Original article

Kardiologia Polska
2011; 69, 9: 881–888
ISSN 0022–9032

Is evaluation of complex polymorphism helpful in the assessment of prognosis after percutaneous coronary intervention. A prospective study

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Abstract

Background: Coronary artery disease (CAD) is a complex disorder accounting for the majority of cardiovascular deaths and morbidity. It is believed that genetic factors explain part of the excessive risk of major adverse cardiac events (MACE) after percutaneous coronary intervention (PCI).

Aim: To evaluate the influence on long-term prognosis of some genetic polymorphisms affecting renin–angiotensin system, inflammatory response, beta-2 adrenergic receptor, nitric oxide and platelets activity in patients with stable CAD undergoing routine PCI.

Methods: The study population consisted of 110 consecutive male patients with stable angina undergoing elective, single-vessel PCI. Genotyping was performed by polymerase chain reaction and restriction fragment length polymorphism-based techniques. Follow-up data were obtained by postal questionnaires regarding survival, myocardial infarction and revascularisation procedures. The control group consisted of 78 healthy males.

Results: Compared to controls, the distribution of polymorphisms among patients differed with regard to interleukin-1 receptor antagonist and CD14 variants. Patients who had PCI during follow-up in comparison with the remaining patients had a similar genetic profile, but higher triglycerides (1.9 *vs* 1.5 mmol/L, p = 0.01) and atherogenic index (3.8% *vs* 3.1%, p = 0.03) and lower percentage of HDL (21.8% *vs* 25.0%, p = 0.02). Among subjects with any revascularisation procedures, a similar clinical profile was observed. However, they differed from those without any procedures regarding the distribution of angiotensinogen M235T variants (MM%/TM%/TT%) 28%/64%/8% *vs* 19%/50%/31%, p = 0.048. Stratification for myocardial infarction showed association with selectin E variants (AA%/AC%/CC%) 57.1%/28.6%/14.3% *vs* 78.8%/21.2%/0%, p = 0.055 and higher triglycerides (2.11 *vs* 1.57 mmol/L, p = 0.055).

Conclusions: Although we cannot exclude the role of polymorphism in angiotensinogen and selectin E genes, the prognosis of patients post-PCI in our study was mainly influenced by risk factors related to lipid metabolisms.

Key words: angioplasty, polymorphism, prognosis

Kardiol Pol 2011; 69, 9: 881–888

INTRODUCTION

Coronary artery disease (CAD) is a complex disorder accounting for most cardiovascular (CV) deaths and morbidity. Apart from the general CV risk profile, genetic determinants play an important role in CAD pathophysiology. For almost three decades, percutaneous coronary intervention (PCI) and stent implantation have remained the established treatments for CAD. Several clinical variables have been proposed to be associated with major adverse cardiac events (MACE) after PCI, with restenosis being the most frequent.

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Received: 13.01.2011 **Accepted:** 11.05.2011
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There are suggestions that genetic factors may explain part of the excessive risk of MACE including restenosis, independently from clinical variables. Many studies have demonstrated that complex mechanisms determined by genetic variants might influence the incidence of MACE . The mechanisms most often proposed included infammatory processes, platelets activity, neurohormonal activities (mainly including renin–angiotensin system), lipids metabolism and oxidative stress as well as nitric oxide synthase activity.

The aim of this study was to evaluate the distribution of some genetic polymorphisms in patients with stable CAD undergoing routine PCI of one coronary artery, and assess the role of genetic predisposition in the long-term prognosis.

METHODS

Study group

We studied consecutive patients with stable angina undergoing elective, single vessel PCI (artery not responsible for previous Q wave myocardial infarction [MI] with lumen > 2 mm). All the patients were males in sinus rhythm, without recent (i.e within the previous six months) Q wave MI or PCI. Exclusion criteria included: signs and symptoms of heart failure or significant valvular heart disease, neoplastic diseases and current treatment with tissue angiotensin converting enzyme inhibitors (ACEI) or diabetes treated with insulin. Data on clinical history as well as standard biochemical test results: total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels, HDL-ratio, atherogenicity index ([TC-HDL–C]/ /HDL-C) and pharmacotherapy were collected. Follow-up questionnaires (regarding MI and revascularisation procedures) were sent to all participants to obtain data on clinical events and survival (missing data was supplemented from the National Death Registry).

We used blood samples from 78 male volunteers from the general population, declared as being free from CV diseases, for control of genetic variability in the Polish population. They constituted the control group for genetic variants analysis.

Polymorphism analysis

Genomic DNA was extracted from fresh blood leukocytes using the phenol-based method. Polymorphisms were determined in the following genes: angiotensin-converting enzyme gene (ACE-insertion/deletion, intron 16), glycoprotein IIIa gene (GPIIIa) — p. Leu33Pro, g.C1565T, angiotensinogen gene (AGT) — p. M235T, c. T704C, angiotensinogen gene (AGT) — p. T174M, c. C521, angiotensin II receptor gene (AT1) — p. A1166C, interleukin-1 receptor antagonist gene (IL-1Ra) — Intron 2-VNTR, endothelial nitric oxide synthase gene: eNOS-Glu298Asp, eNOS-T786C, eNOS-intron 4VNTR (27 bp), phox22 NADPH gene (Phox22NADPH) — C242T, p. His72Tyr, E-selectin gene (SelE) — p. Ser128Arg, c. A128C, apolipoprotein E gene (ApoE) — Cys112Arg, Cys158Arg (ε2-112Cys,158Cys; ε3-112Cys,158Arg; ε4-112Arg,158Arg), CD14 receptor gene (CD14) — C(-260)T, CD18 receptor gene (CD18) — T1323C, beta-2-adrenergic receptor gene (β-2-AR) — Arg16Gly, beta-2-adrenergic receptor — Gln27Glu, and beta-2-adrenergic receptor — Thr164Ile. Genetic typing was performed by polymerase chain reaction (PCR) amplification, nested PCR, mismatched PCR, restriction fragment length polymorphism (RFLP) or variable number tandem repeat (VNTR) analysis. All chemicals were purchased from the Sigma Company. Restrictases and Taq polymerase were purchased from the Fermentas Company. The primers sequences, restrictases and PCR conditions are available on request [1, 2].

Statistical analysis

Results are presented as mean ± SD or numbers and percentages. Hardy Weinberg equilibrium (HWE) was analysed by Fisher exact test using software available at http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa2.pl. Two markers (nitric oxide synthase VNTR and angiotensinogen T174M SNP) with distribution significantly deviating from HWE ($p < 0.05$) either among patients or controls were not analysed further. The influence of genetic and clinical factors on a patient's prognosis was evaluated by univariate survival analysis. Univariate comparisons of genotype distribution among patients and controls were performed by Armitage's trend test using software available at http://ihg2.helmholtz-muenchen.de/cgi-bin/ /hw/hwa2.pl. For markers with more than two alleles (APOE and IL1RA), genotype distribution was compared by Fisher exact test. In case of statistically significant difference, the frequencies of individual alleles were analysed by 2 × 2 tables using Fisher exact test (SPSS). Group comparison was done using χ^2 test (categorical variables) and Student's t test (for continuous variables). In each case $p < 0.05$ was required for statistical significance. We did not use multivariable models due to the small number of events, resulting in insufficient power.

The study protocol was accepted by the Human Bioethical Committee at the Institute of Cardiology and all the patients signed informed consent.

RESULTS

Baseline characteristics of studied group

The study population consisted of 110 patients recruited between 2001 and 2003. Follow-up ranged from 4.2 to 7 years. Mean age was 57.5 years (range 41–76). Baseline intensity of angina assessed by CCS was 2.19 ± 0.8. Both mean average body mass index (BMI) and waist circumference were above normal. Heart rate and blood pressure values were within normal values. Regarding risk factors, 20% of patients had a positive CV family history; hypertension and smoking were also frequent and the mean values of TC, LDL-C, TG and HDL-C were abnormal. All the remaining morphological and

Table 1. Baseline characteristics

Parameter	Data
History	
ACS — non-ST/ST elevation	41% (45)/20% (22)
Angioplasty	12% (1)
Coronary artery bypass graft	5% (5)
Positive family history	22% (24)
Diabetes	11% (12)
Hypertension	54% (59)
Smoking	34% (36)
Clinical characteristic	
Body mass index [kg/m^2]	27.8 ±3.2
Waist/hip circumference [cm]	95.9 ± 8.6/98.9 ± 6.7
Waist/hip ratio	0.9 ± 1.1
Heart rate [bpm]	65.7 ± 9.6
SBP [mm Hg]	125.3 ± 17.2
DBP [mm Hg]	80.2 ± 11.9
Laboratory test results	
Leukocyte [× 10^9/L]	7.4 ± 1.9
Platelets [× 10^9/L]	210.4 ± 62.3
TC [mmol/L]	4.6 ± 1.0
LDL-C [mmol/L]	2.8 ± 0.8
HDL-C [mmol/L]	1.1 ± 0.2
TG [mmol/L]	1.7 ± 0.7
HDL [%]	25.8 ± 10.3
Atherogenic ratio	3.3 ± 1.2
Uric acid [mg/dL]	5.5 ± 1.4
Fasting glucose [mmol/L]	5.7 ± 1.4
Potassium [mmol/L]	4.5 ± 0.5
Sodium [mmol/L]	141 ± 3.3

ACS — acute coronary syndrome; SBP — systolic blood pressure; DBP — diastolic blood pressure; TC — total cholesterol; LDL-C — low density lipoprotein cholesterol; HDL-C — high density lipoprotein cholesterol; TG — triglycerides; continuous variables presented as means ± SD

biochemical variables were within normal ranges (Table 1). Although participants were qualified for single PCI, 54% of subjects had significant (> 75% stenosis) changes in the remaining main coronary arteries, with similar distributions of two and three vessels disease (24% and 22%, respectively). Stents were implanted in 84% of subjects. All patients were on aspirin and thienopiridines blockers. The majority of them received statins (85%) and beta-blockers (79%), followed by long-acting nitroglicerine (65%), ACEI (other than tissue ACEI) (55%) and calcium-channel blockers (25%). Fibrates were used by 5% of patients.

Polymorphism distribution

The results of analysis of the candidate genes polymorphism are presented in Table 2. Both groups (patients and controls) had a similar distribution of genetic variants studied, except for significant differences observed for interleukin-1 receptor antagonist and CD14 gene.

Major cardiovascular events

A detailed description of CV events in the study group occurring during follow-up is presented in Table 3. Clinical and demographic parameters were similar in the study subgroups stratified by survival status. Likewise, there were no major differences in the distribution of genetic variants.

Percutaneous coronary intervention

Subjects with angioplasty during follow-up (regardless of the artery with culprit lesion), compared to those free from PCI, had higher waist/hip ratio, TG, and atherogenicity index, but lower HDL-C percentage and leukocyte count (Table 4). Conversely, there were no significant differences in the distribution of polymorphism of the analysed genes.

Revascularisation (either PCI or CABG)

Participants undergoing revascularisation procedure during the follow-up had higher waist/hip ratio, LDL-C, TG and atherogenic index, but lower percentage of HDL-C, compared to subjects free from the intervention. There was also a difference in genetic variation of angiotensinogen gene M235T (MM 28% *vs* 19.1%, TM 64% *vs* 50%. TT 8% *vs* 30.9%, p = 0.048) for those who had revascularisation compared to those without this procedure, respectively (Table 5). Although Cox proportional hazard did not reveal differences between the groups with regard to genetic variants, comparison between homozygotes and heterozygotes opposite homozygotes for the other allele (a dominant model of genetic effect) showed significant differences in the cases of variants of E selectin (CC *vs* AA and AC) (HR = 9.4, p = 0.032) and angiotensinogen gene M235T (TT *vs* MM and TM) (HR = 0.49, p = 0.029). In the case of E selectin and M235T, homozygotes AA and MM along with heterozygotes AC and MT respectively are regarded as mostly neutral with respect to CV risk, whereas homozygotes CC and TT are disadvantageous.

Myocardial infarction

Stratification of the study population by MI during the follow-up revealed that the group with the event had higher TG level. Moreover, there was a borderline difference in distribution of variants of selectin E gene (p = 0.055) and angiotensinogen M235T gene (p = 0.086; Table 6). By Cox proportional hazard, there were significant dissimilarities with regard to selectin E (p = 0.05) and trends for NOS GLU298ASP (p = 0.06) and angiotensinogen M235T polymorphisms (p = 0.076). Analysis under dominant model (combination of homozygotes and heterozygotes *vs* opposite homozygotes) showed significant differences for selectin E (TT *vs* MM and TM) (HR = 35.7, p = 0.002).

Table 2. Distribution of variants in the studied genes among patients and healthy controls

Gene	Allele distribution	Study subjects	Controls	P/OR
Angiotensin converting enzyme*				NS
	DD	26.36% (29)	20.8% (16)	
	ID	55.45% (61)	48.1% (37)	
	II	18.18% (20)	31.2% (24)	
Angiotensin II receptor (AT1)*				NS
	AA	55.45% (61)	56% (42)	
	AC	41.82% (46)	37.3% (28)	
	CC	2.73% (3)	6.7% (5)	
Angiotensinogen M235T*				NS
	MM	21.82% (24)	25% (19)	
	TM	55.45% (61)	39.5% (30)	
	TT	22.73% (25)	35.5% (27)	
Angiotensinogen T174M*				NS
	MM	5.45% (6)	1.3% (1)	
	TM	21.82% (24)	23.7% (18)	
	TT	72.73% (80)	75% (57)	
Beta adrenergic II receptor*				NS
BIIA Arg16Gly				
	ARG	18.18% (20)	11.8% (9)	
	ARGGLY	43.64% (48)	43.4% (33)	
	GLY	38.18% (42)	44.7% (34)	
BIIA Gln27Glu				NS
	GLN	36.36% (40)	30.3% (23)	
	GLNGLU	49.09% (54)	52.6% (40)	
	GLU	14.55% (16)	17.1% (13)	
BIIB Thr164Ile				NS
	Thr	98.18% (108)	98.7% (75)	
	ThrIle	1.82% (2)	1.3% (1)	
Platelet receptor GPIIIA*				NS
	A1	76.36% (84)		
	A1A2	21.82% (24)		
	A2	1.82% (2)		
Nitric oxide synthase*				NS
Glu298ASP	GG	50.00% (55)	53.8% (42)	
	GT	43.64% (48)	42.3% (33)	
	TT	6.36% (7)	3.8% (3)	
				NS
T 786	CC	11.82% (13)	15.6% (12)	
	CT	51.82% (57)	41.6% (32)	
	TT	36.36% (40)	42.9% (30)	
Selectin E*				NS
	AA	77.27% (85)	73.3% (55)	
	AC	21.82% (24)	24% (18)	
	CC	0.91% (1)	2.7% (2)	
Apolipoprotein E*				NS
	CC (E4/E4)	2.75% (3)	4.1% (3)	
	DC (E2/E4)	1.83% (2)	1.4% (1)	
	DT (E2/E4)	12.84% (14)	11% (8)	
	TC (E3/E4)	16.51% (18)	23.3% (17)	
	TT (E3/E3)	66.06% (72)	60.3% (44)	
CD14*				0.05 (OR = 1.54)
	CC	24.55% (27)	38.7% (29)	
	CT	58.18% (64)	49.3% (37)	
	TT	17.27% (19)	12% (9)	
CD18*				NS
	A1 (T/T)	13.64% (15)	14.5% (11)	
	A1A2 (T/C)	46.36% (51)	44.7% (34)	
	A2 (C/C)	40.00% (44)	40.8% (31)	
Antagonist of interleukin-1 receptor (IL1RA)*				0.021[#] [$]
	AA	57.27% (63)	48.7% (37)	
	AB	27.27% (30)	40.8% (31)	
	AC	4.55% (5)	0% (0)	
	AD	0.91% (1)	0% (0)	
	BB	5.45% (6)	10.5% (8)	
	BC	4.55% (5)	0% (0)	

*Alleles with potentially increased cardiovascular risk are underlined; [#]comparison of allele frequencies using 2 × 2 tables showed a significant difference in frequency of alleles B and C among patients *vs* controls; OR = 0.607 (65% CI 0.379–0.97), p = 0.04 and OR = 1.048 (95% CI 1.018–1.07), p = 0.007), respectively; [$]Fisher exact test genotype comparison; differences between study group and controls reported as significant if p ≤ 0.05

Table 3. Major cardiovascular events

Total number of events	%* (N)
Death	6% (7)
MI	6% (7)
Percutaneous angioplasty	19% (21)
CABG	6% (6)
Coronary events (angioplasty, MI)	23% (25)
Revascularisation procedures (CABG, angioplasty)	23% (25)
Composite end-point (death, angioplasty, CABG, MI)	29% (32)

CABG — coronary artery bypass graft; MI — myocardial infarction; *as some of the subjects experienced multiple events, the total does not equal 100%

DISCUSSION

In our study population, comprising 110 subjects with confirmed CAD who were qualified for PCI, the only genetic differences detected in comparison with controls regarded the distribution of IL1RN and CD14 variants. The IL-RN counter regulates IL-1 activity and its polymorphism is associated with an increased risk of inflammatory disease [3]. Thus, our findings, showing a higher prevalence of this genetic variant in patients *vs* controls, are in line with previous findings. However, data from literature are not consistent, as some authors have found no association between IL-RN polymorphism and increased risk of coronary morbidity [4]. Thus, the association between the IL-1 system and atherosclerosis and its complications appears to be complex and may vary with clinical phenotype and extent of disease [5].

Table 4. Comparison between patients who did and who did not undergo percutaneous coronary intervention (PCI) during follow-up. Only parameters with significant differences are shown

	No PCI (n = 69)	PCI (n = 21)	P
Waist/hip ratio	0.96 ± 0.5	0.99 ± 0.4	0.07
Leukocytes (× 10^9)	7.6 ± 1.9	6.8 ±1.4	0.07
Triglycerides [mmol/L]	1.5 ± 0.6	1.9 ± 0.8	0.01
HDL [%]	26.0 ± 6.9	21.8 ± 5.5	0.02
Atherogenic index	3.1 ± 1.1	3.8 ± 1.1	0.03

Table 5. Association of studied factors with revascularisation procedure, by group comparison

	No revascularisation: N = 68 (73%)	Revascularisation: N = 25 (27%)	P
Angiotensinogen M235T* MM% (n)/TM% (n)/TT% (n)	19% (13)/50% (34)/31% (21)	28% (7)/64% (16)/8% (2)	0.048
Waist/hip ratio	0.96 ± 0.01	0.99 ± 0.01	0.03
LDL-cholesterol [mmol/L]	2.7 ± 0.8	3.05 ± 0.7	0.055
Triglycerides [mmol/L]	1.5 ± 0.6	1.90 ± 0.8	0.03
HDL [%]	26.4 ± 6.9	21.9 ± 5.2	0.01
Atherogenic index	3.09 ± 1.1	3.75 ± 1.1	0.03

*Homozygote MM and heterozygote TM regarded as neutral, TT detrimental

Table 6. Association of studied factors with myocardial infarction (MI), by group comparison

	No MI (n = 85)	MI (n = 7)	P
Angiotensinogen M235T* MM% (n)/TM% (n)/TT% (n)	19% (16)/55% (47)/26% (22)	43% (3)/57% (4)/0% (0)	0.086
Selectin E** AA% (n)/AC% (n)/CC% (n)	79% (67)/21% (18)/0% (0)	57% (4)/29% (2)/14% (1)	0.055
Triglycerides [mmol/L]	1.57 ± 0.1	2.11 ± 0.3	0.055

*Homozygote MM and heterozygote TM regarded as neutral, TT detrimental; **homozygote AA and heterozygote AC regarded as neutral, CC detrimental

The CD14 may contribute to atherosclerosis by stimulating macrophages to produce active substances, causing endothelial and smooth muscle cells activation. In fact, it has already been shown that the polymorphism of CD14 gene (-260)T increases the risk of earlier manifestation of CAD or its complications [6]. Moreover, CD14 gene polymorphism (-260)T was found to be more frequent in subjects after-MI compared to controls [7] and has been suggested as increasing the risk for the development of atheromatous plaque vulnerability in patients with CAD [8]. Nevertheless, Unkelbach et al. [9] did not find any association between this genetic variant and previous MI or extent of CAD. Despite the link with atherosclerosis, our data do not support the role of IL1RN or CD14 variants in modulating the post-PCI risk. Regarding IL1RN, our results are consistent with the conclusions of Zee et al. [10] but in contrast with the suggestions of Kastrati et al. [3] who found that the presence of allele 2 in the IL1RN gene was associated with lower risk of restenosis. Likewise, our observation with respect to CD14 is not consistent with the data of Zee et al. [11] who observed a higher risk of restenosis events with CD14 polymorphism, whereas our results were neutral. A possible explanation may be related to the differences in population characteristics and sample size.

The only genetic factors which were associated with post-PCI prognosis were variants in angiotensinogen and selectin E genes. Polymorphisms of the RASS system, including angiotensinogen M235T, have been previously postulated as important modifiers of clinical prognosis in patients with CAD, but the data are inconclusive. In one of the studies, restenosis was observed in almost one in three subjects and AGT M235T polymorphism was pointed to as a risk factor [12]. In an interesting study, Volzke et al. [13] were unable to show an association between genetic factors (M235T) and prognosis post artery bypass surgery. Nevertheless, more detailed analysis revealed that M235T modulated the effects of age on CV mortality or revascularisation, even showing a tendency towards decreased risk of CV complications with age in subjects with the T allele. Our findings, showing that carriage of the T allele is advantageous are unexpected and may be by chance, but still somehow in agreement with previous publications.

Regarding selectin E which is expressed on activated endothelial cells, an involvement in vascular pathology due to adhesive reactant properties has been suggested. Increased concentration of selectin E has been proposed as a risk factor of MI [14]. In a few studies evaluating the association between the selectin E polymorphism (Ser128Arg), subjects with coronary or peripheral atherosclerosis had a higher prevalence of Arg variant, or subjects with Arg polymorphism had an earlier onset of atherosclerosis [15, 16]. As the inflammatory response may also contribute to the development of restenosis, this problem was studied by Rauchhaus et al. [17] who found that the 128Arg allele of selectin E was an independent predictor of restenosis. As selectin E is considered as a pivotal modifier of the immune response of injured endothelial cells, its polymorphism is likely to play a major role in the restenosis process. Thus, it might serve not only as a CAD risk factor, but also as a prognostic parameter in patients post-PCI intervention.

Despite the wide variety of new CV risk factors, standard clinical parameters like hyperlipidaemia, smoking, and hypertension still play a major role in prognosis post-PCI, which is mainly modified by coronary restenosis or nonculprit lesion progression. In previous publications, besides the typical dyslipidemias, the roles of triglycerides and HDL-C as important prognosis predictors post revascularisation procedures have also been documented. In the paper by Sabik et al. [18] assessing a large group of patients after coronary bypass grafting, a higher level of TG was an important negative predictor of coronary reintervention. Similar findings regarding the effects of TG on prognosis were reported in a study on patients post-PCI, though it was relatively weaker compared to LDL-C [19]. Likewise, low HDL-C has been pointed to as a risk factor of one year mortality in subjects after PCI [20]. Thus, our findings, although showing the prognostic role of less frequent lipids disorders, are also in the line with previous observations, despite presenting a neutral effect of other conventional clinical parameters such as hypertension, smoking and BMI [19].

Clinical impact

Our data confirm a significant, predictive role of lipid-related standard risk factors in patients after revascularisation procedure, thus stressing the importance of secondary prevention aimed at the risk profile. Although the presented results do not support the important role of genetic variability in influencing patients' prognosis, we cannot exclude its role as a modifier of the standard risk factors. This aspect is still under evaluation.

Limitations of the study

Our study has some limitations which should be addressed. We have no data on the characteristics of the control group; thus we were unable to provide the comparison with the study group. Analysis of study end-points was based on posting questionnaires, thus they were not verified objectively. Another aspect is a relatively small number of MACE, which made it impossible to develop reliable, multivariable models. For this reason, our results and conclusions are based on univariate comparisons. Also, a relatively small size of the study group might be a limiting factor. Nevertheless, we believe that the presented data add important information to current knowledge.

CONCLUSIONS

Based on the literature, the role of genetic variants in the prognosis of patients undergoing revascularisation procedures is

controversial. In our study of post-PCI patients, we were unable to document significant impact of a range of polymorphisms on MACE. In fact, our data confirmed the importance of lipids related risk factors as the most significant modifiers of prognosis post-PCI. A significantly larger group is required to give a full explanation of the possible impact of the multiple polymorphisms associated with the pathological mechanism related to atherosclerosis.

This study was supported by internal research grant number 2.48/II/07 from the Institute of Cardiology and by research grant number 1WY/W1/10 from Warsaw Medical University.

Conflict of interest: *none declared*

References

1. Paczkowska A, Szperl M, Malek L et al. Polymorphisms of the beta-1 and beta-2 adrenergic receptors in Polish patients with idiopathic dilated cardiomyopathy. Kardiol Pol, 2009; 67: 235–241.
2. Szperl M, Dzielinska Z, Roszczynko M et al. Genetic variants in hypertensive patients with coronary artery disease and coexisting atheromatous renal artery stenosis. Med Sci Monit, 2008; 14: CR611–CR616.
3. Kastrati A, Koch W, Berger PB et al. Protective role against restenosis from an interleukin-1 receptor antagonist gene polymorphism in patients treated with coronary stenting. J Am Coll Cardiol, 2000; 36: 2168–2173.
4. Woods A, Brull DJ, Humphries SE, Montgomery HE. Genetics of inflammation and risk of coronary artery disease: the central role of interleukin-6. Eur Heart J, 2000; 21: 1574–1583.
5. Andreotti F, Porto I, Crea F, Maseri A. Inflammatory gene polymorphisms and ischaemic heart disease: review of population association studies. Heart, 2002; 87: 107–112.
6. Rizzello V, Liuzzo G, Trabetti E et al. Role of the CD14 C(-260)T promoter polymorphism in determining the first clinical manifestation of coronary artery disease. J Cardiovasc Med (Hagerstown), 2010; 11: 20–25.
7. Hubacek JA, Rothe G, Pit'ha J et al. C(-260)–>T polymorphism in the promoter of the CD14 monocyte receptor gene as a risk factor for myocardial infarction. Circulation, 1999; 99: 3218–3220.
8. Arroyo-Espliguero R, El-Sharnouby K, Vazquez-Rey E, Kalidas K, Jeffery S, Kaski JC. CD14 C(-260)T promoter polymorphism and prevalence of acute coronary syndromes. Int J Cardiol, 2005; 98: 307–312.
9. Unkelbach K, Gardemann A, Kostrzewa M, Philipp M, Tillmanns H, Haberbosch W. A new promoter polymorphism in the gene of lipopolysaccharide receptor CD14 is associated with expired myocardial infarction in patients with low atherosclerotic risk profile. Arterioscler Thromb Vasc Biol, 1999; 19: 932–938.
10. Zee RY, Fernandez-Ortiz A, Macaya C, Pintor E, Fernandez-Cruz A, Lindpaintner K. IL-1 cluster genes and occurrence of post-percutaneous transluminal coronary angioplasty restenosis: a prospective, angiography-based evaluation. Atherosclerosis, 2003; 171: 259–264.
11. Zee RY, Hoh J, Cheng S et al. Multi-locus interactions predict risk for post-PTCA restenosis: an approach to the genetic analysis of common complex disease. Pharmacogenomics J, 2002; 2: 197–201.
12. Ohishi M, Fujii K, Minamino T et al. A potent genetic risk factor for restenosis. Nat Genet, 1993; 5: 324–325.
13. Volzke H, Kleine V, Robinson DM et al. Renin-angiotensin system and haemostasis gene polymorphisms and outcome after coronary artery bypass graft surgery. Int J Cardiol, 2005; 98: 133–139.
14. Matsumoto K, Fujishima K, Moriuchi A, Saishoji H, Ueki Y. Soluble adhesion molecule E-selectin predicts cardiovascular events in Japanese patients with type 2 diabetes mellitus. Metabolism, 2010; 59: 320–324.
15. Wenzel K, Felix S, Kleber FX et al. E-selectin polymorphism and atherosclerosis: an association study. Hum Mol Genet, 1994; 3: 1935–1937.
16. Wenzel K, Ernst M, Rohde K, Baumann G, Speer A. DNA polymorphisms in adhesion molecule genes: a new risk factor for early atherosclerosis. Hum Genet, 1996; 97: 15–20.
17. Rauchhaus M, Gross M, Schulz S et al. The E-selectin SER128ARG gene polymorphism and restenosis after successful coronary angioplasty. Int J Cardiol, 2002; 83: 249–257.
18. Sabik JF, 3rd, Blackstone EH, Gillinov AM, Smedira NG, Lytle BW. Occurrence and risk factors for reintervention after coronary artery bypass grafting. Circulation, 2006; 114: I454–I460.
19. Park MW, Seung KB, Kim PJ et al. Long-term percutaneous coronary intervention rates and associated independent predictors for progression of nonintervened nonculprit coronary lesions. Am J Cardiol, 2009; 104: 648–652.
20. Ghazzal ZB, Dhawan SS, Sheikh A et al. Usefulness of serum high-density lipoprotein cholesterol level as an independent predictor of one-year mortality after percutaneous coronary interventions. Am J Cardiol, 2009; 103: 902–906.

Czy kompleksowa ocena polimorfizmów może być przydatna w ocenie rokowania po zabiegach angioplastyki wieńcowej: badanie prospektywne

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Streszczenie

Wstęp: Choroba wieńcowa (CAD) jest złożonym zespołem odpowiedzialnym za większość zgonów i nowych przypadków zachorowań na choroby sercowo-naczyniowe. Na podstawie danych z piśmiennictwa nie można wykluczyć, że predyspozycje genetyczne są odpowiedzialne za podwyższone ryzyko wystąpienia głównych powikłań sercowo-naczyniowych po zabiegach angioplastyki (PCI).

Cel: Głównym celem badania była ocena wpływu wybranych polimorfizmów modyfikujących aktywność układu renina–angiotensyna–aldosteron, receptora beta-2 adrenergicznego, tlenku azotu i aktywność płytek, a także nasilenie odpowiedzi przeciwzapalnej u pacjentów ze stabilną CAD, u których wykonuje się rutynowy zabieg angioplastyki wieńcowej.

Metody: Badaniem objęto grupę 110 kolejnych mężczyzn ze stabilną CAD, u których przeprowadzono zabieg PCI pojedynczego naczynia (które nie było odpowiedzialne za zawał z załamkiem Q i miało średnicę > 2 mm). Genotypowanie wykonano metodą amplifikacji znanych regionów genomu, połączoną z analizą restrykcyjną (PCR-RFLP). Dane dotyczące zdarzeń w trakcie obserwacji odległej uzyskiwano drogą pocztową i dotyczyły one przeżywalności, wystąpienia zawału serca i zabiegów rewaskularyzacji.

Wyniki: Grupa badana różniła się od grupy kontrolnej w odniesieniu do rozkładu polimorfizmów antagonisty receptora interleukiny-1 oraz CD14. W grupie osób badanych pacjenci, u których w trakcie dalszej obserwacji było konieczne wykonanie PCI, nie różnili się pod względem polimorfizmów wybranych genów, natomiast mieli wyjściowo wyższe stężenia triglicerydów (1,9 *v.* 1,5 mmol/l; p = 0,01) i wyższy wskaźnik aterogenności (3,8% *v.* 3,1%; p = 0,03), a niższy odsetek HDL (21,8% *v.* 25,0%; p = 0,02). Natomiast pacjenci z jakimkolwiek przebytym zabiegiem rewaskularyzacji w porównaniu z resztą chorych w trakcie obserwacji różnili się rozkładem polimorfizmów genu dla angiotensynogenu M235T (MM%/TM%/TT%: 28%/64%/8% *v.* 19%/50%/31%; p = 0,048). Dodatkowo osoby, u których wystąpił zawał serca, różniły się w porównaniu z pozostałymi badanymi chorymi rozkładem polimorfizmów dla selektyny E (AA%/AC%/CC%) 57,1%/28,6%/14,3% *v.* 78,8%/21,2%/0%; p = 0,055), a także stwierdzano u nich wyższe stężenia triglicerydów (2,11 *v.* 1,57 mmol/l; p = 0,055).

Wnioski: Na podstawie przedstawionych danych należy zwrócić uwagę na potencjalną rolę prognostyczną polimorfizmu genów dla angiotensynogenu i selektyny E, jednak w niniejszym materiale główne znacznie miały zaburzenia lipidowe związane z nieprawidłowym stężeniem triglicerydów i cholesterolem frakcji HDL.

Słowa kluczowe: polimorfizm, angioplastyka, rokowanie

Kardiol Pol 2011; 69, 9: 881–888

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Praca wpłynęła: 13.01.2011 r. **Zaakceptowana do druku:** 11.05.2011 r.