VIA MEDICA

EDITORIAL

Cardiology Journal
2008, Vol. 15, No. 4, pp. 299–302

ISSN 1897–5593

In search of understanding the endothelium

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In the current issue of Cardiology Journal, Qi-ming Liu et al. [1] present the study in which they prove that in the group of patients with microvascular angina (myocardial ischemia without stenosis in coronary arteries confirmed by means of several methods) more intense lipid disorders occur than in the control group (precisely selected in terms of gender and age) and additionally that it is associated with endothelial function impairment. This function was evaluated by measuring the extent of flow mediated dilatation of brachial artery (FMD, flow mediated dilatation). The negative correlation between concentration of lipoprotein (a) and LDL cholesterol and FMD [1] was also demonstrated.

This work touches upon the present questions — the problem of microvascular angina pathogenesis, that is of syndrome X as well as the problem of endothelial dysfunction and methods of its investigation.

In patients with syndrome X among others the following disorders were diagnosed: decreased density of capillary vessels in the myocardium [2], increased blood viscosity [3], platelet aggregation disorders [4], hormone disorders [5], abnormal reactions of autonomous nervous system [6] and variously expressed endothelial dysfunction [7].

Endothelial dysfunction is regarded as the first stage in the development of atherosclerosis [8]. It is not a local process, but it refers to all arterial vessels. It was proved that all classical risk factors can impair the function of endothelial [9–12]. In one of our papers we demonstrated that endothelial dysfunction assessed with FMD intensifies with the increasing number of co-existing atherosclerosis risk factors [13].

Endothelial dysfunction is primarily associated with decrease of nitric oxide (NO) secretion by endothelial cells, but also with the increase of concentration of von Willebrand factor (vWF), endothelin (ET), plasminogen activator inhibitor-1 (PAI-1) and with tPA (tissue plasminogen activator) concentration decrease [14]. This results in reduced dilatation ability, predisposition to intravascular thrombosis, leucocyte adhesion to vascular wall, intense proliferation of smooth muscle cells in tunica intima [9]. Since the credible measurement of NO secretion is impossible because of its instability, the research in order to find other methods of endothelial function assessment was conducted. For this evaluation could assess the concentration of other substances secreted by endothelial cells. Endothelial-dependent dilatation of one of easily accesible arteries, such as brachial artery, can also be evaluated. Artery dilatation is caused by the release of nitric oxide provoked by 'shear stress' generated by hyperemia which follows the manometer cuff release. The latter method (FMD), as simple and easily repeatable, is accepted and recommended as the way of endothelial function assessment. The Working Group was created for this method [15]. But so far standarization of the FMD research outcomes and norms has not been achieved [16]. The FMD values considered as reference oscillate in wide range from 4 to 10% [16].

Until recently there was no research which would demonstrate the correlation between concentration of substances secreted by endothelium and FMD. In one of the recently published papers Maas et al. proved a direct relation between the decrease of systemic NO production by endothelial NO synthase (eNOS) and reduction of FMD [9]. In one of our studies we documented that patients with syndrome X have significantly higher PAI-1 concentrations than healthy people and patients with

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atypical chest pain. It was associated with a trend towards lower FMD values [13]. The correlation between brachial artery FMD and extent and intensity of atherosclerotic alterations in coronary arteries [10] was also confirmed.

In their study, Liu et al. [1] showed that in the group of patients with microvascular angina, in comparison with control group, the levels of total cholesterol (TC), LDL cholesterol, apolipoproteine B and lipoproteine (a) were significantly higher and were associated with FMD reduction. In the group of patients with FMD values ≤ 4%, a significant negative correlation was observed between FMD and concentration of LDL cholesterol and lipoprotein (a) [1]. First studies describing endothelial dysfunction in patients with hypercholesterolemia were published in the late 90s [9]. Not all the studies later conducted confirmed the existence of such relations. The mechanism in which hypercholesterolemia influences the decrease in production and/or NO bioaccessibility is not clear. The following are regarded as possible reasons: limited substrate, that is L-arginine availability, increase in endogenous eNOS inhibitors activity (ADMA, asymmetrical dimethyloarginine), oxidative stress leading to eNOS function impairment and negative influence of free radicals [8]. In his work Maas et al. [9] showed that secretion of 15N-labeled nitrate metabolites is 40% lower in patients with hypercholesterolemia than in normocholesterolemic patients. It was connected with 36% reduction of FMD and with considerably lower eNOS expression in platelets [9]. However, this research showed no influence of cholesterol level on concentration of ADMA and 8-iso-PGF (prostaglandin F metabolite), which indicates that increased oxidative stress cannot be considered the reason for reduced NO secretion. However, there are studies documenting that hypercholesterolemia (LDL ≥ 160 mg/dL) contributes to the enhacement of oxidative stress in advanced stages of atherosclerosis.

The key role of eNOS in the development of organ damage induced by hyperglycemia was presented on mice with homozygotic diabetes in relation to lack of eNOS [17]. It was stated that in individuals with diabetes the lack of eNOS has greater adverse impact on microcirculation than on great vessels — the alterations were observed in renal glomerular vessels but not in the aorta. Despite worse glycemia control, the changes in the vessels were more benign in mice with diabetes, but with eNOS preserved. In another study the influence of hyperglycemia and hyperinsulinemia on dilatative vessel reaction was assessed. The outcomes of this study give the evidence that hyperglycemia and hyperinsulinemia increase oxidative stress expressed through 5–10% reduction of plasma antioxidants (in patients with diabetes as well as in healthy individuals), which did not cause the reduction of vasodilatative reaction in response to acetylcholine [18]. So far the oxidative stress was believed to play a key role in the development of vessel complications in patients with diabetes. But in one of the studies conducted to date was proved that the administration of rosiglitazone [a drug from thiazolidinedione class of drugs which are PPAR--gamma receptor (peroxisome proliferator-activated receptor gamma) agonists] brings the improvement in endothelial function expressed with the increase of FMD without any impact on ADMA and concentration of oxidative stress markers [19]. Rosiglitazone was compared to glyburide (a derivative of sulphonylurea), which showed no influence on endothelial function and oxidative stress markers in spite of comparable to rosiglitazone influence on glycemia, insulin concentration during fasting stomach and concentration of peptide C. The favourable influence of thiazolidinediones, resulting most probably from their pleiotropic effects, was confirmed in the PROactive study, which showed a significant reduction in non-fatal myocardial infarction and stroke incidence, with the trend towards the reduction of all-cause mortality and reduction of number of cardiovascular events and interventions [20].

Endothelial dysfunction expressed with FMD reduction and PAI-1 concentration increase was documented in cigarette smokers [21]. In patients with arterial hypertension a variously expressed endothelial dysfunction was also diagnosed [22].

The division of the group (45 patients — 21 with microvascular angina and 24 healthy volunteers) investigated by Liu et al. [1] into subgroups with FMD ≤ 4% and FMD > 4% proved the significant negative correlation between FMD ≤ 4% and concentration of LDL cholesterol and Lp(a).

Patients with microvascular angina as well as patients without symptoms of angina were in the group with lower FMD and higher concentration of LDL cholesterol and Lp(a). It indicates that more advanced endothelial dysfunction is not necessarily connected with the presence of syndrome X. Therefore a question arises why microvascular angina does not occur in all patients with endothelial dysfunction since every patient with microvascular angina has this dysfunction only with the difference in its intensity? It suggests multifactorial pathogenesis of syndrome X. It is also unk-

nown what extent of cardiovascular risk is associated with this kind of myocardial ischemia?

It is clear that the evaluation of cardiovascular risk based on classical atherosclerosis risk factors occuring in a particular individual, especially in younger age groups, does not provide complete risk assessment. That is why it is suggested to use the FMD evaluation in combination with the IMT evaluation (evaluation of the thickness of the intima-media complex in carotid artery) in order to complete the assessment of the threat of cardiovascular events [23]. The results of the research conducted by Qiming Liu et al. imply the same.

It was demonstrated that endothelial dysfunction can improve after treatment with statins [24], ACEI [25], some of the hypoglycemic drugs (irrespective of the glycemic control — rosiglitazone) [19], after physical exercise [22, 26], smoking cessation, supplementation with folic acid or vitamin C.

We should also expect that there will be further studies searching for the links between endothelial function enhancement and the improvement of the myocardial perfusion together with subsiding of anginal symptoms in patients with microvascular angina after the therapy aiming to normalize an endothelial function. Obviously if the endothelial dysfunction constitutes a pathogenetic basis for syndrome X and is not only the 'by-stander' phenomenon, the modification of the lifestyle (physical activity) and application of drugs which are known to improve endothelial function should bring effects such as the improvement in FMD and clinical status as well as the increase in myocardial perfusion proved by means of different methods. The work by Liu et al. indicates how many efforts should yet be made in order to explain the pathogenesis of syndrome X, its diagnostics and treatment. It underlines also that we have good diagnostic tools at our disposal and that they should find wider use.

Acknowledgements

The authors appreciate help of Agnieszka Syska with preparation of the authorized English version of the manuscript.

References

1. Liu Q.M., Zhou S, Qi S et al. Significance of lipid profile and endothelium-dependent vasodilatation in the pathogenesis of microvascular angina. Cardiol J, 2008; 15: 324–328.
2. Antonios TFT, Kaski JC, Hasan KM et al. Rarefaction of skin capillaries in patients with angina chest pain and normal coronary angiograms. Eur Heart J, 2001; 22: 1144–1148.
3. Libionka A, Figiel W, Maga P et al. Blood viscosity in cardiac syndrome X and other cardiovascular disorders. Folia Cardiol, 2005; 12: 465–470.
4. Lanza GA, Andreotti F, Sestito A. Platelet aggregability in cardiac X syndrome. Eur Heart J, 2001; 22: 1924–1930.
5. Rosano GM, Collins P, Kaski JC et al. Syndrome X in women is associated with estrogen deficiency. Eur Heart J, 1995; 16: 610–614.
6. Mizia M, Mizia-Stec K, Gąsior Z et al. Mental stress, heart rate and endothelial function in patients with syndrome X. Cardiology J, 2007; 14: 180–185.
7. Sax FL, Canzon III RO, Hanson C et al. Impaired forearm vasodilatator reserve in patients with microvascular angina. Evidence of a generalized disorder of vascular function. N Engl J Med, 1987; 317: 1366–1370.
8. Baykan M, Erem C, Erdogan T et al. Impairment of flow-mediated vasodilatation of brachial artery in patients with primary hyperparathyreoidizm. Int J Cardiovasc Imaging, 2007; 23: 323–328.
9. Maas R, Schwedhelm E, Khal L et al. Simultaneous assessment of endothelial function, nitric oxide synthase activity, nitric oxide-mediated signaling and oxidative stress in individuals with and without hypercholesterolemia. Clinical Chemistry, 2008; 54: 292–300.
10. Celermajer DS, Sorensen KE, Gooch VM et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet, 1992; 340: 1111–1115.
11. Forte P, Copland M, Smith LM et al. Basal nitric oxide synthesis in essential hypertension. Lancet, 1997; 349: 837–842.
12. O'Byrne S, Forte P, Roberts LJ et al. Nitric oxide synthesis and isoprostane production in subjects with type 1 diabetes and normal urinary albumin excretion. Diabetes, 2000; 49: 857–862.
13. Grąbczewska Z, Thews M, Góralczyk K, Kubica J. Endothelial function in patients with chest pain and normal coronary angiograms. Kardiol Pol, 2007; 65: 1199–1206.
14. Chłopicki S. Zapalenie śródbłonka w atherotrombosis. Kardiologia po Dyplomie, 2005; 4: 77–88.
15. Corretti MC, Anderson TJ, Benjamin EJ et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated dilatation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol, 2002; 39: 257–265.
16. Peretz A, Leotta DF, Sullivan JH et al. Flow mediated dilation of the brachial artery: an investigation of methods requiring further standardization. Cardiovascular Disorders, 2007; 7: 11.
17. Mohan S, Reddick RL, Musi N et al. Diabetic eNOS knockout mice develop distinct macro- and microvascular complications. Laboratory Investigations, 2008; 88: 515–528.
18. Natali A, Baldi S, Vittone F et al. Effects of glucose tolerance on the changes provoked by glucose ingestion in microvascular function. Diabetologia, 2008; 51: 862–871.
19. Kelly AS, Thelen AM, Kaiser DR et al. Rosiglitazon improves endothelial function and inflammation but not asymmetric dimetyloarginine or oxidative stress in patients with type 2 diabetes mellitus. Vascular Medicine, 2007; 12: 311–318.
20. Domandy JA, Charbonnel B, Eckland DJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes mellitus in the PROactive Study (Prospective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet, 2005; 366: 1279–1289.
21. Celermajer DS, Sorensen KE, Georgakopoulos D et al. Cigarette smoking is associated with dose-related and potentially

reversible impairment of endothelium-dependent dilatation in healthy young adults. Circulation, 1993; 88: 2149–2155.
22. Westhoff TM, Franke N, Schmidt S et al. Beta-blockers don't impair benefits of endurance training in hypertensives. J Human Hypertens, 2007; 21: 486–493.
23. Erzen B, Sabovic M, Sobestjen M et al. Endothelial dysfunction, intima-media thickness, ancle-brachial pressure index and pulse pressure in young post-myocardial infarction patients with various expression of classical risk factors. Heart Vessels, 2007; 22: 215–222.
24. Koh KK, Quon MJ, Han SH et al. Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients. Diabetes Care, 2008; 31: 776–782.
25. Bots ML, Remme WJ, Lüscher TF et al. ACE inhibition and endothelial function: main findings of PERFECT, a sub-study of EUROPA Trial. Cardiovasc Drugs Ther, 2007; 21: 269–278.
26. Trzos E, Kurpesa M, Rechcinski T et al. The influence of physical rehabilitation on arterial compliance in patients after myocardial infarction. Cardiol J, 2007; 14: 366–371.