Atherosclerosis and Dyslipidaemias
An official Journal of the Russian National Atherosclerosis Society (RNAS)
2016 №3 (24)
ABSTRACTS

Reviews

The role of PCSK9 in coronary vascular disease development

AB Popova, DN Nozadze, IV Sergienko

Russian Cardiology Research Complex, Moscow, Russia

Abstract
Proprotein convertase subtilisin/keksin type 9 (PCSK9) is a promising target to lower serum cholesterol. PCSK9 binds to the receptor of low-density lipoprotein (LDL-R), and complex PCSK9/LDL-R leads to degradation in endosomes and lysosomes and LDL concentration has increased in blood. Gain-of-function mutations in the gene encoding PCSK9 induse high-plasma LDL levels and increase of cardiovascular risk. Loss-of-function mutations in the gene encoding PCSK9 induse low-plasma LDL levels and decrease of cardiovascular risk without known unwanted effects on individual health. Clinical studies have demonstrated that inhibition of PCSK9 alone and in addition to statins therapy highly reduces LDL concentrations in serum. This review presents the current data on the regulation of PCSK9, its molecular function in lipid homeostasis and new fact on the extra-hepatic effects PCSK9.
Keywords: proprotein convertase subtilisin/keksin 9, hypercholesterolemia, familial hypercholesterolemia.

Safety issues of atorvastatin usage in patients with a chronic kidney disease

N. G. Gogolashvili

Scientific Research Institute of medical problems of the North, Krasnoyarsk, Russia
Krasnoyarsk State Medical University, Krasnoyarsk, Russia

Abstract
Chronic kidney disease (CKD) has a high prevalence in patients with some cardiovascular diseases, as well as in the general population. In many large-scale studies have shown the value of CKD as an independent predictor of the risk of cardiovascular complications and death. At the moment, a number of studies carried out, during which studied the efficacy and safety of individual statins in patients with CKD. A large number of studies conducted with atorvastatin possible to evaluate the safety of the latest high in patients with CKD is not only to reduce the decrease in glomerular filtration rate (GFR), but in some cases, to increase the value of this indicator. The results of a post hoc analysis of large randomized clinical trials (RCTs) have demonstrated the possibility of atorvastatin to reduce the risk of adverse clinical outcomes in patients with various cardiovascular diseases and CKD
Keywords: chronic kidney disease, statins, atorvastatin, glomerular filtration rate, cardiovascular disease.

Original Articles

Evaluation of the utility of manual thromboaspiration for coronary blood flow recovery in patients with ST elevation myocardial infarction

A. S. Tereshchenko, G. K. Arutyunyan, V. M. Mironov, E. V. Merkulov, A. N. Samko

Russian Cardiology Research Complex, Moscow, Russia

Abstract
Chronic kidney disease (CKD) has a high prevalence in patients with some cardiovascular diseases, as well as in the general population. In many large-scale studies have shown the value of CKD as an independent predictor of the risk of cardiovascular complications and death. At the moment, a number of studies carried out, during which studied the efficacy and safety of individual statins in patients with CKD. A large number of studies conducted with atorvastatin possible to evaluate the safety of the latest high in patients with CKD is not only to reduce the decrease in glomerular filtration rate (GFR), but in some cases, to increase the value of this indicator. The results of a post hoc analysis of large randomized clinical trials (RCTs) have demonstrated the possibility of atorvastatin to reduce the risk of adverse clinical outcomes in patients with various cardiovascular diseases and CKD
Keywords: manual thromboaspiration, myocardial infarction, myocardial reperfusion.

Risk assessment of clinical atherosclerosis complications by the estimation of common carotid and femoral arteries' intima-media thickness

A.Ye. Filippov[1, 2] , A. G. Obrezan[1, 2] , B. V. Pomogaybo[3] , P. V. Bovtyushko[4]

[1] Saint-Petersburg State University, Saint Petersburg, Russia
[2] International medical center «SOGAZ», Saint Petersburg, Russia
[3] 413 military hospital, Volgograd, Russia
[4] Medico-military academy named after Kirov, Saint Petersburg, Russia

Abstract
The carotid and femoral arterials intima-media thickness (IMT) was investigated in an isolated sample of 207 men without clinical evidence of atherosclerosis (2414 observations). It was established that risk factors such as age, systolic blood pressure and blood serum cholesterol level, which are the main components of the SCORE model, have direct correlation with IMT (of medium strength ($r=0,57$, $p<0,0001$), which allows to explain the variance of IMT value no more than 33%.
It was shown that the evaluation of the common carotid and femoral arteries of IMT in men with risk value of >1 % and<5 % according to the SCORE model may significantly improve sensitivity of the coronary risk evaluation. At the same time, a significant number of individuals free from cardiovascular events were put into a group of poor prognosis probably due to a high probability of false positive response.
Keywords: atherosclerosis, arterial intima-media thickness, risk factors, low and moderate cardiovascular risk cohort, cardiovascular events.

Serum levels of soluble form of receptor for advanced glycation end products in type 2 diabetes mellitus patients with restenosis after intracoronary drug eluting stent implantation

S. V. Byazrova, S. G. Kozlov, Z. A. Gabbasov, O. S. Saburova, V. P. Masenko

Russian Cardiology Research and Production Complex, Moscow, Russia

Abstract

Aim. To assess blood concentrations of soluble receptor for advanced glycation end products (sRAGE) involvement in restenosis development after drug-eluting stent (DES) implantation in patients with stable angina pectoris (AP) and type 2 diabetes mellitus (DM).

Material and Methods. The study comprised 126 male and female patients, including 55 patients with type 2 diabetes mellitus, with stable AP who underwent elective percutaneous coronary angioplasty with DES and followup coronary angiography within 6–12 months thereafter. According to the follow-up angiograms, the patients were assigned to the group with restenosis or group without restenosis. Both groups of patients were compared in regard to the level of sRAGE at the time of follow-up angiography.

Results. Serum levels of sRAGE in patients with restenosis were lower compared with those patients without restenosis. This difference was related to the difference in the levels of sRAGE in patients with and without restenosis who had type 2 DM. Serum levels [median (25th; 75th percentile)] of sRAGE in DM patients with restenosis were lower compared with those DM patients without restenosis [1,08 (0,91; 1,19) vs. 1,27 (0,99; 1,58) ng/ml, $p<0,001$]. Serum levels of sRAGE in non-DM patients did not differ significantly in those patients with or without restenosis.

Conclusion. Our data suggest that serum levels of sRAGE are associated with restenosis occurrence in type 2 DM patients after DES implantation for stable AP.

Keywords: coronary artery stenting, restenosis, diabetes mellitus, advanced glycation end products, receptor for advanced glycation end products.

The values of cardio-ankle vascular index in patients with impaired glucose metabolism according to research «ECVE-RF» in the Kemerovo region

AN Sumin, NA Bezdenezhnykh, NV Fedorova, AV Shcheglova, EV Indukaeva, GV Artamonova

Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russia

Abstract

Objective. To identify the prevalence of abnormal cardio-ankle vascular index (CAVI) in patients with impaired glucose metabolism (IGM) and factors correlated with its value.

Patients and methods. The study was held on within the cross-sectional multicenter trail «Epidemiology of Cardiovascular Diseases and Their Risk Factors in the Russian Federation» (ECVE-RF) conducted from March to October 2013. The random population sample of adult males and females aged 25–64 years from Kemerovo region with particular investigation of CAVI. Each participant has given written informed consent. Standard research protocol ECVE-RF extended by further study of peripheral arterial stiffness on the VaSeraVS-1000 (Fukuda Denshi, Japan) with automatically measured CAVI. From a sample of 1619 people participants with IGM were isolated: diabetes mellitus (DM) type 1 and 2, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) – a total of 318 people. Two patients with type 1 diabetes, 29

patients with values of ankle-brachial index (ABI) of less than 0.9 (to avoid distortion values CAVI) and 5 patients in whom CAVI has not been studied were excluded from analysis. Thus, the final sample included 282 patients with type 2 diabetes and prediabetes (IFG, IGT), they were divided into two groups: I (n=41) patients with CAVI≥9.0 (pathological CAVI), II (n=241) patients with CAVI <9.0 (normal CAVI).
Results. Pathological CAVI was detected in 14.5% of sample patients with IGM. There was a positive correlation of CAVI value and age (r=0.450; p<0.001), smoking history (r=0.494; p<0.001), increase in systolic and diastolic blood pressure (r=0.303 and r=0.309, respectively, p<0.001), visceral obesity (r=0.123; p=0.031), total cholesterol level (r=0.136; p=0.019), LDL cholesterol (r=0.153; p=0.010) and glucose (r=0.135; p=0.023) levels, negative – with a body mass index (r=-0.121; p=0.042), and glomerular filtration rate CKDEPI (r=-0,365; p<0.001).
Conclusions. The measurement of CAVI in patients with impaired glucose metabolism allows revealing patients with an increased risk of cardiovascular complications.
Keywords: cardio-ankle vascular index, diabetes, prediabetes, factors of cardiovascular risk.

Dynamics of lipid spectrum and markers of inflammation in the patients receiving atorvastatin in hypertensive patients combined with chronic obstructive pulmonary disease

N. A. Sukhaterina

«City Clinical Hospital № 2», Medical University Novosibirsk State Medical University Medical University, Novosibirsk, Russian Federation

Abstract
Objective. To evaluate the performance of lipid profile and markers of inflammation in the dynamics of patients receiving atorvastatin in patients with arterial hypertension and chronic obstructive pulmonary disease.
Material and methods. The study involved 158 patients aged 18–65 years, of which 53 patients with hypertension, 51 patients with COPD, 54 patients with a combination of hypertension and COPD control group consisted of 25 patients without hypertension and COPD.
Special methods of research: – Determination of carbohydrate, protein and lipid metabolism, the concentration of cytokines (IL – 1β and TNF – alpha), blood levels of adipokines (free leptin, resistin, adiponectin), assessment of body composition by bioimpedance component. Patients with comorbid over hypertension and COPD received standard therapy, as well as within six months of atorvastatin 40 mg per day and then re-lipid status were evaluated and markers of inflammation.
Results. Initially, the patients with a combination of hypertension and COPD revealed an increase in fat mass, total and extracellular fluid. Just decreased lean (lean) mass. Revealed atherogenic dyslipidemia, deficiency of protein fractions, high content of negative adipokines – leptin and resistin, adiponectin levels decline. Just found an increased concentration of inflammatory mediators IL – 1β and TNF – α. The dynamics on the background of atorvastatin therapy showed a significant improvement in lipid profile and inflammatory mediators.
Conclusions. For patients with comorbid hypertension and course of COPD is characterized by marked changes in body composition, dyslipidemia, disorders of protein metabolism and adipotsitokinin status. The therapy with atorvastatin 40 mg per day showed a significant improvement in lipid profile, as well as a reduction in the concentration of markers of systemic inflammation.
Keywords: arterial hypertension, chronic obstructive pulmonary disease, dyslipidemia, inflammatory markers, atorvastatin.

The relationship of hormones of adipose tissue with inflammatory markers and homocysteine in coronary atherosclerosis

E. M. Stakhneva[1] , E. V. Kashtanova[1] , Ya. V. Polonskaya[1] , A. V. Kurguzov[2] , O. V. Kamenskaya[2] , Yu.I. Ragino[1] , A. M. Chernyavskiy[2]

[1] Federal State Budgetary Scientific Institution of Internal and Preventive Medicine, Novosibirsk, Russia
[2] Meshalkin Institute of Circulatory Diseases, Ministry of Health of the Russian Federation, Novosibirsk, Russia

Abstract
Research purpose. To study the relationship of hormones of adipose tissue with inflammatory markers and homocysteine in coronary atherosclerosis.
Material and methods. The study included 92 men aged 46–79 years with verified coronary angiographic coronary atherosclerosis. In the serum was determined the concentrations of adiponectin, leptin, resistin, tumor necrosis factor α (TNFα), interleukin 1β (IL1β), interleukin 6 (IL6), interleukin 8 (IL8), C-reactive protein (CRP), homocysteine. The activity of processes of lipid peroxidation in isolated from the serum the low-density lipoproteins (LDL) was determined by the concentration of malondialdehyde (MDA).
Results. IIn men with coronary atherosclerosis, the concentration of adiponectin in blood was 9,04±0,92 mg/ml, resistin was 8.3±0.58 ng/ml. the level of leptin was increased – 20,64±3,69 ng/ml Direct correlation with the body mass index was identified for leptin ($p<0.01$).
Correlations were also found between resistin and CRP ($r=0,520$, $p<0.01$), resistin and IL ($r=0,324$, $p<0.05$), resistin and the initial level of malonic dialdehyde ($r=0,401$, $p<0.01$). The average levels of key proinflammatory cytokines interleukin 6 and interleukin 8 were elevated, 11,73±2,01 PG/ml and of 8.79±1,07 PG/ml, respectively. The level of products of malonic aldehyde in the blood was significantly elevated, compared with the average population values.
Conclusions. In the case of coronary atherosclerosis detected elevated concentrations of the major markers of inflammatory activity (IL, IL, PSA, MDA). The content of adipose tissue hormones adiponectin and resistin corresponds to normal values, and the level of leptin is elevated. Direct correlation between leptin and the degree of oxidative stress between resistin and PSA, resistin and IL, resistin, and baseline levels of MDA.
Keywords: adiponectin, leptin, resistin, coronary atherosclerosis, cytokines, homocysteine.

Association of TLR gene polymorphisms with the severity of coronary atherosclerosis in patients with stable coronary artery disease

A. V. Ponasenko[1] , M. V. Khutornaya[1] , A. G. Kutikhin[1] , I. I. Zhidkova[1] , A. S. Golovkin[3] , O. L. Barbarash[1], L.S. Barbarash[1, 2]

[1] Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russia
[2] Kemerovo State Medical Academy, Kemerovo, Russia
[3] Federal Almazov North-West Medical Research Centre, Institute of Molecular Biology and Genetics, St. Petersburg, Russia

Abstract
Aim. To investigate the associations of the Toll-like receptor (TLR) gene polymorphisms with the severity of coronary atherosclerosis (CA) estimated by SYNTAX (Systematic Coronary Risk Evaluation) score.

Methods. We recruited 292 patients with stable coronary artery disease (CAD). Genotyping was performed in 96-well format using the TaqMan SNP genotyping assay.
Results. We revealed that the C/C genotype of the rs3804099 polymorphism within the TLR2 gene was significantly associated with severe (SYNTAX ≥23) coronary atherosclerosis (OR=2.03, 95%CI=1.09–3.77, p=0.025). However, there were no statistically significant associations of the TLR1 (rs5743551 and rs5743611), TLR2 (rs5743708), TLR4 (rs4986790 and rs4986791), and TLR6 (rs3775073 and rs5743810) gene polymorphisms with the severity of coronary atherosclerosis. When we performed stepwise logistic regression using 16 clinical risk factors, left ventricular ejection fraction (LVF) < 2 affected CA were associated with 1.92-fold higher and 6.25-fold lower risk of severe coronary atherosclerosis, respectively, with the area under the ROC curve (AUC) of 0.677 (0.620–0.730). However, when we added all 8 TLR gene polymorphisms into the regression, we found that the C/T genotype of the rs5743551 polymorphism within the TLR1 gene and the A/G genotype of the rs4986790 polymorphism within the TLR4 gene were associated with 1.83-fold higher and 3-fold lower risk of severe coronary atherosclerosis, respectively. Moreover, AUC increased to 0.710 (0.654–0.762).
Conclusion. The C/T genotype within the rs5743551 polymorphism within the TLR1 gene and left ventricular ejection fraction (LVF) <55% and < 2 affected CA were associated with 1.92-fold higher and 6.25-fold lower risk of severe coronary atherosclerosis, respectively, with the area under the ROC curve (AUC) of 0.677 (0.620–0.730). However, when we added all 8 TLR gene polymorphisms into the regression, we found that the C/T genotype of the rs5743551 polymorphism within the TLR1 gene and the A/G genotype of the rs4986790 polymorphism within the TLR4 gene were associated with 1.83-fold higher and 3-fold lower risk of severe coronary atherosclerosis, respectively. Moreover, AUC increased to 0.710 (0.654–0.762).
Conclusion. The C/T genotype within the rs5743551 polymorphism within the TLR1 gene and left ventricular ejection fraction <55% are associated with severe coronary atherosclerosis in patients with stable CAD.
Keywords: atherosclerosis; immunity; coronary artery disease; Toll-like receptors; gene polymorphisms; SYNTAX.

Factors of inflammation, antioxidant protection and myocardial damage in coronary artery bypass graft in patients with single and multivessel coronary disease

O. A. Rubanenko[1, 2] , O. V. Fatenkov[1] , S. M. Khokhlunov[1, 2] , O. A. Kirichenko[1] , T. M. Kuzmina[1]

[1] Samara State Medical University, Samara, Russia
[2] Samara regional cardiology centre, Samara, Russia

Abstract
Purpose. To estimate the dynamics of factors of inflammation, antioxidant protection and myocardial damage during coronary artery bypass surgery (CABG) in patients with single and multivessel coronary disease.
Methods. Studied were 101 patients who were divided into 2 groups: 1 group comprised 16 patients (68,8% males, mean age 59.1±8.2 years) with single coronary disease, 2 group – 85 patients (80.0% males, mean age 62.2±7.7 years) with multivessel coronary disease. Interleukin – 6 (IL-6), Interleukin – 8 (IL-8), Interleukin – 10 (IL-10), C – reactive protein (CRP), fibrinogen, superoxide dismutase (SOD), troponin I were studied on admission and after operation on 3.8±1.4 days.
Results. The mean levels of C-reactive protein, interleukin – 8 and interleukin – 10 after CABG increased, but their concentration remained within normal range. Mean interleukin – 6 levels in

postoperative period were significantly higher in patients of the 2 group comparing with the 1 group (59,0±29,4 pg/ml vs 34,3±28,2 pg/ ml, p=0,03). Superoxide dismutase levels before operation in patients of the both groups were high, but in the 2 group the level of this indicator was significantly higher compared with the patients of the 1 group (3128,0±2286,6 u/g vs 2389,0±1998,7 u/g, p=0,03). After CABG we observed significant lowering of superoxide dismutase levels wherein in patients of the 2 group concentration of this indicator remained higher (1966,9±1635,1 u/g vs 1182,5±965,2 u/g, p=0,03). Troponin I levels increased after CABG in both groups but differences between groups were not significant.

Conclusion. Our work showed significant rising of interleukin – 6 and superoxidedismutase level in early postoperative period, which demonstrated a high activity of factors of inflammation, antioxidant protection and myocardial damage during reconstructive operations. Troponin levels after CABG also rise but the differences between groups are not significant.

Keywords: coronary artery bypass graft, inflammation, antioxidant, troponin.

Multifocality and progression of non-coronary atherosclerosis in patients undergoing coronary artery bypass grafting

A. V. Bezdenezhnykh, A. N. Sumin, Y. V. Kazachek, A. V. Osokina, Y. V. Bayrakova, N. V. Kondrikova, S. V. Ivanov, O. L. Barbarash

Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russia

Abstract

Purpose: To investigate the prevalence and progression of polyvascular disease (PolyVD) one year after coronary artery surgery (CABG).

Patients and methods. 732 consecutive patients (586 males, 146 females, age median 59 yrs), underwent CABG. After One year after CABG 504 patients (391 men and 113 women) were succeeded to invite clinic for examination. Patients are divided into groups based on the preoperative amount of affected arterial beds: Group 1 (n=243) – lesion of one region; Group 2 (n=178) – lesion of two regions, group 3 (n = 83) – lesion of three or more arterial beds. Any stenosis of 30% or more, and non-cardiac vascular surgery previously carried were considered as an arterial bed lesion. The PolyVD diagnosis was considered in case of two or more affected regions detection. The progression of PolyVD was estimated.

Results. There was a trend to an increase in patients age with a raise of the number of affected beds (p=0.006). Glomerular filtration rate (GFR) was lower in patients with PolyVD as before surgery (p=0,036), and 1 year after it (p=0,041). The logical trend of increasing the intima-media thickness with the number of affected arterial beds affected (p (p<0.001) was revealed. Within 1 year after CABG PolyVD progression occurred in 33 (6.5%) patients. Progression of atherosclerosis was significantly more frequent in patients with PolyVD: the increase in non-coronary artery stenosis was detected in 0.8% of patients with lesions of the pool (group 1), at 10.1% and 15.7% of patients of groups 2 and 3, respectively (p <0,001 when compared to group 1). In a univariate analysis, the likelihood of PolyVD progression increases in case of presence of history of stroke (OR 5.716, 95% CI 2.430–13.444, p=0.001), with a decrease in GFR (OR 0.982, 95% CI 0.968–0.997, p=0.015) and the preoperative PolyVD presence (OR 3.358, 95% CI 2.046–5.513, p<0.001). In multivariate analysis, statistically significant effect on the probability of detecting the progression of IPA preserved defeat several arterial regions (OR 3.064, 95% CI 1.649–5.592, p<0.001) and the presence of suffering a stroke earlier (OR 3.670, 95% CI 1.151–11.699, p=0.027).

Conclusions. One year after CABG non-coronary atherosclerosis progression observed in 6.5% of patients. Factors influencing the likelihood of progression of atherosclerosis are stroke history and preoperative presence of PolyVD.
Keywords: multifocal atherosclerosis, coronary bypass surgery, progression, non-coronary artery.

APOE gene polymorphism is a risk factor for dyslipidemia and potential pharmacogenetic marker of lipid-lowering therapy

N. V. Kokh[1, 2] , E. N. Voronina[1] , G. I. Lifshits[1, 2]

[1] Institute of Chemical Biology and Fundamental Medicine SB RAS, Novosibirsk, Russia
[2]Novosibirsk State University, Novosibirsk, Russia

Abstract
Aim. APOE genotype is widely discussed as a risk factor for lipid disorders and cardiovascular disease pathogenesis of which is atherosclerosis. Statins are the most widely used group of drugs for the treatment of hyperlipidemia and prevention of the atherothrombotic cardiovascular complications. Our purpose is to investigate the role of polymorphisms ε2/ε3/ε4 APOE gene in the risk of hyperlipidemia and its impact on the effectiveness and safety of statin therapy in Russian.
Materials and methods: Genotype APOE was determined in 152 patients, with hyperlipidemia IIa and IIb the WHO types, with evaluation on a scale SCORE high cardiovascular risk and 268 people of population control. For the 107 patients were identified dynamic indicators of clinical and biochemical parameters after 3 months of statin therapy. Efficacy of therapy based on the genotype APOE was investigated on a group of 59 patients receiving 10 mg of rosuvastatin based on the change in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) after 3 months of treatment.
Results: Revealed a protective effect of APOE genotype ε3/ε3 against hyperlipidemia IIa and IIb risk, the relative risk (RR) was 0.69, (p=0.031). Among patients with disorders of lipid metabolism (hypercholesterolemia and/ or an increase in atherogenic index and some additional hypertriglyceridemia), APOE ε3 genotype is associated with better lipid profile: lower level of LDL and TG, (p=0,002 p=0,04 respectively). APOE allele ε2 was a risk factor for type IIb hyperlipidemia (RR=4.15, p=0.00044) compared with carriers of genotype ε3/ε3. APOE genotype had no effect on the change in cholesterol levels after 3 months use of rosuvastatin 10 mg (p=0,46). It was identified, APOE ε4 allele carriers, association with idiopathic muscle pain in patients who received statin therapy (OR=3.40, p=0.028).
Conclusions: APOE ε3/ε3 genotype ε3 is a protective factor for the hyperlipidemia IIa and IIb. APOE ε2 allele is a risk factor not only for the type III, but also for the type IIb hyperlipidemia. Research APOE genotype may be useful to assess the risk of cardiovascular disease, and to identify patients with additional risk factor statin-induced myopathy.
Keywords: APOE, statins, hypercholesterolemia, hypertriglyceridemia, statin-induced myopathy.

Digest

of the International Satellite Symposium of the 84th Congress of the European Atherosclerosis Society, dedicated to the problems of the study of lipoprotein (a)