AUTHOR'S TRANSLATION

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Association of phosphodiesterase 4D gene polymorphism with the risk of myocardial infarction in a group Chornobyl NPP accident clean-up workers

Polymorphism rs966221 of gene phosphodiesterase 4D (PDE4D) was studied among men, the clean-up workers (CUW) of the Chornobyl Nuclear Power Plant accident (192 persons) and control group (84 persons). In the control carriage of TT genotype increased the risk of myocardial infarction (MI) among persons over 60 years with more traditional risk factors, the odds ratio (OR)=9.2 (95% confidence interval (CI), 1,11–15,96, p=0.016). Among the CUW carriers of the TT genotype risk of MI was increased regardless of the age of its development: OR=2.44 (95% CI 1.22–4.894, p=0.010). In addition, the radiation dose of patients subjected to infarction at age below 60 years was higher compared to the CUW with infarction that appeared at the age over 60 years (34.10±10.44 cSv and 10.42±3.12 cSv, respectively, p=0.039). It is assumed that the presence of a genetic predisposition (TT genotype at rs966221 polymorphism of gene PDE4D) promotes the emergence of endothelial dysfunction, especially against ionizing radiation and increases the risk of MI.

Keywords: clean-up workers of the Chornobyl accident, ionizing radiation, myocardial infarction, gene polymorphism rs966221 phosphodiesterase 4D (*PDE4D*).

Introduction

A correlation of the presence of *PDE4D* polymorphisms with ischemic stroke was found (Gretarsdottir et al., 2003; Kakita et al., 2011; Milton et al., 2011), but the number of studies on associations with the risk of MI is small (Lynch et al., 2012 ; Sinha et al., 2013). Furthermore, phenotypic manifestations of *PDE4D* polymorphisms under the influence of IR were not studied. In view of this, the aim of our study was to determine the role of a functionally significant SNPs (SNP83) of gene *PDE4D* as a genetic risk factor for myocardial infarction in victims of the Chornobyl accident.

Subjects and methods

The main study group included 192 Chornobyl CUW males (171 people – CUWs of 1986, 9 persons - 1987, 10 people - 1988 and 2 persons were participants of clean-up works of 1989). Absorbed dose was known in 126 people and was on average 23.65 ± 2.67 cSv (median 14.01 cSv). The maximum dose was received by the CUW of 1986 (Table 1). In the aftermath of the Chornobyl accident 52 patients suffered MI: 28 (53.8%) - at the age of under 60 years, 24 patients (46.2%) - in older age.

Table 1

Radiation doses absorbed by persons surveyed the main group, depending on the year of participation in the clean-up of the Chornobyl accident aftermath

Clean-up workers of Chornobyl NPP accident		Irradiation doses	
year of participation	quantity	M±m	median
1986	111	25.17±2.96	17.3
1987	6	16.01±8.3	8.6
1988	7	11.52±3.88	4.99
1989	2	4.99	4.99

The control group amounted to 84 men, residents of Kyiv, who had no history of direct exposure to IR. During 1993-2012 56 studied individuals of the control group underwent infarction: 11 patients (19.6 %) under the age of 60 years, 42 (75 %) - in older age, three persons (5.4%) exact time of myocardial infarction could not be established. The main and control groups were comparable by the time of MI with respect to Chornobyl accident, except for an increase in the proportion of patients of the main group, which developed MI in the first 20 years after the accident (Table 2). These data are consistent with the results obtained by us in the analysis of cases of MI among CUW included in Clinical and Epidemiological Registry of NRCRM: among 482 men with MI in anamnesis 217 patients (45%) developed it in the first 10 years after the accident. All patients in both groups were subjected to anthropometric data measuring (height, body weight), a history (smoking in the present and in the past, the presence of CVS diseases in the nearest relations) general clinical examination, electrocardiography, differential blood count and general blood chemistry investigation. Excess body mass index >30 kg/m^2 was classified as obesity. Boundary cholesterol level was considered below 5.2 mmol/L, parameters 5.2-6.5 mmol/L were considered as insignificant, 6.5-7.8 mmol/L - moderate and >7.8 mmol/L - a significant hypercholesterolemia.

Table 2

The distribution of patients with myocardial infarction by years with respect to the Chornobyl accident

Myocardial infarction by years after accident	Groups			
	main		control	
	quantity	%	quantity	%
first 10	13	25,0	7	13,2
11-20	20	38,5	28	52,8
over 20	19	36,5	18	34,0
Probability of differences	0.031			

Peripheral blood samples for the molecular genetic studies were collected in tubes with anticoagulant. DNA was obtained using QIAamp Blood Mini Kit (Qiagen, UK) according to the manufacturer's instructions. Polymerase chain reaction (PCR) for the detection of SNP83 (rs966221) of *PDE4D* gene (T>C) was performed by (Saleheen et al., 2003) using2720 Thermal cycler (Applied Biosystems, USA). Reaction products were visualized in 5% agarose gel with propidium iodide and restricted by TaiI restrictase (Fermentas, Latvia, restriction site ACGT) at the temperature of 65^0 for 30 min. Polymorphic variants of the gene were determined by re-electrophoresis: at the presence of the T allele no restriction of reaction product took place (product 492 bp), at the presence of polymorphic allele C 2 fragments of 204 bp and 288 bp were found (Fig. 1).

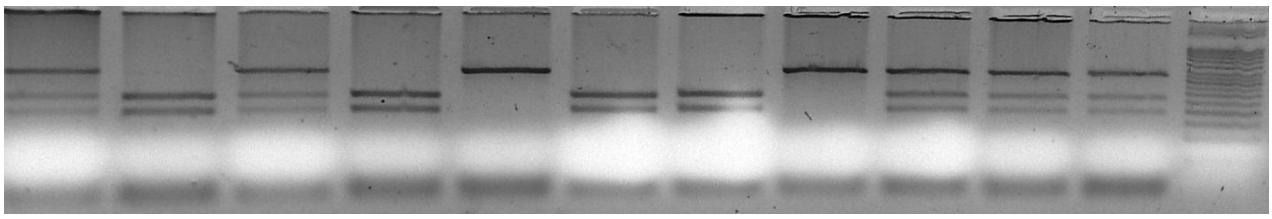

Figure 1. Results of determination of *PDE4D* gene polymorphism rs966221 by polymerase chain reaction followed by restriction of received products by TaiI restrictase. CT, CC, TT - genotypes for SNP83 polymorphism of *PDE4D* gene; M - molecular weight markers.

Results and discussion

The frequency of TT genotype in the study of SNP83 polymorphism of *PDE4D* gene was increased among patients with old myocardial infarction in both groups (Table 3).

Table 3

***PDE4D* gene genotypes distribution depending on arisen myocardial infarction**

Surveyed persons	*PDE4D* gene genotypes, quantity of surveyed (%)			p
	TT	TC	CC	
Main group				
MI arose, n=52	15 (28.8)	19 (36.5)	18 (34.3)	0.110;
MI absent, n=140	22 (15.7)	66 (47.1)	52 (37.1)	0.040*
Control group				
MI arose, n=56	13 (23.2)	21 (37.5)	22 (39.2)	0.072;
MI absent, n=28	1 (3.6)	14 (50.0)	13 (46.4)	0.023

Note: * probability when comparing TT genotype against TC and CC genotypes.

Noteworthy is the difference in the frequency of TT genotype among those with myocardial infarction in the study and control groups. This is due to the fact that the control group, except for patients with MI, included practically healthy persons without cardiovascular diseases. In the main group only 67 surveyed CUW had no signs of coronary artery disease. The distribution of genotypes in them was as follows: TT genotype - 5 persons, TC - 30 and CC - 32 people. At the same time, in the study group 73 patients were suffering from coronary heart disease, nosological form stable angina (distribution of genotypes: TT – 17, TC - 36, CC - 20 people). Increased frequency of TT genotype in the study group among patients undergoing MI was observed only compared with those without CHD (χ 2 = 9.57 , p = 0.002), while compared with patients with diagnosed coronary heart disease differences were unlikely (χ 2 = 0.492 , p = 0.527). Development of MI cases in the control group under 60 years were observed only in carriers of C allele (Table 4). Increased frequency of TT genotype in men with myocardial infarction after 60 years was significant compared with persons of matched age without MI (p = 0.043 when comparing the distribution of genotypes, p = 0.016 when comparing the genotype TT vs. TC and CC genotypes). The risk of myocardial infarction in men TT genotype carriers older than 60 years increased: (OR =9.2; 95 % confidence interval 1.11-15.966, p = 0.016). No effects of genotype on the risk of myocardial infarction in patients aged under 60 years were found (p = 0.164).

Table 4

***PDE4D* gene rs966221genotypes distribution depending on age of myocardial infarction onset**

Surveyed persons	*PDE4D* gene genotypes, quantity of surveyed (%)			p
	TT	TC	CC	
MI arose before 60 years				
main group, n=28	10 (35.7)	8 (28.6)	10 (35.7)	0.088;
control group, n=11	0	6 (54.5)	5 (45.5)	0.030*
MI arose after 60 years				
main group, n=24	5 (20.9)	11 (45.8)	8 (33.3)	0.821;
control group, n=42	12 (28.6)	14 (33.3)	16 (38.1)	0.810*

Note: * probability when comparing TT genotype against TC and CC genotypes.

However, in the main group, the prevalence of TT genotype among patients with MI was observed regardless of the age of the patient at the time of disease : OR = 2.44 (95 % confidence interval 1.22-4.894, p = 0.010). Differences in the frequency of TT genotype in men main group and the control group with myocardial infarction, developed at the age of 60 years were significant, whereas for patients with MI, which developed in the older age in both groups did not differ by genotype frequency (see table 4.). The risk of myocardial infarction at the age of under 60 years for men of core group carriers of the TT genotype, in contrast to controls was also high: OR = 5.73 (95 % CI , 1.79-13.33, p = 0.002) . It should be noted that at the time of the Chornobyl accident people, who developed myocardial infarction at the age of 60 years, were younger (36.67 ± 1.61 years) than those patients who developed myocardial infarction at age over 60 (44.25 ± 1.17 years), p = 0.001. There was also a direct correlation between age at the time of the accident and the age in which developed MI (r = 0,673; p = 0,001).

In the control group, the patients' age, TT genotype carriers at the time of MI was higher (mean age 71.55 ± 1.35 years) than carriers of other genotypes (65.88 ± 1.17 years, p = 0.025). In contrast, in the study group in men, carriers of TT genotype MI developed at significantly younger age compared with carriers of other genotypes: 69 years vs. 79 years, p = 0.03. Reducing the age of MI was observed already at the age under 60 years: the median age of MI in men of main group with TT genotype was 56 years comparing to 59 years in carriers of other genotypes (p = 0.009). The average radiation dose absorbed by patients of the main group with MI at the age under 60 years was higher compared to the liquidators with MI at the age over 60 years: 34.10 ± 10.44 cSv and 10.42 ± 3.12 cSv respectively p = 0.039. In addition, some features were found in the study group in patients with myocardial infarction arised in the first 10 years after the Chornobyl accident. Comparing to patients with MI emerged later than 10 years after the accident they absorbed higher external radiation dose (43.32 ± 15.27 cSv vs 12.28 ± 2.9 cSv p = 0.01) and were significantly younger (mean age was 49.06 ± 2.25 years, compared to 59.31 ± 1.29 years, p = 0.001). Only one patient over 60 years developed myocardial infarction in the first 10 years after the accident. There was an inverse correlation relationship between radiation dose and age of MI development: r = -0.588; p = 0.001 (Fig. 2). There were no differences in the frequency of non-radiation risk factors for coronary heart disease between MI patients of main and control groups (Table 5). The total amount of principal risk factors also did not differ in patients of main and control groups who underwent myocardial infarction at the age under 60 years (2.69 ± 0.24 and 2.54 ± 0.38, p = 0.759) and over 60 years (2.76 ± 0.22 and 2.40 ± 0.21, p = 0.259). However, myocardial infarction patients carriers of the TT genotype in the control, but not in the

main group, had higher number of identified risk factors for coronary heart disease was compared with carriers of other genotypes (3.1 ± 0.29 vs 2.36 ± 0.12, p = 0.033). Thus, the carriage of TT genotype of *PDE4D* gene in the control group influenced on the risk and peculiarities of MI: age over 60 years, higher total number of risk factors for coronary heart disease, compared with carriers of other genotypes. These data indicate that the negative effect of the TT genotype is realized against the background of atherosclerosis characteristics: a more advanced age, presence of dyslipidemia, hypertension, whereas at lower severity of atherosclerotic changes the TT genotype plays rather protective role.

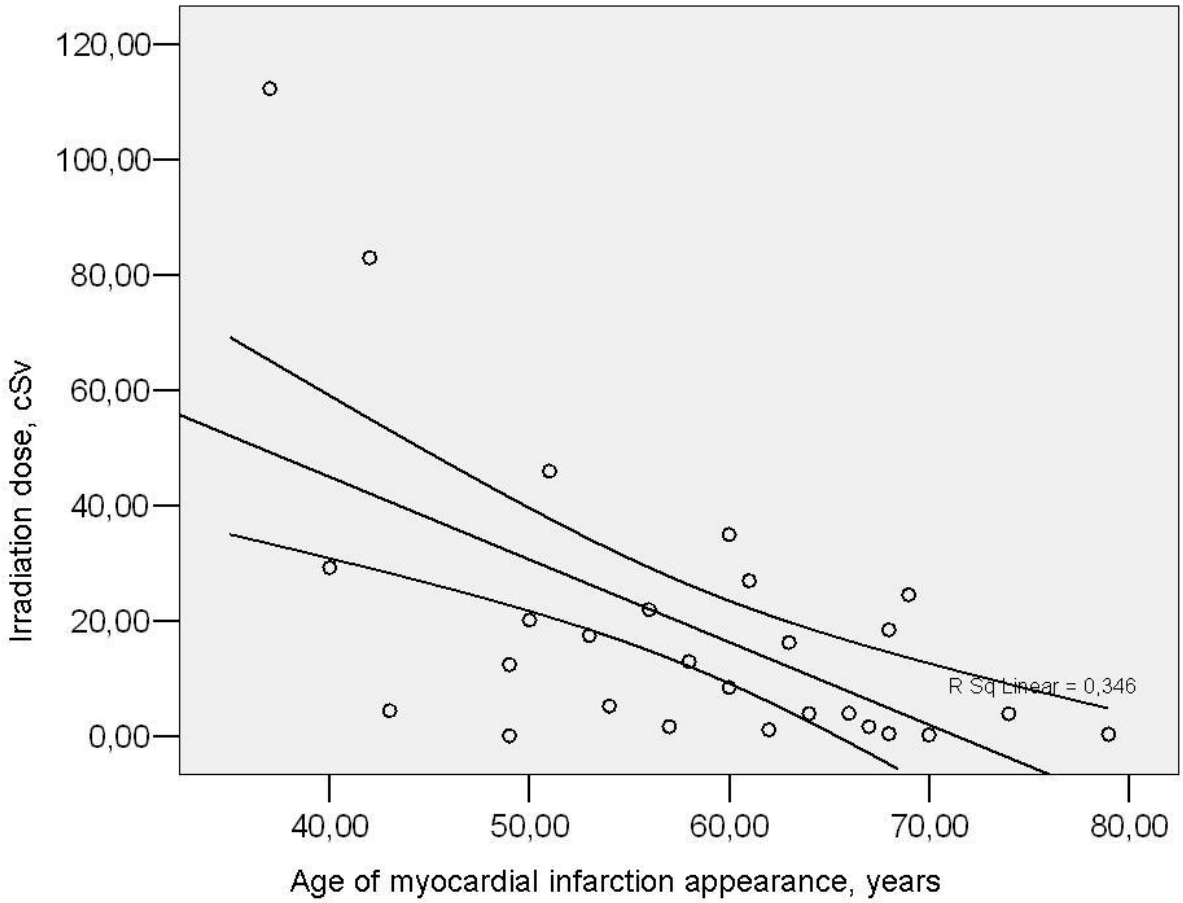

Figure 2. Relationship between the dose of external radiation and age of the patients of the main group at the time of myocardial infarction

Table 5

The frequency of risk factors for coronary heart disease in men with myocardial infarction of main and control groups

Risk factors	Frequency per groups				Probability
	main		control		
	quantity	%	quantity	%	
arterial hypertension	39	75.0	37	66.1	0.171
signs of dyslipidemia	31	59.6	31	55.3	0.892
diabetes mellitus type II	15	29.8	10	17.9	0.277
smoking	22	42.3	23	41.1	0.764
obesity	16	30.7	10	17.9	0.077
the presence of cardiovascular disease in relatives	16	30.7	24	42.8	0.286

For an explanation of the results it should be addressed to the function of phosphodiesterases and polymorphisms influence on the enzyme activity. Polymorphism SNP83 of *PDE4D* gene is localized in the first intron of promoter gene and belongs to the group of SNPs (SNP41-SNP89), in its presence the expression of the long isoform of the enzyme phosphodiesterase - PDE4D7 decreases (Gretarsdottir et al., 2003). These data suggest that CC genotype carriers (homozygotes by the polymorphic alelle SNP83) PDE4D7 activity is reduced and vice versa, in carriers of the TT genotype (homozygote by the dominant alelle SNP83), the enzyme activity is increased. PDE4D7 isoform is composed of domains UCR1 and UCR2, by which it interacts with various proteins and controls the concentration of second messenger cAMP in certain areas of the cell (Rababa'h et al., 2013). Just this effect is due to the activity of phosphodiesterase in the course of many intracellular processes, which can have the opposite character, depending on the protein adapters that interact with the enzyme and modulate its activity. It is known, that the key events of the atherosclerotic process are endothelial dysfunction, inflammation and proliferation of vascular smooth muscle cell (VSMC) (Wildgruber et al., 2013 ; Dessi et al., 2013). The accumulation of VSMC in the intima of vessels is one of the main stages in the development of atherosclerosis. Proliferation of these cells is conditioned by any damage to the vessel wall and the action of such growth factors like platelet-derived growth factor (PDGF), transforming growth factor beta, endothelial growth factor, insulin-like growth factor 1. The action of growth factors was established to be mediated by activation of intracellular kinases - EKK, PI3k, Akt. At low activity of phosphodiesterases, especially isoform PDE4D, locally in cells near activated kinase EKK cAMP is accumulated, which inhibits the kinase and, consequently, the VSMC proliferation (Yoo et al., 2010). Thus, in mice knock-outs for *PDE4D* VSMC proliferation is 26-37 % reduced by action of PDGF (Liu et al., 2011). Inhibition of PDGF growth signal has anti-sclerotic property (Boucher et al., 2003). In contrast, elevated activity of PDE4D (in the

context of our study - TT genotype), reduces the concentration of cAMP, which contributes to the transmission of intracellular signal activation under the influence of PDGF and proliferation of smooth muscle cells of blood vessels.
Another mechanism that links the activity of phosphodiesterases with the development of atherosclerotic process is the interaction of the long isoform of enzyme through the UCR1 domain with EPAC protein of vascular endothelium (Rampersad et al., 2010). EPAC Heras is activated by cAMP and inhibits inflammation in the endothelium and protects cells from apoptosis through multiple mechanisms (Parnell et al., 2012):
- suppresses the activity of transcription factor C / EBP (a transcription factor that binds to a CAAT sequence in gene promoter) and reduces the gene expression of the inflammatory process induced by interleukin;
- in combination with cAMP reduces the penetration of vessels through the activation of integrins, which provide adhesion to endothelial basement membrane;
- enhances the interaction between endothelial cells via activation of a kadheryn-mediated homologous adhesion.
Accordingly, if phosphodiesterase joins to the complex EPAC-cAMP, the cAMP quantity is locally reduced and mentioned effects disappear. Therefore, the use of PDE4D inhibitors, which increases local levels of cAMP, significantly reduces the permeability of vessels, the development of apoptotic changes induced by the action of vascular endothelial growth factor (Rampersad et al., 2010). In contrast, elevated activity of PDE4D (in the context of our study - TT genotype), reduced the concentration of cAMP, resulting in insufficient EPAC activation and disrupted endothelial function .
Thus, it can be assumed that the genotype TT carriage entailed by increased activity of the enzyme is a risk factor for myocardial infarction in patients older than 60 years because of the effects on the key initial stages of atherosclerosis: the VSMC proliferation and increased permeability of blood vessels. At the same time, PDE4D plays a significant role in the functioning of cardiomyocytes directly, and a protective role against the development of myocardial infarction has, just the contrary, increased enzyme activity.
In cardiomyocytes phosphodiesterases are involved in the transmission of intracellular signals when activated β- adrenergic receptors to which they are joined together with a protein β-arrestine reduce the concentration of cAMP and prevent excessive cell activation (Rampersad et al., 2010 ;. Salazar et al., 2013).
Accordingly, at the lowered PDE4D activity (CC genotype) reducing the concentration of cAMP occurs more slowly, which can lead lo hyperactivation of cardiomyocytes under hypoxic conditions, that is, increase the risk of MI in relatively young patients with less severity of atherosclerosis signs.
In contrast to the control group in the study group the negative effect of TT genotype was manifested not only among those over 60 years, but among younger persons at a larger dose of external radiation.
As it was already mentioned, the basis of the pathological impact of IR on the CVS is endothelial dysfunction - disturbances of endothelial membranes, increasing their permeability, cell death with possible formation of blood clots. Over the longer term myocardial ischemia and interstitial fibrosis are developing (Milliat et al., 2008). It was shown in experiments on exposure of genetically modified mice with apolipoprotein E deficiency, that IR enhances the development of atherosclerotic changes (Hildebrandt, 2010; Mitchel et al., 2011; Kumarathasan et al., 2013). The impact of IR on vessels is realized through induction of inflammatory changes and the effects of transforming growth factor beta (Monseau et al., 2013). To summarize current data of experimental and epidemiological studies, Borghini et al. (2013) noted that the effect of high doses of IR in experimental models accelerated the development of atherosclerosis, formation of inflammatory changes, plaque formation, especially on condition of genetic predisposition. Data on the effects of low doses of IR are controversial and need more thorough investigation. In view of these results, we can assume that in men who had absorbed a relatively large dose of external radiation (43.32 ± 15.27 cSv), its effect was realized mainly through the development of atherosclerotic changes in vessels. Therefore, the presence of genetic susceptibility (genotype TT for rs966221 polymorphism gene *PDE4D*), which contributes to the appearance of endothelial dysfunction has a negative expression in the younger age group of CUW than in non-irradiated individuals, and is an independent risk factor for myocardial infarction.

Conclusions

1. Men who are not exposed to ionizing radiation TT genotype is a risk factor for myocardial infarction at the age of over 60 years: OR = 9.2 (95 % confidence interval, 1.11-15.96, p = 0.016). However, the development of myocardial infarction at the age under 60, was observed only in carriers of genotypes CC and CT .
2. General features of MI in carriers of the TT genotype who were not exposed to ionizing radiation are: the development of myocardial infarction in older age (mean age 71.55 ± 1.35 years) than carriers of other genotypes (65.88 ± 1.17 years, p = 0.025), with a relatively greater total number of factors for CHD (3.1 ± 0.29 vs 2.36 ± 0.12, respectively, p = 0.033).
3. Among men who had been exposed to ionizing radiation an independent effect of *PDE4D* gene TT genotype carriage on the risk of myocardial infarction was revealed: OR = 2.44 (95 % confidence interval 1.22-4.894, p = 0.010). MI in exposed men, TT genotype carriers, developed at a much younger age compared to carriers of other genotypes: median 69 years vs. 79 years, p = 0.03. In contrast to the comparison group, the negative effect of TT genotype was manifested not only among those over 60, but also among persons of younger age (p = 0.002).
4. The main features of MI at the age of 60 years for men of main study group were: higher dose of external radiation compared to CUW with a MI arised at the age over 60 years (34.10 ± 10.44 cSv and 10.42 ± 3.12 cSv respectively, p = 0.039) and increased risk of MI with the TT genotype (OR = 5.73 (95 % CI, 1.79-13.33, p = 0.002) .

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