Endothelial Dysfunction and Chlamydia Pneumoniae Infection Among Patients with Coronary Atherosclerosis

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Coronary atherosclerosis is a major cause of morbidity and mortality in humans worldwide. By the year 2020 it is predicted to be the leading cause of death and disability in the world (5). Recently, understanding at the molecular level revealed that atherosclerosis is an inflammatory disease. Thus, an infection being linked to coronary atherosclerosis is biologically plausible (10). A focus on the triggers of the earliest changes of atherosclerosis (endothelial dysfunction) and inflammation that precede atherosclerotic lesions has centered on several microorganisms. An association between coronary atherosclerosis and microorganisms such as Cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae has been reported in an epidemiological study (4). Chlamydia pneumoniae is the microorganism attracting the greatest interest in this context (14). *In vitro* study it has been shown that Chlamydia pneumoniae is capable of infecting three cellular components of the human vascular wall – namely endothelial cells, smooth muscle cells and macrophages and can proliferate in these components (6). The macrophages may adhere to coronary vessels, where they can cause chronic cytokine-mediated inflammatory reactions inflicting direct endothelial damage (14). Beside this it has been shown that Chlamydia pneumoniae antibody prevalence increases significantly with age (8) and there is an evidence of an association between smoking and Chlamydia pneumoniae seropositivity in the general population (9,13).

The aim of the present trial was to study prevalence of endothelial dysfunction and Chlamydia pneumoniae infection in patients with coronary atherosclerosis. It is well known that platelet hyperaggregation is associated with endothelial dysfunction (1,2), hence in addition platelet aggregation was examined as well. Association between endothelial dysfunction and Chlamydia pneumoniae infection was one of the goals of our investigation.

Material and methods. The present trial is the cross-sectional study of outpatients who are under observation in the Department of Secondary Prevention of Coronary Heart Disease (CHD) of Emergency Cardiology Center. 164 patients were enrolled in the trial, of these 108 (66%) had undergone coronary artery bypass graft operation, 45 (27%) — percutaneous coronary intervention and 11 (7%) patients had CHD without myocardial revascularization. Endothelial function was estimated by plasma nitric oxide (NO) concentrations (normal value 15 – 24 mkmol/L), platelet

aggregation — by platelet aggregation test, titers of Chlamydia pneumoniae IgG (normal titer <1.1) were determined as well.

The results were analyzed by variational statistical method. Mean square deviation and standard deviation were measured. To estimate association between two parameters Pearson correlation coefficient and odds ratio were calculated.

Results. The mean age of patients was 55.8 ± 10.0 years (range — 38 – 72 years). 107 (65%) patients were male. The mean levels of investigated biochemical parameters in patients with coronary atherosclerosis are shown in Table 1.

Table 1. Plasma concentrations of biochemical parameters

Parameters	Mean value
Nitric oxide (mkmol/L)	20.4±14.7
Chlamydia pneumoniae IgG	75.1±78.1
Platelet aggregation (%)	96.6±9.0

Prevalence of endothelial dysfunction was 82% (n=134), the mean value of NO ─ 20.4±14.7 mkmol/L (range — 2 – 49 mkmol/L). In 75% (n=123) of patients Chlamydia pneumoniae IgG was upper limit of normal, the mean titer of IgG was 75.1±78.1 (range — 0.8 – 339.7). Endothelial dysfunction was associated with Chlamydia pneumoniae IgG titers (OR=1.9, CI — 1.6-4.9, p=0.02) (Figure 1).

Among studied patients 60% (n=98) had platelet hyperaggregation, mean aggregation level was 96.6±9.0% (range — 70 - 108%). It was associated with endothelial dysfunction (OR=6.9, CI 2.7 – 17.4, p=0.001). There was statistically significant positive correlation between platelet aggregation and Chlamydia pneumoniae IgG titer — r=0.1, p=0.01 (Table 2).

Figure 1. Association between Chlamydia pneumoniae IgG titers and endothelial dysfunction estimated by odds ratio

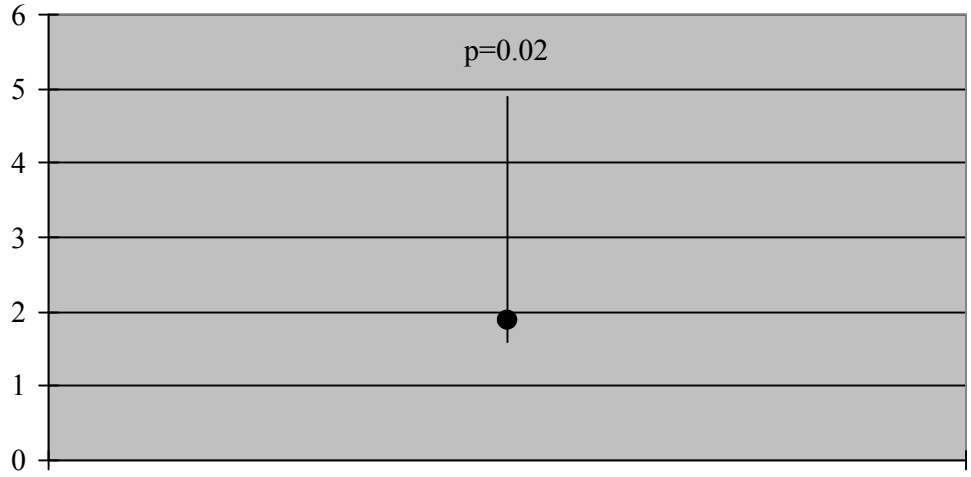

Table 2. Correlation coefficient between Chlamydia pneumoniae IgG titers and platelet aggregation

Parameter	Correlation coefficient	P
Platelet aggregation (%)	0.1	0.01

Discussion. According to our results there was a high prevalence of endothelial dysfunction — 82%. It means that endothelial dysfunction as nontraditional risk factor is an ordinary event in patients with coronary atherosclerosis. In 75% of patients Chlamydia pneumoniae IgG were upper limit of normal. According to our data endothelial dysfunction was associated with Chlamydia pneumoniae infection. It is well known that Chlamydia pneumoniae is characterized by tropism to endothelial cells and the result of this process is endothelial dysfunction (12).

Despite this fact that most of the patients were on aspirin treatment, 60% of them had platelet hyperaggregation. It was associated with endothelial dysfunction in such a category of the patients. For today the fact that nitric oxide has antiaggragative effect is no disputable, it is connected to inhibition of thromboxane A_2 synthesis. It is natural that in nitric oxide abnormal concentration condition activation of platelet adhesion and aggregation occur (3,11). Consequently, according to our study obtained data concerning association between platelet aggregation and endothelial dysfunction are logical.

It is known that Chlamydia pneumoniae bacteria characterized by high adhesion on platelet is a trigger of platelet aggregation (7). The positive correlation between platelet aggregation and Chlamydia pneumoniae IgG titer can be explained by this fact. It is natural, that aspirin is not able to improve endothelial function and treat Chlamydia pneumoniae infection. According to our data these two factors are closely associated with platelet hyperaggregation. Possibly this finding may be related to secondary resistance to aspirin.

In conclusion, most of the patients with coronary atherosclerosis have endothelial dysfunction and Chlamydia pneumoniae infection. These nontraditional risk factors should be considered as some of the goals of the treatment in secondary prevention of CHD. The prevalence of platelet hyperaggregation was high enough as well. This is associated with endothelial dysfunction and Chlamydia pneumoniae infection and is extremely important, particularly in patients following myocardial revascularization. Future prospective studies will provide new insights of disease burden among patients with coronary atherosclerosis.

REFERENCES

1. Марков Х.М. Оксид азота и сердечно-сосудистая система. Успехи физиол. наук. 2001;32:3:49 – 65.
2. Chapidze G., Kapanadze S., Dolidze N. et al. Endothelial dysfunction and hyperlipoperoxidemia in patients with coronary atherosclerosis. Pleotropic effects of cardirat. Experimental & Clinical Medicine. 2006;3:39-42.
3. Chapidze G., Kapanadze S., Dolidze N. et al. Prevention of coronary atherosclerosis by the use of combination therapy with antioxidant coenzyme Q10 and statins. Georgian Medical News. 2005;1:20-25.
4. Fong I.W. Emerging relations between infectious diseases and coronary artery disease and atherosclerosis. CMAJ 2000;163(1):49-56.
5. Gaziano JM. Global burden of cardiovascular disease. In:Braunwald E., Zipes DP., Libby P., eds. *Heart Disease:* A Textbook of Cardiovascular Medicine. Vol 1. 6th ed. Philadelphia, Pa: WB Saunders Co; 2001:1-18.
6. Godzik KG., O'Brien ER., Wang SK., Kuo CC. In vitro susceptibility of human vascular wall cells to infection with Chlamydia pneumoniae. J Clin Microbiol 1995; 33: 2411–4.

7. Hayashida K., Tanaka M., Morita H. et al. Chlamydia pneumoniae seropositivity predicts the risk of restenosis after percutaneous transluminal coronary angioplasty. Heart Vessels. 2002;6:137–145.
8. Karvonen M., Tuomilehto J., Pitkaniemi J., Naukkarinen A., Saikku P. Chlamydia pneumoniae IgG antibody prevalence in south-western and eastern Finland in 1982 and 1987. Int J Epidemiol 1994; 23: 176–84.
9. Karvonen M., Tuomilehto J., Pitkaniemi J., Naukkarinen A., Saikku P. Importance of smoking for Chlamydia pneumoniae seropositivity. Int J Epidemiol 1994; 23: 1315–21.
10. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001;104:365-372.
11. Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. Circ Res. 2001;88:756–762.
12. Mallika V., Goswami B., Rajappa M. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. Angiology 2007; 58:513-522.
13. Ridker PM., Kundsin RB., Stampfer MJ., Poulin S., Hennekens CH. Prospective study of Chlamydia pneumoniae IgG seropositivity and risks of future myocardial infarction. Circulation 1999; 99: 1161–4.
14. Scheller B., Hennen B., Markwirth T., Schieffer H. Evaluation of the role of Chlamydia pneumoniae in the pathogenesis of atherosclerosis - a review. Journal of Clinical and Basic Cardiology 2000; 3:155-158.

ენდოთელიუმის დისფუნქცია და Chlamydia Pneumoniae-ს ინფექცია პაციენტებში კორონარული ათეროსკლეროზით

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აკად. გ. ჩაფიძის სახელობის გადაუდებელი კარდიოლოგიის ცენტრი

კვლევაში შეყვანილი იქნა 164 პაციენტი (საშუალო ასაკი 55.8±10.0 წელი) კორონაროანგიოგრაფიულად მანიფესტირებული კორონარული ათეროსკლეროზით. პაციენტთა 66%-ს გადატანილი ჰქონდა კორონარული შუნტირების ოპერაცია, 27%-ს – კორონარული ანგიოპლასტიკა, დანარჩენ 7%-ში კი დიაგნოსტირებული იყო გულის კორონარული დაავადება მიოკარდიუმის რევასკულარიზაციის გარეშე. კორონარული ათეროსკლეროზის არატრადიციული რისკის ფაქტორებიდან შესწავლილი იქნა ენდოთელიუმის დისფუნქცია მისი ბიოქიმიური მარკერის — სისხლში აზოტის ოქსიდის (NO) კონცენტრაციის მიხედვით, Chlamydia pneumoniae IgG და თრომბოციტების აგრეგაცია. ენდოთელიუმის დისფუნქციის პრევალენტობამ 82% შეადგინა, სისხლის პლაზმაში NO საშუალო კონცენტრაცია 20.4±14.7 მკმოლ/ლ იყო. პაციენტთა 75%–ს Chlamydia pneumoniae IgG ტიტრი ნორმაზე მაღალი აღმოაჩნდა. ენდოთელიუმის დისფუნქცია დაკავშირებული იყო Chlamydia pneumoniae IgG-ის მომატებულ ტიტრთან. აღნიშნული გამოთვლილი იქნა შანსების ფარდობის მიხედვით. მიუხედავად იმისა, რომ პაციენტთა უმრავლესობა იმყოფებოდა ასპირინთერაპიაზე, შემთხვევათა 60%-ში გამოვლინდა თრომბოციტების ჰიპერაგრეგაცია. აღინიშნა სარწმუნო პოზიტიური კორელაციური კავშირი Chlamydia pneumoniae IgG-ის ტიტრსა და თრომბოციტების აგრეგაციას შორის. შანსების ფარდობის გამოთვლის საფუძველზე ასევე გამოვლინდა კავშირი ენდოთელიუმის დისფუნქციასთან, რაც შესაძლებელია დაკავშირებული იყოს ასპირინის მიმართ მეორადი რეზისტენტობის განვითარებასთან. აღნიშნულ ფაქტს უდიდესი მნიშვნელობა გააჩნია პაციენტებში კორონარული ათეროსკლეროზით, განსაკუთრებით კი მიოკარდიუმის რევასკულარიზაციის შემდეგ. მიღებული შედეგების შეჯამებით გამოვლინდა, რომ პაციენტებში კორონარული ათეროსკლეროზით ადგილი აქვს ენდოთელიუმის დისფუნქციას, Chlamydia pneumonia ინფექციას. აღნიშნული არატრადიციული რისკის ფაქტორების შეფასება გულის კორონარული დაავადების მეორადი პრევენციის ერთ-ერთ მნიშვნელოვან სტრატეგიას წარმოადგენს.