 (46,4%)	10 (41,7%)	0,12
Left atrium, mm		37,5±3,9	43,8±3,5	<0,001
Left ventricle end-systolic dimension, (mm)		35,3±7,5	37,3±7,7	0,34
Left ventricle end-diastolic dimension, (mm)		53,2±6,4	55,7±6,8	0,12
Left ventricle end-systolic volume, (ml)		58,7±15,4	53,9±8,6	0,53
Left ventricle end-diastolic volume, (ml)		129,5±34,9	128,7±21,6	0,82
Left ventricle ejection fraction, %		55,6±10,3	57,9±9,7	0,49
Left ventricle posterior wall, (mm)		10,8±1,4	10,4±2,3	0,47
Interventricular septum, (mm)		11,3±1,8	11,8 ±2,2	0,09
Left coronary artery stenosis ⩾50%, n (%)		9 (16,1%)	6 (25,0%)	0,04
Off-pump, n (%)		10 (17,9%)	2 (8,3%)	0,04
Aortic cross clamping time, min		35,2±13,5	36,5±17,7	0,81
Time of artificial circulation		59,7±17,5	60,8±16,4	0,57
Time of ischemia, min		15,4±7,4	14,8±7,9	0,36
Number of grafts		2,6±0,9	2,7±0,9	0,47
Glomerular filtration rate, ml/min/1,73 m^2 (CKD-EPI)		74,1±16,6	76,8±17,5	0,54
Mean hospital stay, days		17,6±3,8	17,1±3,5	0,66

A8202G was found in 39,3% patients of the 1 group and in 16,7% patients of the 2 group (p=0,04), genotype AG — in 44,6% and 54,1% respectively (p=0,4), genotype GG — in 16,1% and 29,2% respectively (p=0,06). Genotype CC TIMP-1 C536T was found in 98,2% and 100% patients in 1 and 2 group respectively (p=0,72), genotype CT — in 1,8% patients of the 1 group. We did not find genotype TT among the patients of 1 or 2 group (table 2).

According to the multivariate analysis (figure 1) odds ratio of POAF development in patients with stable angina grade III was 1,8 (95% confidence interval (CI) 0,5-7,5, p=0,4), NYHA III — 0,85 (95% CI 0,2-3,5, p=0,55), history of CAD more than 20 months — 1,8 (95% CI 1,2-8,1, p=0,03), LA diameter more than 39 mm — 4,2 (95% CI 1,6-9,5, p<0,0001), allele G of MMP-9 A8202G — 2,6 (95% CI 1,2-7,5, p=0,03). Other indicators such as off-pump and left coronary

Table 2

Genetic polymorphisms of MMP-9 and TIMP-1

		1 group (n=56)	2 group (n=24)	p
MMP-9 A8202G	genotype AA, n (%)	22 (39,3%)	4 (16,7%)	0,04
	genotype AG, n (%)	25 (44,6%)	13 (54,1%)	0,4
	genotype GG, n (%)	9 (16,1%)	7 (29,2%)	0,06
	allele G, n (%)	34 (67,9%)	20 (83,3%)	0,02
TIMP-1 C536T	genotype CC, n (%)	53 (98,2%)	24 (100%)	0,72
	genotype CT, n (%)	2 (1,8%)	0 (0%)	0,72
	genotype TT, n (%)	0 (0%)	0 (0%)	1,0

Table 3

Sensitivity and specificity in predicting of AF development in patients undergoing CABG surgery

Indicator	AUC	Sensitivity	Specificity	+LR	-LR	p
History of CAD >20 months	0,76	89%	60%	2,7	0,2	0,003
LA diameter >39 mm	0,92	77%	83%	4,2	0,37	<0,001
allele G MMP-9	0,67	85%	37%	1,7	0,43	0,02

Notation: +LR — positive likelihood ratio, -LR — negative likelihood ratio.

artery stenosis became insignificant with p value much more than 0,05.

Table 3 shows sensitivity and specificity of different indicators in predicting POAF development in patients undergoing CABG surgery.

History of CAD more than 20 months had the highest sensitivity and the lowest negative likelihood ratio. LA diameter more than 39 mm had the highest specificity and positive likelihood ratio.

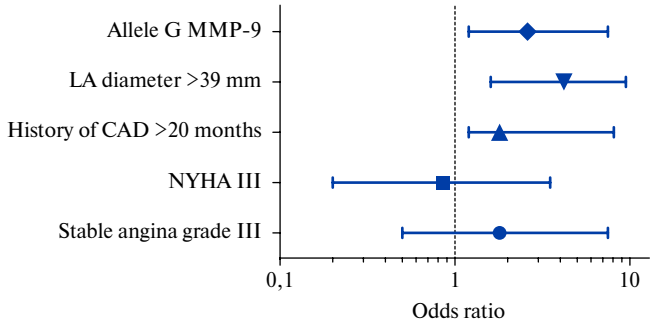

Figure 1. Odds ratio of POAF development in patients undergoing CABG surgery.

Discussion

In our investigation the prevalence of AF after CABG surgery was 30%, which matches the other authors data [8].

We showed that patients with POAF had longer history of CAD and also higher NYHA class of heart failure, that is in many ways similar to Kotecha D, et al. (2016) [9]. In our study LA diameter showed significantly association with occurrence of AF after CABG surgery, which is comparable to Parsaee M, et al. (2014) [10], but is different from Jakubova M, et al. (2012), who did not find significant differences between LA diameter in patients with POAF as compared to patients without POAF [11]. We showed that LA diameter was independent predictor of AF development after CABG surgery because the p value remained significant according to multivariate regression analysis. The other significant indicator in POAF development was also history of CAD. Our data is comparable to Parsaee M, et al. (2014) [10].

One of important factors which have an influence on AF development is artificial circulation. We found that patients with POAF had more often on-pump CABG surgery as compared to patients without POAF (p=0,04), but this factor was insignificant according to multivariate regression analysis. Literature data for this factor is controversial: Davoodi S, et al. (2014) showed that patients with POAF had more often on-pump CABG surgery as compared to patients without POAF (6% vs 3%, p=0,028) [12] but on the other side Wittwer T, et al. [13] showed that incidence of POAF was compared in patients with on-pump and off-pump surgery.

We did not find any significant differences in hospital bed days in patients who underwent CABG which is compared to Davoodi S, et al. (2014) [12] and is different from the data of Philip F, et al. (2014) who showed that patients with POAF had more bed days as compared to patients without POAF [1].

Nowadays we know that genetic polymorphisms may influence AF occurrence [13]. Several studies demonstrated the influence of genetic polymorphisms of matrix metalloproteinases on AF occurrence [5]. MMP-9 is from the family of endopeptidase which participate in extracellular matrix degradation. Myocardial fibrosis formation is to some extent due to disbalance of matrix metalloproteinase activity and their inhibitors. This process leads to extracellular matrix collagen remodeling and also to heart chambers dilatation [3].

Myocardial expression of TIMP-1 and TIMP-2 is stimulated in chronic pressure overload and is linked to interstitial fibrosis [14].

MMP-9 is produced with inflammatory cells and expressed in damaged arteries and acts as systemic inflammation marker [4]. The role of inflammation in AF development was shown in several genetic studies [6, 15]. Inflammatory factors may lead to structural atrial remodeling which leads to initiation and maintenance of AF. Inflammatory infiltrates, necrosis and fibrosis of cardiomyocytes were found in atrial bioptate material in patients with AF [14]. Tissue metalloproteinase inhibitors are the proteins which inhibit MMP activity and maintain the balance between destruction and matrix formation.

In our study we showed that allele G MMP-9 A8202G was associated with POAF (p=0,04). That is why we suggest that in patients with G allele (AG and GG genotype) the risk of POAF after CABG surgery occurrence is significantly higher comparing with patients with AA genotype.

Conclusion

In elderly patients undergoing coronary artery bypass graft surgery left atrial diameter more than 39 mm, history of coronary artery disease more than 20 months and the presence of G allele of MMP-9 A820G are significantly associated with postoperative atrial fibrillation occurrence.

Conflicts of Interest. The authors state no conflict of interests.

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